HIV Psychiatry

A Practical Guide for Clinicians

James A. Bourgeois
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Foreword

Effective HIV care remains challenging and complex, despite great advances in the treatments that have reduced side effects and allow survival durations approaching those of uninfected persons. HIV infection must be seen as much more than an isolated illness. Rather, it exists in a social context, where issues as seemingly separate as stigma, isolation, substance use, as well as an array of comorbid illnesses may contribute to healthcare disparities and compromise treatment outcomes. Persons with HIV often experience mental health stressors or co-incident psychiatric disorders, and care systems and clinicians must understand and address these issues to optimize the full health of their patients. Fortunately, they now have an ally in a new book, *HIV Psychiatry: A Practical Guide*.

Dr. Mary Ann Cohen, one of the world's leading experts in HIV psychiatry, and her colleague, Dr. James Bourgeois, have assembled an impressive group of authors to provide a wide-ranging review of the multifaceted interactions among HIV infection, its social setting, and the common mental health comorbidities. They highlight the multidirectional nature of these relationships, how HIV infection can lead to or exacerbate psychosocial conditions, and how those conditions may compromise the medical management of HIV itself. Each chapter aims to provide truly practical advice for busy clinicians who may feel untrained and poorly supported in these crucial aspects of high-quality, comprehensive care.

The Practical Guide brings our attention to a wide range of topics. Some are, of course, expected, including HIV and psychiatric co-morbid illnesses such as anxiety, depressive, and bipolar disorders, as well as suicide risk. While some HIV care settings have created models of integrated care that bring together teams of medical, mental health, and psychosocial experts, many HIV clinicians must provide a wide range of care themselves. The Practical Guide addresses both ends of this care spectrum by reviewing models of care to help bring teams together, while also offering direct advice on managing the full array of medical and mental health conditions seen commonly in busy practices. The book includes reviews of screening tools to better identify co-morbid psychiatric illnesses, particularly those tools that are practical in application and available without charge. One of the most admirable directions taken by the editors and authors of this new book is their attention to the social

setting of HIV infection, including stigma, discrimination, healthcare access barriers and disparities, and how these must be understood to optimize care outcomes. The book identifies these complex medical and societal interactions as syndemics, an important approach to better address these challenges.

HIV Psychiatry: A Practical Guide is also current with today's many changes. The review of HIV and HCV incorporates newly developed curative HCV medications, and another chapter reviews the still-evolving story of HIV and COVID-19. In a useful chapter on legal and ethical aspects of HIV care, the topic of the unfortunate but still-in-place and actively debated regulations preventing gay men from donating blood is considered.

This new book provides a unique benefit for effective, comprehensive, and compassionate HIV care. Its editors and authors are to be congratulated. This is a timely and important contribution.

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Preface

Many HIV physicians who take care of persons with HIV and AIDS are infectious disease specialists who, over the past 40 years, have helped to revolutionize treatments and transform HIV and AIDS into a chronic manageable illness. Now, HIV physicians are ensuring that their patients stay well, get the best HIV care, and also get the care they need for other multimorbid illness. They know well that HIV can be prevented and make use of the remarkable resources that enable their patients to prevent transmission to others. These include "U=U"–Undetectable=Untransmittable, "PEP" – Post-Exposure Prophylaxis, and "PrEP" – Pre-Exposure Prophylaxis. However, most HIV physicians, because of their superb and competent care of persons with HIV, do not see persons who are not infected with HIV.

It is up to all the rest of us to be sure that we are able to make use of resources for prevention.

It is the pediatrician who cares for adolescents, the geriatrician who sees older adults, the internist, primary care physician, neurologist, obstetrician-gynecologist, surgeon, emergency room physician, general psychiatrist, dentist, as well as nurses, physician assistants, social workers, psychologists, and addiction counselors who see patients long before they become infected with HIV.

All clinicians need to know that even after a potential inadvertent or coerced exposure to HIV that HIV infection can be protected with PEP. All clinicians need to be able to recognize and risk behaviors and make recommendations to help with changes just as they routinely recommend the use of sunscreen for skin cancer prevention, exercise and healthful eating for general health and well-being, smoking cessation for prevention of lung disease and oropharyngeal cancers and other vitally important preventive measures such as physicals, dental care, obstetrical care, vaccinations, and screening for breast, colon, and prostate cancer.

In this practical guide for clinicians, we hope to empower clinicians to understand how to prevent HIV transmission, to recognize risk behaviors, and to add something else to their repertoires. We hope to give all clinicians a sense of security and competence with the recognition and understanding of some of the psychiatric illnesses that complicate and perpetuate the HIV pandemic that continues to persist throughout every area of the world despite the magnitude of the progress that has

transformed the illness from a rapidly fatal to chronic illness that is no longer life limiting. In 2018, there were still a total of 37.9 million persons living with HIV throughout the world, 1.7 million newly infected, and 770,000 deaths.

There were 17 million orphans left behind by AIDS.

Missing in most of the literature on HIV is the subtle, and sometimes not so subtle, contribution of psychiatric symptoms, psychiatric illness, and risk behaviors that drive the pandemic and serve as catalysts for new infections.

In this practical guide, we provide you with the state-of-the-art understanding of not only prevention but also a way to recognize risk behaviors, psychiatric symptoms, and psychiatric illnesses that will demystify and decode for you the sometimes enigmatic and frustrating reasons for nonadherence with diagnostic procedures and life-saving treatments and care.

We cover all of the behaviors and pathology as well as the resources and treatments available.

Intimately related to the psychiatric illness, and potentiating the overall suffering of early HIV patients, is the social stigma experienced by HIV patients. The elements of such social stigma include HIV itself, psychosocial and psychiatric vulnerability, and discrimination of a more "systemic" nature, e.g., inadequacy of optimized medical care, patients being uninsured or underinsured for healthcare, and other areas of poor social support for the management of a chronic and severe illness. Regrettably, stigma continues to apply to patients with other psychiatric illnesses, not necessarily those associated with HIV.

From prevention to exposure, transmission, infection, and course of illness, the human immunodeficiency virus (HIV) and acquired immune deficiency syndrome (AIDS) are inextricably related to risk behaviors and mental health. HIV stigma and fear further complicate the HIV pandemic. Comprehensive and collaborative care play a vital role in the prevention of suffering and adherence to care. An understanding of the psychiatric and psychosocial aspects of the HIV pandemic is key to the prevention of HIV transmission and the prevention of suffering in persons with HIV and AIDS. Nearly four decades later, some of the principles we have learned may be applicable to the COVID-19 pandemic. Of particular note is the disparate impact of pandemics on populations and on healthcare. The magnification of racism in society and healthcare disparities is once again apparent. While the modes of transmission, the immediacy and terror invoked by droplet infection, and specific vulnerabilities make these very different pandemics, the clear need for changes in both society and healthcare are similar.

As the world struggles to come to grips with yet another international pandemic with COVID-19 (which disproportionately impacts socially marginalized and stigmatized populations, as has been the case with HIV), medical professionals and other advocates must come up with strategies to accommodate to the realities of the COVID-19 pandemic, while continuing the yet unfinished work in managing the multitudinous complications and intricacies of HIV disease. As one pandemic has passed the initial, acute phase to be transformed to a complex chronic illness, another has supplanted it. The editors hope that this guidebook, written by many authors with the challenges and honors of managing the COVID-19 pandemic,

gives enduring guidance to medical and other professionals caring for complicated clinical patients.

An understanding of the role of psychiatric aspects of HIV and AIDS is crucial for both prevention of HIV transmission and for the care of persons with HIV. It is in this spirit that we have written this book. All editors have been closely involved in HIV psychiatry. Our goal is to produce a book for three audiences. For the psychiatrist who may not specialize in HIV psychiatry per se, there is a need for a refresher on the current state of psychiatric illness management among people living with HIV. For primary care physicians, specialists, and subspecialists, there is a need for a concise volume on the psychiatric aspects of HIV prevention and treatment that substantially impacts the overall care of the patient. Finally, for those health and mental health professionals from clinical psychology, nursing, physician assistant, social work, and for clinicians and professionals in other disciplines, there is a need for similar understanding of psychiatric catalysts of the pandemic.

HIV began as a dramatic, unexpected epidemic. Due to the efforts of many, it has been transformed into a generally manageable chronic illness, albeit with its persistent specific complications. From the beginning of the pandemic to the present, psychiatric multimorbidity remains an important element in prevention of HIV and the illness experience and care for persons infected with and affected by HIV. The editors hope that this volume provides useful guidance for our health-profession colleagues as they face ongoing challenges in working with persons with HIV and AIDS.

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Chapter 1
The Definition and Scope of HIV Psychiatry: How to Provide Compassionate Care

Mary Ann Adler Cohen, Jonathan Artz, Hameed Azeb Shahul, Caitlin Gonsolin, Ripal Shah, Dennis Dacarett-Galeano, Luis F. Pereira, and Kelly L. Cozza

Persons who are at risk for, affected by, or infected with the human immunodeficiency virus (HIV) are exquisitely vulnerable and deserve compassionate care. In this first chapter, and throughout this book, we present clinicians with approaches for prevention and care for persons with HIV that may diminish clinician anxiety and thus empower clinicians to make their work easier, more enjoyable, and less time-consuming and frustrating.

HIV medicine and HIV psychiatry developed in the 1980s during the first years of the pandemic by pioneering internists, infectious disease specialists, pediatricians, and psychiatrists who recognized the specific psychosocial complexities of

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this new and, at the time, devastating illness, an acquired immunodeficiency (AIDS) of unknown cause. The early years of the HIV pandemic were characterized by intense advocacy and activism by both gay men and by clinicians to counter profound apathy and AIDSism and, thus, contributed to the discovery of the cause of AIDS and to the development of the first antiretroviral treatments. Over the four decades since 1981, HIV/AIDS has become a complex severe manageable illness, and today, HIV psychiatry is closely associated with the broader field of consultation-liaison (C-L) psychiatry. However, many significant contributions to HIV psychiatry were made, and continue to be made, by general psychiatrists and other psychiatrists who are not C-L psychiatrists as well as by other mental health clinicians. The field of HIV psychiatry may be thought of broadly and inclusively to honor the contributions of all in the specialty who are involved with prevention of HIV infection and care of persons with HIV.

HIV/AIDS psychiatry is defined as the sub-subspecialty of consultation-liaison psychiatry that focuses on prevention, care, and treatment of HIV and AIDS; psychiatric aspects of risk behaviors and their antecedents; psychiatric manifestations of HIV and its stigma; psychological consequences of HIV infection and its multimorbidities and their impact on persons infected with and affected by HIV; and the imperative for an integrated biopsychosociocultural approach to prevention, care, and adherence [1–16].

No matter what your field of medicine, you can help decrease transmission of HIV and HIV-related stigma and discrimination and decrease morbidity and mortality in persons at risk for HIV or living with HIV and AIDS. No matter which specialty, subspecialty, or discipline, you can make a difference in the prevention of HIV and the care of persons with HIV. See Table 1.1 for specific details.

Psychiatrists of every specialty and subspecialty can play important roles in the HIV epidemic. Clinicians can work together as teams and communicate in order to play a crucial role in both prevention and care. This comprehensive compassionate care of persons with HIV is exemplified in the concept of a biopsychosociocultural approach as first applied to HIV and AIDS by Cohen and Weisman [3]. In this chapter, we will illustrate the importance of compassion and a comprehensive biopsychosociocultural approach [1–6]. Persons with HIV/AIDS are seen from the standpoint of their systemic medical illnesses, comorbid psychiatric illnesses, and psychological responses to illness. In addition, attention is paid to social aspects and stressors, cultural, political, and societal factors. Persons with HIV/AIDS are treated

Table 1.1 Making a difference in HIV prevention and care

Medical specialists: cardiologist, dermatologist, emergency room physician, endocrinologist, gastroenterologist, geriatrician, infectious disease specialist, internist, intensivist, psychiatrist, surgeon, obstetrician-gynecologist, nephrologist, neurologist, ophthalmologist, pediatrician, psychiatrist, and urologist
Psychiatric subspecialists: ambulatory, child and adolescent, consultation-liaison, emergency, geriatric, HIV/AIDS, and inpatient
Mental health disciplines: social workers, nurses, psychologists, neuropsychologists, and addiction specialist counselors

with respect and dignity as part of a family and community deserving of care, taking into account their personal concerns and understanding of their illness as well as wishes, preferences, and goals for care. See Fig. 1.1 for an illustration of this comprehensive approach to prevention and care.

This chapter gives clinicians and other caregivers a clear, practical guide to psychiatric aspects of HIV care, including definition, stigma prevention, and competent, compassionate care for the psychiatric multimorbidities and manifestations of HIV and AIDS. The scope of the book includes a comprehensive biopsychosociocultural approach to HIV/AIDS prevention, assessment, and care throughout the life cycle. Important elements covered include the management of stigma, identification and understanding of the signs and symptoms of comorbid psychiatric disorders, and their bidirectional impact on the individual and HIV-related illness. We present comprehensive, collaborative approaches to care from conception and pregnancy to childhood, adulthood, older age, dying, and death.

Many persons throughout the world do not believe that there is still an HIV pandemic and that the epidemics of acquired immunodeficiency syndrome (AIDS) and HIV stigma still exist. As we will see, throughout the world, there is ample evidence of an ongoing HIV pandemic: 36.9 million persons worldwide are living with HIV, despite the fact that HIV and AIDS are entirely preventable [7]. There are 17 million children orphaned by the loss of one or both parents to AIDS, all of whom are affected by loss and some of whom are living with HIV as a result of maternal transmission.

Although HIV is very easy to diagnose with rapid HIV testing, throughout the world, 19 million, or 54% of persons with HIV, are unaware that they are infected [7]. In the United States, despite access to HIV testing and care, HIV is still an epidemic, with 1.1 million people living with HIV and 37,600 people becoming

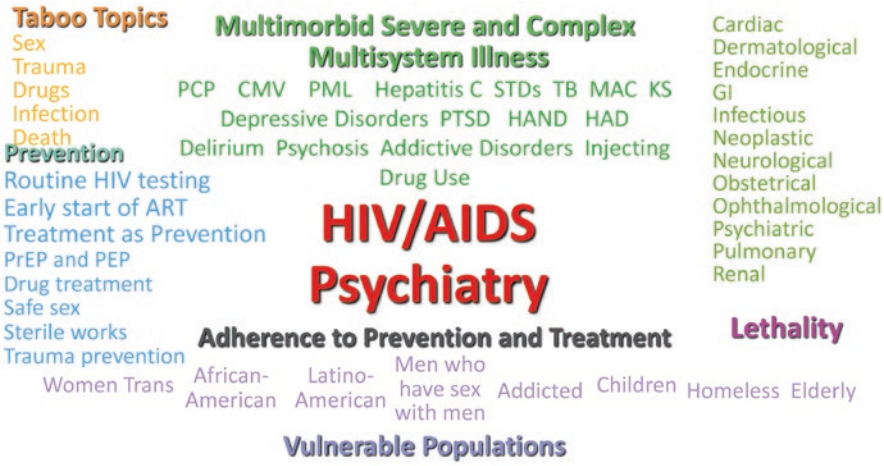

Fig. 1.1 Biopsychosociocultural aspects of HIV/AIDS

infected each year. In the United States, 1 in 7 (162,500) persons with HIV is unaware of being infected and can unknowingly transmit the virus to others [8, 9].

The treatment of persons with HIV needs to be multidimensional and includes ascertainment of social determinants of stigma. There is a need to determine how HIV stigma and discrimination interfere with access to care, amelioration of risk behaviors, and adherence to treatment. Caring for persons with HIV requires an emphasis on an understanding of the syndemics (synergistic epidemics) of substance use disorders, depressive disorders, violence, and post-traumatic stress disorder [13–16] in addition to HIV-associated neurocognitive disorders in both older and younger persons with HIV and AIDS. If systemic lupus erythematosus, multiple sclerosis, malaria, Lyme disease, and syphilis are "The Great Masqueraders" because many of their symptoms are similar to those of other illnesses, HIV is "The Great Magnifier" of both illness and aspects of healthcare. HIV magnifies healthcare disparities, stigma, and discrimination in both society and healthcare delivery systems and leads to HIV transmission and lack of access to care [10]. As long as HIV is stigmatized, persons who have risk behaviors or suspect that they have HIV may well fear discrimination or ostracism and may thus delay or avoid getting tested, being diagnosed, disclosing HIV to potential partners, or accessing care [11]. The stigma and discrimination that are magnified by HIV were described as AIDSism and comprised of homophobia, misogyny, addictophobia, psychiatric illness stigma, racism, fear of infection, and multiple other interpersonal, societal, and political determinants [12]. For more detailed information about AIDSism, stigma, and discrimination, see Chap. 3.

This chapter will introduce the reader to practical aspects of HIV psychiatry based on the tenets of compassion, de-stigmatization, prevention, and provision of lifetime care. Specific and defining features include an emphasis on confronting and managing stigma, HIV prevention, humanism, compassion, diagnosing and treating psychiatric disorders, and the utilization of biopsychosociocultural approach to collaborative and integrated care.

The following case vignettes will serve to illustrate this concept.

Case Vignette 1.1

Ms. A was a 48-year-old single, domiciled, disabled, unemployed former actress with a 20-year history of AIDS diagnosed late, with profound wasting and opportunistic infections. She was started on antiretroviral medications which led to lipodystrophy. She subsequently was diagnosed with Stage 4 lung cancer and treated with surgery, radiotherapy, and chemotherapy. She developed severe hypothyroidism related to radiation therapy. Several years later, Ms. A had a massive myocardial infarction and was diagnosed with severe coronary artery disease related to chest radiation and requiring coronary artery bypass surgery. Twenty years after her diagnosis with AIDS, she developed breast cancer requiring mastectomy. The patient presented in an existential crisis with depression, sadness, and other emotional perturbation due to the feeling that her disfigurement from lipodystrophy was compounded by disfigurement from mastectomy.

Case Vignette 1.2
Mr. B was a 29-year-old single, domiciled, computer engineer unknowingly infected with HIV. While intoxicated with alcohol and in a blackout, he had a sexual encounter with a man whom he met online. As soon as he awakened the next morning, he called to find out if his partner had used a condom and what his partner's HIV status was. He learned that he had indeed experienced anal penetration without a condom and that his partner was HIV-positive. Mr. B had had a recent test for HIV and tested negative, and this encounter was his first experience with anal penetration. He immediately tried to obtain a month's supply of medicine for post-exposure prophylaxis (PEP) but was unable to get it in an emergency room or a hospital clinic. He was unable to obtain PEP until 74 h had elapsed. He knew that he was likely to be infected since the maximum time – 72 h – had passed for prevention of infection following an accidental exposure. Ten days following the sexual encounter, Mr. B developed a serum sickness, flu-like reaction heralding seroconversion and infection with HIV. He was depressed, suicidal, and angry that the medical system had failed to help, or even try, to prevent HIV infection. Online, Mr. B found a methodology for assisting himself to die. He obtained and self-administered the drugs. He was rescued by a friend, and, after an inpatient stay on a psychiatric unit, he self-referred for outpatient care for depression. He committed suicide at the end of his second year of psychotherapy and antidepressants.

Case Vignette 1.3
Mr. C was a 72-year-old disabled married domiciled former chef who was diagnosed with HIV when he was 43 years of age and using heroin by injection. Although he was never treated with antiretroviral therapy, Mr. C's viral load remained undetectable, and his HIV was never symptomatic in the 29 years following his positive test. Mr. C was referred for psychiatric care and was diagnosed with major depressive disorder with suicidal ideation, history of multiple suicide attempts since testing HIV positive, and PTSD following early childhood neglect and physical trauma. He was chronically depressed and suicidal following his HIV diagnosis. He had a history of rheumatic heart disease, increasingly worsening heart failure, and emphysema requiring 24-h oxygen dependence. He was abstinent from heroin (and on methadone as agonist therapy) and alcohol for 25 years and from cigarettes for 8 years. He was treated with psychodynamic psychotherapy, family psychotherapy, and antidepressants. He was coping well, less depressed, and not suicidal. He was enjoying a relationship with his family for 6 years until he developed severe and unremitting dyspnea and tachypnea and was diagnosed with Stage 4 lung cancer. He died after 1 year of palliative, and then hospice, care.

HIV/AIDS is a highly stigmatized, preventable illness caused by a virus and transmitted through human risk behaviors, for which psychiatric disorders can serve as both vectors of illness and obstacles to adherence. Psychiatric treatment can have a significant impact on morbidity and mortality and special implications for public health and general medical and psychiatric care.

With the advances in HIV treatment, HIV has become a chronic, manageable illness for people with access to HIV medical care and treatment with antiretrovirals. However, if HIV medical care is unavailable and/or if comorbid psychiatric illness impedes access to diagnosis and treatment, individuals with HIV are vulnerable to progression of illness, as was common in the early stages of the HIV epidemic. Clinicians in every subspecialty and discipline can play a role in the prevention of HIV transmission and access to and retention in care.

The central nervous system is an independent reservoir for HIV, increasing the risk for HIV-associated neurocognitive disorders and vulnerability to other opportunistic infections and cancers of the central nervous system, such as cryptococcal meningitis, toxoplasmosis, and lymphoma. See Chap. 10 for HIV-associated neurocognitive disorders and delirium. HIV is also associated with multiple systemic medical illnesses, including hepatitis C, nephropathies, endocrinopathies, and neoplasms, as illustrated in the case vignettes of Ms. A and Mr. C.

The HIV epidemic has a disproportionate impact on people of color and people who are LGBTQ, homeless or marginally housed, psychiatrically ill, and/or economically disadvantaged. HIV is more prevalent in individuals with premorbid psychiatric illness, and psychiatric illness and suicidal ideation are prevalent following infection with HIV.

The HIV/AIDS epidemic magnifies psychiatric illness stigma and AIDSism and decreases access to psychiatric care and HIV testing. Syndemics of substance use disorders, PTSD, depressive, and other co-morbid psychiatric disorders complicate and perpetuate the epidemic and decrease adherence to HIV care [13–16]. See Chap. 14 for details about the syndemics of HIV. The psychiatric treatment of depressive disorders, PTSD, and addictive disorders can prevent suicide and improve adherence to both risk reduction and medical care [17, 18]. For further details, see Chap. 6 for depressive disorders, Chap. 7 for PTSD, Chap. 11 for addictive disorders, and Chap. 13 for suicide.

Psychiatric Disorders

A complex, bidirectional relationship exists between HIV and psychiatric disorders [19–28]. There is a high prevalence of HIV in persons with psychiatric disorders and a high prevalence of psychiatric disorders in persons with HIV (Fig. 1.2) [19–28]. The complexity of this relationship emerges from numerous factors (Fig. 1.3). The factors may be the direct result of psychiatric symptoms, such as disinhibition, on risk of HIV infection, and contextual social factors that arise in conjunction with psychiatric disorders, such as homelessness [27, 28].

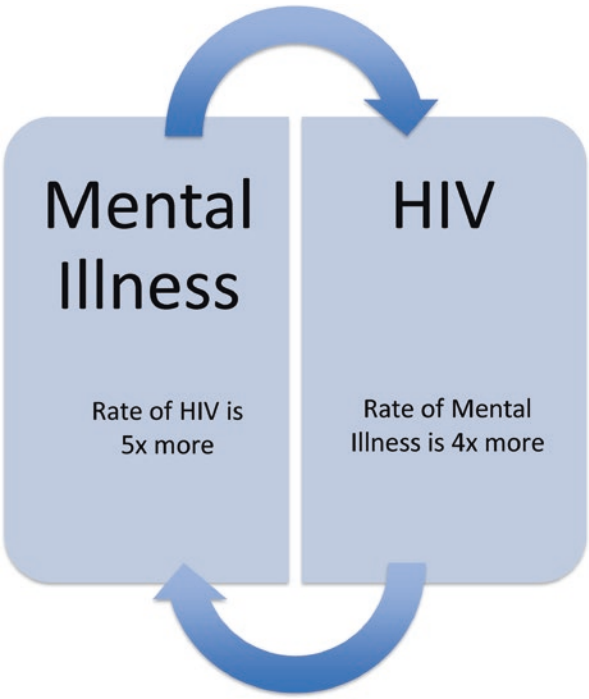

Fig. 1.2 Bidirectionality of HIV and mental illness. (Based on data from Ref. [18])

Complexity Of Bidirectionality
May be due to direct results of symptoms (disinhibition)
May be due to contextual factors (homelessness)
May lead to other factors that increase risk (SUDs)
May be related to a shared third variable (material consequences of violence)

Fig. 1.3 Complexity of bidirectionality. (Based on data from Refs. [27, 28])

Psychiatric disorders serve as vectors of illness and present barriers to adherence (Fig. 1.4). PTSD can impair self-care, affect partner choice, and interfere with the development of trust in clinicians. Early childhood trauma has been shown to be associated with the development of multimorbid psychiatric disorders in persons with HIV (other than PTSD) (Fig. 1.5). Furthermore, early childhood trauma-induced PTSD in persons with HIV has been shown to present barriers to diagnosis and treatment (Fig. 1.6) [20, 21, 25, 32–35]. Refer to Chap. 7 for further details on trauma and stressor-associated disorders.

Psychiatric Disorders - Vectors of HIV + Barriers to Adherence	
PTSD	Impairs self-care, partner choice, trust in clinicians, adherence
Depressive Disorders	Decrease in self-care & self-worth impairs adherence
Anxiety Disorders	Concerns about HIV stigma may impair adherence
Neurocognitive Disorders	Impairs risk reduction, executive functioning, adherence
Addictive Disorders	Direct transmission & non-adherence
Psychotic Disorders	Impairs self-care & adherence
Bipolar Disorders	Hypersexuality & non-adherence

Fig. 1.4 Psychiatric disorders – vectors of HIV and barriers to adherence. (Based on data from Refs. [20, 29])

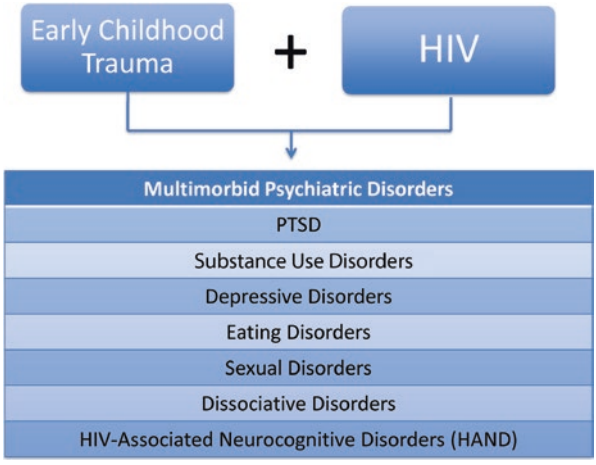

Fig. 1.5 Early childhood trauma is associated with multimorbid psychiatric disorders in persons with HIV

A link between PTSD and substance use disorders is posited in persons with HIV. PTSD may contribute to high rates of risky behaviors, predisposing to infection with HIV. Base rates for alcohol and other drug abuse are considerably higher among persons with HIV and result in further risk of exposure to traumatic events leading to PTSD. A number of syndemics (synergistic epidemics) have been described, such as the syndemic of substance abuse, intimate partner violence, and HIV [13–16]. Refer to Chap. 11 for further discussion of substance-related and addictive disorders and Chap. 14 for HIV syndemics.

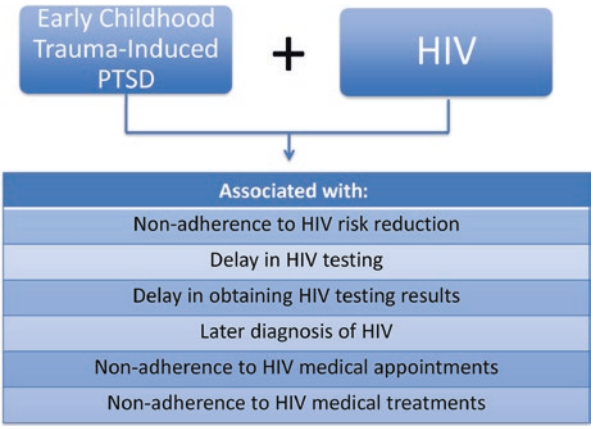

Fig. 1.6 Early childhood trauma-induced PTSD in persons with HIV. (Based on data from Refs. [30, 31])

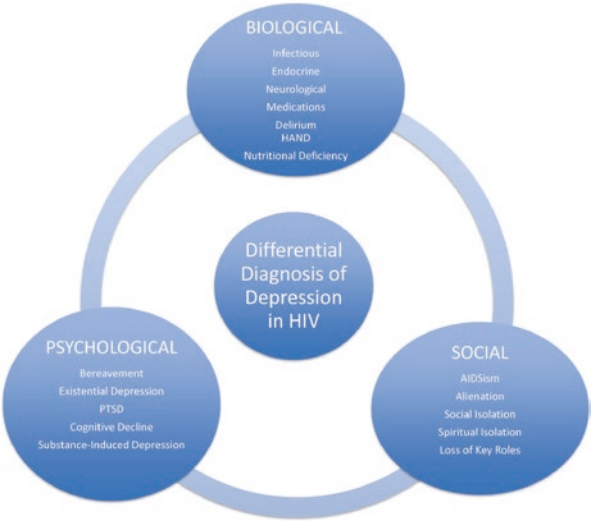

Fig. 1.7 Biopsychosocial approach to depression in HIV

Depressive disorders are psychiatric disorders that have a significant impact on adherence to HIV treatment and may even be a cause of mortality in persons with HIV. Adopting a biopsychosociocultural approach to the differential diagnosis of depression in persons with HIV is a potentially valuable method to appreciating the full scope of the problem and for developing focused interventions (Fig. 1.7). Furthermore, the impact of depressive disorders on persons with HIV is compounded by its impact on caregivers. Refer to Chap. 6 for more on depressive disorders.

Differentiating psychiatric disorders in person with HIV can prove to be key to developing treatments that are geared to address specific psychiatric symptom clusters (Fig. 1.8). A history of trauma, nightmares, and symptoms of intrusive thoughts, hypervigilance, and exaggerated startle response suggests a PTSD diagnosis,

Differentiating Psychiatric Disorders	
PTSD	History of childhood or adulthood trauma, nightmares, intrusive thoughts, hyper-vigilance, easily startle
Mania	Irritability, rapid speech, difficult to follow, excitable
Psychosis	Delusions, difficult to understand, guarded
Depression	Sadness; crying; suicidal thoughts or attempts; guilt; low self-esteem; soft; slow speech; makes clinician feel sad or angry
Delirium	Confusion; nodding out; disorientation; fluctuating behaviors; illusions; hypoactive delirium can masquerade as depression
Dementia	Slow speech & responses, slow movements, problems recalling dates / history
Substance Use Disorders	How much can you hold/use in a day? What happens if you do not use for a day?

Fig. 1.8 Differentiating psychiatric disorders in persons with HIV

whereas a guarded patient who is difficult to understand and who verbalizes delusions may suggest psychotic disorder. Refer to Chap. 5 for detailed information on screening and brief interventions for psychiatric disorders.

Psychiatric Disorders and Adherence to HIV Care

One of the most significant ways that psychiatric illness influences outcomes in HIV is through disruption of adherence to HIV care. Nonadherence with clinic appointments can lead to poorer outcomes for persons with HIV [17–28, 32, 33] and has been found to be independently associated with all-cause mortality [19]. Treatment adherence is considered to be one of the strongest, if not the single strongest, determinant of overall survival and is markedly improved with treatment of comorbid psychiatric disorders, such as depressive disorders and trauma and stressor-related disorders [20–28, 32–35]. Over the past two decades, substance use disorders, trauma and stressor-related disorders, and depressive disorders have been associated with nonadherence to HIV care and antiretroviral medication and are particularly relevant to morbidity and mortality in persons with HIV [17–28, 32–35]. Inadequate adherence to HIV care can also lead to more widespread consequences including increased overall viral load within the surrounding community or increased likelihood of antiretroviral therapy-resistant strains developing [20–28, 32–35]. It is difficult to adhere to medical care, antiretrovirals, and risk reduction for

Table 1.2 Psychiatric disorders and summary of associated barriers to adherence

Psychiatric disorder	Barriers to treatment adherence
Post-traumatic stress disorder	Impairment of self-care, partner choice, trust in clinicians, and adherence to medical care and risk reduction efforts, rapport with clinicians as a result difficulty forming trusting relationships, and retrograde amnesia or repression
Depressive disorders	Apathy and decreased self-worth impairing adherence with care
Anxiety disorders	Increased anxieties related to HIV stigma may impair initiation of care and adherence related to anxiety about forced disclosure
Neurocognitive disorders	Impairment in executive function and adherence to care
Substance use disorders Psychotic disorders Bipolar disorders	Impairment due to drug-seeking behavior, intoxication, and withdrawal Impair self-care and adherence Hypersexuality and nonadherence

persons with psychotic disorders and/or neurocognitive disorders. Psychotic disorders may impair adherence because of paranoia, preoccupation with delusional thought processes, suspiciousness, and difficulty with formation of trusting relationships with HIV physicians and other clinicians. Table 1.2 outlines some of the specific barriers to care adherence associated with each disorder.

Substance use disorders, PTSD, and depressive disorders, in particular, have been shown to be strong predictors of inadequate medication adherence [17–28, 32–35]. Active substance abusers are also less likely to initiate treatment with antiretroviral medications, which is an additional factor contributing to substance abusers having overall poorer outcomes [21]. Importantly, being a *prior* substance abuser has *not* been linked to poorer outcomes [21], which again emphasizes the importance of treating psychiatric disorders in persons with HIV. Inadequate adherence to HIV treatment is especially prevalent in persons with PTSD or a history of early trauma [17–28, 32–35]. It is thought that avoidant behavior in trauma and stressor-related disorders may be one of the symptoms most responsible for poor adherence [17–28, 32–35]. Depressive disorders have been shown to have a strong impact on treatment adherence and may be a stronger indicator of medication adherence than PTSD [32]. Even the presence of depressive symptoms that do not meet full diagnostic criteria for a specific depressive disorder can negatively impact treatment adherence, showing that there may be a strong incremental relationship between depressive symptom severity and outcomes in persons with HIV [32].

Treatment of comorbid psychiatric disorders can lead to improved adherence and thus decreased morbidity, mortality, and alleviation of public health concerns [17–24]. Individual, group, and family psychotherapy, support groups, motivational interventions and interviewing techniques, and appropriate psychopharmacotherapy are possible interventions for improving HIV care adherence through treatment of comorbid psychiatric conditions.

Psychiatric Treatment Modalities for Persons with HIV and Psychiatric Disorders

While in this chapter we touch only briefly on the psychotherapeutic treatments for persons with HIV and psychiatric disorders, it is important to note that psychotherapeutic treatments can serve multiple roles in the care of persons with HIV and the prevention of HIV transmission. Motivational interventions are relevant for prevention and care of persons with HIV. By motivating an individual to decrease or stop using drugs by injection or treating depressive disorders and/or PTSD, we can not only alleviate distress but also improve adherence to medical care and antiretrovirals, decrease morbidity and mortality, and decrease viral load and HIV transmission [1–6, 17–28, 30–35].

Psychotherapy

Psychotherapy can be a helpful therapeutic intervention for processing and addressing the psychological distress of living with a chronic systemic medical illness, such as HIV and AIDS. The emotional distress of living with HIV and AIDS can be viewed as secondary to biological aspects of the disease as well as to more direct biopsychosocial factors [1–6, 31]. The factors involved with distress in persons with HIV are summarized in Table 1.3.

For further understanding of the psychosocial factors at play in vulnerable populations, including persons who are socially disadvantaged, victims of intimate partner violence, marginally housed, or homeless, please see Chaps. 3, 15, and 21. The psychological needs of HIV-positive persons can be complex, requiring a

Table 1.3 Biopsychosociocultural determinants of distress in persons with HIV

Bio	Multimorbid systemic medical and psychiatric illnesses
Psycho	Difficulty coping, shame, guilt
	Loss, bereavement, mourning
	Conflicts regarding sexuality and dependency
Social	Questions regarding the meaning of life and spirituality
	stigma and discrimination
	Negotiation of social and intimate relationships, disclosure of HIV status
	Unemployment, financial stress, access to care, benefits, housing
Cultural	Cultural norms re sexual behavior
	Cultural norms re gender identity
	Cultural use of illness metaphors and illness experience
	Cultural aspects of relocation/isolation/etc.

multidisciplinary approach that is highly dependent on available resources. When these needs are optimally addressed and psychological distress is minimized, we see increased adherence to treatment and improved immune system function in those living with HIV and AIDS. For a primer on the principles of HIV from pathophysiology to treatment, please see Chaps. 16, 17, and 18.

Psychotherapeutic interventions may take various forms, such as individual psychotherapy (e.g., supportive, cognitive-behavioral, psychodynamic/psychoanalytic, interpersonal), motivational interventions, or psychotherapy for a couple, family, or group [36, 37]. Motivational interventions, including motivational interviewing, can both prevent HIV transmission and serve as a therapeutic modality for persons with HIV [38]. Meaning-centered psychotherapy, bereavement interventions, and reflection can be therapeutic at any stage of the life cycle and especially at or near the end of life [39–41].

Support groups have been shown to be helpful for persons living with HIV and AIDS, particularly for enhancing coping with the stress of the illness, treatments, and stigma [41–44]. The use of cognitive behavioral therapy (CBT) strategies through cognitive-behavioral stress management has been linked to increased CD4 counts, while interpersonal psychotherapy (IPT) for those living with HIV showed better or comparable outcomes to medications and psychotherapy (CBT or supportive) combined [45]. The importance of psychotherapeutic interventions in the treatment of psychiatric illness in those living with HIV and AIDS is woven throughout this book, particularly in Chaps. 6, 7, 9, and 11. Caring for persons living with HIV and AIDS in a collaborative, integrated way is an important aspect of treatment and is discussed in Chap. 19.

Integrative Medicine Modalities

Because patients living with HIV and AIDS were previously assumed unlikely to survive at the start of the epidemic, many powerful agents for sleep, anxiety, and pain were more liberally prescribed in the past due to the perceived "decreased" risks associated with long-term use. Improved survival in persons living with HIV and AIDS, due in large part to advancements in antiretroviral therapy, has shifted attention toward time-limited treatment options for symptom management. In part due to this shift in approach to illness management, increasing numbers of patients living with HIV and AIDS turn to integrative medical remedies, such as vitamins, minerals, and herbal supplements. In fact, more than half of people living with HIV and AIDS report using integrative medicine in addition to antiretrovirals and other medications [46].

Many of the herbal remedies, vitamins, and mineral supplements used by those living with HIV and AIDS are intended to address physical symptoms, and several have been studied in the treatment of psychiatric symptoms. Chaps. 6, 9, and 20 include information on the use of integrative medicine remedies for mood symptoms. Considerations toward providing a safe, non-judgmental space for a patient to

discuss their use of integrative agents, compliance, high-risk behaviors, as well as other sensitive issues are discussed in Chaps. 3, 4, and 5.

Psychopharmacology

The introduction of protease inhibitors (PIs) and non-nucleoside reverse transcriptase inhibitors (NNRTIs) in 1995–1996 was a tipping point in the treatment of HIV/AIDS. The combination of different classes of potent antiretrovirals led to a significant decrease in AIDS-related morbidity and mortality and an increase in life expectancy that is now close to that of people not infected with HIV. Over the years, significant developments in antiretrovirals have permitted once-a-day dosing and fewer significant side effects. This was a consequential advancement as older antiretrovirals were not only well-known to cause disabling side effects but also required to be taken several times a day with predictable pernicious effects on adherence and quality of life. Antiretroviral therapy (ART), previously known as "highly active antiretroviral therapy (HAART)" and later known as "combination antiretroviral therapy (CART)," decisively transformed the landscape of pharmacotherapeutic options for people living with HIV/AIDS. Pharmacotherapies involved in viral suppression include nucleoside reverse transcriptase inhibitors (NRTIs), non-nucleoside reverse transcriptase inhibitors (NNRTIs), protease inhibitors (PIs), integrase strand transfer inhibitors (INSTIs), entry inhibitors/CCR5 antagonists, fusion inhibitors, and CD4-directed post-attachment inhibitors. Currently, combination antiretroviral therapy typically comes co-formulated in the form of a single pill, simplifying treatments that used to be cumbersome and overwhelming.

Nevertheless, lifetime daily adherence is required, which for many patients can be a challenge [12]. From a psychiatric perspective, adherence to both antiretroviral therapy and psychotropic medication can be impacted by factors, such as psychiatric symptoms or disorders including depressive disorders, PTSD, and addictive disorders, and challenges related to social support and stigma [8, 10–12]. The relationship between antiretroviral adherence and mental health has been shown to be complex and bidirectional; effective antiretroviral treatment has been associated with a decrease in the severity of many psychiatric disorders including depression, mania, delirium, and psychosis as well as decreased morbidity and mortality in persons with HIV [17–28, 30–35, 47]. In addition to the profound impact on health and life, some antiretroviral medications, such as efavirenz, cause psychiatric side effects, while others, such as ritonavir, interact with psychotropic and other medications. Efavirenz may cause depression and suicidality in some patients [48]. Several antiretrovirals are inducers of CYP450 3A4 and can drastically reduce the level of methadone causing the patient to experience opioid withdrawal and lead to nonadherence with discontinuation of antiretrovirals. Other antiretrovirals are inhibitors of CYP 3A4 and can raise the level of medications such as methadone to dangerous levels.

Most psychotropic medications are efficacious and tolerable for patients living with HIV/AIDS. However, persons with HIV are extremely vulnerable to both the anticholinergic and extrapyramidal side effects of antidepressants and antipsychotic medications. Mood-stabilizing anticonvulsants and some antidepressants have pharmacokinetic properties that may interfere with tolerable and effective antiretroviral therapy. When choosing psychotropic medications, clinicians need to be aware of side effects, toxicities, and potential drug-drug and drug-illness interactions [1–6].

Clinicians need to be aware of the drug-drug and drug-illness interactions that can further complicate treatment. Medical and psychiatric clinicians need to work together care for persons with HIV and multimorbidities in an effort to synergistically improve their care. Side effects of antiretrovirals and drug-drug effects are reviewed in Chap. 17.

HIV Risk Behaviors: Recognition and HIV Prevention

The US Centers for Diseases Control and Prevention (CDC) recommends that everyone between the ages of 13 and 64 years be tested for HIV at least once in their lifetime, with at-risk individuals undergoing routine HIV testing – at least once a year [49]. It therefore remains a critical and salient point for all clinicians to ensure they are able to identify persons who may be at risk. Normalizing risk assessment protocol questions during appointments in addition to normalizing routine HIV testing can aid in identifying and protecting persons with risk factors and behaviors. Ensuring that testing is readily available, discussed, normalized, and encouraged by clinicians is paramount in establishing this first line of defense against HIV. See Table 1.4 for recognition of risk behaviors for HIV transmission.

An important aspect of prevention is recognizing and acknowledging that different vulnerable subpopulations (e.g., women, men who have sex with men, injection drug users) have varying risk dynamics to be addressed for adequate psychotherapy, counseling, and education. One of the infallible benefits of routine HIV testing for at risk individuals is that early detection can lead to early initiation of treatment. By

Table 1.4 Recognition of HIV risk behaviors in persons who are HIV negative

HIV risk behaviors
Inconsistent condom use Monogamous long-term relationship with an HIV-positive partner or a partner who is injecting drugs
Sex work/exchange of sex for drugs
Intimate partner violence
Receptive anal intercourse
Intravenous drug use/needle sharing
Frequent change in sexual partners
Indiscriminate partner choice

identifying infection as early as possible and referring patients for antiretroviral therapy, viral load can be suppressed. Antiretrovirals, if started early, may also decrease the chances of the virus entering the brain and central nervous system, which may then serve as an independent reservoir for HIV replication. HIV viral load is a key determinant in its transmission from one individual to another. The concept U = U, Undetectable = Untransmittable, was born from the advent of antiretroviral therapy (ART) showing that reduced viral loads from ART were associated with reduced transmission. U = U highlights the powerful preventive effect that treatment can provide (TasP – treatment as prevention) [49, 50].

For persons who are HIV negative but may be at risk due to an ongoing relationship with an HIV-positive partner or risky behaviors, pre-exposure prophylaxis, or PrEP, is an effective prevention tool, requiring increased accessibility and affordability. PrEP is a long-term ongoing medical intervention prescribed to at-risk, eligible individuals that can decrease the risk of acquiring HIV through sexual activity by more than 90 percent for those who strictly adhere to the daily regimen [51–53]. PrEP is also recommended for persons who are HIV negative but continue to use drugs by injection. Post-exposure prophylaxis or PEP is a short-term, 28-day emergency intervention for an HIV-negative person inadvertently exposed to HIV during a consensual or coerced sexual encounter or injection drug use. In a similar manner, PEP, or post-exposure prophylaxis, can reduce the risk of infection if started promptly (within 24–72 h) after exposure [54]. See Chap. 2 for further details on prevention of HIV transmission, routine testing, treatment as prevention (TasP), PrEP, PEP, and U = U.

It is clear that recognition of HIV risk behaviors and viral suppression with antiretroviral treatment empower both clinicians and their patients to prevent HIV. Awareness and knowledge that treatment of psychiatric disorders reduces sexual risk behavior and improves adherence to care and treatment remains of utmost importance.

Collaborative Care, Prevention of HIV, and Improvement of Clinical Outcomes

Collaborative psychiatric and HIV care can help alleviate stigma, increase adherence to HIV medical appointments and treatment, decrease morbidity and mortality, and decrease HIV transmission through viral suppression. All clinicians can help prevent transmission of HIV by eliciting risk behaviors, encouraging routine HIV testing, suggesting early care engagement and antiretroviral treatment for viral suppression, and becoming aware of the availability of pre- and post-exposure prophylaxis [49–54].

Persons with HIV have a higher-than-average prevalence of multimorbid systemic medical and psychiatric illnesses and face a significant amount of stigma and discrimination associated with their diagnosis. HIV also affects vulnerable

populations in a disproportionate fashion. These factors need to be taken into consideration to provide complete care, necessitating comprehensive and more collaborative approach to care. Collaborative care provided by a multidisciplinary team of healthcare professionals may improve adherence, reduce suffering and stigma, and improve viral suppression [1–6, 55, 56]. Refer to Chap. 19 for more on collaborative care models in HIV.

The HIV/AIDS epidemic magnifies healthcare disparities and the salience of social determinants of overall health. Understanding psychiatric aspects of HIV can help clinicians prevent HIV transmission, ameliorate the stigma associated with HIV and psychiatric illness, and care for people infected and affected with HIV. In this chapter and throughout this practical guide, clinicians will be able to find ways of preventing transmission and improving the care of persons with HIV and AIDS.

Multiple-Choice Questions and Associated References

Question 1: Stem [18, 24–26]

1. Which of the following statements best exemplify the bidirectional nature of HIV transmission and psychiatric illness?
   Question 1: Key (correct answer)
   (a) Treatment and referral of an HIV-negative injection drug user for medication-assisted therapy and methadone maintenance.
   Question 1: First distractor
   (b) Ensuring that condoms are not readily accessible on inpatient psychiatric units.
   Question 1: Second distractor
   (c) Awareness that more than one million persons are living with HIV in the United States. Question 1: Third distractor
   (d) The prevalence of HIV in persons with mental illness is the same as that of persons in the general population.

Question 2: Stem [7]

2. Recent global epidemiological data relating to HIV suggest that:
   Question 2 Key (correct answer)
   (a) There is ample evidence to suggest the continued existence of an HIV pandemic.
   Question 2: First distractor
   (b) There is a clear downward trend in global HIV incidence rates.
   Question 2: Second distractor
   (c) There is ample data to suggest that the HIV pandemic is in a state of resolution compared to the 1980s and 1990s.
   Question 2 Third distractor
   (d) Most people with HIV infection are aware that they are infected.

Question 3: Stem [1, 2, 37]

3. Which of the following is most accurate regarding the relationship between HIV/AIDS and psychiatric disorders?

   Question 3 Key (correct answer)

   (a) There is a complex bidirectional relationship between HIV/AIDS and psychiatric disorders, with the latter serving as vectors of illness and obstacles to adherence.

   Question 3: First distractor

   (b) Historically, rates of mental illness were higher in the HIV-infected population, but recent advances in treatment have resulted in rates comparable to the general population.

   Question 3: Second distractor

   (c) Rates of mental illness in HIV patients are significantly higher, but the rates of HIV in psychiatric patients are not significantly higher.

   Question 3: Third distractor

   (d) HIV infection and psychiatric disorders overlap or co-vary only when a third variable such as intravenous substance use and low socioeconomic status is present.

Question 4: Stem [19, 32, 34]

4. Which of the following has been shown to result in better health outcomes for persons with HIV?

   Question 4 Key (correct answer)

   (a) Keeping HIV clinic appointments

   Question 4: First distractor

   (b) The presence of depressive symptoms meeting clinical criteria for a depressive disorder

   Question 4: Second distractor

   (c) A history of early life exposure to a traumatizing event

   Question 4: Third distractor

   (d) A current diagnosis of generalized anxiety disorder with untreated symptoms

Question 5: Stem [8, 47]

5. Which of the following describes the impact of the HIV epidemic on people of color, LGBTQ, homeless or marginally housed, and/or economically disadvantaged people?

   Question 5 Key (correct answer)

   (a) The HIV epidemic has a disproportionate impact on people of color and people who are LGBTQ, homeless or marginally housed, mentally ill, and/or economically disadvantaged people.

   Question 5: First distractor

   (b) The HIV epidemic has a disproportionate impact on people of color, but not on LGBTQ, homeless or marginally housed, mentally ill, and/or economically disadvantaged.

Question 5: Second distractor

(c) The HIV epidemic has the same impact on general population and as it does on people of color, LGBTQ, homeless or marginally housed, and/or economically disadvantaged people.

Question 5: Third distractor

(d) The HIV epidemic has an impact on people of color, LGBTQ, homeless or marginally housed, and/or economically disadvantaged people only in a few states and areas of the United States.

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Chapter 2
HIV Testing and Prevention

Mark V. Bradley, Luis F. Pereira, and Mary Ann Adler Cohen

Introduction

There is substantial evidence that having psychiatric illness may increase the risk of HIV infection. Early convenience samples of patients in psychiatric clinical settings found substantially higher rates of HIV infection in psychiatric patients than those in the general population [1]. Subsequent research using larger Medicaid data sets found a 50% prevalence of HIV in people with schizophrenia and a prevalence of schizophrenia in persons with HIV six times that in the general population [2]. One rapid-testing study of over 1000 patients in inpatient and outpatient psychiatric settings found an HIV prevalence of 2–6% [3]. Other psychiatric disorders have also been associated with HIV risk, including depressive disorders, posttraumatic stress disorders, and substance use disorders [4–6]. Such research over the decades of the AIDS pandemic have underscored the links between psychiatric disorders and HIV infection.

Given the increased risk for HIV infection that is often conferred by psychiatric illness, all clinicians working with patients with psychiatric disorders should be aware of current best practices in preventing HIV transmission and in detecting HIV infection in order to refer patients to HIV medical care. This chapter includes an overview of current public health practices for HIV testing and prevention, followed by a review of the psychiatric illness-related factors that lead to increased HIV risk.

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Finally, we will discuss some of the specific practices and challenges in HIV prevention when working with people living with psychiatric illness.

Public Health Strategies for HIV Prevention

The knowledge base regarding factors that support HIV transmission has developed continuously since the early 1980s, and as a consequence, approaches to HIV prevention have evolved steadily in the ensuing decades. Early approaches to HIV transmission focused on education and dissemination of knowledge. Subsequent publicly funded trials of increasingly sophisticated behavioral interventions drew from existing theories of health behavior change and incorporated the influence of gender and culture on HIV-related behaviors [7]. In addition, a steadily growing literature showed that psychiatric symptoms and disorders played an important role in the behavioral aspects of HIV [8]. Many interventions focused on behavioral outcomes such as condom use, frequency of high-risk sexual acts, and/or HIV transmission risk through intravenous drug use behaviors. Some of these interventions have demonstrated positive outcomes in clinical trials to reduce HIV transmission risk behaviors and are endorsed by the US Centers for Disease Control and Prevention (CDC) as effective interventions. However, these interventions have also been challenged by barriers to widespread uptake and implementation [9]. In addition, it has generally been difficult to demonstrate that these interventions reduce HIV incidence in addition to changing individual risk behaviors.

In recent years, prevention efforts have also come to include biomedical approaches that complement and reinforce behavioral prevention interventions [10]. For a number of years, there has been evidence that the infectiousness of an individual with HIV depends upon the concentration of viral particles in the blood, a measurement known as *viral load*. This, in turn, led to research that demonstrated that suppressing an individual's viral load with antiretroviral medication renders them unable to transmit the virus, underscoring the importance of identifying persons with HIV in order to initiate virus-suppressing treatment. The following sections discuss some of the major current public health concepts and strategies for the prevention of HIV transmission.

Treatment as Prevention

Based on prior evidence that HIV transmissibility is heavily dependent on viral load, in recent years, there have been several large prospective observational studies examining the risk of HIV transmission within mixed HIV status couples who

engaged in condomless sex [11–13]. These studies examined heterosexual and homosexual couples from Europe, South America, Asia, and Australia. These studies found that in serodifferent couples, when the viral load of the HIV-positive partner is suppressed to undetectable levels with antiretroviral medication, the risk of HIV transmission is effectively zero. Thus, the systematic early identification of individuals infected with HIV – in order to start them on antiretroviral treatment for the purpose of suppressing viral load – is seen as a critical goal in reducing new HIV infections within populations. Specifically, *Treatment as Prevention (TasP,)* or use of combined antiretroviral therapy as a means to prevent people living with HIV from infecting others, has formed a cornerstone public health HIV prevention strategy.

In order to accomplish the goal of suppressing viral loads within populations so as to reduce HIV incidence globally, in 2014, the Joint United Nations Programme on HIV/AIDS (UNAIDS) launched the *90-90-90* target for HIV prevention [14]. This plan comprised three aspirational goals: by the year 2020, 90% of all individuals living with HIV will know their HIV status, 90% of all people with diagnosed HIV infection will receive sustained antiretroviral therapy, and 90% of all people receiving antiretroviral therapy will be virally suppressed. Mathematical modelling has suggested that achieving these goals by 2020 would lead to the end of the HIV epidemic by 2030 [15]. A number of cities across the globe have taken up the UNAIDS 90-90-90 target as goals around which to organize their programmatic HIV prevention efforts. While these goals have provided significant hope for a strategy to lead to the end of the HIV epidemic, there has been some variability across locales with respect to the success of approaching the 90-90-90 target by 2020 [16, 17].

Another benefit of TasP – and the inability of virally suppressed individuals to transmit HIV – has been progress toward the de-stigmatization of HIV and of people living with HIV/AIDS. From the early days of the epidemic, HIV/AIDS has been met with tremendous public fear, often complicated by a poor understanding of HIV transmission. People living with HIV/AIDS have often been treated as immoral, irresponsible, or a public threat. This HIV stigma has been identified as a barrier to HIV prevention efforts and as negatively impacting the mental health and quality of life of people with HIV. Given that virally suppressed individuals with HIV are no more likely to transmit HIV than people who are HIV-negative, people living with HIV and working in the HIV field recognized new opportunities for stigma reduction. One of these is a public campaign called **U = U**, short for Undetectable = Untransmissible. This campaign is seen as having the potential to reduce HIV shame, increase participation in treatment, improve awareness of the public health importance of HIV treatment, and thus increase the likelihood of success of meeting the 90-90-90 target [18]. The U = U message has been adopted by numerous organizations worldwide and received further legitimization when the CDC declared its support in 2017 for the conclusion that people with undetectable viral loads are effectively unable to transmit HIV [19].

Pre-exposure Prophylaxis

Another important biomedical intervention that has evolved in recent years has been the emergence of pre-exposure prophylaxis for HIV, often abbreviated as *PrEP* [20]. In 2012, the US Food and Drug Administration (FDA) approved the use of a daily two-drug combination pill, emtricitabine and tenofovir disoproxil fumarate (E/TDF or Truvada), by HIV-negative individuals for the prevention of HIV. Clinical trials suggest that under optimal conditions of adherence, PrEP can prevent 99% of new infections. The CDC has subsequently released and updated guidelines on the prescription of PrEP, including recommendations for risk assessment, indications, and laboratory follow-up [21]. The CDC guidelines recommend considering PrEP for individuals who engage in high-risk HIV transmission behavior within the categories of men who have sex with men (MSM), heterosexually active men or women, and people who inject drugs. In 2019, PrEP was classified as a grade A recommendation by the US Preventive Services Task Force. In spite of its potential, PrEP has also been associated with some concerns. The first of these has had to do with cost and access to the medications. In addition, there has been some concern for *risk compensation*, or the idea that individuals taking PrEP will subsequently engage in riskier sexual behavior, such as refraining from barrier methods or increasing high-risk sex frequency, and thus expose themselves to a greater risk of STIs. It remains a matter of scientific debate whether risk compensation is a significant concern in the setting of PrEP use [22].

Post-exposure Prophylaxis

Post-exposure prophylaxis (*PEP*) is the use of antiretroviral medication by an HIV-negative individual to reduce the risk of HIV infection after a high-risk exposure to the virus. PEP was initially used in healthcare settings for medical workers who were accidentally exposed to while working with HIV-positive patients, such as via a needlestick. This form of PEP is now called occupational post-exposure prophylaxis, or oPEP. Subsequently, PEP became recognized as an effective way to reduce the risk of HIV infection in individuals potentially exposed to HIV in a non-work event, such as through sex or injection drug use. HIV-negative people may seek PEP after having unsafe consensual sex, in the setting of failure of other preventive means such as condom breakage, after sharing needles during intravenous drug use, or after surviving a sexual assault. This form of PEP is known as non-occupational post-exposure prophylaxis, or nPEP. Mental health clinicians may be the first line of reporting by patients describing a high-risk potential HIV exposure and thus may have the opportunity to serve their patients by referral for PEP in appropriate circumstances.

Factors That Increase HIV Risk in People with Psychiatric Illness

HIV prevention researchers have increasingly tried to identify the relationships between psychiatric illness and HIV risk in order to develop effective interventions for these populations. Clinicians evaluating HIV risk in patients with psychiatric illness should be aware that these relationships may be complex and require considering factors in a number of different domains.

Symptoms For some patients, active psychiatric symptoms may lead to increased HIV risk. For example, patients in a manic episode of bipolar disorder may experience loss of behavioral inhibition, leading them to engage in high-risk sexual behavior. In contrast, some research has suggested that a subset of people with depressive disorders may engage in sexual behavior as a way to reduce negative affective states [4].

Deficits Although active symptoms are often the most dramatic aspect of psychiatric illness, many psychiatric conditions also comprise losses of adaptive functioning that may place the patient at higher risk of HIV infection. People with schizophrenia may have cognitive limitations that comprise an important determinant of their overall outcomes. Such limitations may impair important decision-making around safe sexual behavior and HIV risk prevention. Other patients who have survived trauma may, as a consequence, experience difficulties negotiating high-threat situations, leading to exposure to high HIV risk.

Substance use Although substance use disorders are themselves considered to be psychiatric disorders, the symptoms and deficits of many psychiatric illnesses, including major depressive disorder, bipolar disorder, schizophrenia, and PTSD, place patients at much higher risk for comorbid substance use disorders. Because substance use is one of the most significant risk factors for HIV, it serves as an important element of the HIV risk environment in psychiatric illness.

Structural factors In addition to substance use, psychiatric illness is associated with a number of social factors which can in turn increase the risk for HIV infection. People with chronic psychiatric illness may be placed at greater risk of homelessness, incarceration, violence, and/or transactional sex, which are themselves associated with HIV risk. Lack of access to healthcare may reduce rates of HIV testing, prevention interventions, and antiretroviral treatment, thus increasing rates of HIV transmission in persons with psychiatric illness. In addition, structural factors may interact with other aspects of social marginalization pertaining to race, gender, and LGBT status, in ways that reduce the ability of persons with psychiatric illness to minimize HIV risk.

Shared causal factors In some instances, a patient may have experienced an exposure which leads to both HIV infection and to psychiatric illness. The most salient example of shared causal factors is that of the sexual assault survivor whose trauma leads to both HIV infection and psychiatric sequelae such as depressive disorders, acute stress disorder, PTSD, or substance use disorders.

HIV Risk Assessment, Screening, and Testing Patients with Psychiatric Illness

The rationale for routine assessment of HIV risk in patients with psychiatric illness for early identification of HIV infection is severalfold. First, the higher risk in this population represents an opportunity for expeditious identification of HIV risk behaviors or other psychosocial risk factors in order to intervene with counseling, initiation of PrEP, referral to services, or other preventive approaches. Second, in patients identified as having HIV, early ART initiation and viral suppression play an important public health role in preventing new HIV infections in the community. Finally, for people with HIV, early initiation of ART is associated with significantly better long-term medical outcomes.

Assessment of HIV risk comprises a detailed understanding of the behavioral and social factors that may increase HIV risk in patients with psychiatric illness. At its most basic level, such assessment starts with an understanding of the type, frequency, number of sexual partners, and risk reduction methods involved in the patient's sexual behavior. For example, it is known that there is a range of HIV transmission risk conferred by specific sexual behaviors, ranging from condomless receptive anal intercourse representing very high risk to condomless penile-oral intercourse representing relatively low risk. In addition, additional risk is conferred by both higher frequency of higher-risk sexual behaviors and higher number of partners with whom the patient engages in higher risk sex. It is also important to understand partner characteristics that may suggest additional risk to the patient, such as whether the patient is aware of partner serostatus, and contextual factors, such as whether sex was transactional or occurred in an incarcerated setting. The presence of other sexually transmitted infections such as herpes simplex or syphilis should also be assessed, as these can increase the risk of HIV infection. Finally, the clinician should inquire about the use of prevention methods such as condoms or PrEP.

In addition to sexual risk behavior, the use of intravenous (IV) drugs is an important mode of HIV transmission. When assessing for current or past IV drug use, key information includes frequency of use, a history of sharing needles with others, and history of other blood-borne infections, such as hepatitis C. Harm reduction practices such as the use of clean, unshared needles should be discussed. Patients with current opioid use disorder should be offered appropriate evidence-based treatment such as buprenorphine/naloxone or referral for methadone maintenance therapy and psychosocial and psychiatric treatment services.

Because HIV testing serves as such an important role in public health efforts to reduce new HIV infection as well as ensuring optimal care for people living with HIV, clinicians working with patients at high risk for HIV should have some understanding of the available HIV tests and their differences. The most commonly used HIV test in clinical settings is the HIV antigen/antibody HIV test, sometimes called fourth-generation testing, which identifies both viral proteins and the patient-generated antibodies which fight infection. When tested on blood drawn from a vein, this test can usually identify HIV infection within 18–45 days after exposure, although there is a fingerstick version of the test which can usually identify infections within 18–90 days after exposure. In addition to the antigen/antibody test, most rapid tests performed by fingerstick or oral swab are antibody tests, as are available HIV home testing kits, which can detect infection 23–90 days after exposure. Positive antigen/antibody and antibody tests results require confirmatory testing. A final type of HIV test measures viral RNA in the blood. This type is typically used to follow the response to antiretroviral treatment and measure the severity of HIV infection in patients living with HIV and is only used for diagnostic purposes in specific situations (see below).

In addition to assessing HIV risk behaviors, clinicians working with patients at high risk for HIV should be aware of the acute retroviral syndrome, marked by fever, malaise, rash, and lymphadenopathy, which commonly occurs in the days or weeks following new HIV infection [23]. Because newly infected patients have high levels of circulating virus and are at a period of high infectiousness, and are typically unaware of their newly infected state, it is important to test patients suspected of acute HIV infection using either a viral antigen/antibody immunoassay or HIV RNA in conjunction with an antibody test, with a negative immunoassay followed by an HIV RNA test. Patients diagnosed with acute HIV infection should be counseled regarding their infectiousness and need for risk prevention and referred for HIV medical care.

PrEP for Persons with Mental Illness

Case Vignette 2.1
Ms. A. was a 27-year-old female who migrated from a small town in El Salvador 5 years ago, to escape gang violence. She had a history of physical, emotional, and sexual abuse and had been in psychiatric treatment for major depressive disorder and PTSD. Ms. A. reported experiencing flashbacks, inability to experience positive emotions, angry outbursts, and hypervigilance for which she self-medicated with alcohol. She admitted to engaging in unprotected vaginal intercourse many times in the previous 3 months with strangers of unknown HIV status and being diagnosed with gonorrhea 3 months previously. She experienced mild flu-like symptoms a few weeks

earlier, including sore throat, myalgias, and low-grade fever, but stated that these symptoms resolved spontaneously 5 days previously. During the interview, Ms. A. requested to be started on PrEP. What is the most appropriate approach?

A. Prescribe daily TDF-FTC as Ms. A. clearly meets criteria for initiation of PrEP.
B. Prescribe daily TAF-FTC as Ms. A. meets criteria for initiation of PrEP and you want to minimize potential renal and bone side effects.
C. Request HIV immunoassay blood test, and, if negative, prescribe either TAF-FTC or TDF-FTC.
D. Request HIV immunoassay blood test, and if negative, complement it with antibody/antigen immunoassay and HIV-1 viral load, deferring initiation of PrEP at this time.

Since the identification of HIV in 1984 as the causative agent of AIDS, the scientific community has focused on behavioral and biomedical strategies to prevent its transmission. Apart from sexual abstinence, the condom was the first method shown to protect from HIV [24], and it was approved by the US FDA for this purpose in 1986. When used consistently and as recommended, the efficacy of condoms in HIV prevention has been calculated to be greater than 90%. In 1994, zidovudine (AZT) was approved by the US FDA for the prevention of peripartum transmission of HIV [25]. It is now recommended that pregnant women living with HIV take combined antiretroviral therapy to reduce the risk of vertical HIV transmission.

During the past decades, the combination of these preventive strategies, in addition to the development of new, potent, and better tolerated antiretrovirals, has led to a continuous decrease in new infections. However, the impact of the available behavioral and biomedical methods has been limited as more people become newly infected with HIV on a daily basis.

Initial studies in macaques showed that systemic use of antiretrovirals (in particular TDF and FTC) led to effective concentrations of these medications in the rectal and vaginal mucosae and might be protective of HIV infection. These findings catalyzed several trials designed to assess their efficacy in humans. As a consequence, in 2012, US FDA approved the first combination of antiretrovirals to prevent HIV transmission in individuals at high risk for HIV infection, tenofovir disoproxil fumarate and emtricitabine (TDF/FTC).

PrEP is currently recommended for use by adults and adolescents who are at significant risk of HIV acquisition, including men who have sex with men (MSM), heterosexually active men and women, and people who inject drugs (PWID). Tables 2.1, 2.2, and 2.3 summarize the recommended indications for PrEP use for at-risk populations.

A negative HIV immunoassay blood test is recommended prior to initiation of PrEP. In the case of a positive result, HIV infection should be treated according to

Table 2.1 Recommended indications for PrEP use by MSM

MSM who are sexually active and have one of the following characteristics:
A serodiscordant sex partner
Inconsistent use of condoms during receptive or insertive anal sex
A sexually transmitted infection (STI) with syphilis, gonorrhea, or chlamydia within the previous 6 months

Based on data from Ref. [26]

Table 2.2 Recommended indications for PrEP use by heterosexually active men and women

Heterosexually active women and men who have one of the following characteristics:
A serodiscordant sex partner
Inconsistent use of condoms during sex with a partner whose HIV status is unknown and who is at high risk (e.g., a person who injects drugs, a man who engages in sexual intercourse with men and women)
A STI with syphilis or gonorrhea within the previous 6 months

Based on data from Ref. [26]

Table 2.3 Recommended indications for PrEP use by persons who inject drugs (PWID)

Persons who inject drugs and have one of the following characteristics:
Shared use of drug injection equipment
Risk of sexual acquisition of HIV

Based on data from Ref. [26]

local guidelines, and PrEP is therefore contraindicated because the use of TDF and FTC as the only antiretrovirals in PLWH can lead to the development of resistances to any of these drugs. In cases where the result is indeterminate, or in patients who have signs or symptoms of acute HIV infection anytime in the prior weeks, it is recommended to exclude the possibility of HIV infection during the prior weeks and confirm negative serostatus with either an antibody/antigen assay or an HIV-1 viral load assay prior to prescribing PrEP. Figure 2.1 summarizes the steps to assess patient's HIV status prior to prescribing PrEP.

Current guidelines were based on trials which studied the efficacy of TDF/FTC in MSM, transgender women, heterosexual men and women, and PWID. Table 2.4 summarizes the results of key PrEP studies. These trials have found that PrEP's efficacy was higher in the studies that also showed a higher PrEP adherence particularly the French "Intervention Préventive de l'Exposition aux Risques avec et pour les Gays" (IPERGAY) and the pre-exposure prophylaxis to prevent the acquisition of HIV-1 infection (PROUD) studies and ineffective in the studies where low adherence was reported (FEM-PrEP and VOICE). Blood levels of tenofovir diphosphate (TDF-DP), the active metabolite of TDF which accumulates in blood cells in a dose-proportional manner [28], have been used as a marker of adherence. For example, in the iPrEX (from Spanish: Iniciativa Profilaxis Pre-Exposición, "pre-exposure prophylaxis initiative") study, when there were detectable levels of study drugs, there was a 92% reduction in the risk of HIV acquisition [29–36].

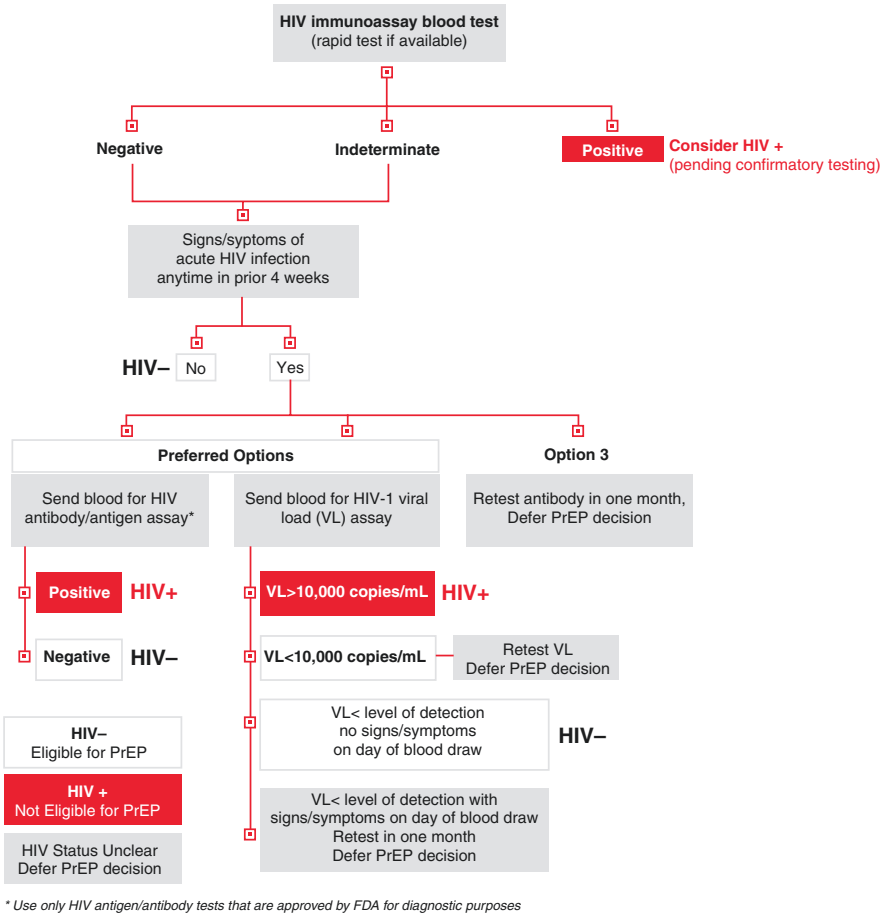

Fig. 2.1 Clinician determination of HIV status for PrEP provision. (Based on data from Ref. [21])

The combination TDF-FTC was generally well tolerated with no significant differences regarding the risk of serious adverse events when compared to placebo. Gastrointestinal side effects (nausea in particular) were the most common but generally resolved with continued use. Grade 1 elevations in creatinine were seen but generally resolved with discontinuation of PrEP [37]. TDF has been associated with bone loss. In particular, the iPrEX and TDF-2 trials showed decreased bone mineral density but no associated risk of fractures. It must be stressed that these studies involved short periods of observation, and longer periods of monitoring are necessary to assess the clinical impact of these findings [38].

It has been a commonly shared concern that the use of PrEP might lead to risk compensation and consequently increased risky behaviors. None of the abovementioned studies found decreased condom use nor increased incidence of sexual transmitted infections (STIs). Interestingly, in both the iPrEX and Partners PrEP studies,

Table 2.4 Key oral PrEP studies

Year	Study	Location	Number of participants	Population studied	PrEP agent	Efficacy	Comments
2010	iPrEX	Brazil, Ecuador, Peru, South Africa, Thailand, USA	2499	MSM and transgender women	TDF-FTC	44%	Poor adherence Overall reduction in number of partners Increased condom use
2011	FEM-PrEP	Kenya, South Africa, Tanzania	1950	18–35yo women	TDF-FTC	0%	Low adherence Low plasma levels of TDF Stopped at interim analysis
2011	Partners PrEP	Kenya, Uganda	4758	HIV-serodiscordant couples	TDF TDF-FTC	75% on TDF-FTC vs 67% on TDF	No difference in efficacy between men and women High adherence
2011	TDF-2	Botswana	1200	Heterosexual men and women	TDF-FTC	63%	High loss to follow-up No change in sexual behavior
2012	VOICE	South Africa, Uganda, Zimbabwe	5029	18–45 yo women	Oral TDF-FTC, oral TDF, TDF vaginal gel	0%	Low rates of adherence Low plasma levels of TDF TDF arm stopped at interim analysis due to futility
2013	Bangkok tenofovir study	Thailand	2413	Intravenous drug users	TDF	49%	No difference compared to placebo during the first 3 years
2015	Kaiser Permanente (Clinical cohort) [27]	USA	388 person-years of PrEP	MSM	TDF-FTC	0 HIV diagnoses in 388 person-years of PrEP use	High rates of STIs Self-reported decrease in condom use

(continued)

Table 2.4 (continued)

Year	Study	Location	Number of participants	Population studied	PrEP agent	Efficacy	Comments
2015	IPERGAY	France, Canada	400	MSM, transgender women	TDF-FTC (*on-demand* dosing)	86%	No change in behavior High adherence
2015	PROUD	UK	544	MSM, transgender women	TDF-FTC	86%	"Real-world setting" Suggestion of risk compensation among some PrEP participants
2020	HPTN-083	Argentina, Brazil, Peru, South Africa, Thailand, USA	4494	MSM, transgender women	CAB-LA vs oral TDF/FTC	Incidence rate of HIV infections: CAB-LA arm: 0.41% Oral TDF/FTC arm: 1.22%	66% reduction in incident HIV infection in the CAB-LA arm, compared to the TDF-FTC arm CAB-LA generally well tolerated but with higher incidence of injection site reactions
2020	HPTN-084	Botswana, Eswatini, Kenya, Malawi, South Africa, Uganda, Zimbabwe	3223	Cisgender women	CAB-LA vs oral TDF/FTC	Incidence rate of HIV infections: CAB-LA arm: 0.21% Oral TDF/FTC arm: 1.79%	89% reduction in incident HIV infection in the CAB-LA arm, compared to the TDF-FTC arm Both drugs were well tolerated Higher incidence of injection site reactions in the CAB-LA arm; higher incidence of gastrointestinal side effects in the TDF/FTC arm

CAB-LA Cabotegravir long-acting injectable

there was an increase in the self-reported use of condom after initiating PrEP. It has been speculated that the results may reflect the comprehensive services offered during the trials, which included counseling and condom distribution. However, in a systematic review of observational studies and one open-label trial, PrEP was associated with an increase in STIs, and most studies showed evidence of decreased overall condom use [39]. These results underscore the importance of risk reduction counseling in addition to PrEP prescription.

Finally, another widely discussed concern is the development of resistance to TDF-FTC. These antiretrovirals are not only used to prevent HIV transmission but they are also commonly used to treat chronic HIV infection, in addition to a third antiretroviral. Although PrEP-associated emergence of drug-resistant viral strains has been described, this has occurred in association with the initiation of PrEP in individuals with unrecognized HIV infection or with low medication adherence.

In 2019, the FDA approved a new formulation of tenofovir (TAF, tenofovir alafenamide) to be used in combination with FTC (TAF-FTC) in adults and adolescents at increased risk for HIV infection. It must be noted that this combination is not approved for cisgender women because the effectiveness in this population has not been well evaluated. In the phase 3 Discover study [29], TAF-FTC was shown to be non-inferior to TDF-FTC in preventing new HIV infections. TAF is converted intracellularly to the active drug form which leads to higher intracellular and lower plasma concentrations of active drugs. It has been hypothesized that this may be the reason why TAF is associated with less bone and renal toxicity than TDF. On the other hand, TAF is associated with greater weight gain and increase in LDL cholesterol in comparison with TDF.

Psychiatric illness can increase the risk for HIV infection by four- to tenfold, and the risk may be even higher in patients with serious mental illness or who have several co-occurring psychiatric disorders, such as depressive disorders, substance use disorders, and PTSD [40]. As an example, in the iPrEX study, increased risk behaviors were more commonly reported in individuals with depressive symptoms [41]. Substance use may also increase the vulnerability to HIV infection, and many other psychiatric illnesses are known to increase the risk for substance use. For these reasons, PrEP should be offered to people living with psychiatric illness who are at substantial risk of HIV infection. It is also advisable to screen for psychiatric disorders when prescribing PrEP, as psychiatric illness is known to affect adherence to antiretrovirals in chronic HIV infection [42], although their effect on PrEP is less clear at this time. Interestingly, it has been suggested that mild-moderate anxiety can *improve* adherence to PrEP as worry regarding potential HIV risk may promote adherence [43].

It is recommended that individuals on PrEP be assessed every 3 months in order to repeat HIV testing and assess for side effects, adherence, and risk behaviors, as well as for STI [21]. Table 2.5 summarizes the recommendations for clinical follow-up and monitoring.

There are no significant drug-drug interactions between approved PrEP options and psychotropic medications.

Table 2.5 Clinical follow-up and monitoring

Every 3 months
Repeat HIV testing and assess for signs/symptoms of acute infection
Test for pregnancy
Prescribe daily PrEP for no more than 90 days (until the next HIV test)
Assess for side effects, adherence, and HIV acquisition risk behaviors
Support medication adherence and risk-reduction behaviors
Conduct STI testing
At least every 6 months
Monitor creatinine clearance
At least every 12 months
Evaluate the need to continue PrEP as a component of HIV prevention

Based on data from Ref. [21]

Because PrEP's preventive effect is highly dependent on adherence, there has been interest in the development of long-acting injectables that don't require daily oral adherence. CAB-LA (cabotegravir long-acting injectable) is a new integrase strand transfer inhibitor that, although not approved for PrEP yet, has shown promising results across three groups: MSM, transgender women, and cisgender women. In yet to be published two randomized, double-blind, double-dummy studies, CAB-LA was found to be well tolerated (despite having higher incidence of injection site reactions) and more effective than oral TDF/FTC, with a 66% reduction in the risk of HIV infection in MSM and transgender women [44] and 89% in cisgender women [45].

Post-Exposure Prophylaxis

Accidental or coerced exposure to HIV constitutes a medical emergency and can be addressed with post-exposure prophylaxis (PEP). PEP provides clinicians the opportunity to intervene to prevent a new HIV infection in an HIV-negative individual who is exposed to HIV. Through timely treatment with PEP, a person who is exposed can prevent HIV from establishing infection if designated PEP antiretroviral treatment is initiated before 72 h after exposure and preferably within 24–36 h after exposure [46]. The duration of the use of PEP is for 28 days after exposure. This section describes non-occupational exposure, since occupational exposure is for the occurrence of exposure in medical settings and is subject to specific infection control protocols tailored to the setting of care.

When a patient reports recent potential exposure to HIV occurring under 72 h from time of presentation, the CDC recommends several factors to consider when determining whether PEP is indicated [46–48]. The first is to clarify the patient's HIV serostatus, and if possible, confirm by rapid HIV antibody testing that the patient is HIV negative. If the patient is seronegative, the potential exposure should

be evaluated for its level of HIV risk. It should be determined if the HIV status of person(s) representing the exposure source is known and, if so, whether this status is HIV positive. The body fluid involved in the potential exposure should be ascertained (e.g., higher-transmission-risk fluids such as blood or semen versus minimal-transmission-risk body fluids such as tears or saliva). Finally, the site of exposure should be determined, with vaginal, rectal, and non-intact skin exposures representing higher risk. These exposures typically occur through condomless anal or vaginal intercourse or through injection drug use with shared needles. The indication for use of PEP is highly specific and medically emergent and not only protects the person affected but has potential public health implications. PEP should be used when potential HIV exposure is a rare, accidental, unintended, or coerced event. PEP, when administered promptly as soon as possible within 72 h after exposure, can prevent HIV infection [43–45].

Patients who present with ongoing risks for HIV exposure should be transitioned to PrEP or other forms of behavioral HIV prevention, such as counseling on the consistent use of barrier methods for sexual intercourse or the use of clean needles for injection drug use practices. For patients presenting with ongoing risks for injection drug use HIV transmission, referral to treatment for substance use disorder should also be strongly considered. In addition, when a patient presents with a likely high-risk exposure for HIV, other risks should be evaluated, such as for hepatitis B, hepatitis C, other STIs, and pregnancy (Fig. 2.2, Table 2.6).

Post-exposure prophylaxis differs from pre-exposure prophylaxis in the indications for use, medications used, the duration of treatment, and the lack of a very strong evidence base for treatment (the evidence for PEP is limited to animal and cohort studies without randomized clinical trials). See Table 2.7 for a summary of the differences between PEP and PrEP.

Nonetheless, PEP is useful in reducing HIV transmission when it is begun as rapidly as possible following an isolated exposure [46–48]. The preferred antiretroviral medications for nPEP in otherwise healthy adults and adolescents are tenofovir disoproxil fumarate (tenofovir DF or TDF) (300 mg) with emtricitabine (200 mg) once daily *plus* raltegravir (RAL) 400 mg twice daily or dolutegravir (DTG) 50 mg once daily for a 28-day course. The medications recommended for PEP for pregnant women and women of a childbearing age are now under review because of concerns for neural tube defects from use of dolutegravir although the evidence is somewhat controversial [49–51]. Thus, the pregnancy status of women should be determined before recommending PEP.

Conclusions

Clinicians should be aware of the special risks for HIV infection in persons with psychiatric disorders. Familiarity with best practices for HIV screening and prevention allows clinicians to take an active role in HIV risk reduction with their patients. Awareness of best practices creates opportunities to reduce the burden of illness in

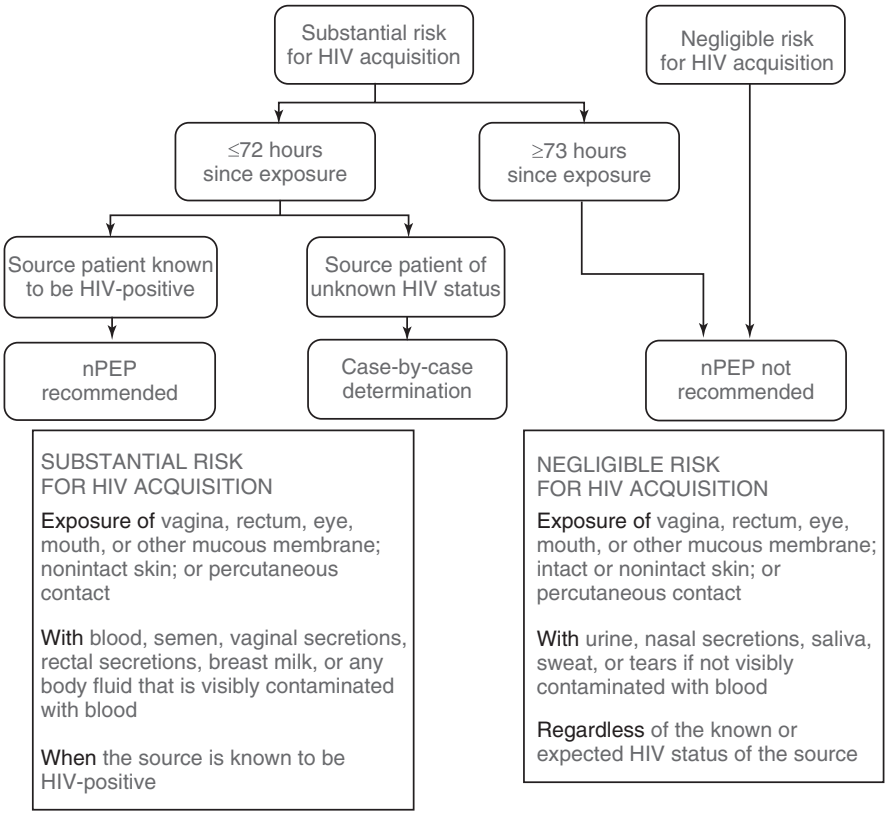

Fig. 2.2 Algorithm for assessing candidacy for PEP. (Adapted from Updated Guidelines for Antiretroviral Post-exposure Prophylaxis After Sexual, Injection Drug Use, or Other Nonoccupational Exposure to HIV— United States, 2016 from the Centers for Disease Control and Prevention (CDC), U.S. Department of Health and Human Services)

vulnerable high-risk patients and contributes to public health efforts to reduce community HIV transmission.

Multiple-Choice Questions

1. Post-exposure prophylaxis differs from pre-exposure prophylaxis in which of the following ways? (Please choose one only.)

   (a) It is helpful in reducing HIV transmission.
   (b) It is recommended for an HIV-negative sexual partner of a person with HIV and needs to be taken on a daily basis for the duration of the relationship, or it is not consistently efficacious in preventing HIV transmission.

Table 2.6 Frequency of infection associated with individual HIV exposure events (from CDC)

Type of exposure	Risk per 10,000 exposures
Parenteral	
Blood transfusion	9250
Needle-sharing during injection drug use	63
Percutaneous (needlestick)	23
Sexual	
Receptive anal intercourse	138
Insertive anal intercourse	11
Receptive penile-vaginal intercourse	8
Insertive penile-vaginal intercourse	4
Receptive oral intercourse	Low
Insertive oral intercourse	Low
Other	
Biting	Negligible
Spitting	Negligible
Throwing body fluids (including semen or saliva)	Negligible
Sharing sex toys	Negligible

Table 2.7 Differences between PrEP and PEP

PEP	PrEP
Emergent use	Harm reduction
Evidence not strong	Evidence is strong
28-day course	Can begin when there is a realization of ongoing risk of HIV infection
Must begin rapidly as soon as possible after exposure	Careful choice of recipients since adherence is crucial
Requires three antiretrovirals, one combination pill once a day and one other pill either once or twice a day	Requires careful monitoring
For use after accidental potential HIV exposure	For HIV-negative persons with ongoing risk of HIV infection through sexual transmission
Unsafe sex	For HIV-negative individuals unable to abstain from drug use by injection
Rape, coerced sex	
Accidental exposure to contaminated drug paraphernalia	

(c) The duration of post-exposure prophylaxis is the same as that of pre-exposure prophylaxis.
(d) Post-exposure prophylaxis is indicated emergently following an accidental exposure of an HIV-negative person to the blood or body fluid of an HIV-positive person during a sexual encounter or injection drug use.
(e) Post-exposure prophylaxis is a response to a medical emergency and but is not comprised of treatment with antiretroviral medications.

(Correct answer is d.)

2. Post-exposure prophylaxis or PEP is indicated for which of the following clinical presentations?

   (a) An HIV-negative man who is in a long-term monogamous relationship with an HIV-positive man experiences condom failure during receptive anal sex.
   (b) A person with opioid use disorder in remission experiences a relapse and shares needles during an instance of injection drug use.
   (c) An HIV-negative person who was drugged and awakened after a sexual encounter while intoxicated with no recollection of the encounter.
   (d) An HIV-negative, non-pregnant woman who is of childbearing age and is in a long-term relationship with an HIV-positive man realizes that her partner "forgot" to put on a condom during vaginal intercourse.
   (e) All of the above.

   (Correct answer is e.)

3. Treatment as prevention (TasP) refers to which of the following HIV prevention strategies:

   (a) Incorporating evidence-based behavioral prevention interventions within the workflow of a primary care clinic
   (b) The collecting of detailed HIV risk behavior information by primary care clinicians during routine visits
   (c) The prescription of pre-exposure prophylaxis (PrEP) by psychiatrists to patients with mental illness and high-risk HIV behavior
   (d) The use of combined antiretroviral therapy to reduce the viral load of people living with HIV and thereby preventing their infection of others
   (e) The use of Medicaid funding to support HIV education efforts

   (Correct answer is d.)

4. Examples of structural factors that contribute to increased HIV risk include which of the following?

   (a) A 32-year-old woman who uses intravenous drugs is ambivalent about entering treatment for opioid use disorder.
   (b) A specific state law criminalizes programs which provide clean needles to people who inject drugs.
   (c) A 55-year-old man discontinues lithium carbonate due to concerns about interactions with his antiretroviral regimen and experiences subsequent mania leading to high-risk sexual behavior.
   (d) A primary care clinician, upon learning that her patient exchanges sex for money, feels embarrassed and uncomfortable discussing methods of reducing HIV transmission risk.
   (e) A 23-year-old man who has sex with men (MSM) does not believe that he is at risk for HIV as he does not identify as gay or bisexual.

   (Correct answer is b.)

5. Which of the following statements is correct regarding PrEP?

   (a) All patients taking TDF/FTC for PrEP should switch to TAF/FTC as the latter combination of antiretrovirals is associated with fewer renal side effects.

(b) It is not necessary to rule out HIV infection prior to initiating PrEP.
(c) PrEP can only be prescribed by infectious disease physicians.
(d) The combination TAF/FTC is not recommended for use in cisgender women because its effectiveness in this population has not been well evaluated.
(e) Individuals on PrEP only need to be reassessed every 12 months in order to repeat HIV testing and assess for adherence, risk behaviors, and side effects.

(Correct answer is d.)

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Chapter 3
HIV Stigma

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Introduction

While remarkable strides have been made in the diagnosis and treatment of persons with human immunodeficiency virus (HIV) and acquired immunodeficiency syndrome (AIDS), stigma and discrimination remain significant barriers to care and complicate and perpetuate the HIV pandemic. Throughout the world, 37.9 million people are living with HIV/AIDS, and an estimated 1.7 million individuals worldwide are newly infected with HIV each year [1]. In the United States, despite access to HIV testing and care, HIV is still an epidemic, with 1.1 million people living with HIV and 37,600 people becoming infected each year. In the United States, 1 in 7 or 162,500 persons with HIV is unaware of being infected and can unknowingly transmit the virus to others [2]. In the United States, only 63% of persons with HIV have attained sustained viral suppression [3].

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While this treatment cascade has multiple biopsychosocial determinants [1–10], HIV stigma, AIDSism [11], and resultant discrimination contribute to HIV transmission, nonadherence to care, and morbidity and mortality in persons with HIV. HIV stigma has been defined by the US Centers for Disease Control and Prevention (CDC) and UNAIDS [12–14]. The CDC defines HIV/AIDS-related stigma as negative beliefs, feelings, and attitudes toward people living with HIV, their families, people who work with them (e.g., HIV clinicians), and vulnerable individuals who have been heavily impacted by HIV, such as gay and bisexual men, homeless people, street youth, and mentally ill people. HIV discrimination refers to the unfair and unjust treatment of someone based on their real or perceived HIV status. Discrimination can also affect family and friends and those who care for people with HIV [12]. HIV discrimination is often fueled by myths of casual transmission of HIV and preexisting biases against vulnerable persons, certain sexual behaviors, drug use, and fear of illness and death. Discrimination can be institutionalized through laws, policies, and practices. UNAIDS defines HIV/AIDS-related stigma as a "process of devaluation" of people either living with or associated with HIV and AIDS [13]. This stigma often stems from the underlying stigmatization of sex and intravenous drug use—two of the primary routes of HIV infection. Discrimination follows stigma and is the unfair and unjust treatment of an individual based on his or her real or perceived HIV status. Discrimination occurs when a distinction is made against a person that results in being treated unfairly and unjustly on the basis of belonging, or being perceived to belong, to a particular group [14].

In educating medical students, physicians, and other clinicians, it is important to use words that do not stigmatize. The use of the words "risk groups" stigmatized all persons in these groups—thus Haitians, persons with hemophilia, and men who have sex with men previously were *all* considered to constitute HIV risk groups. The concept magnified HIV stigma by falsely categorizing all members of the group and falsely reassuring individuals *outside* the groups that they were *not at all* at risk [15]. Gradually, more accurate and less stigmatizing words were introduced. Transmission categories and risk behaviors replaced the concept of risk groups. A clinician in any field of medicine can help decrease HIV transmission and HIV stigma and encourage routine HIV testing and engagement in care.

Stigma has been identified as the most formidable psychosocial factor contributing to treatment nonadherence among HIV-positive individuals [16]. Almost eight in ten persons who are living with HIV report feeling HIV-related internalized stigma, defined by the CDC as integrating negative HIV stereotypes [17]. Internalized stigma may aggravate depression, heighten anxiety, reduce a person's hope, and increase despair, thereby reducing a person's ability to protect and manage health and well-being [18]. According to results from the 2010 AIDS Treatment for Life International Survey (ATLIS) [19], the most common stigmas surrounding HIV/AIDS reported by respondents were the following: (1) the person with HIV/AIDS has or does engage in risky behavior such as sexual promiscuity, drug use, and/or sex work, and (2) people with HIV/AIDS should be avoided. Such stigma may cause HIV-positive individuals to avoid seeking treatment or deliberately skip doses

of medication in the presence of other people, for fear that such exposure would lead to suspicion or inadvertent disclosure of their HIV status [20].

The patient-clinician relationship has consistently appeared in studies as a major factor in treatment adherence and nonadherence [21–23]. Dynamics of the patient-clinician relationship, including issues of power, stigma, and the nature of interactions, may play critical roles in adherence [21]. HIV-positive patients who reported receiving standardized education about adherence and adherence aids during antiretroviral therapy (ART) initiation also reported higher adherence rates than patients not receiving such information [24].

Physician communication is positively correlated with patient adherence, showing a 19% higher risk of nonadherence among patients whose physician communicates poorly than among patients whose physician communicates well [22]. Findings from studies examining dynamics of patient-clinician communication among people living with HIV show that most patient-clinician communication focuses almost exclusively on the biomedical aspects of HIV-related treatment [25].

Perhaps for these reasons, in its 2001 report on healthcare, the Institute of Medicine (IOM) bemoaned modern medicine's narrow focus on disease, ignoring the psychosocial aspects of an individual's illness. In the report, the IOM recommends a patient-centered approach to care as one of six key domains of quality care in the twenty-first century [26]. In reference to patient-centered care, the IOM recommends that healthcare processes be customized based on patient needs and values. "The system should be able to meet the most common needs, but have the capability to respond to individual patient choices and preferences" [26]. Furthermore, "patients should be provided necessary information and the opportunity to exercise the degree of control they choose over health care decisions that affect them" [26]. The IOM recommendations are summarized in Table 3.1. The IOM supports a patient-centered approach to healthcare and with good reason. Research on patient-clinician relationships shows that improved communication can potentially modify stigma, patient mood states, and self-efficacy thereby improving HIV treatment adherence [27]. Moreover, effective patient-clinician communication is linked empirically to outcomes of care including patient satisfaction, health status, recall of information, and adherence [22]. Studies have shown that a patient-centered approach to communication is generally preferred by patients and facilitates improved health outcomes across all disease conditions [28].

In their meta-analysis of publications on physician communication and treatment adherence, Zolnierek and DiMatteo noted four essential elements of the patient-physician relationship, verbal and nonverbal communication, effective questioning and transmission of information, expression of empathy and concern, and partnership and participatory decision-making, summarized in Table 3.2 [22]. Of interest, the analysis revealed that pediatricians and residents had a more positive effect on treatment adherence than more experienced physicians and those not trained as pediatricians. Zolnierek and DiMatteo attribute the results to training that promotes pediatrician communication at the level of both child and parent and to present information about recommended regimens in such a manner as to ensure understanding by both children and parents. Additionally, residents' lower level of

Table 3.1 IOM-recommended six dimensions of patient-centered care

IOM's Recommended six dimensions of patient-centered care
1. Respect for patients' values, preferences, and expressed needs Patient-centered care responds specifically to the patient's individual wants, needs, and preferences. Shared decision-making is a dynamic process, changing as patients' preferences and circumstances change over time
2. Coordination and integration of care Patients rely on providers to coordinate care (e.g., tests, consultation, procedures). Patient-centered care addresses the need to manage a smooth transition from one setting to another or from health care to home care
3. Information, communication, and education Patients want to know what is the problem (diagnosis), what is likely to happen, how it will affect them (prognosis), and what can be done to change or manage their prognosis. Answers should be accurate and in the language they can understand. Patient-provider interactions should provide trustworthy information that is attentive, responsive, and tailored to the patient's needs
4. Physical comfort Attention to physical comfort implies timely, tailored, and expert management of symptoms such as pain, shortness of breath, or other discomfort at all levels of illness. Patients should never need to undergo suffering
5. Emotional support: relieving fear and anxiety Patient-centered care also attends to distressing symptoms other than just physical pain, such as anxiety that accompanies illness, fear of pain, disability or disfigurement, loneliness, financial stressors, or effect of illness on the family
6. Involvement of family and friends Patient-centered care accommodates others on whom the patient relies. When appropriate, they should be involved in decision-making and supported as caregivers. Family and friends should feel welcomed and comfortable in the care delivery setting and their needs and contributions recognized

Based on data gathered from the Institute of Medicine [26]

Table 3.2 Four essential elements of the patient-physician relationship

Four essential elements of the patient-physician relationship
Verbal and nonverbal communication
Effective questioning and transmission of information (task-oriented behavior)
Expression of empathy and concern (psychosocial behavior)
Partnership and participatory decision-making

experience with patient and illness management may require more attention to interpersonal skills of effective communication to achieve better adherence and treatment outcomes. Results of the meta-analysis support the prediction that patient adherence is significantly related to the quality of communication of physicians and that adherence can be improved when physicians are trained to be better communicators [22] (Table 3.3).

In an effort to identify communication strategies to improve HIV treatment, Rochon et al. interviewed nine focus groups consisting of HIV-positive adults of varied ages, ethnicities, and genders at a publicly funded HIV clinic in Houston, Texas [27]. Analysis of the focus group transcripts revealed five constructs

Table 3.3 Constructs amenable to communication to improve treatment adherence

Constructs amenable to communication to improve treatment adherence
1. Cultural beliefs/language
MODIFIER: Experienced translator; culturally appropriate education materials
2. Stigma
MODIFIER: Minimizing the conditions in which a person can be stigmatized has the potential to remove fears about disclosure or alleviate humiliation and increase treatment adherence
3. Cues to action
MODIFIER: Pill boxes; alarms; placing pills near a daily reminder such as a coffee pot or toothbrush; asking someone close to the patient to help remind the patient to take medication
4. Self-efficacy
MODIFIER: A supportive environment and increased health literacy can improve self-efficacy and physical and emotional well-being as well as reduce negative emotional states
5. Mood state
MODIFIER: Worthiness, hopefulness, and a positive attitude can help improve medication taking. Supportive communication with the healthcare team, family, friends, or support groups can help foster worthiness and a positive attitude

especially amenable to using communication to increase patient adherence. These are (a) cultural beliefs/language, (b) stigma, (c) cues to action, (d) self-efficacy, and (e) mood state. With regard to cultural beliefs and language, the focus groups revealed non-English-speaking monolingual patients, particularly Spanish-speaking patients, had difficulty understanding complicated medication regimens. Additionally, cultural variations in attitudes toward health, specifically health or folk beliefs, impacted willingness to adhere to regular medication regimens. Rochon et al. posit that language barriers or cultural beliefs that decrease treatment adherence can be modified using experienced translators or providing culturally appropriate education materials.

With regard to stigma, group members expressed feeling marginalized and ostracized “like a leper” and that their HIV diagnosis gives people a convenient excuse for prejudice and preexisting hostility that includes rejection and humiliation. They mentioned missing medication doses when they have company or are with people who do not know their HIV status. One member explained how a friend helped to minimize his irrational beliefs and hypervigilance by accompanying him to his appointment at the clinic. The friend reminded the patient that everyone was there for the same reason. The friend also noted that he believed the brown bag everyone was carrying must have contained lunches. He did not know the bags contained medications.

Focus group members described affirmative mood states, like worthiness and hopefulness, which were used to clinical advantage in motivating patients for taking medications. Many members reported how they were made to feel unworthy and socially inferior because of their HIV status. Managing one’s own mood state was one of the main strategies that patients employed to cope with their HIV infection and the stresses inherent to medication adherence. Patients who had better treatment adherence found ways to cope with denial and depression, improve their attitudes,

Table 3.4(a) ABC Project's competency framework communicating with patients about medicine

1. Listening Listens actively to the patient	*2. Communicating* Helps patients interpret information in a way that is meaningful to them
3. Context With the patient, defines a mutual understanding of the purpose of the consultation	*4. Knowledge* Has up-to-date knowledge of area of practice and wider health and social services

Adapted with permission from White et al. [29]. Available from: http://pharmacyeducation.fip.org/pharmacyeducation/article/view/254/226

Table 3.4(b) Managing and supporting medicine adherence [29]

1. Understanding Recognizes that the patient is an individual	*2. Exploring* Discusses illness and treatment options, including no treatment
3. Deciding Decides with the patient the best management strategy	*4. Supporting* Supports the patient with medicine taking

Adapted with permission from White et al. [29]. Available from: http://pharmacyeducation.fip.org/pharmacyeducation/article/view/254/226

and organize their lives around the complicated treatment regimens. Built into this self-recovery was a sense that communication was vital, whether it was with health-care clinicians or peers who were also HIV infected. Group members often verbalized the role of support groups in facilitating communication and improved mood states. This latter theme further illustrates the importance of positively perceived patient-clinician communication [27] and also illustrates the value of support groups.

Because of a lack of operationalization, there has been much difficulty integrating patient-centeredness into the current biomedical model of medicine [28]. In an effort to develop a standardized training model for engaging with patients to manage and support medication adherence, White et al. developed an evidence-based framework for improving patient medication adherence as part of the ABC (Ascertaining Barriers to Compliance) project. The framework comprises of eight core competencies that are grouped into two overarching areas: (a) communicating with patients about medicines and (b) managing and supporting medication adherence (see Tables 3.4(a) and 3.4(b)) [29]. A detailed diagram of the framework is available for download at the following link: http://pharmacyeducation.fip.org/pharmacyeducation/article/view/254/226.

Although HIV stigma and discrimination have evolved over the four decades of the pandemic, evidence that AIDSism still exists can be found in the words of patients and in their experiences of care. Descriptions of HIV internalized stigma and societal stigma can be found in patients' words and are summarized in Table 3.5. Suggestions for assessing for stigma and AIDSism can be found in Table 3.6.

Case Vignettes

The following are brief clinical vignettes that poignantly illustrate the impact of HIV stigma and discrimination on patients in both home and healthcare settings.

Case Vignette 3.1: Ms. A was newly diagnosed with HIV infection. After her visit, as she was leaving her physician's office, she fainted in the waiting room, and healthcare workers came to her assistance. She wrote a letter to the hospital praising her caregivers for rushing to her side and for not being afraid of touching her despite her HIV serostatus.

Case Vignette 3.2: Mr. B had HIV for three decades and had developed profound lipodystrophy and lipoatrophy from protease inhibitors. The first four plastic surgeons he consulted for severe facial atrophy refused to provide care for him, although it would have been covered by his insurance.

Case Vignette 3.3. Dr. C was a physician on elective rotation in an HIV clinic who refused the introductory handshake offered by a person with HIV.

Case Vignette 3.4. Mr. D was an HIV patient whose parents refused to allow him into their home after he disclosed his diagnosis. They informed him that they would not be responsible for his burial after his death.

Case Vignette 3.5. Ms. E was a woman with AIDS who refused to enter the front door of the HIV clinic or sit in the waiting room for fear of forced disclosure by being recognized by persons in her neighborhood.

Case Vignette 3.6. Mr. F was a 35-year-old HIV-negative man, the son of a mother with AIDS. Mr. F returned home after attending an informational workshop on HIV in an effort to learn more about AIDS in order to further understand and support his mother. When his wife saw that he returned from an HIV informational workshop, she insisted he remove his clothes in the backyard before entering the house so he would "not bring home AIDS."

Table 3.5 Internalized and societal stigma: in Patients' Words

"It is embarrassing"
"It has an effect on your mind, body, and soul"
"The perception is that you are not a very nice person anymore"
"Everything is limited"
"Before you could do whatever you wanted"
"Relational and career goals seem like a fairy tale"
"I feel awful about myself for lying to my friends"
"I've lost all my goals"
"I am ashamed to come to the clinic because someone may recognize me"
"I have my medicines sent to me by mail because I am ashamed to go to the drugstore for them"

Table 3.6 Assessing for HIV stigma and discrimination

Have you disclosed your serostatus to close friends or relatives?
Have you regretted having told some people that you have HIV?
Have you lost friends by telling them that you have HIV?
Do you feel that you have to hide the fact that you have HIV?
Do you worry that people who know will tell others?
Do you worry that people may judge you if they learn that you have HIV?
Do you feel guilty or ashamed because you have HIV?
Do you worry about people discriminating against you because of your HIV status?
Do you worry about losing your job if your employer knows that you have HIV?
Do you feel that telling people about your status has negatively affected your relationship with them?

Patients living with HIV often experience differential care that visibly marks them to others as living with HIV such as by the inappropriate use of infection control precautions by clinicians or other healthcare workers. An example would be a clinician's use of gloves during non-invasive procedures such as taking vital signs on patients with HIV but not on HIV-negative patients [30]. As a result of HIV stigma persons may avoid accessing HIV testing services, avoid medical care for fear of forced disclosure by the nature and setting of care, and avoid taking antiretrovirals for fear of forced disclosure.

Impact of HIV Stigma on Patients

HIV Testing

Current HIV testing guidelines recommend testing at least once as part of routine healthcare. For persons with risk behaviors such as injecting drug use or condomless anal penetration, annual or more frequent HIV testing is recommended. Once HIV testing becomes a normal and routine part of medical care, the stigma of HIV testing will likely recede and allow for the millions of people living with HIV who

are unaware of their status to get tested [31]. Increasing availability of HIV self-test kits improves HIV testing [32].

Obtaining Test Results

Even after testing for HIV is conducted, the stigma associated with a positive diagnosis can lead to delay in or avoidance of obtaining testing results for fear that the result will be positive. This can lead to delay in treatment and thus poorer health outcomes in patients with a positive HIV diagnosis.

Disclosure

The stigma associated with an HIV diagnosis can discourage disclosure of serostatus for fear of discrimination, rejection, or ostracism. Nondisclosure to friends or family members can lead to feelings of isolation, loss, and depression by eliminating an important source of social support [33]. Nondisclosure to current sexual partners due to stigma can also potentially elevate risk of infection for partners [34], and establishment of care or treatment may be delayed due to fear of forced disclosure through the context of treatment [35].

Accepting Referral for Care

The delivery of HIV test results should be tailored to the patient's emotional response. Test results should be delivered promptly after results are available and interpreted to ensure that the patient clearly understands the meaning of the test results. Key information such as disclosure, confidentiality of test results, early referral to care, initiation of treatment, and support services should be delivered. Test and treat guidelines recommend rapid initiation of antiretroviral therapy for all people living with HIV with a confirmed HIV diagnosis. ART should be offered on the same day for people who are ready to start [36].

Engagement in Care

Barriers to obtaining HIV services and engagement in care can be overcome through providing collaborative and integrated care, embedded psychiatrists and mental health clinicians, as well as outreach and social services. Integrated services can increase uptake and prevent isolation of patients accessing HIV care [32].

Accepting Recommendations for PrEP

Current guidelines recommend pre-exposure prophylaxis (PrEP) use for individuals who are at substantial risk of acquiring HIV infection, particularly persons with an HIV-positive sexual partner, persons who inject drugs, persons with a high number of sexual partners, persons with a history of inconsistent or no condom use, and persons who engage in sex work [4].

Adherence to PrEP

Individuals who are HIV negative as well as individuals in an ongoing relationship with HIV-positive partners and on PrEP to prevent infection also experience barriers to treatment adherence, including HIV-related stigma. PrEP uptake can be low among youth, minority groups, or marginalized communities due to individual, social, and structural barriers summarized in Table 3.7. In a PrEP study among HIV-negative young men of color who have sex with men, participants reported experiencing stigma from within the gay community as well as from healthcare providers, family, friends, and strangers, thus causing barriers to maintaining regular medication adherence, avoiding taking medication in front of others, or not seeking PrEP treatment at all [37]. Stigma toward individuals using PrEP often stems from assumptions about increased risk-taking behaviors and promiscuity while on PrEP or assumptions that taking the medication means one is HIV-positive [38].

Missing Clinic Appointments

Individuals who miss their scheduled medical appointments are more likely to have higher viral loads and lower CD4 counts [39, 40]. Differentiated care models such as multi-month prescriptions and reduction of clinical visits to every

Table 3.7 Barriers to PrEP uptake

Individual	Social and structural
Medical distrust	Cost
Pill burden	Access to healthcare
Concerns over side effects	Need for regular visits
Daily adherence	Stigma and negative attitudes
Limited awareness of PrEP	

3–6 months should be implemented for stable patients and tailored to their needs [41, 42].

Nonadherence with Medications

HIV-related stigma can be a major contributor to medication nonadherence through several different mechanisms. Fear of forced disclosure can lead to attempts to conceal treatment which can make consistent adherence difficult [33]. HIV stigma may intensify symptoms of depressive disorders, such as low self-esteem, low self-worth, and self-devaluation, which can indirectly lead to nonadherence to care or medication. Stigma can also cause nonadherence indirectly through intensification of anxiety. Both depressive disorders and anxiety disorders have a strong independent association with nonadherence to care and antiretroviral treatment [43].

Treatment Cascade Versus Viral Suppression

The HIV care cascade is a model which tracks patient involvement through the steps of care occurring after HIV status is known. The steps of the continuum include linkage to care, engagement and retention in care, initiation of antiretroviral treatment, and finally achievement of viral suppression. Analysis of attrition at each step can help locate possible deficits in care [44]. HIV-related stigma can disrupt the cascade of care at any point along its continuum, even after establishment of initial diagnosis. Disruption of treatment at any stage of the cascade can have downstream effects resulting in failure to achieve viral suppression as shown in Fig. 3.1 [3]. Discriminatory attitudes toward persons with HIV by healthcare workers can contribute to poor adherence to medication, retention in care, and viral load suppression [45].

Delay in Beginning a 28-Day Course of PEP

Post-exposure prophylaxis (PEP) is a 28-day-long course of antiretroviral drugs that should be administered within 72 h of potential HIV exposure to prevent infection. PEP is a highly time-sensitive intervention, and delays in administration can result in reduced efficacy [46]. HIV-related stigma has been shown to be a factor contributing to delay in initiation of PEP, with fear of judgment from healthcare providers, fear of discrimination, or fear of sexual orientation disclosure being commonly cited fears of individuals seeking PEP [47].

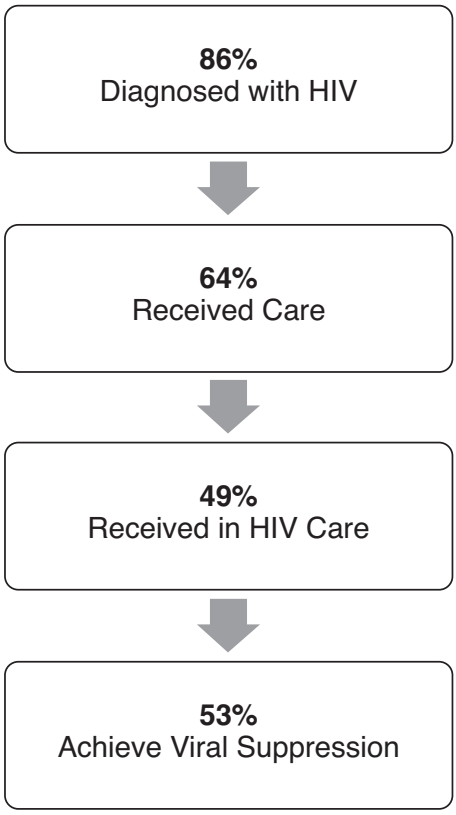

Fig. 3.1 The HIV treatment cascade of the estimated 1.1 million persons living with HIV in the United States (2017). (Based on data from Ref. [3])

Impact of HIV Stigma on Healthcare

Multiplicity of HIV-Associated Stigma

HIV

At the outset of the HIV pandemic in 1981, HIV-associated stigma arose out of the fear of infection, contagion, and fatality [10, 48]. A pervasive lack of understanding among both the medical community and society at large drove many of the negative attitudes displayed toward people with HIV. "AIDSism" is comprised of the unique stigma and discrimination that people with HIV/AIDS experience [11]. It is built on the foundation of other experiences of discrimination, such as racism, sexism, and homophobia, and can be manifested both interpersonally and structurally [9]. This unfounded fear has contributed to the elevated isolation, withdrawal, and depression that patients living with HIV experience on an individual level [49]. In practice, stigma translates to discriminatory practices, which in turn increases many social inequities, such as rates of unemployment and homelessness

[9, 49]. For many, AIDSism oftentimes synergistically works with other experiences of marginalization, such as mental illness-based stigma and specifically "addictophobia" [9]. These telescoping forms of stigma have many implications for both patients who live with HIV and those who may be at higher risk of contracting HIV [34].

Psychiatric Illness and Addictophobia

Many patients living with HIV also have multimorbid psychiatric disorders [50]. Internalization of negative social attitudes may be heightened by HIV stigma and, thereby, increase prevalence of depressive disorders and symptoms of anxiety and depression. Stigma toward psychiatric illness is another layer of marginalization that can contribute to the suffering of patients living with HIV and a comorbid psychiatric disorder. Negative attitudes toward people with psychiatric illness include the ideas that all patients with psychiatric illness are dangerous to others, unpredictable, and difficult to interact with. Many believe that patients with psychiatric illness are in some way responsible for their condition [51]. Whether with or without other psychiatric illnesses, patients with substance use disorders are also often made to feel to blame for their condition.

Homophobia

HIV disproportionately burdens men who have sex with men (MSM). Compared to heterosexual men, MSM are 88 times more likely to receive an HIV diagnosis in their lifetime. In fact, estimates demonstrate that at the current rates of diagnosis, about 1 in 6 MSM in the United States will contract HIV in their lifetime. This disparity is highest among African American and Latino MSM, who face a lifetime risk of 1 in 2 and 1 in 5, respectively [52]. Stigma is among the many reasons MSM are disproportionately burdened by the epidemic. Internalization of negative societal attitudes about homosexuality and/or having multiple sexual encounters negatively impacts rates of HIV testing and treatment [9, 53].

Race and Ethnicity

Since the beginning of the HIV epidemic, racial and ethnic minorities have been disproportionately impacted. When HIV had become the third leading cause of death in the United States among adults aged 25 to 44 in 1990, it was also the leading cause of death among black men and Hispanic men in the same age group [54]. Stigma associated with the vulnerability to HIV, and the concept of "risk groups," magnifies various other experiences of stigma and discrimination. For example, in a qualitative study [55] by the US Centers for Disease Control and Prevention

assessing the prevalence of stigmatizing beliefs about people living with HIV, the authors found that negative attitudes were more frequently demonstrated by participants who were white, male, and 55 years or older, had a high school education, had an annual income less than $30,000, and/or had poorer health [56]. Racial and ethnic identification is thought to possibly act as a moderator of the deleterious effects of discrimination; however, the relationship has been shown to be complex [57, 58].

Overall, HIV stigma has been shown to be declining in the United States. Nevertheless, globally, it continues to persist [48]. Stigma and discrimination are contextually mediated, and there is variation of how they both manifest cross-culturally. In many parts of the world, such as in India, people with HIV disease continue to face employment discrimination, eviction, and denial of medical care [9]. In Thailand, where sex work is a significant part of its tourism economy, HIV stigma is closely intertwined with a societal perception that sex work tourism is primarily responsible for the country's epidemic [59]. Sub-Saharan Africa, the region most affected by the HIV pandemic, faces many unique challenges related to stigma particularly because of how the epidemic afflicts many women and young girls [9]. Women are often times seen as vectors of HIV; in Malawi, for example, a sexually transmitted disease is known as a "woman's disease." In parts of Tanzania, an HIV-positive person is called a submarine (nyambizi), implying that the person is inherently menacing [60].

Gendered Stigma and the Effects of Gender-Based Violence

Gendered stigma and the effects of gender-based violence form an additional layer of marginalization for many people afflicted with HIV disease. Women comprise 90% of new HIV infections worldwide. The relationship between gender-based violence and HIV in women is complex. Rape increases the likelihood of HIV transmission due to the abrasions that come with forced sex. Survivors of violence who do not report concurrent sexual assault are still at a higher risk of contracting HIV. This is thought to be due to multiple factors. Male perpetrators are potentially at a higher risk of contracting HIV due to other high-risk behaviors such as substance use, decreased condom use, and having multiple sexual partners. Survivors of violence are also at a higher risk of experiencing re-victimization, experiencing additional violence [9]. The gendered stigma of HIV plays a role in victimization as well. As women in sub-Saharan Africa are oftentimes thought to be vectors of HIV transmission, there have been reports of husbands beating and abandoning their wives who they thought to be HIV-positive [60]. In this context, women may be further victimized if they refuse sex, ask their partner to use a condom, and/or request an HIV test [60]. The relationships among gendered oppression, sex work, and its criminalization also contribute to the disproportionate burden women face in terms of HIV and HIV stigma; 116 countries prohibit sex work under the law [61].

Criminalization creates the norm by which stigma arises; in countries where sex work is criminalized, sex workers suffer higher levels of gender-based violence and oftentimes lack the resources to seek protection from victimization [61]. Both the

vulnerabilities of gender-based violence and the burden of HIV infection are compounded for transgender women and gender-nonconforming individuals. Although the data are limited to middle- and high-income countries where HIV is most concentrated among men who have sex with men, estimates of the burden of HIV among transgender women range from 19% to almost 40% [62]. Transgender and gender-nonconforming individuals face high levels of minority stress due to pervasive experiences of gender-based stigma and discrimination, from family rejection to frank criminalization of "cross-dressing" [62]. In addition to facing discrimination in seeking education, employment, and housing, transgender and gender-nonconforming people face high barriers in seeking healthcare, including lack of competent and/or biased medical providers, refusal of care, and frank harassment and violence [62, 63].

Practical Guidelines and Approaches to Reducing Stigma in Healthcare Settings

In a culture of fear, consistent, timely HIV testing and initiation of care are more difficult [11]. HIV-related discrimination can be addressed by confronting fear-based misconceptions about HIV transmission and increasing awareness among health workers of what stigma itself is and its negative impacts. Although addressing stigma may seem like a large undertaking, many multi-level interventions can be utilized in order to reduce its impact on people affected by HIV infection [10]. These include strong confidentiality protections, providing patients robust social and emotional support, and augmenting the clinical setting's capacity for cultural sensitivity.

Strong Confidentiality Protections

Healthcare workers should know how crucial confidentiality is in taking care of vulnerable populations. Staff should be made aware of how much harm can be caused by confidentiality breaches and neglect of informed consent. Private and confidential counseling, testing, treatment, and support services can help avoid unintentional disclosure. For an in-depth discussion of privacy and confidentiality for persons with HIV, please see Chap. 21 on the legal, ethical, and cultural aspects of HIV and AIDS.

Cultural Sensitivity

As AIDSism does not operate singularly, but rather builds upon other forms of discrimination such as racism, sexism, homophobia, and transphobia, it is important to build a capacity for sensitivity to social difference. One way to approach this competency is to

develop a sense of cultural humility. Cultural humility is an approach to understanding another person according to the aspects of their identity they find the most important [64]. Cultural humility requires a commitment to self-reflection and self-critique as well as an intentional willingness to fix inequitable power dynamics [65].

Patient-Centered Care and Communication

Patient-centered communication, which builds trust and rapport through empathy, promotes a better clinician-patient relationship. Patient-centered communication facilitates improvement in health literacy and promotes self-efficacy. Effective patient-centered communication allows a clinician to better assess potential barriers to adherence and to more fully understand a patient's resilience and vulnerability. Clinicians should be mindful of the language they use that may carry weighted meaning, particularly words with negative connotations, e.g., during a clinical intake interview, it is much less blaming to ask *how a patient learned that they had seroconverted* than to ask *how a patient got infected by HIV*. Creating a culture of patient-centered communication requires active participation and collaboration by the entire team of care providers. For the multiply marginalized, using phrases such as *person living with HIV* or *person with a substance use disorder* intentionally places the person before their diagnosis. Being mindful of person-first language can go far to promote a therapeutic alliance [10].

Emotional Support

People living with HIV often face multiple stressors in their lives. In light of pervasive stigma, people afflicted with HIV may lack a sense of social support to better promote resiliency. In this context, people with HIV oftentimes internalize this shame which can lead to feelings of unworthiness. To combat the profound effects of stigma, clinicians should provide emotional support and consider the need for psychotherapeutic modalities such as supportive psychotherapy, cognitive-behavioral psychotherapy, as well as psychodynamic psychotherapy [10]. Peer support can be powerful and should not be understated; facilitated peer-based support can provide a sense of family and promote openness, honesty, and acceptance in a stigmatizing world.

Conclusion

Stigma, discrimination, and fear may prevent persons with risk behaviors such as unprotected sex and injection drug use from getting HIV testing, learning that they have HIV, and/or accessing care. Thus, HIV stigma worsens health outcomes and

increases HIV transmission. Persons with HIV may experience stigma from multiple sources in addition to HIV infection. Stigma and discrimination complicate and perpetuate the HIV epidemic, are themselves a considerable source of suffering, and can contribute to depression and suicide risk. Utilization of a patient-centered participatory style of communication can minimize stigma, foster resilience, and empower patients toward a more collaborative approach to clinical care. Clinicians are encouraged to play an active role in advocating against stigma and treating the consequences of stigma and discrimination. The use of a collaborative, integrated approach to care helps to ameliorate stigma and discrimination.

Questions

Question 1: Stem

1. In addition to sensitivity and awareness, what is the most direct way that a clinician can ameliorate stigma and discrimination in the care of persons with HIV and AIDS? [26]
   Key – correct answer
   (a) By using patient-centered approaches
   First distractor
   (b) By determining if the patient has a psychiatric disorder
   Second distractor
   (c) By ensuring that the patient is taking antiretrovirals
   Third distractor
   (d) By determining the CD4 count

Question 2: Stem

2. We now utilize concepts of transmission category or risk behavior to replace the previous concept of "risk groups." How does the concept of "risk groups" magnify HIV stigma? [15]
   Key – correct answer
   (a) It assigns risk to entire populations of individuals.
   First distractor
   (b) It is a requirement for HIV reporting an infectious disease.
   Second distractor
   (c) HIV is more prevalent in groups at risk.
   Third distractor
   (d) Risk groups may be related to racism and ethnocentricity.

Question 3: Stem

3. There is a bidirectional relationship between HIV and psychiatric illness and both contribute to stigma in persons with HIV because of the high prevalence of HIV in persons with psychiatric illness. What is the prevalence of HIV in persons with mental illness? [66, 67]

Key – Correct answer

(a) The prevalence of HIV in persons in treatment for mental illness is four times that of the general population.

First distractor

(b) The prevalence of HIV in persons in treatment for mental illness is six times that of the general population.

Second distractor

(c) The prevalence of HIV in persons in treatment for mental illness is two times that of the general population.

Third distractor

(d) The prevalence of HIV in persons in treatment of mental illness is three times that of the general population.

Question 4: Stem

4. In order to end the HIV epidemic, clinicians need to be aware that HIV stigma and discrimination are still barriers to obtaining HIV testing, engaging in care, keeping clinic appointments, and attaining viral suppression. Which of the following statements best supports the need for attaining viral suppression? [40]

Key – Correct answer

(a) Missed clinic appointments is associated with all-cause mortality.

First distractor

(b) Missed clinic appointments is associated with negative transferences.

Second distractor

(c) Missed clinic appointments may be associated with HIV stigma.

Third distractor

(d) Missed clinic appointments may be associated with lack of trust in clinicians.

Question 5: Stem

5. Patient-centered care applies specifically to the patient's individual wants, needs, and preferences. Which of the following questions suggests that the clinician is using patient-centered communication and care? [10, 26]

Key – Correct answer

(a) What is your understanding of your illness?

First distractor

(b) Why did you miss your last three appointments?

Second distractor

(c) When are you going to stop sharing needles?

Third distractor

(d) How did you get infected?

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Chapter 4
Consultation, Assessment, and Evaluation

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Some persons who are at risk for or living with HIV and AIDS have no comorbid psychiatric illness, while others have a multiplicity of complex comorbid psychiatric disorders. Persons with HIV and AIDS may have comorbid psychiatric disorders and may be unrelated to HIV (such as schizophrenia or bipolar disorder). Patients may also develop psychiatric symptoms in response to their HIV/AIDS, its treatments, or associated conditions (such as HIV-associated dementia). Multiple HIV-related co-occurring medical illnesses and their treatments (such as hepatitis C, cirrhosis, HIV nephropathy, and end-stage renal disease) can also result in psychiatric symptoms. Persons with HIV may also have multimorbid-unrelated medical illnesses and treatments (such as coronary artery disease, cancer, and endocrine disorders).

Comprehensive psychiatric evaluations can provide diagnoses, inform treatment, and mitigate anguish, distress, depression, anxiety, and substance use in persons

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with HIV and AIDS. Furthermore, thorough and comprehensive assessment is crucial because HIV has an affinity for brain and neural tissue and thus can cause central nervous system (CNS) complications even in healthy seropositive individuals. These complications are described in Chaps. 6, 9, 10, and 11 of this book.

In this chapter, we provide a basic comprehensive approach to persons at risk for or living with HIV and AIDS who are under the care of you, as a clinician in any specialty or in the field of infectious disease of HIV care. We provide you with a template for understanding and recognizing psychiatric disorders and psychosocial factors that put people at risk for HIV or that contribute to difficulty with engagement, adherence, and retention in care and cause suffering in persons with HIV. This chapter will also help you understand the role of psychiatrists and other mental health clinicians in the care of persons with HIV. Neuropsychological evaluation can be a valuable adjunct in some persons with HIV and AIDS and is covered in detail in Chap. 11.

Psychiatry consultations are requested across a wide variety of settings, requiring the psychiatric consultant to be adept at understanding the needs and resources of each setting. Consults continue to present in traditional settings such as the inpatient and ambulatory settings of acute care facilities and long-term care facilities. Although, as AIDS is increasingly regarded as a chronic severe illness, most persons with HIV and AIDS are seen in outpatient settings, clinics, private offices, and other ambulatory care facilities. These settings have become critical venues for psychiatric assessment of patients, with a particular eye to chronic management and prevention of additional complications. Psychiatric consultations and psychotherapeutic interventions can enhance the survival and quality of life for patients living with HIV/AIDS. Additional specific settings which remain a focus of care include the home care setting, settings of marginal housing (such as shelters, single room occupancy, and transitional housing), correctional facilities, and homeless outreach programs. The complexities of the many special settings where persons with HIV may be evaluated are covered in Chap. 7 as well as in Chap. 10, where correctional facility settings are addressed in further detail.

As the medical care of persons with HIV and AIDS has shifted primarily to the ambulatory setting, various models of integrated care are used:

1. The co-located psychiatrist who works in a comprehensive HIV program can provide evaluations, follow-up care, support groups, consultations to patients admitted in the inpatient setting, curbside consultations, teaching, and supervision.
2. The mental health team leader model finds a clinician directing a diverse group of mental health providers in delivering care to patients through a particular site or program.
3. The triage model in which a mental health clinician participates in the screening of patients, then provides guidance about the appropriate referral to make for a particular patient.

In these various models, the lead clinician can be a psychiatrist or other mental health clinician, with a psychiatrist available for consultation. For a more detailed

description of integrated models of care, please see Chap. 7 of this textbook. It is critical to keep abreast of resources locally available for patients with an eye to providing personalized care.

There is no clear evidence base to determine the best practice model, as the model for delivery of HIV and AIDS medical and psychiatric care is so varied across urban, suburban, rural, and frontier settings. Both inpatient and ambulatory evaluations are presented in this chapter, with the hope that a clinician can develop the tools needed for a comprehensive assessment in any setting.

Given the complexity and severity of HIV/AIDS, there are numerous reasons for clinicians to request a psychiatric consultation. These reasons depend on individual patients' illness severity, psychosocial factors, and psychological aspects of their illness experience (Table 4.1).

Once the need for a psychiatric consultation has been established, a referral to a psychiatrist or other mental health services can be made. Care for patients with HIV and AIDS occurs in a wide variety of settings to include outpatient and inpatient facilities. Psychiatry consultations can be requested in any of these settings, each of which comes with its own unique challenges and resources.

Outpatient Consultation

Primary HIV/AIDS care most often occurs in outpatient settings such as ambulatory clinics or private offices. Involvement of psychiatrists in the care of patients with HIV and AIDs exists primarily in two models:

1. Integrated: The co-located psychiatrist is embedded in the primary HIV care clinic or office. The co-located psychiatrist can provide onsite evaluation, consultation, and follow-up care.
2. Stand-alone: The psychiatrist is located outside of the primary HIV care setting in an independent clinic or office.

An integrated model offers several advantages, including reduced barriers to accessing mental healthcare and increased opportunity for communication among

Table 4.1 Potential reasons for psychiatry consult for persons with HIV/AIDS

Symptoms
Test results (laboratory studies, neuroimaging, etc.)
Psychosocial risk factors
Medical and/or psychiatric history
Substance use/abuse
Medication indications, side effects, interactions, adherence
Consultee's countertransference reactions
Information from collateral sources
Other (e.g., decisional capacity determination, bioethical concerns)

Based on data from Lokko and Stern [1]

clinicians. However, most patients receive care in a stand-alone model that requires them to travel an additional site for mental health services. When referring patients to non-co-located psychiatrists, primary HIV clinicians must be mindful of the added stigma of seeking psychiatric care while being treated for HIV or AIDS.

Inpatient Consultation

Psychiatry consultations during inpatient admission for patients with HIV and AIDS may or may not be directly related to their HIV status. Consulting psychiatrists can assist consultees in refining their consultation question, to allow for a more focused and effective consultation. The inpatient setting can make it easier for psychiatric consultants to gain access to electronic or written patient medical records to supplement the information shared by the consulting clinician.

The specific components and methods of psychiatric consultation referral are discussed in "Communication with Other HIV/AIDS Care Clinicians."

Potential Members of Care Team for Persons with HIV/AIDS

Caring for the global health of persons with HIV/AIDS requires a diverse team of practitioners. The role of a patient's primary HIV clinician can be filled by a physician, nurse practitioner, or physician assistant. These clinicians typically have specialized training in infectious disease or HIV/AIDS care. Their efforts are supported by several allied healthcare professionals, such as nurses, pharmacists, nutritionist/dietitians, and dentists. Social service providers often play a part in addressing a patient's environment and psychosocial needs. This support is coordinated by social workers, case managers, patient navigators, and/or substance abuse specialists. The ideal optimum HIV care team also includes mental health clinicians. They supply specialized expertise and psychological support based on their unique education and training. Commonly utilized mental health clinicians and their respective scopes of practice are outlined below (Table 4.2).

Communication with Other HIV/AIDS Care Clinicians

Patients with HIV/AIDS can be referred for psychiatric care at any stage of their illness in any number of clinical contexts. The content and method of psychiatry referrals are consistent regardless of setting (Table 4.3).

When a referral to a psychiatrist or mental health professional is requested by the team, the primary HIV clinician should inform the patient of this collaboration. Once the patient accepts the referral, the primary provider should emphasize that a

Table 4.2 Multidisciplinary members of mental healthcare team for persons with HIV/AIDS

Position	Role
Psychiatrist	A medical doctor (M.D. or D.O.) who specializes in psychiatry and is qualified to diagnosis, treat, and prevent mental, emotional, and behavioral disorders Utilizes medication, psychotherapy, and other indicated medical procedures (such as electroconvulsive therapy) in treatment
Consult/liaison psychiatrist	A psychiatrist with additional training in the care of patients with comorbid psychiatric and general medical conditions. Additionally, consultation-liaison psychiatrists can specialize in HIV psychiatry
Psychologist	Practitioners with advanced degree (Psy.D. or Ph.D.) and training to help people learn to cope more effectively with life issues and mental health problems, utilize psychotherapy, and can administer tests and assessments to evaluate patients' cognition and non-cognitive status (personality, behavior, and emotions)
Addiction counselor	A mental health counselor specializing in the treatment of patients who have a chemical dependency on drugs or alcohol Can conduct substance abuse evaluations, administer drug/alcohol tests, offer therapy, and develop treatment plan in outpatient or inpatient settings
Social worker	A licensed social worker (LMSW, LCSW) focuses on shaping the patient and their environment to enhance well-being and meet basic needs Assist patients in navigating social services and address social determinants of health. Licensed clinical social workers can provide short-term therapy
Psychiatric nurse specialist	A certified advanced practice nurse (MSN, DNP) who specializes in mental health and is qualified to diagnosis, treat, and prevent mental, emotional, and behavioral disorders Utilizes medication and psychotherapy in treatment

mental health provider is an *integral part* of the HIV care team. A warm introduction from the primary physician or clinician to the psychiatrist or other mental health clinician will reduce patient anxiety and reinforce the importance of psychiatric support in HIV/AIDS care. Primary HIV clinicians continue to work closely with other members of the care team providing pertinent medical history, treatment plans, and collateral information. Psychiatric specialists communicate back to the primary HIV clinicians to inform them of assessments, diagnosis, and management related to patients' mental healthcare. Meaningful communication between HIV providers supports a collaborative biopsychosociocultural approach to prevention, care, and treatment adherence in persons vulnerable to or affected by HIV and AIDS.

As discussed, the care team for persons with HIV/AIDS should involve multiple clinicians with diverse expertise and backgrounds. Just as every clinician knows the patient, the clinician should know the other members of the HIV care team. This manifests in a constant, open, and dynamic dialogue among clinicians. A coordinated care model also keeps the patient informed and involved in all decision-making. The HIV care team is united around the core mission of providing compassionate, patient-centered care that respects the right to privacy and autonomy of persons with HIV and AIDS.

Table 4.3 Setting, goal, and components of psychiatry referral by primary HIV provider

	Outpatient consultation	Inpatient consultation
Setting	Integrated: co-located mental health provider at site of primary HIV care	Inpatient facility
	Stand-alone: mental health provider outside primary HIV care clinic or office	
Goal	Answer clinical question(s) of consultee to aid in providing preventive and therapeutic interventions for those vulnerable to, infected with, or affected by HIV	
Referral content	1. Clinical question posed by consultee 2. Expectations of consultee 3. Urgency of referral 4. Past medical and psychiatric history (to the extent relevant and possible) 5. Patient's emotional state	
Referral methods	Personal contact Telephone call Written request Request through Electronic Health Records (EHR)	

Culture, Structural Competence, and Managing Stigma

There are many elements that shape the way individuals perceive HIV, its risk factors, and its progression of illness. These elements may include geographical origin, religious background, race/ethnicity, language, and socioeconomic status, as well as beliefs and norms that are shared with a larger community [2]. This constellation of elements is broadly referred to as "culture," an idea that does not have a universally agreed-upon definition in the literature. What *is* known, however, is that patients often turn to clinicians of a different background from their own for HIV-related care and that disparities in HIV care, as well as other medical care, may be related to these social differences [3]. Within the context of HIV, there are many experiences including those related to sexuality, gender, family, views of the body, illness, and medical treatment which are understood differently through different cultural lenses. The idea of "cultural competence" was introduced to improve clinician practices regarding cultural differences with patients and increase effective and respectful clinical practice with patients of diverse cultural backgrounds [4]. This approach commonly includes increasing clinician familiarity with a broader range of cultural ideas and practices, particularly with respect to medical illness and treatment.

However, the idea of cultural competence has also been critiqued as an overly static approach to culture which privileges the cultural viewpoint of the clinician. Another proposed approach is known as "cultural humility," which suggests a more

continuous and dynamic stance of self-reflection by the clinician regarding their own culture, particularly how it pertains to social power disparities between clinician and patient [5]. In recent years, some writers have suggested that an emphasis on cultural differences in clinical interactions may in fact obscure larger social, legal, and institutional forces that may lead to worse health outcomes for people from marginalized social groups. Metzl and Hansen have proposed the idea of "structural competency" to increase clinician attention on social disparities and to approach them within a non-medicalized framework, leaving room to consider that the patient's health depends on structural change as well as medical treatment [6]. This perspective may be particularly applicable within the context of HIV, where social structural forces have been key drivers since the inception of the epidemic [7].

In addition to understanding cultural and structural factors, it is essential for HIV clinicians to appreciate the social role of *stigma* in HIV/AIDS. Deriving from the Greek word for "mark," stigma refers to generally held negative reactions toward persons because of a particular attribute, with the result of loss of status and value, exclusion of the stigmatized group from society, and the oppression of the stigmatized group [8]. Stigma in the setting of HIV is a complex phenomenon. For people living with HIV/AIDS, stigma may accrue in part from negative biases directed toward populations historically associated with HIV, including homophobia toward men who have sex with men (MSM) or negative biases toward people who use IV drugs [9]. Stigma is also generated by misconceptions about HIV itself, including negative perceptions about people who become infected. The effects of stigma on people living with HIV are also multifaceted.

At its most extreme, stigma can result in violence toward people living with HIV [10], or may result in overt acts of discrimination in the setting of housing or employment. Much stigma, however, is covert and plays out in everyday interactions with family, friends, and clinicians.

Another element of stigma is known as internalized stigma, in which people living with HIV incorporate negative attitudes about themselves from the surrounding society and the media [11]. Stigma can have significant effects on both HIV prevention [12] and antiretroviral adherence for people living with HIV [13, 14]. HIV stigma is also associated with depressive disorders and other negative psychiatric outcomes [15].

It is essential for clinicians to be mindful of how stigma is shaped by the social and cultural context of their patients with HIV to understand how it may present barriers to retention and adherence in HIV care. It is also important for clinicians to be aware of their own biases toward people with HIV, toward people who engage in practices that place them at high risk for transmission, and toward communities that have been highly impacted by the AIDS epidemic, in order to avoid unintentional enacted stigma within clinical care. Training interventions have been developed to reduce HIV stigma toward people living with HIV/AIDS [16].

Consultation, Assessment, and Evaluation

Screening for Neuropsychiatric Conditions

Psychiatric screening tools can detect symptoms of psychiatric disorders that may otherwise go unnoticed in a clinical encounter. Proper use of these tools can assist clinicians in identifying patients in need of mental health support or treatment. There is an increased need for such tools to detect symptoms of psychiatric disorders, which are more common in people with HIV/AIDS than people who are non-infected [17]. Ideal screening tools are inexpensive, easy to administer, reliable, and valid in the population being evaluated. The assessments introduced below are practical for use in a variety of clinical and nonclinical contexts, to include HIV care.

These screening tools were designed and employed in adult populations. Additional information on special populations, such as youth and adolescents, is briefly discussed at the end of this section. Chapter 5 provides further information on screening as well as brief intervention for psychiatric disorders in people with HIV/AIDS.

Screening for Trauma

Trauma in the life of a person with HIV may manifest in numerous ways and may or may not be directly related to HIV. Experiencing traumatic events may lead to full syndrome post-traumatic stress disorder (PTSD), in which debilitating, stress-related persistent psychiatric illness develops following a traumatic exposure. Lifetime prevalence of PTSD is higher in persons with HIV than those without [18]. Persons with HIV/AIDS have higher rates of exposure to risk factors for PTSD, such as poverty, violence, and lack of social support [19].

Neurobiological changes to stress and fear pathways have been linked to HIV infection. These neurological adaptations may potentiate behavioral changes associated with trauma exposure and serve as a risk factor for PTSD independent of the environment [20]. The diagnosis of HIV itself may constitute a traumatic event and may lead to the development of PTSD [21]. Although experiencing a traumatic event does not invariably lead to PTSD, increased exposure to trauma increases the likelihood of other psychiatric illness, such as major depressive disorder. History of early life trauma and PTSD are associated with nonadherence to antiretroviral therapy (ART) in persons with HIV [22]. Timely recognition of stress-related trauma reactions may reduce the occurrence of a chronic course of PTSD by allowing for early treatment of acute stress disorder [23]. Screening tools for trauma may assist clinicians in identifying a patient's trauma exposure to coordinate more rapid intervention (Table 4.4).

Table 4.4 Screening tools for trauma

Screening tools	Validated in PLWHA?	
Clinician-Administered PTSD Scale (CAPS) 30 items administered by a trained clinician to assess PTSD symptoms, including their frequency and severity Clinician determines if patient meets DSM-5 PTSD diagnostic criteria	Yes	Gold standard in studies of PTSD Checklist for DSM-5 in PLWHA [24]
Post-traumatic Diagnostic Scale (PDS) 49-item self-report measure recommended for use in clinical or research settings to measure severity of PTSD symptoms related to a single identified traumatic event PDS yields a total severity score (ranging from 0 to 51) that largely reflects the frequency of the 17 symptoms of PTSD	No	
PTSD Checklist for DSM-5 (PCL-5) Standardized self-report rating scale for PTSD comprising 20 items that correspond to the key symptoms of PTSD, generally applied to any traumatic event	Yes	In PLWHA, PCL-5 with cutoff ≥33: 78.6% sensitivity, 68.3% specificity [24]
Life Event Checklist (LEC) Self-report questionnaire asking prevalence of 16 potentially traumatic lifetime events	No	Used in PLWHA in combination with PCL-5 [24]
Adverse Childhood Experience (ACE) Questionnaire 10-item self-report measure developed for the ACE study to identify childhood experiences of abuse and neglect	No	

Key: PLWHA persons living with HIV/AIDS, *CAPS* Clinician-Administered PTSD Scale, *PDS* Post-traumatic Diagnostic Scale, *PCL-5* PTSD Checklist for DSM-5, *LEC* Life Event Checklist, *ACE* Adverse Childhood Experience

Screening for Depressive Disorders

Depressive disorder is the most common mental disorder in persons with HIV/AIDS [25] with double the prevalence compared to persons without HIV [26]. Depressive disorder puts persons with HIV at risk for decreased care adherence, increased HIV risk behaviors, and increased mortality [27, 28]. Screening for depressive disorders is associated with improved outcomes in the general population with improved clinician care and increased logistical support for mental healthcare [29] (Table 4.5).

Table 4.5 Screening tools for depressive disorders

Screening tools	Validated in PLWHA?	
Patient Health Questionnaire-9 (PHQ-9) 9-question tool to assess for the degree of depression present in an individual	Yes	In PLWHA, cutoff ≥11: 85% sensitivity, 69% specificity [30]
Patient Health Questionnaire-2 (PHQ-2) 2-question tool to assess the frequency of anhedonia and depressed mood over the past 2 weeks	No	
Beck Depression Inventory (BDI) 21-item, self-report rating inventory that measures characteristic attitudes and symptoms of depressive disorders	No	
Substance and Mental Illness Symptom Screener (SAMISS) 16-question tool to screen for mental health and substance abuse conditions, takes under 15 min to administer	Yes	In PLWHA, cutoff ≥1: 97% sensitivity60% specificity for mental illness (includes bipolar disorder, depressive disorder, panic disorder, anxiety disorder- and trauma-related syndromes) [31] In PLWHA, cutoff/1: 95% sensitivity, 49%specificity for mental illness [32]
Hamilton Depression Rating Scale (HAM-D) Rates severity of depression; original HAM-D has 21 items, but scoring is based only on the first 17	No	
Center for Epidemiologic Studies-Depression scale (CES-D) 20-item measure that asks caregivers to rate how often over the past week they experienced symptoms associated with depression	Yes	CES-D 10 comparable to CES-D 20 In PLWHA, outpatient, cutoff ≥16: 79.8% sensitivity, 83% specificity) [33]

Key: PLWHA persons living with HIV AIDS, *PHQ-9* Patient Health Questionnaire-9, *PHQ-2* Patient Health Questionnaire-2, *BDI* Beck Depression Inventory, *SAMISS* Substance and Mental Illness Symptom Screener, *HAM-D* Hamilton Depression Rating Scale, *CES-D* Center for Epidemiologic Studies-Depression scale

Screening for Substance-Related and Addictive Disorders

Substance-related and addictive disorders are considered a risk behavior for acquiring HIV and occur at a significantly higher rate in persons with HIV when compared to the general population [34]. Substance-related disorders are associated with decreased adherence and acceleration of HIV disease progression [35, 36]. Substances of abuse can alter the metabolism of antiretroviral therapy (ART) and may increase the risk of overdose while on ART [37]. Screening for substance use disorder in a judgement-free manner can identify patients struggling with or at risk for substance-related disorders in order to engage them in the appropriate treatment (Table 4.6).

Table 4.6 Screening tools for substance use disorders

Screening tools	Validated in PLWHA?	
Substance and Mental Illness Symptom Screener (SAMISS) 16-question tool to screen for mental health and substance abuse conditions, takes under 15 min to administer Adult and adolescent versions	Yes	In PLWHA: 94% sensitivity, 85% specificity for substance and alcohol component [31] In PLWA: 86% sensitivity, 75% specificity for substance abuse component [32]
CAGE/CAGE-AID Questionnaires 4-item questionnaire to assess for alcohol or drug abuse or dependence in adults	No	
Alcohol Use Disorders Identification Test (AUDIT/ AUDIT-C) 3-item alcohol screen that can help identify persons who are hazardous drinkers or have active alcohol use disorders	No	
Drugs Abuse Screen Test (DAST-10) 10-item brief screening tool that can be administered by a clinician or self-administered that yields a quantitative index of the degree of consequences related to drug abuse	No	
Tobacco, Alcohol, Prescription medication, and other Substance use (TAPS) tool 4-item screening for tobacco use, alcohol use, prescription medication misuse, and illicit substance use in the past year and brief assessment	No	
NIDA-Modified Alcohol, Smoking, and Substance Involvement Screening Test (NM-ASSIST) NMASSIST is a screening tool for drug use in general medical settings that generates a substance involvement score that suggests the level of intervention needed	No	
Substance Abuse Subtle Screening Inventory (SASSI) 93-item screening measure that helps identify individuals who have a high probability of having a substance dependence disorder	No	

Key: SAMISS Substance and Mental Illness Symptom Screener, *PLWHA* persons living with HIV AIDS, *CAGE* Cut back, Annoy, Guilt, Eye-Opener, *CAGE-AID* Cut back, Annoy, Guilty, Eye-Opener-Adapted to Include Drugs, *AUDIT* Alcohol Use Disorders Identification Test, *DAST* Drugs Abuse Screen Test, *TAPS* Tobacco, Alcohol, Prescription medication and other Substance use, *NM-ASSIST* National Institute on Drug Abuse-Modified Alcohol, Smoking, and Substance Involvement Screening Test, *SASSI* Substance Abuse Subtle Screening Inventory

Screening for Neurocognitive Impairment

Neurocognitive disorders in persons with HIV are referred to collectively as HIV-associated neurocognitive disorders (HAND). HAND encompasses a spectrum of neurocognitive disorders, ranging from asymptomatic neurocognitive impairment to mild neurocognitive disorder to HIV-associated dementia. Cognitive ability and functional status decline as HAND progresses. While the advent of ART drastically reduced HAND, neurocognitive impairments still affect persons with HIV, especially if there are concurrent risk factors such as comorbid mental illness, substance-related disorders, and poor medication adherence. HAND is associated with suboptimal medication adherence and increased HIV risk-taking behaviors. Early treatment of HIV plays a crucial role in preventing HAND [38] (Table 4.7).

Screening for Suicidality

The lifetime rates of suicidal ideation and attempt are higher among persons with HIV when compared to persons without HIV [44]. This is of particular concern immediately after notification of a positive HIV test result and persists through the various stages of HIV illness. Suicide risk in persons with HIV is associated with comorbid factors such as psychiatric diagnoses, substance-related disorder, stigma, and the direct effects of HIV on the brain [45, 46]. Early recognition of suicidality, assessment of risk, and immediate intervention have been shown to prevent suicide in persons with HIV/AIDS [47] (Table 4.8).

Screening in Unique Populations of People with HIV/AIDS

Youth and adolescents with HIV are a diverse group with several distinctions that differentiate them from adults with HIV. Youth with HIV are less likely to be aware of their HIV status, to be linked with timely care, or to have a suppressed viral load than adults with HIV. Increased prevalence of high-risk behaviors and socioeconomic challenges present barriers to securing and maintain healthcare and treatment for HIV (Table 4.9).

Table 4.7 Screening tools for neurocognitive disorders

Screening tools	Validated in PLWHA?	
International HIV Dementia Scale (IHDS) 4-component tool that assesses memory, motor speed, and psychomotor speed	Yes	In PLWHA: 68% sensitivity, 86% specificity [39] In PLWHA: 94% sensitivity, 86% specificity for HAND [40] Moderately useful for HAND screening among ART-naive patients [41]
Montreal Cognitive Assessment (MoCA) 1-page, 30-point test that takes around 10–12 min to complete and assesses several domains of cognitive function	Yes	Weak correlation with IHDS and MoCA [42] MoCA alone is not a sufficient screening for HAND [43]
Mini-mental State Examination (MMSE) 30-point test that takes around 10–12 min to complete and assesses several domains of cognitive function	Yes	Poor screening ability for HAND [41]
Cognitive Assessment Tool- Rapid Version (CAT-rapid) Brief HIV-associated neurocognitive disorder screening tool that includes functional symptom questions and a measure of executive function	Yes	In PLWHA: 94% sensitivity, 52% specificity With IDHS, adequate for detecting HIV-dementia but substandard for detecting HAND [39]

Key: IHDS International HIV Dementia Scale, *PLHWA* persons living with HIV AIDS, *HAND* HIV-Associated Neurocognitive Disorder, *ART* Antiretroviral Therapy, *MoCA* Montreal Cognitive Assessment, *MMSE* Mini-mental State Exam, *CAT-rapid* Cognitive Assessment Tool-Rapid Version

Table 4.8 Screening tools for suicidality

Screening tools	Validated in PLWHA?
Suicide Assessment Five-Step Evaluation and Triage (SAFE-T) Five-step evaluation which addresses the patient's level of suicide risk and suggests appropriate interventions	No
Columbia -Suicide Severity Rate Scale (C-SSRS) Questionnaire that assesses the severity of the lethality of suicidal behaviors and ideation, takes less than 5 min Children and adults	No

Key: SAFE-T Suicide Assessment Five-Step Evaluation and Triage, *C-SSRS* Columbia Suicide Severity Rate Scale

Table 4.9 Screening tools that may be used in youth populations

Screening tools	Validated in PLWHA?	
CRAFFT (Car, Relax, Alone, Forget, Friends, and Trouble) 9-item questionnaire to assess for substance abuse Ages 12–26	Yes	Utilized among youth living with HIV [48]
Columbia -Suicide Severity Rate Scale (C-SSRS) Questionnaire that assesses the severity and lethality of suicidal behaviors and ideation Takes less than 5 min Children and adults	No	
Substance Abuse and Mental Illness Symptoms Screener (SAMISS) 16-question tool to screen for mental health and substance abuse conditions Takes less than 15 min to administer Adult and adolescent versions	No	

Key: *CRAFFT* Car, Relax, Alone, Forget, Friends, and Trouble, *C-SSRS* Columbia Suicide Severity Rate Scale, *SAMISS* Substance Abuse and Mental Illness Symptoms Screener

Postpartum Women (Table 4.10)

Cultural differences can affect a patient's interpretation of and ability to utilize mental health screening tools. Living with and seeking treatment for mental illness carry unique stigmas and challenges in different countries and societies. To address this diversity, certain screeners were modified or developed to improve validity for specific populations or cultural groups (Table 4.11).

Assessing Psychosocial and Psychiatric Barriers to Optimal HIV Outcomes

For clinicians working with patients with HIV/AIDS or who work with populations at high risk for HIV infection, two domains of health behavior assessment are essential as part of routine evaluation. The first is comprehensive screening for behaviors that are high risk for HIV transmission, and the second is assessment of adherence to antiretroviral medications for treatment of HIV or for HIV pre-exposure prophylaxis.

Screening for HIV Transmission Risk Behavior

Patients turn to clinicians with the understanding that their health behavior is collected to encourage healthy practices across a number of domains, and this understanding should contextualize questions about sexual and drug use-related HIV risk

Table 4.10 Screening tool that may be used with postpartum women

Screening tools	Validated in PLWHA?
Edinburgh Postnatal Depression Scale (EPDS) 10-item psychological rating scale for measuring the severity of postnatal depression symptoms	No

Key: EPDS Edinburg Postnatal Depression Scale

Table 4.11 Screening tool developed for a specific cultural group

Screening tools	Validated in PLWHA?	
Shona Symptom Questionnaire (SSQ-14) 14-item screening tool developed in Zimbabwe and used to measure common mood disorders	Yes	In PLWHA, cutoff ≥9: 73% sensitivity, 84% specificity [30]

Key: SSQ-14 Shona Symptom Questionnaire

behaviors. At the same time, for many patients, this information is laden with stigma, shame, and fears that disclosure will result in negative consequences. Many patients fear judgement from the clinician because of their disclosure, and some patients may have experienced negative reactions in the past when disclosing this information. Some patients may live in communities where disclosure of same-sex or extramarital sexual activity, drug use, or sex work would result in ostracism or, even worse, potential violence.

Clinicians screening for HIV transmission risk behavior should take steps to ensure the trust and comfort of the patient to optimize the accuracy and validity of the information reported by the patient. Before asking questions about HIV-related behavior, the clinician should utilize other components of the clinical interview to consolidate a rapport. It is also advisable to ensure the patient's awareness that this clinical information is confidential and to provide a clear rationale for the purpose of these questions. It can be helpful to explicitly frame these questions as analogous to questions pertaining to other health behaviors, such as nutrition, exercise, or seat-belt use, to align them with other routine areas of health and safety.

With a rapport in place and with the rationale for questions provided, the clinician should ask questions about sexual risk behavior in as clear and straightforward a way as possible. Questions about sexual behavior can begin with "do you have sex with men, women, or both?" Follow-up questions should include number of partners, use of barrier methods of STI transmission, and specific forms of intercourse, such as oral, anal, or vaginal. For men who have sex with men, clinicians should also inquire about the use of drugs such as methamphetamines in sexual settings. To screen for intravenous drug use, clinicians should ask whether a patient has ever injected drugs that were not prescribed, about needle-sharing and needle-cleaning practices, and whether patients have ever been treated for opioid replacement medications such as methadone or buprenorphine. The CDC recommends specific HIV risk screening questions for men who have sex for men, heterosexual men and women, and IV drug uses in its practice guidelines for PrEP.

Screening for HIV Medication Adherence

For people living with HIV, adherence to antiretroviral medication is one of the strongest predictors of HIV health outcomes, including progression to AIDS. In addition, nonadherence to antiretrovirals greatly increases the risk of virologic failure, increases the risk of resistant viral strain development, and predicts poorer long-term health outcomes. For HIV-negative patients who take PrEP, medication adherence is necessary to prevent HIV infection in the setting of high-risk behavior.

Antiretroviral adherence has strong associations with comorbid psychiatric illness and thus should be assessed in the mental health evaluations of people living with HIV/AIDS. Although there is no single agreed-upon best method for evaluating adherence, several methods studied in clinical and research settings include self-report methods, including structured adherence screenings, electronic monitoring pill caps, serum medication levels, and pharmacy records, each of which has strengths and limitations [49]. Self-report carries the limitations of social desirability, in which the patient over-reports adherence to gain clinician approval, as well as the possibility of recall biases.

Social desirability effects may be reduced by communicating an attitude that normalizes the experience of antiretroviral medication nonadherence. There is also some evidence that social desirability biases are reduced when adherence is queried using computer methods rather than directly by the clinician [50]. Recall biases may be reduced by using an exact specified time frame that is long enough to capture nonadherence events and reduce ceiling effects, such as "How many times in the last month have you missed a dose of HIV medication?" The clinician may also consider using an antiretroviral adherence screening scale that has been validated in their patient population.

Factors that Increase HIV Risk Behaviors and Nonadherence

HIV risk behaviors and medication nonadherence are complex, multi-determined behavioral outcomes that have been the subject of decades of research. These outcomes are shaped by a wide range of social, psychological, and systemic factors, which may vary greatly from one patient to another. Like all clinical evaluations focused on mental health, evaluations in the HIV setting consider ways to improve behavioral health and to identify barriers to optimal behavioral outcomes. Clinicians should consider factors driving HIV risk behavior and antiretroviral adherence in the following domains.

Psychiatric A number of different psychiatric illnesses have been shown to play a role in driving HIV risk behavior (see Chap. 2), as well as in contributing to antiretroviral nonadherence. These include depressive disorders, PTSD, substance use disorders, and schizophrenia (also see the related chapters on specific disorders). For patients with mental illness, treating the underlying psychiatric condition will be

essential to ensure optimal target HIV-related behavioral outcomes. In addition, it is important to understand the way that the specific psychiatric disorder is impacting behaviors. For example, someone with schizophrenia may have social deficits which impede effective negotiation of safer sex practices with partners, or a patient with depressive disorder may lack the energy and drive for successful daily medication adherence.

Motivation and Health Literacy In addition to psychiatric factors, there are several factors that operate at the individual level to impede HIV risk reduction practices or medication adherence but are not in and of themselves psychopathological. This area of behavioral determinants includes beliefs, norms, and practices that shape motivation to engage in everyday health behaviors [51]. Clinicians should query patients about their knowledge, attitudes, and beliefs about HIV risk behaviors, risk reduction, and the importance of antiretroviral medications. Patients should also discuss their perceived self-efficacy, or belief in their ability to change their behavior, and their perception of the likelihood that behavior change could positively improve their health. Patient community norms should also be discussed, which allows for the opportunity to understand how cultural and social factors shape their HIV behavioral outcomes. Motivational interviewing, an intervention initially developed for behavior change in patients with substance use disorders, can be a useful framework within which to work with patients around optimizing HIV-related behaviors.

Structural Factors HIV risk behaviors and medication adherence are determined not only by forces at the level of the individual patient but also by many factors that shape social, legal, and financial environment in which the patient lives [52]. Some of these factors may be directly assessed in discussing health behaviors with the patient. For example, a patient may have difficulty accessing antiretroviral medication due to a lack of reliable public transportation or because of problems accessing financial assistance for medication in their state. Other structural factors may include the civil rights climate in each area for LGBT people, women, or ethnic and racial minorities [53, 54]. Clinicians can form the most valid assessment of determinants of their patients' HIV-related behaviors, and opportunities for behavior change, if they can sensitively formulate how structural factors interact with individual level factors for a given patient.

Psychiatric Differential Diagnosis in HIV/AIDS

The differential diagnosis of psychiatric symptoms in PLWHA is often challenging. This may be explained by the multitude of diseases that can affect the immunocompromised patient, side effects of antiretrovirals and other medications used to treat or prevent medical comorbidities, as well as the prevalence of co-occurrence of substance-related and other psychiatric disorders in PLWHA. The differential

Table 4.12 HIV-associated opportunistic infections

Opportunistic infection	CD4+ T cell threshold (cells/mm^3)
Coccidioidomycosis	<250
Histoplasmosis	<150
MAC (*Mycobacterium avium* Complex)	<50
PCP (*Pneumocystis jiroveci* Pneumonia)[a]	<200
Toxoplasma gondii encephalitis	<100
Cryptococcal meningoencephalitis	<100
Cytomegalovirus (CMV) retinitis	<50

[a]Previously called *Pneumocystis carinii*

diagnosis is often complicated by the potential simultaneous existence of any and all factors mentioned above.

Immunosuppression and Differential Diagnosis

Untreated chronic HIV infection progressively causes depletion of CD4+ T cell populations, consequently increasing the susceptibility to various diseases. Classically, these have been called opportunistic infections and have been associated with certain thresholds of $CD4^+$ counts, under which prophylaxis may be recommended. Table 4.12 summarizes selected HIV-associated opportunistic diseases.

When the central nervous system (CNS) is affected, patients often present with focal neurological signs, headaches, or seizures. In some cases, these diseases present with nonspecific symptoms and signs such as malaise, confusion, inattention, and disturbances in cognition and therefore require a high level of suspicion by the clinician. CNS opportunistic infections may also present with psychiatric symptoms. For example, symptoms of delusions and auditory hallucinations have been described in patients with acute toxoplasmosis [55, 56] and mania in cryptococcal meningitis [57]. A careful interview, physical examination, and obtaining collateral information regarding patient's psychiatric baseline are often necessary steps to reach the correct diagnosis.

Effects of Medications

Psychiatric symptoms can also be caused or magnified by antiretrovirals. For example, zidovudine (AZT), the first antiretroviral approved for the treatment of chronic HIV infection, has been described to cause mania [58, 59], and nevirapine has been reported to induce persecutory delusions, hallucinations, and depressive symptoms [60].

Efavirenz is the antiretroviral mostly associated with neuropsychiatric side effects. The most frequently reported side effects are dizziness, vivid dreams, and insomnia, but these often improve within 2–4 weeks of efavirenz initiation. Mood changes, including mania and depression, appear to be common and have been described in up to 25% of patients. Efavirenz has also been reported to cause anxiety, suicidal ideation, and psychotic symptoms [61]. Personal history of psychiatric disease, in particular depression, has been thought to increase the risk for efavirenz-related neuropsychiatric side effects, and for this reason, a thorough assessment is indicated prior to initiating this antiretroviral.

Among the most recently developed antiretroviral classes, integrase strand transfer inhibitors (ISTIs) are known to cause psychiatric side effects, although less frequently than efavirenz. The elevated penetration into the central nervous system may explain the psychiatric side effects of this class, which includes insomnia, dizziness, anxiety, and depression [62, 63]. Although these have been associated with all INSTIs, they seem to occur more frequently with dolutegravir [64].

Drugs used to treat HIV-associated comorbid medical illnesses can also cause psychiatric symptoms. Cases of psychosis and/or mania have been described with the use of cephalosporins, trimethoprim/sulfamethoxazole, and metronidazole. Fluoroquinolones have been associated with multiple neuropsychiatric symptoms, including irritability, insomnia, depression, suicidal ideation, mania, and psychosis [65]. Interestingly, beta-lactams act as GABA-A antagonists in a dose-dependent fashion and in higher than therapeutic doses may cause anxiety [65].

Substance-Related and Addictive Disorders and Psychiatric Symptoms

PLWHA have a higher prevalence of substance-related and addictive disorders than the general population [66]. The use of drugs and HIV infection have a bidirectional relationship: on one hand, the use of substances affects the progression of the disease by decreasing adherence to medications as well as retention in care, and, on the other hand, HIV infection may also increase the susceptibility to certain substance-related disorders. In addition to psychosocial factors often present in PLWHA which may increase the risk for the use of substances (stigma, traumatic experiences, poverty, poor social support, comorbid psychiatric disorders), HIV may directly predispose to substance-related disorders as HIV's Tat protein modulates the reward pathway via dopaminergic transmission [67].

The use of substances can cause psychiatric symptoms either during intoxication or withdrawal states. For example, anxiety is commonly reported during cocaine, amphetamine, and caffeine intoxication, but it is also a symptom experienced during alcohol, benzodiazepine, opiate, or nicotine withdrawal.

Depressive symptoms can be seen in chronic alcohol, opiate, and stimulant use, and acute cocaine and amphetamine intoxication are associated with mania, psychosis, delirium, and aggressive behavior.

The potential for drug-induced psychiatric symptoms should always be considered during the evaluation of PLWHA and, when deemed necessary, confirmed using urine toxicology. For more detailed information about substance use disorders in PLWHA, please see Chap. 11.

Other Psychiatric Illnesses

Mental illness is more prevalent in PLWHA than in the general population [68, 69]. In a nationally representative sample of PLWHA in the United States, almost 50% of participants screened positive for a psychiatric disorder [25]. Depressive disorder is one of the most common psychiatric disorders [70, 71] and can be challenging to differentiate from neurocognitive disorders. The latter can vary from mild to severe (ranging from asymptomatic cognitive impairment to HIV-associated dementia) and can present with apathy and psychomotor retardation. Bipolar disorder, in particular manic episodes, can increase the risk for HIV infection as it is associated with impulsivity, hypersexuality, and impaired judgment. Although not as frequent as it once was in the early years of the HIV pandemic, AIDS mania may present in patients with significant immunodepression. This unique entity can be distinguished from classic bipolar disorder as it is more commonly associated with irritability, occurs in patients without a personal or family history of bipolar disorder, and is often associated with neurocognitive impairment [72]. For more information regarding psychiatric disorders in PLWHA, please see Chaps. 6, 7, 8, 9, and 10.

Multiple Choice Questions

1. Persons with HIV/AIDS experience mental illness at a rate far higher than the general population. Of the psychiatric disorders listed below, which is the most common among persons with HIV/AIDS?

   (a) Depressive disorder
   (b) Personality disorder
   (c) Trauma-related disorder
   (d) Psychotic disorder
   Correct answer: (a).

Reference: Parhami I, Fong TW, Siani A, Carlotti C, Khanlou H. Documentation of psychiatric disorders and related factors in a large sample population of HIV-positive patients in California. AIDS Behav. 2013;17(8):2792–801.

2. Persons with HIV/AIDS and mental illness are at increased risk for which of the following, regardless of the specific psychiatric diagnosis?

   (a) Increased HIV risk behavior
   (b) Impaired metabolism of antiretroviral medications
   (c) Decreased adherence to treatment regimen
   (d) Delayed HIV testing

   Correct Answer: (c)

References: Mehta S, Moore RD, Graham N. Potential factors affecting adherence with HIV therapy. AIDS. 1997;11(14):1665–670.
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Chapter 5
Screening for Psychiatric Disorders in HIV Care

Francine Cournos and Karen M. McKinnon

Introduction

In the USA, settings that provide primary care or specialized medical services to people living with HIV include private practice offices, hospital-based clinics, Federally Qualified Health Centers (FQHCs), and community clinics. Given the high rates of psychiatric disorders, including substance use disorders, among people with HIV, these are the settings that can best ensure case finding through the screening for psychiatric disorders using evidence-based tools. Screening is particularly important in clinical settings with few in-clinic integrated behavioral healthcare (BH) resources. There, screening serves to identify which patients have symptoms suggestive of a psychiatric disorder and should be referred to psychiatrists, other mental health professionals, and/or off-site mental health and substance use programs for further psychiatric assessment and care. In addition, screening allows for the provision of supportive measures for patients who have mild symptoms and don't need formal mental healthcare. Finally, screening allows for monitoring and watchful waiting for patients with mild symptoms and for patients with more severe symptoms who are not ready to accept a referral. It is important to acknowledge that

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screening is only one step along the behavioral health continuum of care and always requires resources for the appropriate next steps.

In this chapter we describe mental health and substance use screening tools that can be used in a range of care settings for patients with HIV, as well as how to access these tools at no cost. We discuss the utility of screening and provide clinical site vignettes for how real-world settings have incorporated these screening tools into their services.

As Fig. 5.1 shows, the World Health Organization has created a depiction of the optimal mix of types and intensities of mental health services that healthcare settings need to consider for their patients [1]. Screening is an essential first step to understanding patient care needs and the degree to which those needs can be met through services delivered at one or more of the different levels of care, which include patient self-management and informal community supports (such as Alcoholics Anonymous), shown at the bottom of the pyramid, through skilled non-specialized mental or behavioral health services or through highly specialized psychiatric services, shown at the top of the pyramid.

The degree of integration of general medical and psychiatric services within HIV care varies widely. A relatively small percentage of HIV clinical programs provides fully integrated general medical and psychiatric care. Some of these programs date

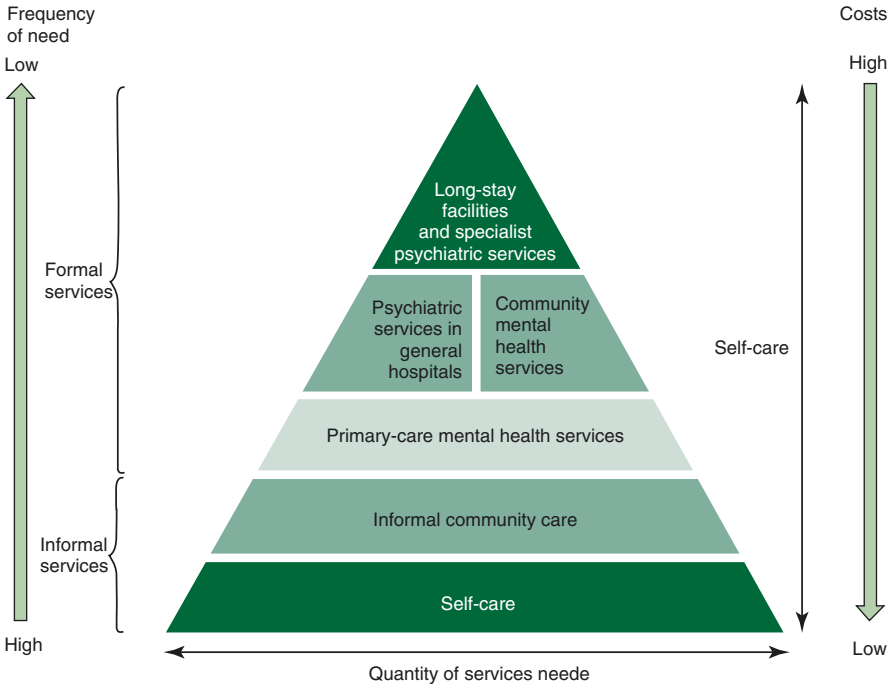

Fig. 5.1 World Health Organization service organization pyramid for an optimal mix of services for mental health. (Adapted from World Health Organization (WHO) [1]. With permission from World Health Organization (WHO))

back to the early days of the HIV epidemic and were established with the help of donor funding and/or efforts to show that such integration reduces the cost of caring for people with HIV. In these model programs, psychiatrists and/or behavioral health clinicians are part of a treatment team that includes all of the multidisciplinary healthcare clinicians treating a given person with HIV, and there is one common treatment plan.

However, it is more common for HIV programs to offer *limited* behavioral health (BH) services and to depend on members of the HIV care team to identify psychiatric conditions and make appropriate referrals, whether to mental health clinicians co-located inside their own system or through off-site referrals outside of their system. A description of the various models for care integration can be found in Chap. 19. Many programs do not follow any specific model for integrating psychiatric care with HIV care but "make do" with what seems realistic under their particular circumstances (e.g., staffing, billing, external funding). Moreover, most models for integrating primary medical care and BH care are not designed for people who have both *complex* general medical *and* BH care needs.

The authors, who have led the behavioral health component of the Northeast/Caribbean AIDS Education and Training Center for more than two decades, have visited hundreds of programs that treat people with HIV in different regions of the USA and have observed the highly variable arrangements used to provide substance use and other mental health services. Available behavioral health clinicians nested within HIV care settings may include social workers, substance use counselors, psychiatric nurse practitioners, physician assistants, psychologists, and psychiatrists, the latter frequently on a part-time basis. Efforts have been made to also encourage primary care practitioners to screen for psychiatric disorders, and when primary care clinicians are very busy, often other non-BH clinicians assume the screening role. Some of these non-BH healthcare clinicians have served as champions who have sought their own training in task-shifting to address the highly prevalent psychiatric disorders their patients face. The most common psychiatric illnesses screened for are depressive disorders, anxiety disorders, PTSD, and alcohol and other substance use disorders. Many HIV care settings also want to understand and screen for suicide risk.

As important as screening can be as a first step in identifying those in need of psychiatric services, what happens following screening is crucial, and it is necessary to create policies and procedures that all staff members are trained to carry out. Patients with symptoms in the milder range may be candidates for watchful waiting and the provision of information about self-care or a brief intervention, whereas patients with moderate-to-severe symptoms are often referred to mental health clinicians. Figure 5.2 shows the steps in the behavioral health continuum that follow positive screens and also shows how the behavioral health continuum maps onto the HIV care continuum for optimal patient health outcomes.

This chapter encourages screening people with HIV for psychiatric disorders but also recognizes that there are both advantages and disadvantages to doing so (Table 5.1).

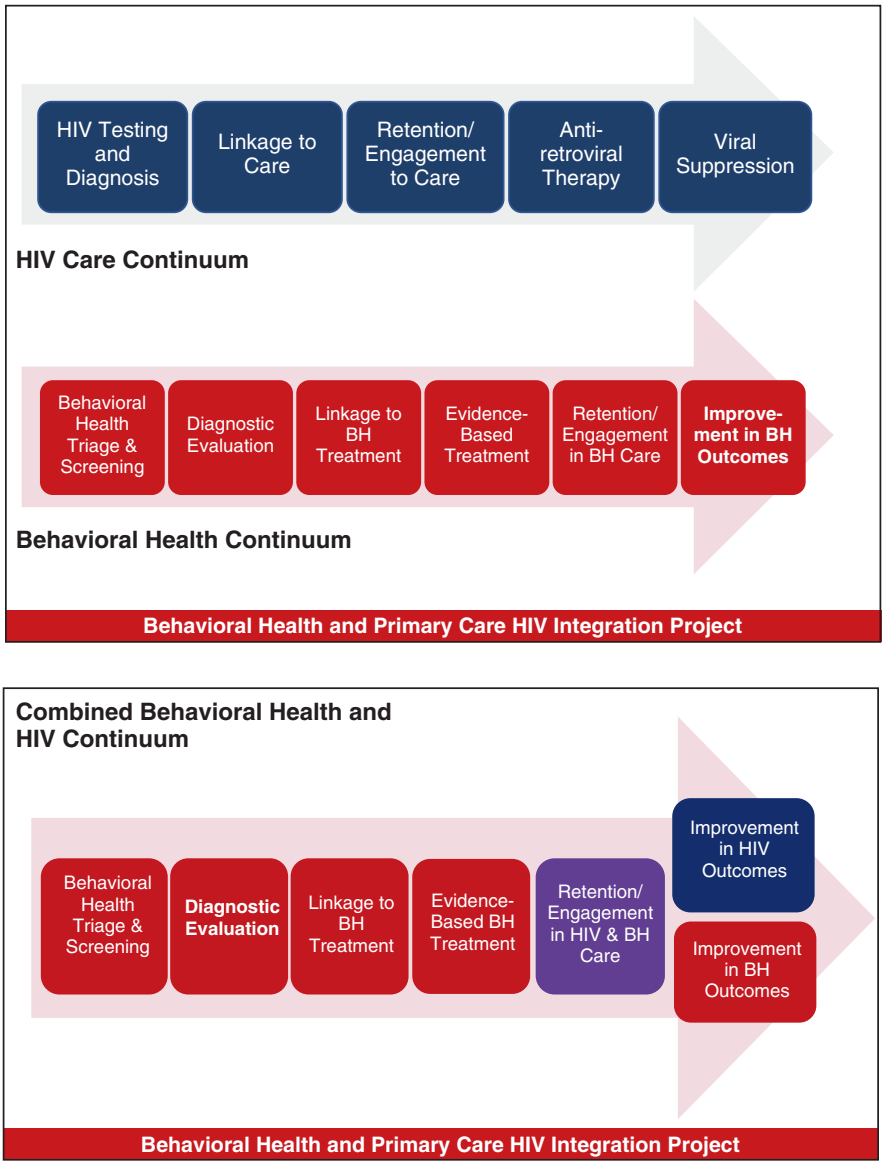

Fig. 5.2 Actions following a positive behavioral health screen [2]

The screening tools most often used in clinical practice are brief to administer and free of charge. The Health Resources and Services Administration (HRSA) has created an impressive National HIV Curriculum (https://www.hiv.uw.edu) [2] that contains evidence-based screening tools for common psychiatric disorders (anxiety, depression, and post-traumatic stress disorder), for alcohol and substance use

Table 5.1 Advantages and disadvantages of screening for frequently encountered psychiatric disorders, including substance use disorders, in HIV care settings

Advantages
Is responsive to the high rates of psychiatric disorders among people living with HIV infection
Reduces stigma by making screening for psychiatric problems a routine part of care
Identifies patients with unmet needs, who do not spontaneously offer psychiatric complaints
Reduces the burden on specialty mental health clinicians to evaluate every patient
Disadvantages
There are some false-positive and some false-negative results
A positive screening test does not establish a diagnosis, so further evaluation is needed following positive screens
There are clearer guidelines for treating psychiatric disorders than there are for responding to psychiatric symptoms that are sub-syndromal
Screening is a poor use of healthcare clinicians' time if there are no links to further evaluation and care for persons who screen positive
Positive screens can result in over-diagnosis and overtreatment of people with psychiatric symptoms who do not have psychiatric disorders

disorders, and for cognitive impairment. Screening for cognitive impairment is important given the frequency of HIV-associated neurocognitive disorders as well as the large number of people who are aging with HIV and may have other conditions associated with cognitive impairment. See Chap. 10 for a full discussion of assessing neurocognitive disorders.

Table 5.2 lists ten tools that can be very conveniently accessed and that have scores automatically calculated online through the National HIV Curriculum [2]. These tools can be found by clicking on the section of the curriculum labeled Tools & Calculators. Other tools are also available without automatic calculators, and these can be found in Module 2, Basic HIV Care, Lessons 5 and 6 of the curriculum which provide narrative information on mental health screening and substance use screening. Module 2, Lessons 5 and 6 also contain extensive information about the sensitivity and specificity of these screening instruments.

In addition to the National HIV Curriculum, a considerable body of information is readily available at no cost online about the use of clinical screening instruments for psychiatric disorders as well as references to public access peer-reviewed articles about the evidence that underlies their use. While a variety of diagnostic research instruments are available that can go beyond screening and establish psychiatric diagnoses, these are generally too time-consuming to be used in clinical practice and will therefore not be reviewed here.

Screening tools indicate if a patient is likely to have a particular disorder. However, screening tools are imperfect and cannot be used to make psychiatric diagnoses as a single data point. This can best be understood by considering the sensitivity and specificity of screening tools (Table 5.3).

If the sensitivity and specificity of a screening tool were each 100%, or at least close to it, screening tests could be used to make diagnoses; however, the screening

Table 5.2 Screening tools for psychiatric symptoms and disorders

Online self-calculating screening tools		
Self-calculating screening tools for mental disorders		
Anxiety:	Generalized Anxiety Disorder 2-item	GAD2
Anxiety:	Generalized Anxiety Disorder 7-item	GAD7
Depression:	Patient Health Questionnaire-2	PHQ-2
Depression:	Patient Health Questionnaire-9	PHQ-9
PTSD:	Primary Care PTSD Screen for DSM-5	PC-PTSD-5
Self-calculating screening tools for alcohol and substance use		
Alcohol:	Alcohol Use Disorders Identification Test	AUDIT-C
Alcohol:	CAGE Questionnaire for Detecting Alcoholism	CAGE
Alcohol/other drug use:	CAGE-AID Questionnaire	CAGE-AID
Drug use:	Two-item Conjoint Screen for Alcohol/Other Drugs	TICS
Opioids:	Opioid Risk Tool	ORT
Other recommended screening tools		
Depression:	2-Item Prime-MD	PRIME-MD
Depression/anxiety:	Hospital Anxiety and Depression Scale	HADS
Panic Disorder:	PHQ for Panic Disorder	PHQ-PD
Bipolar Disorders:	Mood Disorders Questionnaire	MDQ

Used with permission from The National HIV Curriculum [2]

Table 5.3 The sensitivity and specificity of screening tests

Sensitivity refers to the ability of a test *to correctly classify an individual as sick or ill*. It refers to the probability of a test being positive when illness is present
Specificity is a measure of the ability of a test *to correctly classify an individual as healthy or illness-free.* Specificity refers to the probability of a test being negative when illness is absent

tools we have fall below that standard and are not used for diagnosing BH disorders. This concept will be explored further in the discussion of the screening tools for depression.

Screening for Depression, Anxiety Disorders, and PTSD

The most commonly used and well-studied screening tool for depression is the Patient Health Questionnaire-9 [3–5], commonly referred to as the PHQ-9. This chapter looks carefully at the use of the PHQ-9 and its companion instrument, the Patient Health Questionnaire-2 [6], to illustrate the strengths and limitations of all screening tools for psychiatric disorders. Table 5.4 displays the PHQ-9 questions, and Table 5.5 displays the PHQ-2 questions. Table 5.6 displays how to link PHQ-9 scores to the severity of depression and proposed treatment options.

The PHQ-2 uses the first two questions of the PHQ-9 as a very brief screen for depression (see Table 5.5). Each of these two questions is scored on a scale of 0 to

Table 5.4 Patient Health Questionnaire-9 (PHQ-9)

NAME: _____ DATE: _____

Over the last 2 weeks, how often have you been bothered by any of the following problems? *(use "√" to indicate your answer)*	**Not at all**	**Several days**	**More than half the days**	**Nearly every day**
1. Little interest or pleasure in doing things	0	1	2	3
2. Feeling down, depressed, or hopeless	0	1	2	3
3. Trouble falling/staying asleep, sleeping too much	0	1	2	3
4. Feeling tired or having little energy	0	1	2	3
5. Poor appetite or overeating	0	1	2	3
6. Feeling bad about yourself or that you are a failure or have let yourself or your family down	0	1	2	3
7. Trouble concentrating on things, such as reading the newspaper or watching television	0	1	2	3
8. Moving or speaking so slowly that other people could have noticed or the opposite, being so fidgety or restless that you have been moving around a lot more than usual	0	1	2	3
9. Thoughts that you would be better off dead or of hurting yourself in some way	0	1	2	3
Add Columns		+	+	+
(Healthcare professional: For interpretation of TOTAL, please refer to accompanying scoring card).	TOTAL:			

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Table 5.5 Screening for depression – Patient Health Questionnaire-2 (PHQ-2)

Over the last 2 weeks, how often have you been bothered by any of the following problems:
Little interest or pleasure in doing things
0 = Not at all
1 = Several days
2 = More than half the days
3 = Nearly every day
Feeling down, depressed, or hopeless
0 = Not at all
1 = Several days
2 = More than half the days
3 = Nearly every day
If the score is 3 or more, major depression is likely; consider further screening with the PHQ-9. Can also be used as the PRIME-MD yes/no questionnaire; if yes to either question, screen with the PHQ-9

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Table 5.6 PHQ-9 scores and proposed treatment actions

PHQ-9 score	Depression severity	Proposed treatment actions
0–4	Non-minimal	None
5–9	Mild	Watchful waiting; repeat PHQ-9 at follow-up
10–14	Moderate	Treatment plan, considering counseling, follow-up, and/or pharmacotherapy
15–19	Moderately severe	Active treatment with pharmacotherapy and/or psychotherapy
20–27	Severe	Immediate initiation of pharmacotherapy and, if severe impairment or poor response to therapy, expedited referral to a mental health specialist for psychotherapy and/or collaborative management

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3, creating a range of summary scores from 0 to 6. A score of 3 has the best combination of sensitivity and specificity for detecting clinical depression, and the next screening step is to complete the PHQ-9 for those who score 3 or higher. The PHQ-2 questions have also been used in a similar instrument, the two-item PRIME-MD [2]. In this case, an answer of yes to *either* question is followed by administering the PHQ-9. Some settings begin with one of these two question screens and only conduct the PHQ-9 if the 2-item screen is positive, whereas other settings always use and score the entire PHQ-9. The psychometric properties of choosing a two-step vs. a one-step approach are well described in the chapter on mental health screening in the HIV National Curriculum (https://www.hiv.uw.edu) [2]. Both approaches are acceptable.

One clear set of advantages of the PHQ-2 and PHQ-9 questionnaires is that they are widely studied, brief, free of cost, and easily accessible online in multiple languages. Hundreds of peer-reviewed publications have now demonstrated that the PHQ-9 improves the detection of depressive disorders in primary care. Moreover, the online scoring instructions for the PHQ-9 suggest possible next steps (e.g., watchful waiting) to take depending on a patient's score (Table 5.6).

Despite the widespread embrace of the PHQ-9 in the USA, examining the use of this tool illustrates the many limitations of any tool used to screen for psychiatric illness. To begin with, we have no biological tests for diagnosing depressive disorders in clinical practice, so we depend on the reports of the patients, and sometimes significant others, to describe what is wrong. There is a dearth of studies on the numerous factors that could affect self-report (see Table 5.7).

The problem of over-diagnosis of depression based on screening alone is well illustrated by early research studies of rates of mental illness among people with HIV infection. Known as the Health Costs and Services Utilization Study (HCSUS), rates of major depression (and other psychiatric illnesses) were estimated at various time points [7]. At the first follow-up visit, 27% of participants were diagnosed with probable major depressive disorder based on a brief research tool, but only 19% of these participants had major depressive disorder based on a subsample of patients who were reassessed using a full diagnostic interview [8]. Screening in clinical care

Table 5.7 Factors that adversely affect the utility of screening for psychiatric disorders

Limited or no biological tests for specific psychiatric illnesses
Limitations in the sensitivity and specificity of screening instruments
Communication, language, literacy, and/or cultural barriers that are present during the screening process
Examiner asks questions without demonstrating an interest in the answers (e.g., stares at a computer screen, appears hurried)
Patient has reasons to not give honest answers
No services are available to patients with positive screens

can identify the patients at greatest risk for having a current psychiatric disorder, but this needs to be followed up with a diagnostic interview.

Case Vignette 5.1
Site A is a Ryan White HIV/AIDS program which uses a "no-wrong-door" approach to patient flow. For several years, the site has complied with a state department of health requirement to use the PHQ-9 to screen for major depressive disorder. Because there are scarce behavioral health specialists available on site, multiple members of clinical staff have been trained to use the PHQ-9. However, some staff members doubt that their patients are giving them the real story. They recount instances in which a patient completes their PHQ-9 screening with a fairly low score indicating no signs of depression but then 10 minutes later is seen crying and telling their medical case manager, whom they have known for more than a decade, about a recent romantic breakup. These instances are confusing to staff who have not been trained to distinguish between distress and psychiatric disorders. Site A is committed to quality care for its patients, so leadership has encouraged additional training for staff in mental health and first aid for psychiatric symptoms so that staff feel more confident in their use of the screener.

We will next briefly describe a number of other common screening tools without going into depth about their strengths and weaknesses. Anxiety disorders are some of the most common psychiatric illnesses both in the general population and among people with HIV. The GAD-2 and the GAD-7 (see Table 5.8) screen for generalized anxiety disorder (GAD). The GAD-7 is also moderately good at screening for three other disorders: panic disorder, social anxiety disorder, and post-traumatic stress disorder (see information about sensitivity and specificity in Table 5.8) [9–11].

Post-traumatic stress disorder (PTSD) is also considerably more common among people with HIV than it is in the general population. Rather than using the GAD-7, which will miss about a third of cases of PTSD, most practitioners use the PC-PTSD-5 [12, 13] to screen for PTSD (see Table 5.9).

Table 5.8 Generalized anxiety disorder 7-item (GAD-7) scale [5]

Over the last 2 weeks, how often have you been bothered by the following problems?	Not at all sure	Several days	Over half the days	Nearly every day
1. Feeling nervous, anxious, or on edge	0	1	2	3
2. Not being able to stop or control worrying	0	1	2	3
3. Worrying too much about different things	0	1	2	3
4. Trouble relaxing	0	1	2	3
5. Being so restless that it's hard to sit still	0	1	2	3
6. Becoming easily annoyed or irritable	0	1	2	3
7. Feeling afraid as if something awful might happen	0	1	2	3
Add the score for each column	+	+	+	+
Total score (*add your column scores)* =				

Level of Functioning [10]

If you checked off any problems, how difficult have these made it for you to do your work, take care of things at home, or get along with other people?

Not difficult at all ☐	Very difficult ☐
Somewhat difficult ☐	Extremely difficult ☐

Scoring the GAD-7 [2]

Scoring: Scores of 5, 10, and 15 are taken as the cutoff points for mild, moderate, and severe anxiety, respectively. When used as a screening tool, further evaluation is recommended when the score is 10 or greater.

Using the threshold score of 10, the GAD-7 has a sensitivity of 89% and a specificity of 82% for generalized anxiety disorder.

The GAD-7 is moderately good at screening for three other common anxiety disorders:

Panic disorder (sensitivity 74%, specificity 81%)

Social anxiety disorder (sensitivity 72%, specificity 80%)

Post-traumatic stress disorder (sensitivity 66%, specificity 81%)

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Screening for Alcohol and Substance Use Disorders

Table 5.2 lists five screening tools for alcohol and substance use disorders. We discuss some of these tools and introduce one newer tool.

Table 5.10 [2] illustrates a commonly used tool to screen for alcohol use problems, the Alcohol Use Disorder Identification Test, also known as the AUDIT-C [2, 14, 15]. Table 5.11 [2] illustrates a commonly used tool to assess the risk for the misuse of prescription opioid medications known as the Opioid Risk Tool also known as the ORT [2, 16, 17]. Three other commonly used tools to screen for alcohol and other substance use can be accessed through the National HIV Curriculum and have automatic calculators. They are the CAGE, which is another screen for alcohol use disorders, the CAGE-AID, which is a four-item screen for both alcohol and drug use problems, and the TICS, which is a two-item screen for alcohol and other drug use. See Table 5.2 and Reference [2] to access these questionnaires and to score them using automatic calculators. The properties of these instruments are also well described in the National HIV Curriculum [2].

Table 5.9 Primary Care PTSD Screen for DSM-5

Description
The Primary Care PTSD Screen for *DSM-5* (PC-PTSD-5) is a five-item screen designed to identify individuals with probable PTSD. Persons who screen positive require further assessment, preferably with a structured interview.
The measure begins with an item designed to assess whether the respondent has had any exposure to traumatic events. If a respondent denies exposure, the PC-PTSD-5 is complete with a score of 0.
If a respondent indicates a trauma history – experiencing a traumatic event over the course of their life – the respondent is instructed to answer five additional yes/no questions (see below) about how that trauma has affected them over the past month.
Sometimes things happen to people that are unusually frightening, horrible, or traumatic. For example:
☐ A serious accident or fire
☐ A physical or sexual assault or abuse
☐ An earthquake or flood
☐ A war
☐ Seeing someone be killed or seriously injured
☐ Having a loved one die through homicide or suicide
Have you ever experienced this kind of event?
☐ YES ☐ NO
If no, screen total = 0. Please stop here.
If yes, please answer the questions below.
In the past month, have you …
1. Had nightmares about the event(s) or thought about the event(s) when you did not want to?
☐ YES ☐ NO
2. Tried hard not to think about the event(s) or went out of your way to avoid situations that reminded you of the event(s)?
☐ YES ☐ NO
3. Been constantly on guard, watchful, or easily startled?
☐ YES ☐ NO
4. Felt numb or detached from people, activities, or your surroundings?
☐ YES ☐ NO
5. Felt guilty or unable to stop blaming yourself or others for the event(s) or any problems the event(s) may have caused?
☐ YES ☐ NO
PC-PTSD-5 (2015) National Center for PTSD Page 2 of 2
Preliminary results from validation studies suggest that a cutoff point of 3 on the PC-PTSD-5 (e.g., respondent answers "yes" to any 3 of 5 questions about how the traumatic event(s) have affected them over the past month) is optimally sensitive to probable PTSD. Optimizing sensitivity minimizes false-negative screen results. Using a cutoff point of 4 is considered optimally efficient. Optimizing efficiency balances false-negative results. As additional research findings on the PC-PTSD-5 are published, updated recommendations for cutoff point scores as well as psychometric data will be made available.

Adapted from PTSD: National Center for PTSD [13]

Table 5.10 Alcohol Use Disorders Identification Test (AUDIT-C)

Questions	
How often do you have a drink containing alcohol?	
☐ Never	+0
☐ Monthly or less	+1
☐ 2–4 times a month	+2
☐ 2–3 times a week	+3
☐ 4 or more times a week	+4
How many drinks containing alcohol do you have on a typical day when you are drinking?	
☐ 1 or 2	+0
☐ 3 or 4	+1
☐ 5 or 6	+2
☐ 7–9	+3
☐ 10 or more	+4
How often do you have six or more drinks on one occasion?	
☐ Never	+0
☐ Less than monthly	+1
☐ Monthly	+2
☐ Weekly	+3
Interpretation: **Men**, a score of 4 or more is considered positive, optimal for identifying hazardous drinking or active alcohol use disorders **Women**, a score of 3 or more is considered positive, optimal for identifying hazardous drinking or active alcohol use disorders **NOTE**: If all points are from Question 1, assume the patient is drinking below recommended limits, and the medical provider should review the patient's alcohol intake during the past few months	

Based on data from Ref. [14]

Case Vignette 5.2

Site B is a community-based organization (CBO) that is trying to offer a wide range of supportive services to their HIV clients. As a result of a department of health initiative in which new funding has been made contingent upon integrating HIV and behavioral health services, Site B began routine screening for substance use disorders using the CAGE-AID (2). Many patients are also receiving such screening from their medical care settings, but CBOs do not have access to those health records, and so Site B is focusing on screening for Opioid Use Disorder (OUD) because that is a high need among their clients. Although the CAGE-AID broadly focuses on all alcohol and drug use, the CBO wants to focus exclusively on opioids and so have trained their staff to modify the CAGE-AID wording to specify opioids and to give examples and common street drug names for opioids during screening. If a client screens positive for OUD, there may be limited options for referral given how few clinicians in the area are offering Medication-Assisted Treatment (MAT) for OUD (often referred to as MOUD). The only option that staff of the CBO feel that they have is to refer patients for opioid detoxification. The waiting lists

Table 5.11 Opioid Risk Tool (ORT)

The Opioid Risk Tool (ORT) is a brief screening tool for clinicians to use to accurately predict opioid abuse among individuals prescribed opioids for treatment of chronic pain All questions must be answered:	
Sex	☐ Male ☐ Female
Age between 16 and 45 years?	☐ Yes ☐ No
Family history of substance abuse	
Alcohol	☐ Yes ☐ No
Illegal drugs	☐ Yes ☐ No
Prescription drugs	☐ Yes ☐ No
Personal history of substance abuse	
Alcohol	☐ Yes ☐ No
Illegal drugs	☐ Yes ☐ No
Prescription drugs	☐ Yes ☐ No
Personal history of sexual abuse	
Preadolescent sexual abuse	☐ Yes ☐ No
Personal history of psychological disease	
ADD, OCD, bipolar, schizophrenia	☐ Yes ☐ No
Depression	☐ Yes ☐ No
Interpretation: Risk category is based on score Low risk: 0–3 Moderate risk: 4–7 High risk: 8 and greater	

Reprinted with permission from Webster and Webster [16]

for detoxification are long, and often by the time a spot becomes available, the client is no longer motivated to obtain treatment. In cases where clients do avail themselves of the detoxification treatment, the support that they need when they leave the more intensive setting of care is not readily found in their community. At that point, the clients may be so uncomfortable that they may relapse, and overdose risk is then heightened because they can no longer tolerate the same quantity of opioids they were used to consuming. Site B has come to appreciate that screening without additional supports and a strong referral network may have unintended negative consequences, and they are working to build their connections with substance use treatment agencies and individual clinicians to better serve and support their patients.

The Tobacco, Alcohol, Prescription Medications, and Other Substance Tool (TAPS)

The TAPS is a relatively new tool [18, 19]. It became widely available in 2018 and was designed to assess primary care patients for tobacco, alcohol, prescription drug, and illicit substance use. This tool was developed and validated with NIDA support and provides options specific to patients and settings. The paper form, shown in Tables 5.12 and 5.13, divides the TAPS into two parts. The online version takes the user (patient or clinician) through an algorithm based on responses and ends with recommendations for next steps. There may be no need for further action in the case of minimal risk, but higher threshold findings suggest additional services are needed.

The TAPS tool has two components. The first component (TAPS-1) is a four-item screen for tobacco, alcohol, illicit drugs, and non-medical use of prescription drugs (men answer question 2 and women question 3) (Table 5.12). If an individual screens positive on TAPS-1 (i.e., reports other than "never"), the tool will automatically begin the second component (TAPS-2) (see Table 5.13), which consists of brief substance-specific assessment questions to arrive at a risk level for that substance. Clinicians are encouraged to provide positive feedback to patients who screen negative and support their choice to abstain from substances. For patients who have a positive screen on the TAPS-1, a brief assessment (TAPS-2) identifies the specific substance(s) used and risk level, ranging from "problem use" to the more severe substance use disorder (SUD).

One of the main advantages to the TAPS-1 is that it covers prescribed as well as other substances. Additional advantages include being brief (typically 5 minutes or less) and available without cost for patient self-administration or for clinical interviewer administration to detect at-risk, harmful, or hazardous use as well as substance use disorders. The TAPS is intended to be used under a clinician's supervision and functions as a clinician extender to guide self-assessment. It does not take the place of a healthcare professional's clinical judgment. The online version is self-explanatory in plain language and easy to follow and can be accessed at: https://cde.drugabuse.gov/instrument/29b23e2e-e266-f095-e050-bb89ad43472f [19].

Instructions

The TAPS can be used by the patient (self-administered) online or administered as an interview by a health professional. Upon completion, the tool will automatically generate a risk level for each substance class. Implications of the score, along with suggested clinician actions and additional resources, are provided.

Screening Tool Cutoffs and Scoring Thresholds

Endorsement of any substance use during the initial screening phase (TAPS-1) prompts a few additional questions regarding use-related behaviors through a brief assessment (TAPS-2) (Table 5.13).

Table 5.12 TAPS Tool Part 1

NIDA Clinical Trials Network
The Tobacco, Alcohol, Prescription medications, and other Substance (TAPS) Tool

TAPS Tool **Part 1** Web Version: 2.0; 4.00; 09-19-17

General Instructions:
The TAPS Tool Part 1 is a 4-item screening for tobacco use, alcohol use, prescription medication misuse, and illicit substance use in the past year. Question 2 should be answered only by males and Question 3 only by females. Each of the four multiple-choice items has five possible responses to choose from. Check the box to select your answer.

Segment:
Visit number:

1. In the PAST 12 MONTHS, how often have you used any tobacco product (for example, cigarettes, ecigarettes, cigars, pipes, or smokeless tobacco)?
   ☐ Daily or Almost Daily ☐ Weekly ☐ Monthly
   ☐ Less Than Monthly ☐ Never

2. In the PAST 12 MONTHS, how often have you had 5 or more drinks containing alcohol in one day? One standard drink is about 1 small glass of wine (5 oz), 1 beer (12 oz), or 1 single shot of liquor. (Note: This question should only be answered by **males**).
   ☐ Daily or Almost Daily ☐ Weekly ☐ Monthly
   ☐ Less Than Monthly ☐ Never

3. In the PAST 12 MONTHS, how often have you had 4 or more drinks containing alcohol in one day? One standard drink is about 1 small glass of wine (5 oz), 1 beer (12 oz), or 1 single shot of liquor. (Note: This question should only be answered by **females**).
   ☐ Daily or Almost Daily ☐ Weekly ☐ Monthly
   ☐ Less Than Monthly ☐ Never

4. In the PAST 12 MONTHS, how often have you used any drugs including marijuana, cocaine or crack, heroin, methamphetamine (crystal meth), hallucinogens, ecstasy/MDMA?
   ☐ Daily or Almost Daily ☐ Weekly ☐ Monthly
   ☐ Less Than Monthly ☐ Never

5. In the PAST 12 MONTHS, how often have you used any prescription medications just for the feeling, more than prescribed or that were not prescribed for you? Prescription medications that may be used this way include: Opiate pain relievers (for example, OxyContin, Vicodin, Percocet, Methadone), Medications for anxiety or sleeping (for example, Xanax, Ativan, Klonopin), Medications for ADHD (for example, Adderall or Ritalin)
   ☐ Daily or Almost Daily ☐ Weekly ☐ Monthly
   ☐ Less Than Monthly ☐ Never

Adapted from NIDA CTN Common Data Elements [19]

Scores on these questions generate a risk level per substance endorsed, based on a range of possible scores per substance.

TAPS score	Risk category
0	No use in the past 3 months
1	Problem use
2+	Higher risk

For identifying DSM-5 substance use disorders at the recommended cutoff of 2+, the TAPS Tool has adequate sensitivity (>70%) only for tobacco, alcohol, and marijuana. Further assessment should be conducted for patients with a score of 1+ for other substances. This assessment is a high priority for patients with a TAPS score of 2+, given its high positive predictive value for most substance classes.

Case Vignette 5.3
Site C is a stand-alone clinic that provides comprehensive services to patients with HIV. Because of its history of grant-funded activities, it has in place a complex set of screening processes for psychiatric conditions that were designed to satisfy multiple funders. For example, the AUDIT-C, CAGE-AID, and ORT are all given at intake to screen for substance use disorders, and they are also given at 6-month visits by both the clinical care team and the supportive care team due to funder requirements. However, some sources of funding have ended, and the current workflow could be streamlined for more efficient time management and improved patient experience. In addition to those goals, the clinic has taken up a tobacco cessation initiative and is in a high opioid overdose area and so has decided to find a tool that incorporates screening for tobacco and both prescribed and illicit opioids (the ORT looks only at the risk for misusing prescribed opioids). Having received training on how to use the relatively new TAPS, the clinic leadership decides to replace the three-screen protocol with a face-to-face administration of the TAPS. Clinic leadership is also looking to expand access to tablets for their patients so that they can self-administer the TAPS in the waiting room and simply print the results and recommended next steps for the care team member to review with the patient in the examination room.

Screening for HIV-Associated Neurocognitive Disorders (HAND)

Screening for HIV-associated neurocognitive disorders (HAND) presents a greater challenge than screening for other psychiatric disorders, primarily because it is difficult to screen for HAND until cognitive impairment has reached the level of dementia. The International HIV Dementia Scale (IHDS) can be used to detect HIV-associated dementia. Please see Chap. 10 for a full description of HAND, the available screening tools for dementia, and approaches to documenting less severe cognitive changes associated with HIV infection.

Screening for Suicide Risk

Suicide risk is not a diagnosis in the DSM-5, although it is in the 10th version of the International Classification of Diseases. Regardless of whether suicide risk should be included as a disorder, it's a problem of great concern in medical and psychiatric settings alike.

A single question about suicide is incorporated in the PHQ-9, but by itself it's not a sufficient assessment tool for suicide risk and suicidal ideation [20]. More

Table 5.13 TAPS Tool Part 2
Adapted from NIDA CTN Common Data Elements [19]

NIDA Clinical Trials Network
The Tobacco, Alcohol, Prescription medications, and other Substance (TAPS) Tool

TAPS Tool **Part 2** Web Version: 2.0; 4.00; 09-19-17

General Instructions:
The TAPS Tool Part 2 is a brief assessment for tobacco, alcohol, and illicit substance use and prescription medication misuse in the PAST 3 MONTHS ONLY. Each of the following questions and sub questions has two possible answer choices-either yes or no. Check the box to select your answer.

1. In the PAST 3 MONTHS, did you smoke a cigarette containing tobacco? □ Yes □ No
If "Yes", answer the following questions:
a. In the PAST 3 MONTHS, did you usually smoke more than 10 cigarettes each day? □ Yes □ No
b. In the PAST 3 MONTHS, did you usually smoke within 30 minutes after waking?

2. In the PAST 3 MONTHS, did you have a drink containing alcohol? □ Yes □ No
If "Yes", answer the following questions:
a. In the PAST 3 MONTHS, did you have 4 or more drinks containing alcohol in a day?* (Note: This question should only be answered by females). □ Yes □ No
b. In the PAST 3 MONTHS, did you have 5 or more drinks containing alcohol in a day?* (Note: This question should only be answered by males). □ Yes □ No
*One standard drink is about 1 small glass of wine (5 oz), 1 beer (12 oz), or 1 single shot of liquor.
c. In the PAST 3 MONTHS, have you tried and failed to control, cut down or stop drinking? □ Yes □ No
d. In the PAST 3 MONTHS, has anyone expressed concern about your drinking? □ Yes □ No

3. In the PAST 3 MONTHS, did you use marijuana (hash, weed)? □ Yes □ No
If "Yes", answer the following questions:
a. In the PAST 3 MONTHS, have you had a strong desire or urge to use marijuana at least once a week or more often? □ Yes □ No
b. In the PAST 3 MONTHS, has anyone expressed concern about your use of marijuana? □ Yes □ No

4. In the PAST 3 MONTHS, did you use cocaine, crack, or methamphetamine (crystal meth)? □ Yes □ No
If "Yes", answer the following questions:
a. In the PAST 3 MONTHS, did you use cocaine, crack, or methamphetamine (crystal meth) at least once a week or more often? □ Yes □ No
b. In the PAST 3 MONTHS, has anyone expressed concern about your use of cocaine, crack, or methamphetamine (crystal meth)? □ Yes □ No

5. In the PAST 3 MONTHS, did you use heroin? □ Yes □ No

Table 5.13 (continued)

If "Yes", answer the following questions:
a. In the PAST 3 MONTHS, have you tried and failed to control, cut down or stop using heroin? □ Yes □ No
b. In the PAST 3 MONTHS, has anyone expressed concern about your use of heroin? □ Yes □ No

6. In the PAST 3 MONTHS, did you use a prescription opiate pain reliever (for example, Percocet, Vicodin) not as prescribed or that was not prescribed for you? □ Yes □ No
If "Yes", answer the following questions:
a. In the PAST 3 MONTHS, have you tried and failed to control, cut down or stop using an opiate pain reliever? □ Yes □ No
b. In the PAST 3 MONTHS, has anyone expressed concern about your use of an opiate pain reliever? □ Yes □ No

7. In the PAST 3 MONTHS, did you use a medication for anxiety or sleep (for example, Xanax, Ativan, or Klonopin) not as prescribed or that was not prescribed for you? □ Yes □ No
If "Yes", answer the following questions:
a. In the PAST 3 MONTHS, have you had a strong desire or urge to use medications for anxiety or sleep at least once a week or more often? □ Yes □ No
b. In the PAST 3 MONTHS, has anyone expressed concern about your use of medication for anxiety or sleep? □ Yes □ No

8. In the PAST 3 MONTHS, did you use a medication for ADHD (for example, Adderall, Ritalin) not as prescribed or that was not prescribed for you? □ Yes □ No
If "Yes", answer the following questions:
a. In the PAST 3 MONTHS, did you use a medication for ADHD (for example, Adderall, Ritalin) at least once a week or more often? □ Yes □ No
b. In the PAST 3 MONTHS, has anyone expressed concern about your use of a medication for ADHD (for example, Adderall or Ritalin)? □ Yes □ No

9. In the PAST 3 MONTHS, did you use any other illegal or recreational drug (for example, ecstasy/molly, GHB, poppers, LSD, mushrooms, special K, bath salts, synthetic marijuana ('spice'), whip-its, etc.)? □ Yes □ No
If "Yes", answer the following questions: In the PAST 3 MONTHS, what were the other drug(s) you used?

Comments:

complex tools to screen for suicide risk are available, though they are more likely to be implemented in BH care settings rather than in medical settings [21].

The two most widely used suicide assessment scales are the Beck Scale for Suicide Ideation (BSI) and the Columbia Suicide Severity Rating Scale (C-SSRS) [21–23]. All instruments to assess suicide risk have worrisome limitations, and there is no single instrument considered to be the gold standard [21].

There are multiple versions of the C-SSRS. The authors present the screening version because of its brevity and because it parallels the clinical training that many psychiatrists receive to consider suicide risk on a continuum from low to high risk. The questions in the C-SSRS screening scale spell out this continuum (see Fig. 5.3). Other versions of C-SSRS are available [23]. But it's important to bear in mind that the prediction of suicide, whether by a psychiatric interview or the use of a screening instrument, remains limited [21].

COLUMBIA-SUICIDE SEVERITY RATINGS SCALE

Screening

	Past Month		Lifetime (Worst Point)	
Ask questions that are in bold and underlined.	**YES**	**NO**		
Ask Questions 1 and 2				
1) ***Have you wished you were dead or wished you could go to sleep and not wake up?*** Person endorses thoughts about a wish to be dead or not alive anymore, or a wish to fall asleep and not wake up.				
2) ***Have you actually had any thoughts of killing yourself?*** General non-specific thoughts of wanting to end one's life/die by suicide without general thoughts of methods, intent, or plan.				
If YES to 2, ask questions 3, 4, 5, and 6. If NO to 2, go directly to question 6.				
3) ***Have you been thinking about how you might do this?*** Person endorses thoughts of suicide and has thought of at least one method. *e.g., "I thought about taking an overdose, but I never made a specific plan as to when, where or how i would actually do it... and i would never go through with it."*				
4) ***Have you had these thoughts and had some intention of acting on them?*** Active suicidal thoughts of killing oneself and reports having some intent to act on such thoughts. *e.g., "I have the thoughts, but I definitely will not do anything about them."*				
5) ***Have you started to work out or worrked out the details of how to kill yourself? Do you intend to carry out this plan?*** Thoughts of killing oneself with details of a plan fully or partially worked out and person has some intent to carry it out,				
6) ***a) Have you ever done anything, started to do anything, or prepared to do anything to end your life?*** Examples: Collected pills, obtained a gun, gave away valuables, wrote a will or suicide note, took out pills didn't swallow any, held a gun but changed your mind or it was grabbed from your hand, went to the roof but didn't jump; or actually took pills, tied to shoot yourself, curt yourself, tried to hang yourself, etc.			**Lifetime** YES / NO	
b) IF YES, ask: ***Was this within the past three months?***			**Past 3 months** YES / NO	

Low Risk

Moderate Risk

High Risk

Fig. 5.3 Columbia Suicide Severity Rating Scale Screener. (Adapted with permission from Screener Columbia Suicide Severity Rating Scale: Six levels of risk severity (C-SSRS) [22])

Conclusions

In closing, the use of screening tools for psychiatric disorders expands the range of clinicians who can briefly assess people with HIV for psychiatric disorders in need of further assessment and care. Patients whose symptoms fall below the clinical cutoffs for psychiatric disorders may greatly benefit from brief interventions at the primary care level, from supportive services in the community, and from learning techniques that will help them improve their own self-care strategies. Positive scores on screening tools require further diagnostic assessment. This can lead to the diagnosis of common psychiatric disorders such as major depressive disorder, generalized anxiety disorder, PTSD, and alcohol and substance use disorders. Screening can also unmask suicidal ideation. Screening is only the first step in a continuum of services needed to diagnose and treat psychiatric disorders, which in turn can lead to the alleviation of suffering, improve adherence, and save lives.

Multiple-Choice Questions

1. If the GAD-7 has a sensitivity of 89% and a specificity of 82% for detecting generalized anxiety disorder at a cutoff score of 10, this would mean that when using that score:

   A. 11% of people who DO NOT have generalized anxiety disorder will test positive on the GAD-7
   B. *11% of people who DO have generalized anxiety disorder will not be identified by the GAD-7*
   C. 18% of people who DO have generalized anxiety disorder will not be identified by the GAD-7
   D. 89% of people screened with the GAD-7 who have generalized anxiety disorder will be accurately diagnosed by using this tool

   Explanation of Question 1

   - Sensitivity refers to the ability of a test to correctly identify those people who have the problem, e.g., “true positives.”
   - At a cutoff score of 10, the GAD-7 will fail to identify 11% of the people screened who have generalized anxiety disorder.
   - Specificity is a test’s ability to identify people who do not have a problem, e.g., “true negatives.”
   - At a cutoff score of 10, the GAD-7 will falsely identify 18% of the people screened as having generalized anxiety disorder when, in fact, they don’t have this condition.
   - The GAD-7 is a screening tool, not a diagnostic tool. Further evaluation is needed following a positive screen for generalized anxiety disorder.

2. Screening tools for psychiatric disorders can be used to:

   A. Establish DSM-5 psychiatric diagnoses
   B. Identify which patients will attempt suicide
   C. Establish that a patient does not have a psychiatric diagnosis
   D. *Suggest the possible presence of a psychiatric diagnosis*

   Explanation of Question 2

   - Screening tools help to identify patients who are likely to have a psychiatric disorder but, because of the limitations in their sensitivity and specificity, they do not definitely establish or rule out a psychiatric diagnosis.
   - Screening tools to identify suicide attempts remain imperfect.

3. Which statement is true:

   A. *It's difficult to screen for mild symptoms of HIV-associated neurocognitive impairment*.
   B. The GAD-7 for generalized anxiety disorder cannot detect other anxiety disorders.
   C. The PC-PTSD-5 is sometimes positive even if there's no report of experiencing a traumatic event.
   D. The AUDIT-C for alcohol use problems scores men and women in the same way.

   Explanation of Question 3

   - Detecting mild symptoms of HIV-associated neurocognitive impairment usually requires neuropsychological testing because current screens are insensitive to mild symptoms.
   - The GAD-7 is moderately good at detecting panic disorder, social anxiety disorders, and PTSD.
   - PTSD is unique among psychiatric diagnoses in requiring an external event to make a diagnosis.
   - On the AUDIT-C, women will test positive at a lower score than men.

4. Which statement is false:

   A. *The Opioid Risk Tool focuses on both prescribed and illicit opioids.*
   B. There is no gold standard screening test for suicide risk.
   C. Psychomotor speed is a component of testing for HIV-associated dementia.
   D. The Drug Abuse Screening Test (DAST-10) excludes alcohol.

   Explanation of Question 4

   - The Opioid Risk Tool is designed to help clinicians predict which patients who are prescribed opioid medications for pain are at risk for opioid abuse.
   - The other statements are all true.

5. A cutoff score for a screening tool is established to:

   A. Maximize the ability to detect people who have a given disorder
   B. Minimize the problem of falsely identifying people as having a disorder when the disorder is not present
   C. *Balance the ability to identify people who have an illness without including those who don't have the illness*
   D. Find a score that best matches the diagnostic criteria in the DSM-5

   Explanation of Question 5

   • A screening tool tries to balance capturing all the people who are likely to have a given illness while excluding people who are free of this illness. This success in achieving these goals is reflected in the sensitivity and specificity of a screening tool.

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Chapter 6
Depressive Disorders

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Major depressive disorder (MDD), the most common neuropsychiatric complication in HIV-infected patients [1], is up to four times more prevalent among HIV-infected individuals than in the general population [2], particularly in certain subpopulations, such as women or socially disadvantaged persons [3]. Comorbidity of HIV/AIDS with MDD and other disorders in the depressive spectrum is described in all phases of HIV infection and impacts massively on various clinical aspects of both comorbid conditions [1, 4]. Unfortunately, MDD is often not recognized in persons living with HIV/AIDS (PLWHA), not only as a result of underestimation but also as a consequence of several confounding factors, such as HIV-associated neurocognitive disorders (HAND) and substance-related disorders. Moreover, even when properly diagnosed, MDD may be inadequately managed because of many reasons, including concerns related to side effects of psychotropics and potential drug-drug interactions [3, 5]. Since the introduction of effective antiretroviral therapy (ART), the impact and course of HIV infection have changed from a rapidly debilitating and deadly illness to a chronic, manageable illness with a long-term life

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expectancy, and the ability to provide an effective treatment of comorbid MDDs assumes even more relevance to the improvement of quality of life of patients [5].

The pathogenic basis for the association of MDD and HIV-infection is complex and remains to be fully clarified. Potential etiologies may include the disruption of immune balance, via HIV-promoted activation of inflammatory mediators, e.g., pro-inflammatory cytokines, chemokine receptors, extracellular matrix-degrading enzymes, and glutamate receptor-mediated excitotoxicity. The same pathogenetic pathways may be involved in determining effectiveness of antidepressant treatments [1, 6]. The identification of MDD biomarkers, such as pro-inflammatory cytokines, in PLWHA may improve diagnostic and therapeutic strategies for MDD, potentially increasing adherence to ART, improving quality of life, and decreasing morbidity and mortality [7].

In this chapter, we provide an update on the comorbidity of HIV/AIDS with MDD and other disorders on the depressive spectrum, synthesizing existing evidence from epidemiology, clinical features, explanatory models, and effective therapeutic options. Special attention is given to the role of inflammation and immune function as an explanatory model, as well as to the most frequent obstacles and pitfalls in clinical diagnosis and management.

Epidemiology

Prevalence and Risk Factors Associated with Depressive Disorders in Persons with HIV

The World Health Organization (WHO) estimated that, by the end of 2018, nearly 38 million people in the world were living with HIV, disproportionately affecting African regions where over two-thirds of the population living with HIV reside [8]. The US Centers for Disease Control and Prevention (CDC) estimates that there are just over one million PLWHA in the USA, with one in seven estimated to be undiagnosed [9]. Depressive disorders are even more prevalent, with 2017 data estimating 17.3 million adults in the USA having had at least one major depressive episode, representing over 7% of the entire population [10]. Given the significant morbidity associated with HIV infection, it is not surprising that depressive disorders are more common among this population than that of non-infected controls, as well as associated with an increased risk of HIV disease progression and mortality.

While more common in PLWHA, the exact prevalence of MDD and other disorders on the depressive spectrum among this group varies across the literature. There are a variety of factors contributing to this, largely due to the lack of a unified definition of "depression." A systematic review by Sherr et al. found that studies rarely adopted the same cutoff points when using various scales to measure depressive symptoms. Studies using the Beck Depression Inventory (BDI), for example, had prevalence estimates that ranged from a cutoff of +/= 15 to a cutoff of +/= 20 among seven different studies, yielding prevalence rates which ranged from 12% to 71%

[11]. This clearly contributes to the difficulty in determining the true prevalence of depressive disorders among PLWHA. Multiple studies suggest a prevalence of two- to fourfold the rate of depressive when compared to non-HIV-infected individuals in the general population [12]. The best recent estimate of the prevalence of depression in PLWHA comes from a 2019 systematic review and meta-analysis by Rezaei et al., the first study to analyze the global impact of comorbid depressive disorders, which found an overall prevalence of 31% across 118 studies including 51,143 subjects [3]. Of these PLWHA, 14,942 were diagnosed with moderate to severe depression [3]. Prevalence was noted to be highest in developing/underdeveloped countries, suggesting that governmental support, access to care, and increased awareness in developed countries positively impact on the rate of diagnosis and management of MDD among PLWHA.

Subgroup analyses of various studies can provide insight into prevalence rates differing from the standard PLWHA population, highlighting potential at-risk and vulnerable groups. Pregnant women with HIV, for example, have about one and a half times the odds of experiencing antenatal and postnatal depressive disorders when compared to non-HIV-infected controls [13]. Men who have sex with men and former blood/plasma donors were found to have significantly higher rates of depressive disorders in a Chinese systematic review and meta-analysis of over 20,000 PLWHA, with 43.9% and 85.6% experiencing depressive disorders, respectively [12]. Further analyses are warranted to identify other at-risk subgroups to guide targeted interventions.

Risk Factors

The relationship between HIV and depressive disorders is multifactorial and varies depending on geographic region. Depressive disorders can occur in all phases of HIV infection with more prevalence in advanced-stage HIV illness [1]. This suggests the importance of depressive symptom screening and clinical monitoring throughout treatment of HIV and AIDS. Some key risk factors include female sex, preexisting depressive disorder and family history of depressive disorders [5], as well as a combination of neurobiological changes and psychosocial and behavioral factors [1].

The neurobiological changes are related to lower CD4 counts, higher viral loads [1, 12], chronic neuroinflammation, reduction in trophic factors, and alterations in dopamine and other neurotransmitters [5]. Psychosocial factors such as early life trauma, violence exposure, limited healthcare access, financial instability, lower educational attainment, and underemployment can increase risk. Behavioral factors such as drug and alcohol abuse as well as limited physical activity are also implicated [5].

Unfortunately, depressive disorders continue to be underdiagnosed and undertreated [1] in the HIV-infected population. In addition to treatments focused on prevention and cure of HIV/AIDS, attention should be aimed at the quality of life in PLWHA [13], including the diagnosis and treatment of depressive disorders. Addressing and modifying the risk factors for depressive disorders may improve

adherence to antiretrovirals and mitigate progression of HIV. This can help people cope with this illness and ultimately decrease mortality [13] (Table 6.1).

Diagnosis

Despite the importance of detecting and treating depressive disorders in HIV-infected patients, this syndrome frequently goes unrecognized [14, 15], and, even when clinically recognized, it often goes untreated. Moreover, even when treating depressive disorders concomitant with HIV, clinicians' adherence to best-practices guidelines about dosing, duration, and monitoring of antidepressants is low, meaning that many patients fail to receive an adequate treatment course and therefore fail to benefit from treatment [14].

The ascertainment of depression in HIV-infected patients may be expected to be difficult or biased due to several factors:

1. The etiology of depression in HIV is a complex, multidimensional phenomenon comprised of various components of psychiatric, psychological, neurological, systemic medical, and toxic factors which are summarized in Table 6.2. Stressful life events and other psychosocial factors (such as stigma) related to the fact of being infected by HIV may lead to an adjustment disorder with depressive symptoms ("psychological" depression). Further, HIV-related conditions and HIV-associated inflammation with an impact on the central nervous system could also present with depressive symptoms ("neuropsychiatric" depression). Moreover, some systemic medical conditions caused by HIV infection, such as hypothy-

Table 6.1 Risk factors for depressive disorders in HIV patients (classified into related categories)

Sociodemographic	Female gender Lower education Poor income adequacy Homelessness Limited healthcare access Lack of social support Unemployment/underemployment
Related to somatic status/illness	Pregnancy Limited/decreased physical activity
Related to HIV	High viral load Low CD4 count Men who have sex with men Former blood/plasma donors
Psychological/psychiatric	Violence exposure Early life trauma Active substance abuse Personal/family history of depressive/mood disorder Transgender individual Poor self-efficacy

Table 6.2 Clinical features of depression in HIV patients

Standard DSM-5/ICD-10 criteria for depression	Endicott's supplement criteria for use with medical patients
Poor appetite or changes in weight	Tearfulness or depressed appearance
Loss of energy and fatigue	Social withdrawal, decreased talkativeness
Insomnia or hypersomnia	Brooding, self-pity, pessimism
Diminished ability to think or to concentrate	Lack of reactivity, cannot be cheered up

roidism or hypogonadism, can produce depression-like symptoms ("medical" depression). Finally, some treatments given to PLWHA can produce psychiatric side effects ("toxic" depression). Once we have ruled out systemic medical or toxic conditions, it may be very difficult to differentiate between MDD ("psychiatric" depression), reactive depression ("psychological" depression), or depression due to HIV infection in the brain ("neuropsychiatric" depression). In many cases, in HIV patients, these three explanatory models of depressive disorders represent a continuum of depressive symptoms rather than three separate categorical diagnoses.

2. The clinical criteria commonly used to diagnose depressive disorder in the general population have some limitations when they were applied to PLWHA, due to the confounding effect of physiological changes associated with HIV illness progression or multimorbid other medical systemic illnesses (such as cancer, cardiovascular illness, or diabetes mellitus), the physical symptoms of infection, and/or side effects of HIV medications. For example, both symptoms of depression and physiological changes associated with HIV illness share appetite changes, lack of motivation, fatigue, sleep disturbances, anergia, loss of libido, impaired sexual functioning, and cognitive impairment. Thus, prevalence rates vary greatly across studies [16]. Relying excessively on somatic symptoms for depressive disorder diagnoses may lead clinicians to mistakes in diagnosis, either over- or underestimation of depression risk, since these somatic symptoms are less specific in patients with systemic medical comorbidities. Cognitive-affective criteria, similar to those proposed by Endicott for diagnosing depression in cancer patients, could be more helpful in HIV patients and make diagnosis more accurate [17]. Symptoms and signs such as depressed appearance, self-pity/pessimism, hopelessness, and social withdrawal or lack of reactivity, instead of poor appetite, fatigue, insomnia, or diminished ability to think clearly could be more useful to diagnose psychiatric/psychological depression in PLWHA (see Table 6.2).
3. The clinical setting of care may complicate the diagnosis of depressive disorders in PLWHA. Depressed patients may only tend to report somatic symptoms to their HIV physician, and they may not refer to their mood state if not assessed specifically. Further, physicians who are not psychiatrists may feel less confident asking about depressive symptoms. In some cases, the brief duration of medical encounters may prevent clinicians from including psychosocial issues or evening asking the simple question "Are you depressed?". Finally, there may be a

misconception that depression is "normal" or even "acceptable" in PLWHA, leading to diagnostic and therapeutic nihilism.

Tools for Assessment

Clinicians need effective tools to diagnose depressive disorders in PLWHA. The utilization of self-report scales can also improve clinicians' ability to screen for depression in patients with HIV and AIDS. Most of the instruments commonly validated and used to screen or measure depressive symptoms were created to be used in the general population. Table 6.3 describes some of the scales used to screen and measure depressive symptoms. Most of the scales include somatic symptoms of depression, which, as mentioned before, may be confounded with somatic symptoms due to HIV infection or other multimorbid illness. The Hospital Anxiety and Depression Scale (HADS) [21] is a self-report scale specially designed to assess anxiety and depression in people with systemic medical illness. The depression subscale mainly assesses anhedonia and does not include any somatic item that can be confused with symptoms of systemic medical illness. The HADS has a major advantage over other existing depression measures. Accumulating data suggest that the HADS provides a valid and reliable assessment of depression and anxiety for a wide variety of populations.

Table 6.3 Evidence-based tools to diagnose depression in HIV patients

Screening instrument	Administration	Items	Measurements	Primary use
Beck Depression Inventory (BDI) [18]	Self-report	20	Cognitive, somatic subscales	Clinical
Center for Epidemiological Studies-Depression (CES-D) [19]	Self-report	20	Cognitive, somatic subscales (cutoff scores for clinically relevant symptoms)	Epidemiologic research
Hamilton Rating Scale for Depression (HAM-D) [20]	Clinician	17	Affective, vegetative subscales	Clinical research
Hospital Anxiety and Depression Scale (HADS) [21]	Self-report	7	Screens for depression and anxiety; excludes somatic symptoms	Clinical
Patient Health Questionnaire-9 (PHQ-9) [22]	Self-report	9	Screens for depression according to DSM criteria	Clinical research
General Anxiety Disorder-7 (GAD-7) [23]	Self-report	7	Screens for generalized anxiety disorder according to DSM criteria	Clinical research

Case Vignette 6.1
J was a 68-year-old man known to be infected by HIV for 25 years, when he was using substances intravenously. He was on ART with undetectable viral load. Past medical history included type 2 diabetes mellitus on insulin for 2 years, diabetic nephropathy, and benign prostate hypertrophy and chronic obstructive pulmonary diseases because of smoking. The patient was on beta-adrenergic-blocking drugs for hypertension and on allopurinol for hyperuricemia. He had surgery for facial lipo-injection and abdominal and cervical liposuction in 2007.

He had had AD treatment with paroxetine in the past, due to depression and anxiety. He had a very good job as chief operating officer in a company, but had retired. He had a stable partner relationship for years. With the time, he reduced the amount of social relations. He preferred to avoid interpersonal relationships because he did not want to disclose his HIV condition. He used to be a meticulous person with obsessive traits of personality. After a long time, he went back to the psychiatrist who had given him treatment in his previous depressive and anxiety episode, because he started to have depressive symptoms, with feelings of hopelessness and suicidal thoughts. As concurrent events he related that he had started a long-distance relationship and was considering not continuing with his current partner. However, he was afraid of abandonment, if he broke his long-time relationship. He also referred difficulties in assuming the deterioration due to getting older and due to his medical illnesses. He admitted having difficulties in being adherent to the ART treatment. He often forgot to take the medication. He was also afraid of starting to have cognitive impairment. Neuropsychological examination was recommended, but he refused.

What care strategies would you consider for the case?
What clinical problems would you prioritize?

Case Vignette 6.2
D was a 30-year-old gay man, known to be infected by HIV and HCV through unprotected sex for 10 years. He started ART when his CD4 lymphocyte count was 212 cell/ml and his viral load was 182,000 copies. After starting ART, these values improved to almost 600 CD4 cells/ml and undetectable viral load. He went to his regular visit to his HIV physician, and after a short time of interview, he reported that he had feelings of low energy and some memory difficulties for the previous 8 months. He started to increase the intake of cocaine to get more energy, but this was useful only during a short time. He was living alone after he broke off his relationship with his partner, 1 year before. Laboratory tests showed no relevant deviations of the normal ranges, except from low testosterone levels. Scores on the HADS were 6 on the anxiety subscale and 17 on the depression subscale. The HIV care provider started

testosterone treatment and sent D to the psychiatrist. After 8 weeks of testosterone replacement, D still referred depressive symptoms such as anhedonia, hopelessness, suicidal thoughts, increased social isolation, poor appetite, and sleep disturbances. Difficulties with memory and concentration also persisted. The depressive subscale of the HADS still scored above 10. D was given, antidepressant medications and almost all depressive symptoms improved after 4 weeks of treatment. Cognitive impairment did not improve. Neuropsychological testing showed Frascati criteria for mild neurocognitive disorder.

What do you think may be the "take-home" message in this case?
Would you have acted differently in a similar situation?

Table 6.4 Inflammatory phenomena relevant in the etiology of MDD

1. Elevated circulating pro-inflammatory cytokine levels
2. Significant associations between markers of inflammation and neuropsychiatric symptoms [24]
3. Frequent experience of psychiatric symptoms among individuals suffering from immune-related disorders with high levels of circulating cytokines
4. Depressive symptoms induced by acute experimental activation of the immune system with endotoxin (e.g., Lipopolysaccharide – LPS) or therapeutically used cytokines, such as interferon-α (IFN-α); these symptoms are responsive to antidepressant (AD) therapy

Etiology

The pathogenic causal pathways for the increased risk of MDD in HIV-infected subjects remain to be fully understood but are based on the complex interaction among biopsychosocial factors. The biological mechanisms include neurobiological changes caused by the persistent viral presence in the CNS and systemic and intra-CNS immune-inflammatory and neuroendocrine phenomena induced by HIV. The HIV-related immune imbalance could contribute to the development of depression via activation of inflammatory mediators, cytokines, chemokine receptors, extracellular matrix-degrading enzymes, and glutamate receptor-mediated excitotoxicity. All of these mediators have been proposed to play a role in mediating depressive symptoms and response to depression treatment in general (not only in HIV-related depression), but such a role could be even more important or apparent in persons with HIV. Additionally, HIV may act via direct infection of astrocytes, oligodendrocytes, and neuronal progenitor cells, and HIV proteins may activate brain glial cells with a further contribution to inflammation. Evidence favoring the role of pro-inflammatory cytokines in the pathogenesis of MDD has been confirmed in recent years and includes different molecules and mechanisms, as described in Table 6.4.

Among the cytokines likely to be involved in MDD and its treatment, there are pro-inflammatory cytokines, including interleukin (IL)-1, IL-6, IL-18, IL-12, IL-23,

tumor necrosis factor (TNF)-α and IFN-α, and chemokines, such as monocyte chemoattractant protein (MCP)-1 [25]. The same pro-inflammatory cytokines may play a role in the development of MDD in HIV-infected persons, as significant changes in the levels of expression of pro-inflammatory cytokines (including IL-18 and INF-γ and TNF-α) in peripheral blood mononuclear cells of a sample of HIV-infected subjects were confirmed [26]. The neurotrophin brain-derived neurotrophic factor (BDNF) is also known to be involved in the pathogenesis and treatment of MDD: significantly lower levels of BDNF mRNA were found than in healthy subjects compared to the expression of BDNF in peripheral blood mononuclear cells of HIV-infected patients [26]. Pro-inflammatory cytokines may affect BDNF expression and release in a human glioblastoma-astrocytoma cell line, suggesting that cytokines may contribute to the development of depression by reducing the neurotrophic support in the brain.

Systemic immune activation during HIV infection is also a consequence of the effects of HIV on the structure and functioning of the gut mucosa; HIV negatively impacts on the functioning of the enteric immune system, reducing its effectiveness in surveillance to the gut barrier. As a consequence, translocation across the gut mucosa of bacterial products, such as LPS, may be easier, leading to engagement of a massive inflammatory response mediated by further production of pro-inflammatory cytokines. Further events include interference with the tryptophan metabolism, activation of inflammasomes, and direct stimulation of the CNS immune system. Neuroinflammation is also enhanced by the occurrence of co-infection by opportunistic pathogens or by abuse of drugs and alcohol.

Pro-inflammatory cytokines are known to also impact on the effectiveness of the treatment of MDD, since increased inflammatory markers in depressed patients have been associated with non-response to treatment with AD, and anti-inflammatory therapy is beneficial in depression, including observations of the adjuvant role of NSAIDs such as ASA toward serotoninergic AD [27]. A circular etiopathogenetic interrelationship among effects of AD medications and biomarkers of depression may be hypothesized, with biomarkers possibly associated with or predicting clinical response to AD [6]. The rate and severity of depression also seem to correlate to prescription and effectiveness of ART, a further demonstration that de-activation of the immune system and consequent reduction in cytokine levels also impact on psycho-behavioral phenomenology.

In HIV-infected individuals, identification of specific biomarkers for MDD may support diagnostic and therapeutic strategies by informing clinicians about the onset of comorbid depression or supporting recommendations for AD therapy. The final positive results of identifying biomarkers may be better adherence to ART, improvement of quality of life, and decreased morbidity and mortality.

Psychosocial mechanisms are also relevant, such as the burden of having a life-threatening and chronic disabling disease and factors more specific to HIV such as isolation, stigma, lack of support, violence, and drug abuse; such issues become even more significant when other psychosocial risk factors are present, e.g., migrant status and poor coping. HIV-related psychosocial mechanisms may lead to depressive disorders via activation of some of the neurobiological pathways as previously

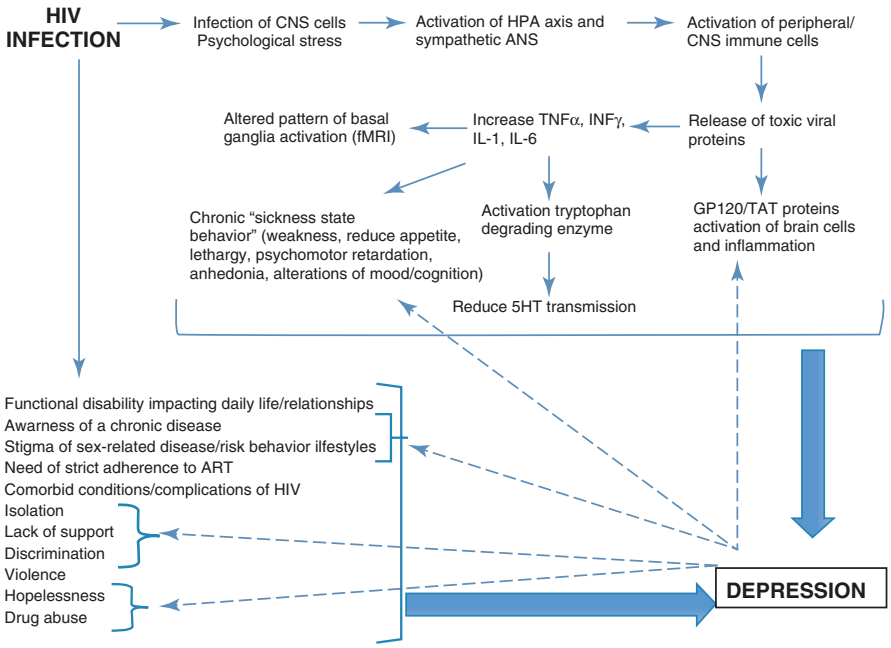

Fig. 6.1 Possible causative mechanisms of depression in HIV subjects. (Reprinted from Nanni et al. [1]. With permission from Springer Nature)

described, e.g., altered activity of the hypothalamic-pituitary-adrenal axis as a consequence of chronic exposition to stress [1]. Figure 6.1 sums up mechanisms that could be implied in determining depression among HIV-infected subjects.

Clinical Interventions

Pharmacotherapy

AD pharmacotherapy remains a mainstay of treatment for PLWHA and concomitant MDD. The indications to begin pharmacotherapy are the same regardless of HIV status, but with HIV-positive patients, there are additional considerations. Challenges related to antidepressant treatment of persons with HIV and depressive symptoms include an increased risk of nonadherence as well as drug-drug interactions with the patient's antiretroviral medications [28]. Additionally, adequate treatment in the HIV population is critical, as HIV-positive individuals with depressive symptoms are shown to have increased HIV illness progression and higher mortality rates compared with HIV-positive individuals without symptoms of depressive disorders [29]. However, treatment of depressive symptoms has also been shown to

increase adherence to ART, thus emphasizing that treatment of depression may also lead to better treatment of the HIV infection [1].

A recent meta-analysis of over 700 patients showed that treatment with AD pharmacotherapy was superior to placebo when assessing depressive symptoms with the Hamilton Depression Rating Scale (HAM-D) score [30]. This study supports that the pharmacotherapies we use to treat the general population will also be effective for PLWHA. Many classes of ADs have been studied in this patient population with similar results; thus, choosing therapy is based on tolerability and side effects. In general, SSRIs/SNRIs are first-line agents that tend to be tolerated well with few side effects, with sexual dysfunction being a common complaint. See also Chap. 17 for a detailed discussion on combining antiretrovirals and psychotropics. In addition, bupropion seems to be well tolerated and effective with more favorable side effect profiles [31]. Bupropion's activating characteristics may also help with the fatigue that may be experienced by individuals living with HIV and depression and has been shown to be effective regardless of HIV clinical staging [32].

In a survey performed by 62 HIV mental health clinicians, almost all of whom were psychiatrists, citalopram/escitalopram emerged as the preferred first-line treatment option for MDD. In the case of no response to treatment for 8 weeks, a switch to a serotonin/norepinephrine reuptake inhibitor (SNRI) AD was considered a first-line treatment by consensus, followed by bupropion or another SSRI as other appropriate first-line options. Respondents considered a switch to mirtazapine as a second-line option. Fluvoxamine, amitriptyline, and monoamine oxidase inhibitors (MAOIs) were clearly considered third-line treatments.

In the case of augmenting a partial response to the initial treatment, clinicians chose to add a second (non-SSRI) AD as a first-line strategy. Use of lithium, psychostimulants, second-generation antipsychotics, and thyroid hormone replacement were viewed by a majority as second-line options. The addition of buspirone was relegated to third-line status [33].

In addition to starting AD therapy, it is also important to assure close follow-up of patients for re-assessment and dose adjustments, since only about half of patients fully respond to initial treatment [34].

To be noted, there is also a theoretical risk of CYP modulation that could lead to altered drug levels as well as lead to dangerous adverse events such as serotonin syndrome: this is specific to persons with HIV since they are likely to be taking other medications such as antiretrovirals that may alter drug metabolism [31, 35]. The use of ADs in patients who are on ART should follow similar principles as in the case of older patients or patients with other systemic medical illnesses: start with lower doses and increase progressively to standard full-recommended dose, and use the least complicated possible dosing schedules [36].

In addition to managing the pharmacotherapy for the treatment of the patient's depressive symptoms, it is important to consider that many of the ART commonly used to treat HIV infection have their *own* neuropsychiatric side effects. The US CDC recommends screening for depression and suicidality for people with HIV who are taking a regimen that includes efavirenz. The same CDC guidelines include

Table 6.5 AD medications[a] commonly used in HIV patients [28, 29]

Class	Examples	Considerations
SSRIs	Fluoxetine, sertraline	Increased/decreased concentrations due to many CYP interactions (i.e., CYP2D6), especially cobicistat or ritonavir-containing regimens; QTc prolongation, SIADH, serotonin syndrome, bleeding etc.
SNRIs	Duloxetine, venlafaxine	CYP interactions as above; may help with fatigue/ neuropathic pain
Serotonin receptor modulators and partial SSRI	Trazodone, vilazodone	Potential interaction with protease inhibitors, priapism
Dopamine-NE	Buproprion	Potential interactions with protease inhibitors
Reuptake inhibitors		May lower the seizure threshold
TCAs	Amitriptyline, nortriptyline	Effective but often third line due to anticholinergic side effects, delirium
Noradrenergic/ specific serotonergic	Mirtazapine	Associated with dizziness/sedation, increased appetite, decreases nausea

Abbreviations: *SSRIs* selective serotonin reuptake inhibitors, *SNRIs* selective serotonin-norepinephrine reuptake inhibitors, *NE* norepinephrine, *TCAs* tricyclic antidepressants
[a]Please see Chap. 17

concern about an increased risk of suicidal ideation in patients taking dolutegravir. Moreover, integrase strand transfer inhibitors report depression as an adverse event [37]. In general, clinicians should discuss in advance the potential onset of depressive symptoms with their patients taking ART, to plan adequate management accordingly, if necessary (Table 6.5).

Psychotherapy

Alternatively, many patients and clinicians desire psychotherapy as a first-line treatment of MDD. In the American College of Physicians' 2016 clinical guidelines for the treatment of MDD, they found that most comparative studies showed no significant difference in outcomes between pharmacologic and non-pharmacologic therapy for mild/moderate cases, although this was studied in the general population [38]. More specifically for PLWHA, large meta-analyses have shown that cognitive behavioral therapy has improved depressive symptoms in PLWHA patients with both depression and anxiety. Additionally, a review of group psychotherapy has shown that it may be beneficial as a treatment for depression in PLWHA [39]. As seen in Table 6.6, there have been many studies demonstrating the effectiveness of multiple different psychotherapies. While cognitive behavioral therapy has been the most studied [40], the specific approach to psychotherapy may be left to the patient and clinician to choose.

Table 6.6 Evidence-based non-pharmacological therapeutic options for depressed HIV patients

Cognitive behavioral therapy
Group psychotherapy
Information and supportive psychotherapy [38]
Interpersonal therapy (including teletherapy) [39]

Notably, HIV often affects individuals in lower socioeconomic areas with poor access to healthcare. Typically, this may be a barrier to psychotherapy treatment, as the patient may be unable to travel to obtain ongoing psychotherapy from their mental health clinician or may have economic limitations to access. Although traditionally a significant barrier to time-intensive psychotherapy, recent data suggest that brief telehealth/teletherapy appointments may be able to bridge this gap and have meaningful reductions in patients' depressive symptoms [41]. As telehealth capabilities continue to improve, psychotherapy becomes an increasingly viable treatment option also for PLWHA. This increase in accessibility of care should encourage greater use of psychotherapy for the treatment of depression in PLWHA regardless of location. Please see Chap. 16 for further discussion on psychotherapy and other psychotherapeutic modalities.

Case Vignette 6.3
A 22-year-old man with known HIV-positive status presented to the clinic with complaints of fatigue for the previous 6 months. He stated that he just felt overly exhausted by the end of the day despite having no increase in activity level. He also found it exceedingly difficult to get out of bed each morning, which had a significant impact on his schoolwork as a college student. In addition to this, he was having trouble at work as he cannot concentrate as well as before. Despite these problems, he stated he "knows [he] should care about these problems" but feels "almost too tired to care." On further questioning, he also noted that he had feelings of guilt regarding his HIV-positive status and was anxious about how this would affect him long term for both his health and relationships. He also had noticed a decreased appetite that started about 6 months previously, but he was unsure if he lost any weight. His HIV diagnosis was made over a year previously, and the patient had not had any AIDS-defining illnesses. The patient was taking a combination pill of an integrase strand transfer inhibitor, a nucleoside reverse transcriptase inhibitor (NRTI), and a prodrug of another NRTI. He stated that he had been taking the medication as instructed without any side effects. In addition to his HIV medications, he also took a daily multivitamin and drank whey protein shakes following workouts, but had not been to the gym recently due to his symptoms. Recently, he saw his clinician managing his HIV and stated his CD4+ counts

were "good" and the rest of his laboratory work came back "normal." He had no additional past medical or surgical history. His family history was pertinent for a mother with anxiety disorder and a father with type 2 diabetes mellitus. He denied any suicidal ideation or homicidal ideation.

What is the patient's most likely diagnosis?

How would you initially manage this patient if you saw him in clinic?

Other Therapeutic Options

Pharmacotherapy and psychotherapy remain the most researched and supported therapies for MDD in HIV-positive individuals; however, additional therapeutic options are being studied. These therapies include a wide array of approaches and levels of invasiveness. A more invasive technique is the use of vagal nerve stimulators to modulate CNS function. While the traditional surgical approach to implant the stimulators is invasive, newer noninvasive transcutaneous VNS may be a future intervention for refractory depression in HIV patients, but future studies and official approval are still needed [42].

Electroconvulsive therapy (ECT) has been used to treat depressive disorders that are refractory to traditional therapies; however, response to ECT for PLWHA has not been widely studied. There are a series of case reports that show profound improvement of symptoms from a MADRS with a mean score of 36 before treatment to 6 following ECT [43]. Given the other medical risks for these immunocompromised patients, it is important to exclude other central nervous system pathology with neuroimaging and laboratory studies prior to considering ECT.

Another neuromodulation therapy being studied for its potential benefit in depressive disorders is transcranial magnetic stimulation (TMS). As a potentially effective therapy for treatment-resistant depressive disorder with fewer cognitive side effects than ECT, it is a promising new technology [44, 45]. There have not been major studies investigating TMS specifically in depressive disorder in PLWHA specifically, but it is an emerging area of interest. Additionally, there may be future uses of TMS for the treatment of neuropathic pain in PLWHA [46].

Ketamine, a dissociative anesthetic, has been demonstrated to be effective in the treatment of MDD and clinically useful in treatment-resistant MDD, including ECT-resistant MDD. While IV ketamine is studied in most trials, oral and intranasal ketamine have demonstrated significant antidepressant effects with good overall tolerability, making it a preferred treatment option, given its lower cost and ability to be administered outside the hospital setting [47]. Unfortunately, data on the efficacy of ketamine in PLWHA with MDD are not yet available in the literature. Future randomized-controlled trials, especially among treatment-resistant MDD in PLWHA, are warranted in this population.

Finally, there have been studies showing that improvements in lifestyle factors may be effective on depression scores as an adjunct to traditional treatment. Aerobic exercise, acupuncture, meditation/mindfulness, and massage therapy all have

multiple small sample size studies that both support and refute their ability to augment depression treatment in PLWHA [48]. These interventions have little or no side effects and thus are encouraged in addition to traditional pharmacotherapy or psychotherapy. Please see Chap. 16 for further discussion of psychotherapy and other psychotherapeutic modalities.

Conclusions

A timely and precise diagnostic framing of depressive disorders in HIV-positive patients is essential to provide appropriate management of the two comorbid conditions. Both psychiatrists and specialists in infectious diseases should be aware of the high rates of depression in their HIV-positive patients as well as of the many factors interfering with appropriate management. The study of MDD in HIV provides a specific model of the roles of inflammation and immune system activation in the etiology of depressive disorders in general and not only facilitates improvements in basic science knowledge on the topic but also may identify powerful and reliable tools for the clinician to be used in everyday practice. The evolution of HIV from a life-threatening, acute condition to a manageable, chronic illness presents an imperative for clinicians and persons with HIV to diagnose and treat depressive disorders.

Disclosure The opinions and assertions expressed herein are those of the author(s) and do not necessarily reflect the official policy or position of the Uniformed Services University or the Department of Defense.

Multiple-Choice Questions

1. Which ART medications have the CDC recommended for a careful assessment of suicidality?

   (a) Efavirenz, zidovudine, and ritonavir
   (b) Efavirenz and dolutegravir (correct)
   (c) Ritonavir and dolutegravir
   (d) Efavirenz and ritonavir
   (e) All integrase inhibitors

2. Among the following, which psychometric tool to screen persons with HIV for anxiety and depression may be considered to be more suitable?

   (a) Hospital Anxiety and Depression Scale (correct)
   (b) Beck Depression Inventory
   (c) Hamilton Depression Rating Scale
   (d) PHQ-9

(e) Montgomery-Asberg Depression Rating Scale

3. Which of the following are relevant risk factors for depressive disorders among HIV patients?

   (a) Male gender, practicing regular physical activity, high CD4 count
   (b) Low viral load, male gender, migrant status
   (c) Female gender, high viral load, family history (correct)
   (d) Heterosexuality, high socioeconomic status, female gender
   (e) Neuroticism, low CD4 count, long-term ongoing ART

4. Which of the following mechanisms are considered to be relevant in the pathogenesis of MDD in HIV-positive subjects?

   (a) De-sensitization of CD4 and CD8, stimulation of anti-inflammatory cytokines, altered thyroid metabolism
   (b) Reduced effectiveness of the gut barrier, activation of inflammatory mediators, direct stimulation of the CNS immune system by HIV (correct)
   (c) Hypo-activation of the HPA axis, increased permeability of the gut barrier, release of histamine
   (d) Increased effectiveness of the gut barrier, release of anti-inflammatory cytokines, high levels of BDNF mRNA
   (e) Low levels of BDNF mRNA, hypo-activation of the HPA axis, altered thyroid metabolism, poor response to antidepressant medications

5. According to the recent meta-analysis by Rezaei and colleagues (2019), what is the prevalence of MDD and other depressive disorders among PLWHA?

   (a) 55%
   (b) 20%
   (c) 15%
   (d) 30% (correct)
   (e) 75%

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Chapter 7
Trauma and Stressor-Associated Disorders

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Overview: What Is Trauma?

Trauma is an event, series of events, or, in some cases, a chronic set of circumstances which overwhelms an individual's ability to cope with the severity of the experience. It can be a single catastrophic event, such as a sexual assault; a series of related events, such as exposure to combat during wartime; or a long-term experience, such as growing up in an abusive household or spending time as a prisoner of war. As research has developed a better conception of the nature of trauma, the range of experiences understood to be potentially traumatic has expanded. For example, some research has demonstrated that certain medical illness experiences can be traumatic [1], including work that has suggested that a new HIV diagnosis can itself be traumatic [2].

Trauma can result in varied painful and debilitating emotional responses, depending on the circumstances and the individual, including a range of psychiatric sequelae. On the other hand, some individuals may demonstrate *resilience,* or the ability to withstand the damaging effects of trauma [3]. Others may even experience *post-traumatic growth,* or the development of new strengths and capacities as the result of surviving their traumatic experiences [4]. Although post-traumatic stress

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disorder (PTSD) is one of the most common and familiar conditions seen after a traumatic event, other psychiatric sequelae, including major depressive disorder and substance use disorders, can also emerge as sequelae to a traumatic event; these psychiatric conditions are often comorbid in traumatized patients.

Post-traumatic Stress Disorder PTSD is a disorder characterized by a set of emotional, cognitive, and sympathetic nervous system arousal symptoms that follow the experience of a traumatic event. The diagnostic criteria for PTSD are codified in the fifth edition of the *Diagnostic and Statistical Manual of Mental Disorders* (DSM-5,) (Table 7.1) [5], and the criteria have evolved over time since the diagnosis was first introduced in the 1970s. According to DSM-5 criteria, the precipitating trauma can be "exposure to actual or threatened death, serious injury, or sexual violence" and may be experienced directly as victim, witnessed, learned about as occurring to a loved one, or experienced more indirectly through learning details of a horrific event. Patients with PTSD experience symptoms in four areas: intrusion symptoms, re-experiencing symptoms, avoidance symptoms, and negative alterations in mood and cognition.

Intrusion symptoms represent involuntary experiences of reliving the trauma, which may include intense and distressing memories and nightmares. Other intrusion symptoms include intense distress or physiologic reactions to reminders of the trauma, as well as dissociative experiences called *flashbacks* wherein the individual feels as though they are reliving the experience.

In avoidance symptoms, the patient makes marked efforts to avoid thoughts, conversations, or external cues that serve as reminders of the trauma. Avoidance is believed to have a role in the ongoing pathophysiology of the disorder, as it serves to prevent the successful integration of traumatic events into the patient's overall emotional functioning.

Negative alterations in cognitions and mood refers to a broad set of symptoms that include amnesia for the traumatic event, exaggerated negative beliefs about the world, a distorted sense of blame of oneself or others for the event, and other persistent negative emotional reactions.

Finally, in *marked alterations in arousal and reactivity*, the individual may experience symptoms such as heightened irritability, reckless behavior, hypervigilance, an exaggerated startle response, problems with concentration, or insomnia.

To meet DSM-5 criteria for PTSD, the symptoms need to be present for more than a month and must cause significant distress or problems in functioning. There are different theories about how PTSD develops in traumatized individuals, although the disorder is far from completely understood. Some theories have emphasized abnormalities in the glucocorticoid and sympathetic stress responses, while others have focused on problems with processing of fear stimuli in the central nervous system [6]. A number of evidence-based manualized psychotherapies have been developed for PTSD, as well as recommended pharmacologic approaches [7].

Acute Versus Chronic Trauma When the concept of PTSD was first introduced, it was conceived as describing a set of pathological reactions to a specific discrete

Table 7.1 DSM-5 diagnostic criteria for post-traumatic stress disorder

Note: The following criteria apply to adults, adolescents, and children older than 6 years. For children 6 years and younger, see corresponding criteria below.
A. Exposure to actual or threatened death, serious injury, or sexual violence in one (or more) of the following ways:
1. Directly experiencing the traumatic event(s).
2. Witnessing, in person, the event(s) as it occurred to others.
3. Learning that the traumatic event(s) occurred to a close family member or close friend. In cases of actual or threatened death of a family member or friend, the event(s) must have been violent or accidental.
4. Experiencing repeated or extreme exposure to aversive details of the traumatic event(s) (e.g., first responders collecting human remains; police officers repeatedly exposed to details of child abuse).
Note: Criterion A4 does not apply to exposure through electronic media, television, movies, or pictures, unless this exposure is work related.
B. Presence of one (or more) of the following intrusion symptoms associated with the traumatic event(s), beginning after the traumatic event(s) occurred:
1. Recurrent, involuntary, and intrusive distressing memories of the traumatic event(s).
Note: In children older than 6 years, repetitive play may occur in which themes or aspects of the traumatic event(s) are expressed.
2. Recurrent distressing dreams in which the content and/or affect of the dream is related to the traumatic event(s).
Note: In children, there may be frightening dreams without recognizable content.
3. Dissociative reactions (e.g., flashbacks) in which the individual feels or acts as if the traumatic event(s) were recurring. (Such reactions may occur on a continuum, with the most extreme expression being a complete loss of awareness of present surroundings.)
Note: In children, trauma-specific reenactment may occur in play.
4. Intense or prolonged psychological distress at exposure to internal or external cues that symbolize or resemble an aspect of the traumatic event(s).
5. Marked physiological reactions to internal or external cues that symbolize or resemble an aspect of the traumatic event(s).
C. Persistent avoidance of stimuli associated with the traumatic event(s), beginning after the traumatic event(s) occurred, as evidenced by one or both of the following:
1. Avoidance of or efforts to avoid distressing memories, thoughts, or feelings about or closely associated with the traumatic event(s).
2. Avoidance of or efforts to avoid external reminders (people, places, conversations, activities, objects, situations) that arouse distressing memories, thoughts, or feelings about or closely associated with the traumatic event(s).
D. Negative alterations in cognitions and mood associated with the traumatic event(s), beginning or worsening after the traumatic event(s) occurred, as evidenced by two (or more) of the following:
1. Inability to remember an important aspect of the traumatic event(s) (typically due to dissociative amnesia and not to other factors such as head injury, alcohol, or drugs).
2. Persistent and exaggerated negative beliefs or expectations about oneself, others, or the world (e.g., "I am bad," "No one can be trusted," "The world is completely dangerous," "My whole nervous system is permanently ruined").
3. Persistent, distorted cognitions about the cause or consequences of the traumatic event(s) that lead the individual to blame himself/herself or others.

(continued)

Table 7.1 (continued)

4. Persistent negative emotional state (e.g., fear, horror, anger, guilt, or shame).
5. Markedly diminished interest or participation in significant activities.
6. Feelings of detachment or estrangement from others.
7. Persistent inability to experience positive emotions (e.g., inability to experience happiness, satisfaction, or loving feelings).
E. Marked alterations in arousal and reactivity associated with the traumatic event(s), beginning or worsening after the traumatic event(s) occurred, as evidenced by two (or more) of the following:
1. Irritable behavior and angry outbursts (with little or no provocation) typically expressed as verbal or physical aggression toward people or objects.
2. Reckless or self-destructive behavior.
3. Hypervigilance.
4. Exaggerated startle response.
5. Problems with concentration.
6. Sleep disturbance (e.g., difficulty falling or staying asleep or restless sleep).
F. Duration of the disturbance (Criteria B, C, D, and E) is more than 1 month.
G. The disturbance causes clinically significant distress or impairment in social, occupational, or other important areas of functioning.
H. The disturbance is not attributable to the physiological effects of a substance (e.g., medication, alcohol) or another medical condition.
Specify whether:
With dissociative symptoms: The individual's symptoms meet the criteria for post-traumatic stress disorder, and in addition, in response to the stressor, the individual experiences persistent or recurrent symptoms of either of the following:
1. *Depersonalization:* Persistent or recurrent experiences of feeling detached from, and as if one were an outside observer of, one's mental processes or body (e.g., feeling as though one were in a dream; feeling a sense of unreality of self or body or of time moving slowly).
2. *Derealization:* Persistent or recurrent experiences of unreality of surroundings (e.g., the world around the individual is experienced as unreal, dreamlike, distant, or distorted).
1. *Note:* To use this subtype, the dissociative symptoms must not be attributable to the physiological effects of a substance (e.g., blackouts, behavior during alcohol intoxication) or another medical condition (e.g., complex partial seizures).
Specify if:
With delayed expression: If the full diagnostic criteria are not met until at least 6 months after the event (although the onset and expression of some symptoms may be immediate).

violent event, as might be experienced by a soldier in wartime. However, subsequent research has found that much trauma is experienced in an ongoing fashion and includes trauma of multiple types. In the 1990s, the concept of complex PTSD (CPTSD) was introduced to describe the emotional effects on people who have experienced enduring forms of trauma and proposed more pervasive effects on personality and self-regulation than those seen in single-event associated PTSD [8].

CPTSD has been described in people who were exposed to prolonged traumas from which there was no escape, such as childhood sexual abuse, captivity in concentration camps, or severely abusive adult relationships. In contrast with

single-event PTSD, CPTSD emphasizes symptoms such as increased somatization, dissociation, affective dysregulation, pathological changes in identity, and changes in ability to relate to others. The concept of CPTSD is an important clinical consideration in working with people living with HIV/AIDS (PLWHA), as childhood sexual abuse is linked to HIV risk behavior later in life [9, 10], and PLWHA experience higher rates of multiple occurring stressors, including sexual assault, interpersonal violence, and higher rates of psychosocial instability, including housing and financial insecurity.

Trauma and Development When working with patients who have experienced trauma, it is important to view trauma through a developmental perspective. In short, the impact of trauma can be vastly different depending on when it occurs in a person's life cycle. The effect of early trauma can have several ramifications for survivors which are different from that experienced in later life.

First, children experiencing trauma have not acquired the internal coping resources that may provide resilience, allow for sufficient processing of the trauma, and allow for the potential for post-traumatic growth. Second, trauma in childhood often disrupts other developmental processes, complicating the acquisition of such developmental milestones as the capacity for attachment to others, cognitive and educational achievements, the development of a stable identity, and the ability to relate to peers [11]. These interruptions in development have secondary effects in adult life that go beyond the specific symptoms of PTSD.

Finally, childhood trauma appears to have neurobiological effects in development that have implications for adult emotional functioning. When working with survivors of childhood trauma, clinicians should consider the various developmental stages and related domains of functioning that may have been affected.

Association Between Trauma and HIV

Research has found that PLWHA (as a population) have experienced higher rates of trauma, including interpersonal violence, compared to the general population. 2864 HIV-infected adults in a survey who were receiving medical care and were enrolled in the HIV Costs and Service Utilization Study during 1996 and 1997 were asked about violence exposure since HIV diagnosis. Violence since diagnosis was reported by 20.5 percent of women, 11.5 percent of MSM, and 7.5 percent of men not reporting sex with men [12]. Of these, half of women and between one third and one half of men reported this violence to be related to their HIV diagnosis.

In addition, PLWHA also tend to report high rates of early trauma, especially childhood sexual abuse [10]. Cisgender women, transgender women, and men who have sex with men (MSM) consistently report high rates of prior sexual trauma [13–15]. In addition to higher rates of trauma, the prevalence of PTSD diagnosis among PLWHA is higher than in the general population. A recent meta-analysis of 38 studies found that, globally, PLWHA have a PTSD prevalence of 28%, greatly

exceeding that of the general population [16]. Another meta-analysis of women in the United States with HIV estimated a prevalence of 30 percent [17]. The fact that some studies point to early trauma in the lives of PLWHA suggests that this may represent a risk factor for the later acquisition of HIV and that post-traumatic psychiatric and behavioral sequelae, including PTSD, may play a role. DSM-5 includes reckless and self-destructive behaviors (RSDBs) as a core symptom of PTSD, and while not all individuals with PTSD engage in RSDBs, there may be an association between increased PTSD severity and increased RSDBs [18].

Increased frequency or number of different types of trauma is associated with more HIV risk behaviors, including younger age at sexual debut, more frequent unprotected sex, multiple sexual partners, sex work, illicit drug use, and excessive alcohol consumption [19, 20]. Rate of transmission may be increased in communities that suffer high rates of community violence, social discrimination, and socioeconomic hardship, all of which contribute to higher rates of traumatic stress, less access to care, or lower adherence to ART.

Types of Trauma Experienced by People Living with HIV/AIDS

The use of singular diagnostic categories such as PTSD, although useful for guiding research, clinical diagnosis, and treatment, can also obscure the myriad forms that trauma can take clinically, particularly in the lives of people living with or at risk for HIV. In addition, higher likelihood of trauma exposure is conferred by specific forms of socially marginalized status; for example, being homeless and having an LGBTQ identity both serve as risk factors for violence [21, 22]. Below are specific types of trauma that have been examined and may be relevant for patients in the HIV setting.

Sexual Assault Sexual assault may be linked to HIV by transmission that occurs during the assault itself, by creating psychological sequelae that place survivors at higher downstream risk of HIV exposure, and by shared psychological or socioeconomic factors that place individuals at higher risk for both sexual assault and HIV infection. In addition, sexual assault history increases mental health burden on PLWH. One study found that survivors of sexual assault living with HIV/AIDS were more likely to report symptoms of depression, anxiety, and borderline personality, and were more likely to engage in unprotected anal intercourse, than participants with HIV/AIDS without a sexual assault history [23].

Clinicians should be mindful that sexual assault history is common among PWLHA and that this may represent a risk factor for *both* HIV risk behaviors and compromised mental health. In addition, clinicians should be familiar with protocols for post-exposure prophylaxis (PEP) for HIV, in order to prescribe or make referrals for HIV-negative immediate sexual assault survivors.

Intimate Partner Violence There has been a clear link established between intimate partner violence (IPV) and the risk of HIV infection [24]. IPV is defined as threatened or actual physical or sexual violence, or the use of psychological coercion, by a current or former intimate partner. Women with a history of IPV are more likely to show risk factors for exposure to HIV, as well as other behavioral risk factors, and women living with HIV are significantly more likely to experience intimate partner violence. In addition, the disclosure of seropositivity to a partner may increase the likelihood of IPV toward the disclosing partner. Intimate relationships with abusive power dynamics may include forced sex and sex without the use of barrier protection, thus resulting in exposure to HIV or other STIs. Coercive relationships may also reduce the likelihood of accessing appropriate HIV testing or care.

Military Trauma Military veterans represent a population with high rates of trauma exposure and high rates of psychiatric sequelae of trauma including PTSD and substance use disorders [25]. Women veterans also experience high rates of sexual assault while serving in the military [26]. In addition, military veterans who have combat-related PTSD have been found to have high rates of other physical or sexual trauma history.

Many veterans have become infected with HIV via IV drug use [27], a practice which for some began during military service and, for some, may represent a substance use disorder that developed in the wake of combat trauma exposure. In spite of the 2010 repeal of the Clinton era "Don't Ask, Don't Tell" policy against disclosing lesbian, gay, or bisexual orientation while in US military service, anti-LGBT stigma remains significant in military communities and may create further barriers to HIV treatment or care. The Department of Veterans Affairs provides HIV care for any veterans who qualify for medical care within the VA system.

Migration Trauma Increases in mass migration in recent years have highlighted the traumas that are and can be incurred during migration experiences, particularly when movement occurs in the setting of socioeconomic instability and/or human rights violations. Studies of migrants have suggested relationships between migration-related traumas and HIV exposure [28, 29]. Pre-migration trauma refers to events that precede migration, such as assault or torture in the country of origin. Post-migration traumas may relate to poor working or housing conditions and vulnerability to assault or exploitation.

Intergenerational Trauma Intergenerational trauma is the theory that the psychological effects of trauma may be transmitted from one generation to the next. The concept has been used to explain physical and mental health vulnerabilities experienced by specific discriminated-against social groups as partly located in traumatic events experienced by prior generations. The idea of intergenerational trauma has been applied specifically to understand the health effects of trauma and stress in African-American [30], Native American [31], and Jewish families who have survived the Holocaust [32]. The concept of intergenerational trauma may be useful for

individuals seen in the HIV care setting whose personal trauma histories are embedded in a larger context of family and intergenerational traumatic stressors.

Impact of Traumatic Stress on HIV Outcomes

Trauma and Adherence

Antiretroviral adherence serves as the cornerstone for health maintenance in PLWH, as well as for population-level strategies for preventing HIV infection. As such, adherence has been a focus in HIV research, which has attempted to identify structural and individual-level factors that impede consistent use of antiretrovirals. Within this work, numerous studies have found trauma, including PTSD, to be an important factor driving nonadherence [33].

Traumatic and stressful experiences have been found to increase rates of nonadherence and virologic failure [34]. While some work has suggested that avoidance and problems with coping may undergird these relationships, there is some evidence that dissociation plays a role in antiretroviral adherence difficulties in traumatized individuals with HIV [35]. Other work has suggested that the overall life contexts of individuals exposed to trauma, including problems with substance use and unstable housing, play a role in problems with adherence and treatment retention. Reducing the negative effects of trauma on antiretroviral adherence has been identified as an area for developing behavioral interventions focusing on symptoms reduction and improved coping [36].

Trauma and HIV Medical Outcomes

The higher rates of trauma seen among patients with HIV appear to lead to worse medical outcomes. Higher lifetime trauma exposure has been linked to all-cause mortality [37], and severe trauma has been associated with worse quality of life in PLWH [38]. In addition, trauma has been found to be associated with lower CD4 count and higher likelihood of progression to AIDS, as well as faster development of an opportunistic infection or AIDS-related death after starting ART [39]. PLWHA with PTSD have been found to have higher viral loads, lower CD4 counts [37], or increased rates of infection or reactivation of latent infection despite relatively high CD4 counts than PLWHA without PTSD [38].

It is likely that these deleterious effects on medical outcomes are explained in large part by the negative impact of trauma and PTSD on medication adherence as described above. However, several proposed biological mechanisms have also been proposed to explain these links. Acute stress may increase sympathetic activation, and autonomic arousal has been shown to be associated with increased rates of

retroviral replication [40]. In addition, HIV infection is associated with chronic increases in circulating cytokines, the disruption of which may transiently increase viral replication rates [41].

Practical Guidelines for Trauma-Informed Care

Trauma-informed care (TIC) is a systems-level approach to trauma which emphasizes critical role of the context in which trauma is addressed and services for trauma survivors are delivered. The TIC model arose from growing awareness that patient-level clinical interventions are not enough to achieve optimal outcomes for trauma survivors without incorporating key trauma principles into the organizational culture [42].

Adopting principles of TIC and formally integrating it into daily clinical and administrative flow of HIV clinics should be a collaborative effort that engages clinic personnel at all levels, from front desk staff to nurses, physicians, other clinicians, and administration. Psychiatrists consulting in HIV clinics can be impactful at multiple levels of this process. This may include raising awareness of high prevalence of trauma among PLHWA and its detrimental impact on health behaviors and HIV clinical outcomes. It may be helpful to introduce the concept of trauma re-enactment through relationships and day-to-day interactions with the clinic personnel (e.g., clinical space and routine clinical practices can potentially trigger re-traumatization or, if done right, provide sense of safety). Psychiatrists may have a role in validating the emotional toll that dealing with trauma survivors can have on the clinic personnel (including vicarious traumatization and emphasizing importance of self-care). Psychiatrists can further take leadership in initiating implementation of specific protocols and procedures based on TIC principles.

Table 7.2 summarizes the *SAMHSA's Concept of Trauma and Guidance for a Trauma-Informed Approach.* Rather than prescribing specific practices and procedures, this document outlines four key premises on which a trauma-informed system is built, six key principles of TIC, and ten domains of organizational change for implementation of TIC. Full document is available at https://www.integration.samhsa.gov/clinical-practice/trauma-informed. The UCSF Helen Diller Medical Center's Women's HIV Program is an example of integrating TIC model into multidisciplinary clinic serving PLWHA [43].

SAMHSA's National Center for Trauma-Informed Care recommends the following four "Rs" for a trauma-informed approach to treatment [42]:

1. *Realizes* the widespread impact of trauma and understands potential paths for recovery
2. *Recognizes* the signs and symptoms of trauma in clients, families, staff, and others involved with the system
3. *Responds* by fully integrating knowledge about trauma into policies, procedures, and practices

Table 7.2 Summary of SAMHSA's Guidance for Trauma-Informed Care

4 Key Premises of TIC (4 Rs)	6 Key Principles	10 Implementation Domains
1. ***R**ealizing* the widespread impact of trauma and understanding potential paths for recovery	1. *Safety:* the physical space is safe; interpersonal interactions promote safety; safety (as understood by recipients of care) is a high priority.	*1. Governance and Leadership:* the leadership supports and invests in implementing and sustaining TIC; there is an identified point of responsibility.
2. ***R**ecognizing* the signs and symptoms of trauma in individuals involved with the system (e.g., patients, families, staff, clinicians)	2. *Trustworthiness and Transparency:* operational decisions are conducted in a manner that builds and maintains trust among those involved (e.g., patients, clinicians, staff)	2. *Policy:* written policies and procedures establishing TIC are fully integrated into the organizational mission.
3.***R**esponding* by fully integrating knowledge about trauma into policies, procedures, and practices	3. *Peer Support:* promoting mutual self-help among trauma survivors to establish safety and facilitate recovery and healing.	3. *Physical Environment:* promotes safety and collaboration.
4. ***R**esisting* re-traumatization by actively identifying ways in which the system (inadvertently) re-traumatizes individuals	4. *Collaboration and Mutuality:* recognizing that everyone involved, from clerical staff to professionals and administrators, has a role in the TIC model.	4. *Engagement and Involvement:* trauma survivors, patients, and their families are involved in all levels of organizational functioning.
	5. *Empowerment, Voice, and Choice:* understanding the power differentials while recognizing that experience of trauma may be a unifying force among the consumers and providers of care; operations, workforce development, and services are designed to foster development of staff and patients alike; patient input is solicited in shared decision-making.	5. *Cross-sector Collaboration:* understanding how awareness of trauma can affect achievement of an organization's mission plays a key role in building collaborations.
	6. *Cultural, Historical, and Gender Issues:* policies, protocols, and procedures are responsive to the needs of those served; recognizing and addressing historical trauma	6. *Screening, Assessment, and Treatment Services* are acceptable, effective, and available for individuals and families seeking services.
		7. *Training and Workforce Development: trauma-informed principles are incorporated into hiring, supervision, and staff evaluation.*

Table 7.2 (continued)

4 Key Premises of TIC (4 Rs)	6 Key Principles	10 Implementation Domains
		8. *Progress Monitoring and Quality Assurance* of effective implementation of TIC principles are ongoing.
		9. *Financing* is available to support trauma- and TIC-related resources.
		10. *Evaluation:* measures and program evaluation tools reflect understanding of trauma and TIC principles

4. *Resists* re-traumatization

Clinicians can begin to implement these recommendations in clinical practice and examine ways to more systematically educate and train residents and fellows to bring these practices to their care settings. Clinicians can advocate for system-wide policies, procedures, and practices that would prevent further re-traumatization of HIV-positive patients in outpatient and medical settings. At a practical level, recognizing that many persons in the health professions also have a history of trauma and need support may also further these practices as standard of care.

Conclusions

In this chapter, we have described associations of trauma and post-trauma conditions, most importantly post-traumatic stress disorder with nonadherence to risk reduction and medical care in persons with HIV. Adherence to medical care in all severe and complex medical illnesses has significant implications for clinicians, patients, families, and caregivers. Nonadherence results in pain, suffering, complications, and increased morbidity and mortality, as well as frustration for caregivers. In persons with HIV, nonadherence to risk reduction and medical care also has serious public health implications. HIV clinicians frequently encounter individuals who are nonadherent to both prevention and care interventions.

Some nonadherent patients have a history of trauma and may have PTSD and/or other psychiatric disorders. Childhood (and/or later) trauma leading to post-traumatic stress disorder is associated with multifactorial reasons for nonadherence. These include difficulty with trust, low self-esteem, difficulty caring for the self and body, high levels of anxiety and depression, and a sense of a foreshortened future. For HIV clinicians to help their patients to adhere to care, they need to understand

how to assess for trauma and its sequelae. Understanding how to evaluate and care for persons with HIV, trauma, and PTSD may enable the clinician to mitigate suffering, improve adherence to risk reduction and HIV care, and decrease morbidity and mortality in persons with HIV.

Multiple-Choice Questions

1. Which of the following overshadowing and associated psychiatric disorders best explain why early childhood trauma-induced PTSD is difficult to diagnose?

   (a) Borderline personality disorder
   (b) Depressive disorder
   (c) Schizophrenia
   (d) Attention deficit disorder
   Correct answer: (b)

2. Characteristic clinically observable signs and symptoms of posttraumatic stress disorder can include all of the following except:

   (a) Jumpiness (exaggerated startle)
   (b) Cognitive impairment
   (c) Fearfulness
   (d) Watching the doorway or glancing around frequently
   Correct answer: (b)

3. On first clinician encounter, persons with HIV who have experienced trauma *are likely NOT to do which one of the following*:

   (a) Report amnesia
   (b) Demonstrate repression of horrific events
   (c) Refuse to discuss the traumatic event
   (d) Demonstrate difficulty in developing trusting relationships with their clinicians
   Correct answer: (d)

4. The 4 Rs of trauma-informed care include which one of the following:

   (a) Regulating
   (b) Resilience
   (c) Responding
   (d) Resonating
   Correct answer: (c)

5. Ideally, an initial psychiatric assessment of a person with HIV who reports a history of traumatic life events should include:

   (a) Assessment of mood or anxiety-related complaints
   (b) Assessment of cognitive function
   (c) Assessment of substance abuse history, current or prior
   (d) Assessment for psychotic symptoms
   (e) All of the above
   Correct answer: (e)

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Chapter 8
Bipolar Disorders

Antoine Douaihy, Grace Kang, and Tianyi Zhang

Introduction

Psychiatric disorders including major depressive disorder and bipolar disorder are common in patients with HIV illness. Patients with co-occurring bipolar disorder and HIV face significant challenges in the process of accessing and adhering to care in order to maintain optimal health. Some of the challenges include encountering stigma, engaging in risky behaviors such as using substances to self-medicate, and struggling with multiple psychosocial stressors.

Prevalence and Risk Factors

There is a higher prevalence of bipolar disorder (BD) in people living with HIV than in the general population. A report from the National Epidemiologic Survey on Alcohol and Related Disorders found that the 12-month prevalence of bipolar disorder among respondents with HIV infection was 10.8%, compared to 3.7% among people who are HIV-negative [1]. In the NIMH Multisite Acute HIV Infection Study, approximately 53% of persons with HIV had a lifetime history of major depressive disorder or BD [2]. Another study done in Brazil showed that the

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prevalence of BD type I was 5.6% in persons with HIV, nearly six times higher than in the general US population [3].

The risk of HIV transmission for persons with comorbid BD and HIV infection is elevated; persons with both illnesses were more likely to report unprotected intercourse with HIV-negative partners *and* less likely to adhere to antiretroviral therapy (ART) [4]. Additionally, the most common psychiatric multimorbidity in persons with HIV infection and bipolar disorder is substance use disorder (61.5%), itself an independent risk factor for HIV transmission [3]. With the spread of HIV infection in persons with co-occurring psychiatric and substance disorders, the "triple diagnosis" of HIV and psychiatric and substance use disorders has emerged as a clinically challenging condition for primary care physicians, addiction medicine specialists, psychiatrists, and other physicians. Existing data support the high prevalence of triple diagnosis in patients seen in different treatment settings, e.g., inpatient and ambulatory general psychiatry, addiction psychiatry, and HIV medicine [5].

Assessment and Diagnosis

The factors causing difficulties in the diagnosis of bipolar disorder in people living with HIV include poor recollection of prior hypomanic or manic episodes and more frequent depressive episodes. In addition, in persons with BD, HIV prevention interventions to reduce HIV transmission risk behaviors are crucial [4]. Furthermore, manic episodes in people living with HIV may be due to other causes such as metabolic disturbances, systemic infections, neurological and endocrine disorders, illicit substances, and prescribed medications. A full comprehensive workup is necessary to distinguish between bipolar disorder and mania secondary to HIV or other medical comorbidities. Mania can occur in people living with HIV as an entity known as AIDS mania or secondary mania. AIDS mania is uniquely associated with late-stage HIV infection, and it is characterized by typical mania and additional cognitive impairment in the setting of a lack of previous personal or family history of bipolar illness. The clinical picture of AIDS mania is more of irritability than euphoria, which is more associated with idiopathic bipolar mania, and more of a chronic course. The prevalence of AIDS mania has greatly diminished over the past 2 decades due to the advent of effective ART; however, AIDS mania is still a risk in persons who have poor access to care and are nonadherent to ART [6].

Differential Diagnosis

New onset of mania or hypomania in persons living with HIV should prompt consideration and workup of systemic medical etiologies. Neuropsychiatric complications of HIV infection can closely resemble primary psychiatric illness. Mania secondary to central nervous system (CNS)-related manifestations of HIV typically

presents late in the course of HIV infection. As mania secondary to HIV may herald the progression to late-stage HIV infection, it is crucial to distinguish this from separately co-occurring bipolar disorder. Individuals with mania secondary to HIV are less likely to have personal or family history of bipolar or depressive disorders and more likely to demonstrate cognitive slowing and impairment in comparison to individuals with comorbid HIV and BD [7]. Other systemic medical etiologies for mania should be considered. There are case reports describing manic episodes due to a variety of systemic diseases including thyroid disease, Cushing's syndrome, traumatic brain injury, multiple sclerosis, brain tumors, and systemic lupus erythematosus [8]. Certain substances and medications, including the antiretroviral medication zidovudine, which is significantly less frequently prescribed in recent years, are also associated with reports of mania [9].

Case Vignette 8.1

Mr. A was a 37-year-old man brought to the emergency room by his partner, who was worried about his recent unusual behaviors. Mr. A dismissed his partner's concerns, saying that he felt "fantastic." He reported that he had returned home yesterday after completing a weeklong road trip across several states to go to concerts of various famous musicians. He said this trip was motivated by his belief that the musicians were in love with him because God had given him a blessing of heightened desirability. During his trip, he spent $3000 on concert memorabilia and slept about 2 hours every night on average due to feeling too energetic for sleep.

He denied any past psychiatric history including past psychiatric hospitalizations or holds prior episodes of depression and, before these past 2 weeks, any prior history of manic symptoms.

He denied any family history of psychiatric illness. He endorsed a prior history of methamphetamine use, including intravenous use, which began 4 years previously and ended 8 months before presentation. He denied any known past medical history. He did not have a primary medical physician and could not recall the date of his last physical examination. All the above history was corroborated by his partner, who tearfully added that he had never seen Mr. A behave this way before during their 14-year-long relationship.

Mr. A's mental status exam was notable for pressured speech, expansive affect, and flight of ideas. He did not demonstrate any perceptual disturbances. An MMSE yielded a score of 21 out of 30, which was abnormally low for his college-level education and consistent with mild cognitive impairment. He demonstrated high distractibility during testing and poor attention, including his being unable to spell "WORLD" backward or to complete serial sevens subtractions. His poor attention made the remainder of his testing unreliable for interpretation.

His vital signs were within normal limits. His physical exam was notable for cervical and axillary lymphadenopathy and was otherwise remarkable. Laboratory testing was notable for a positive anti-HIV-1 antibody test. His CD4 count and viral load were still pending. His CBC, electrolytes, and liver enzymes were normal. The remainder of his diagnostic workup including RPR, TSH, and vitamin B12 were pending.

The differential for this case of new-onset mania in an individual with HIV includes bipolar disorder and secondary mania. Although mania secondary to HIV infection became less common as the result of advances in diagnosis and treatment of HIV, it may still occur, particularly in individuals with lack of access to care and/or nonadherence to ART. The features of this patient's presentation that would raise suspicion for mania secondary to HIV include no personal history of a mood disorder, no family psychiatric history of bipolar disorder, and older age of onset of first episode mania, which is atypical for bipolar disorder.

Bipolar Disorder and Adherence to ART

An estimated 40% of patients with BD do not adhere to their psychiatric medications (e.g., mood stabilizers) as prescribed; one-third take less than 30% of their mood stabilizer doses [10]. Individuals with BD who are nonadherent to their psychiatric medications are at a greater risk for relapse and recurrence of manic and depressive episodes and psychiatric hospitalization [10, 11]. Previous research suggesting poor adherence in persons living with HIV and BD has been sparse. In one of the studies to use electronic tracking of ART medication in a group of PLWH with serious psychiatric illness, adherence varied widely, between 50% and 90% [12]. To our knowledge, just one study focused exclusively on people living with HIV and bipolar disorder [13]. This study reviewed medication adherence among 44 people living with HIV with comorbid BD as compared to 33 demographically and medically comparable people living with HIV without BD. Classification of medication adherent (≥90%) or nonadherent (<90%) based on proportion of correctly taken doses over 30 days was determined using electronic medication monitoring devices. The study showed that people living with both HIV and bipolar disorder were significantly less likely to be ART adherent (47.7%) as compared to people living with HIV without BD (90.9%). Within the people living with HIV and BD group, mean psychiatric medication adherence was significantly worse than ART medication adherence, although there was a significant correlation between ART and psychiatric adherence levels. Importantly, 30-day ART adherence was associated with plasma virologic response among people living with HIV and BD. Monitoring and optimizing adherence to *both* ART and psychotropic medications in people living with HIV and BD is warranted [13].

Pharmacological, Psychosocial Treatment, and Mobile Health Approaches

Pharmacological Interventions

Pharmacological treatment for bipolar disorder in persons with HIV is similar to treating bipolar disorder in the general population, but there are very few studies specifically focusing on the efficacy of these treatments for this population. As for the general population, mood stabilizers and antipsychotic medications are regularly used for acute mania in persons with HIV. Mood stabilizers, such as lithium and valproic acid, are effective but require extra caution due to possible drug-drug interactions with antiretroviral therapy and their own specific toxicities. Lithium should be titrated carefully, and trough levels should be checked every 4 days during dose escalation and adjustment due to its narrow therapeutic window. A case series reviewing treatment with lithium for bipolar disorder in persons living with HIV showed that 8 out of 10 patients developed symptoms of lithium toxicity [14]. Lithium use in patients with secondary mania can lead to potential complications such as delirium and dehydration because of unpredictable fluctuations in lithium level and HIV-associated nephropathy (HIVAN). Valproic acid also requires close monitoring due to its potential risk of hepatotoxicity, hyperammonemia, and pancreatitis [15]. This medication should be avoided in patients with preexisting severe liver or pancreatic dysfunction or history of hyperammonemia. Antipsychotic medications are very effective in treating acute mania in persons with HIV and can show quicker results than mood stabilizers but carry the potential of extrapyramidal side effects [16]. Persons with HIV are more vulnerable to the anticholinergic and extrapyramidal side effects of antipsychotic medications. Care must be taken when prescribing mood stabilizers in the context of ART. It is essential to monitor for untoward side effects, as well as to examine possible drug-drug interactions and potential toxicities. Controlled studies of mood-stabilizing agents in HIV illness are needed. Please see Chap. 17 for further details on psychopharmacologic interventions.

Psychosocial Interventions

A review of PubMed yielded no studies on psychosocial interventions specific to individuals living with HIV and bipolar disorder or HIV and mania secondary to any other cause. In 2018, van Luenen et al. published a meta-analysis reviewing the effectiveness of psychosocial treatments for people living with HIV and psychiatric disorders such as support interventions (e.g., peer support), interpersonal therapy, family interventions, stress management interventions, meditation and mindfulness interventions, cognitive behavioral therapy, motivational interviewing, and psychoeducation. None of the included studies measured outcomes prevention of mania or

depression in people with co-occurring HIV and bipolar disorder in particular. The included studies mainly focused on outcomes of depression, anxiety, and overall well-being and found a small positive benefit on these measures [17]. The outcomes of those studies might not be transferable to people living with HIV and bipolar disorder per se, as psychosocial interventions in practice serve a different and more adjunctive role in the treatment of bipolar disorders, as opposed to the treatment of anxiety or depression in which they are often featured in a first-line role. Further research is warranted to identify and evaluate psychosocial interventions that can be of benefit for people with co-occurring HIV and bipolar disorder.

Mobile health (mHealth)-based strategies represent a promising new healthcare intervention direction to address HIV prevention and medication adherence [18]. A recent 30-day randomized controlled trial of a two-way text messaging system, iTAB, compared to an active comparison (CTRL) to improve antiretroviral (ARV) and psychotropic (PSY) adherence and dose timing was conducted [19]. Both groups received medication adherence psychoeducation and daily texts assessing mood. The iTAB group additionally received personalized medication reminder texts. Participants responded to over 90% of the mood and adherence text messages. Mean adherence was high and comparable between groups for both ARV and PSY medications. However, iTAB participants took ARVs significantly closer to their intended dosing time than CTRL participants. This promising study suggested that daily contact via text messaging is feasible even in vulnerable populations such as people living with HIV and BD and that text messaging in conjunction with psychoeducation improves ARV dose timing in people living with HIV and BD who are at high risk for nonadherence to life-saving medications. Larger-scale interventions are needed to evaluate the long-term efficacy of such interventions.

Case Vignette 8.2

Mr. H. was a 47-year-old man who started using various substances at an early age as a way of escaping many stressors, including traumatic experiences, and more recently losing his job and experiencing relationship issues. He was diagnosed with HIV at age 30 after presenting to the hospital with pneumonia. Since his initial presentation, he continued using various substances, primarily alcohol and crack cocaine while cycling in and out of residential treatment programs. He was on a medication regimen of ART, divalproex sodium, and mirtazapine, but he reported intermittent adherence to all these medications. He reported that he significantly decreased his substance use since the birth of his son a few years previously. He described a history of hypomanic episodes, but mostly depressive episodes linked to periods of increased substance use. Mr. H. met the criteria for a "triple diagnosis" of bipolar disorder type II, cocaine/alcohol use disorders, and HIV illness. He reported limited social support system because of his substance use and had been struggling to find employment because of his past legal problems.

Components of an integrated approach to working with Mr. H. include establishing a multidisciplinary care team, a person-centered collaborative approach incorporating psychoeducation about triple diagnosis, pharmacological and psychosocial treatments addressing his substance use and bipolar disorder, HIV prevention interventions, and providing support and coaching for ART and psychotropic medications. An ideal way to optimize outcomes for Mr. H. would be a comprehensive collaborative program of "one-stop shopping" in which he could receive all services in one treatment program such as a primary care HIV clinic. A program with embedded psychiatric and other mental health services would be ideal to optimize outcomes. If this is not possible, coordination of care among clinicians is essential to ensure appropriate delivery of services. Encouraging involvement in mutual support groups such as 12-step recovery programs could help Mr. H. establish substance use recovery and a social support system. Case management and patient navigation can assist with scheduling and adherence to appointments, transportation, and vocational resources.

Conclusion and Future Directions

Individuals with bipolar disorder are disproportionately affected by HIV compared to their counterparts with no history of psychiatric disorder. Improved recognition of the high prevalence of the co-occurrence of HIV and bipolar disorder may prompt clinicians to counsel their patients with bipolar disorder about HIV testing and screen them for high-risk behaviors including injection drug use and risky sexual behaviors such as condom-less sex. All clinicians working in primary care or HIV care settings need to be familiar with the diagnostic criteria for bipolar disorder, be able to screen routinely for signs and symptoms of bipolar disorder, and coordinate care with mental health practitioners. This approach facilitates early engagement in treatment and enhanced retention in medical and mental healthcare and a better integration of prevention efforts to reduce HIV risky behaviors. When not recognized early and aggressively treated, both HIV infection and bipolar disorder are associated with high levels of morbidity and mortality.

Significant pharmacologic advances have been achieved over the past couple of decades, including the development of antiretrovirals and newer mood stabilizers as treatments for HIV and bipolar disorder, respectively. These treatments improve quality of life and daily functioning, reduce symptoms, decrease hospitalizations and mortality, and, in the case of antiretrovirals, reduce transmission of HIV. These life-saving treatments require high levels of adherence to be effective. Of primary concern is the effect of co-occurring bipolar disorder and HIV on both psychotropic and antiretroviral medication adherence.

Healthcare practitioners should consistently incorporate interventions to optimize patients' adherence to antiretrovirals and psychotropic medications.

Additionally, there is no quality research on the use of psychosocial interventions in this population. Further research is necessary to examine the interface between HIV infection and bipolar disorder to inform pharmacological and psychosocial interventions, aimed at reducing risky behaviors, optimizing adherence to medications, increasing engagement and retention in care, and thereby reducing improving quality of life in people living with HIV.

Multiple-Choice Questions

1. How does the prevalence of bipolar disorder in persons living with HIV compare with that of persons who do not have HIV?

   A. Higher
   B. Equal
   C. Slightly lower
   D. Significantly lower

   Answer: A

2. Which is *not* considered an obstacle for diagnosing bipolar disorder in people living with HIV?

   A. Frequent hospitalizations
   B. Poor recollection of prior manic episodes
   C. More frequent depressive episodes
   D. Unknown diagnosis of HIV

   Answer: A

3. Elevated rates of HIV transmission are reported among people with bipolar disorder as compared to that of the general population. Bipolar disorder has been linked to several conditions and behaviors that could increase an individual's risk of HIV transmission. Which of the following describes the risk factors experienced by people with bipolar disorder, relative to the general population?

   A. Similar prevalence of substance use
   B. Higher rates of sexual intercourse without a barrier method of protection
   C. Lower prevalence of HIV testing
   D. Similar rates of medication nonadherence

   Answer: B

4. A small number of individuals living with HIV/AIDS develop mania secondary to their underlying medical illness. Which of the following features is more commonly found in people with secondary mania than in people with bipolar disorder?

   A. Older age of onset
   B. Family history of bipolar disorder
   C. Personal history of depressive disorder

D. Normal-range cognitive testing

Answer: A

5. Which component is not characteristic of an integrated treatment approach for patients with HIV and bipolar disorder?

A. Psychoeducation
B. Motivational strategies
C. Interventions addressing adherence to medications
D. Medical and psychiatric services provided in separate settings

Answer: D

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Chapter 9
Anxiety Disorders

Jordi Blanch, Tianyi Zhang, Steven C. Beall, Steven J. Gibson, and Grace Kang

Introduction

In this chapter, we review significant practical data about the prevalence, etiology, and diagnosis of anxiety in people living with HIV, as well as the relation between anxiety and the outcomes of HIV infection. We also provide an update of the most relevant information about comorbid psychiatric disorders and psychopharmacological and psychotherapeutic interventions for anxiety symptoms and anxiety disorders in people living with HIV.

Symptoms of anxiety may be a normal and expected reaction to stress. If this reaction includes excessive anxiety and worry and is disproportionate to the stressor and/or has a major impact on a person's function, it may be diagnosed as an anxiety disorder as defined in DSM-5 (1). Anxiety disorders have standardized categories that fulfill diagnostic criteria according to both the International Classification of Diseases, Clinical Modification (ICD-10-CM) and DSM-5. Anxiety is characterized by cognitive emotional symptoms such as excessive worry, fear, irritability, and physical symptoms such as fatigue, dyspnea, heart palpitations, and muscle tension. The anxiety disorders appear in a variety of clinical forms such as generalized anxiety disorder, panic disorder, and specific phobias [1].

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Since HIV infection has become a chronic illness for persons with access to HIV care and antiretroviral therapy, many persons with HIV infection and longer life expectancy are confronted with new challenges. Persons with HIV and access to care have to confront a long course of chronic illness that includes ongoing medical visits, diagnostic tests, medication intake, side effects, HIV stigma, and HIV serostatus disclosure, all of which may produce anxiety symptoms or trigger anxiety disorders. On the other hand, anxiety can also have an impact on the processes related to the HIV infection, such as adherence to treatment, inflammation, immune status, and systemic medical and psychiatric comorbidities. Clinicians caring for people with HIV need to become familiar with the prevalence, characteristics, diagnosis, differential diagnosis, impact, and the treatment of anxiety symptoms and anxiety disorders.

Epidemiology

Prevalence

As with the study of other psychiatric disorders in people with HIV, the prevalence rates of anxiety disorders and symptoms of anxiety depend on the methodology, characteristics of the population, and selection of diagnostic scales, tool, or other instruments used. In a critical review by Brandt et al. [2], the authors observed that none of the studies had employed an empirically derived representative sample, and only a few had used a control group. Of all the studies that used a diagnostic interview instead of questionnaire-based assessments, prevalence rates for anxiety disorders were notably higher among PLWHA than the general population. The median prevalence of anxiety disorders among PLWHA in the reviewed studies where diagnostic interview were employed was about 23%. When examining specific anxiety disorders, panic disorder, generalized anxiety disorder (GAD), and social anxiety disorder, but not specific phobia, showed higher rates of prevalence in persons with HIV compared to the general population [2].

Diagnosis

Persons living with HIV constitute a unique population of persons who may experience extreme negative social stigma and discrimination related to HIV that puts them at an increased risk of both generalized anxiety disorder and panic disorder as well as other psychiatric disorders [3]. Although anxiety risk factors may be increased in people living with HIV/AIDS, the diagnosis of anxiety disorders, specifically, generalized anxiety disorder (GAD), is made using the same criteria as in the general population (see Table 9.1).

Table 9.1 Criteria for diagnosis of generalized anxiety disorder. According to the DSM-5 [1]

(A) Excessive anxiety for more days but not over 6 months
(B) Difficulty controlling worry
(C) Associated with at least three of these symptoms (restlessness, fatigue, difficulty concentrating, irritability, muscle tension, sleep disturbances)
(D) Significant life impairment
(E) Not attributable to another substance or medical condition
(F) Not being better explained by another medical disorder

Table 9.2 Autonomic symptoms of anxiety

Heart palpitations or pounding
Sweating
Trembling or shaking
Sensation of shortness of breath
Chest pain or discomfort
Nausea or abdominal distress
Feeling dizzy or light-headed
Hot flushes
Muscle tension
Hyperventilation
Sleep disturbance
Fatigue
Increased perspiration
Cold sweats

It is important to note that patients with anxiety disorders and HIV are at a higher risk for other systemic medical disorders that may present with similar symptoms; therefore, it is crucial to rule out other diagnoses as mentioned in criterion E before making the diagnosis. Although we discuss the diagnosis of anxiety disorders in this section, it is important to keep in mind that these disorders do not exist in a vacuum separate from one another. Of HIV-positive individuals with anxiety disorders, about 50% have concomitant depressive or substance use disorders [4]. Identification and treatment of multimorbid psychiatric disorders are crucial for the improvement of outcomes.

Clinical Features

Persons living with HIV and AIDS may have a broad spectrum of clinical presentations and may complain of somatic and autonomic symptoms [5]. See Table 9.2 for the somatic manifestations of symptoms of anxiety disorders. It is important to recognize that patients are at risk for infection, malignancy, and other health emergencies, given their HIV status. With this in mind, physicians and other clinicians

cannot assume that the presenting symptoms are purely due to the somatic manifestations of an anxiety disorder, but must first rule out other medical causes that may be life-threatening, such as pneumonia, sepsis, or anemia.

Differential Diagnosis and Diagnostic Pitfalls

Persons with HIV and AIDS have multimorbid diagnoses and are at a higher risk for health complications than immunocompetent individuals are, so it is important to keep a broad differential (Table 9.3) when you are evaluating a patient with HIV.

Tools for Diagnosis and Assessment

In order to diagnose an HIV-positive patient with a generalized anxiety disorder, the patient must meet the aforementioned DSM-5 criteria. Additionally, the diagnosis is supported by evaluating the patient for risk factors such as caffeine use, poor sleep hygiene, substance abuse, and other comorbid psychiatric illness [5]. Data from clinical experience and case reports suggest that patients on the antiretroviral medication efavirenz may have increased irritability, unusual dreams, and more severe anxiety than patients not on this medication. However, randomized studies do not support this claim, so the link is unclear. Clinicians should ask about these symptoms and use their clinical judgement for additional medication management [5–8].

Additionally, screening tools and questionnaires may be a practical way to assess for anxiety-related symptoms in these patients. The Client Diagnostic Questionnaire (CDQ) is a brief diagnostic screening tool designed for use by non-mental health

Table 9.3 Differential diagnosis of an HIV-positive patient with anxiety symptoms

Anxiety disorders
Generalized anxiety disorder
Panic disorder
Post-traumatic stress disorder
Depressive disorders
Major depressive disorder
Dysthymia/persistent depressive disorder
Bipolar disorders
Substance use disorders (e.g., intoxication or withdrawal)
Other medical conditions/disorders
Thyroid disorders
Cardiopulmonary disorders
Infection (correlate with CD4+ count and opportunistic infections)
Malignancies
Neurological disorders
Side effects of medications

professionals to assess the range of psychiatric disorders known to be prevalent among persons infected with HIV or at high risk of infection including depressive disorders, anxiety disorders, PTSD, and substance use disorders. For the diagnosis of any of these disorders, the CDQ shows a sensitivity of 91% and a specificity of 78% and an overall accuracy of 85% [9]. One benefit of screening tools is that they enable untrained individuals to administer them. This can help identify more at-risk patients without overextending the clinician. The *New York State Department of Health AIDS Institute* guidelines recommend screening for anxiety annually. However, the guidelines also recommend screening for changes in sleep habits, appetite, and suicidal/homicidal ideation at *every visit*. The guidelines do not use formal screening measures for anxiety but suggest asking about periods of anxiety greater than 1 month, sudden "spells or attacks" of anxiety, and autonomic symptoms consistent with a panic attack/anxiety [10].

Measuring HIV symptomatology does not have to be complicated with long questionnaires; simple tools with as few as four questions are effective and valid. One study of women living with HIV found that assessing HIV-related anxiety causing sleeping difficulty, decreased appetite, decreased desire to socialize, and difficulty concentrating was a valid measure of psychological, psychosocial, and physical distress [11].

There are several screening tools for measuring anxiety, but none specifically for the HIV population. Table 9.4 shows the most commonly used instruments for anxiety. There is no clear benefit supporting the use of one tool over the other. In any case, they are meant to supplement the diagnostic approach of the clinician. Please see Chap. 5 for a detailed discussion of the use of screening tools for psychiatric disorders in persons with HIV.

Case Vignette 9.1: Diagnosis

Ms. A was a 28-year-old woman with known HIV-positive status who presented to your clinic complaining of anxiety for the previous 6 months. She stated that she felt worried most days and that it had impacted her ability to concentrate at work as well as enjoy her social life. She also noted difficulty sleeping as well as muscle tension over the previous 6 months. The patient denied suicidal or homicidal ideation. She was diagnosed with HIV 6 years previously and remained clinically asymptomatic on a single combination pill.

What is the most likely diagnosis?

(a) Major depressive episode
(b) Post-traumatic stress disorder
(c) Generalized anxiety disorder
(d) Panic disorder

Correct answer: (c).

Table 9.4 Evidence-based tools to screen for anxiety

Screening instrument	Administration	Items	Time of administration in minutes
Hamilton Anxiety Rating Scale – HAM-A [12]	By clinician	14	10–15
State-Trait Anxiety Inventory – STAI [13]	Self-report	40 (20 state and 20 trait symptoms)	15–20
Profile of Mood States – POMS [14]	Self-report	65 (9-item tension/ anxiety subscale)	10–15
Hospital Anxiety and Depression Scale – HADS [15]	Self-report	14 (7-item anxiety subscale; excludes somatic symptoms)	5–10
General Anxiety Disorder 7 – GAD7 [16] (screening for generalized anxiety disorder, panic disorder, social anxiety disorder, and post-traumatic stress disorder)	Self-report	7	5

Etiology

The etiology of anxiety in persons with HIV and AIDS is poorly understood and likely due to the complex biopsychosociocultural interactions that manifest in a variety of presentations. First, certain pharmacological therapies may cause symptoms of anxiety (e.g., efavirenz, interferon, corticosteroids). Second, biologic factors such as chronic inflammation (i.e., secondary to HIV infection) have been implicated as etiologies of anxiety [17]. Third, the relationship between chronic stress and changes in the hypothalamic-pituitary-adrenal system resulting in immune dysfunction has been described and is correlated with both depression and anxiety, suggesting another potential etiology of these highly multimorbid conditions in HIV infection.

HIV is related to a variety of cognitive and social stressors, such as disease stigma, health worries, and serostatus disclosure concerns [18]. After ruling out biologic mechanisms, other causes should be explored such as social, cognitive, and behavioral etiologies associated with the manifestation of anxiety in persons with HIV and AIDS (Table 9.5.). Furthermore, transdiagnostic domains, such as anxiety sensitivity, distress tolerance, emotion dysregulation, avoidant coping, and personality factors, have been implicated in the psychopathology of anxiety in this population.

Anxiety sensitivity is defined as the extent to which individuals believe anxiety and its related sensations (e.g., racing heart, numbness) may have harmful personal consequences [19, 20]. Cumulative data from cross-sectional studies provides empirical evidence that anxiety sensitivity is related to anxiety and related depressive symptoms, as well as HIV symptoms and poorer medication adherence among

Table 9.5 Possible causative mechanisms of anxiety in HIV subjects

Biologic factors
Medical therapies (e.g., efavirenz, interferon, corticosteroids)
Chronic inflammation (from HIV infection)
Behavioral factors
Maladaptive coping behaviors
Maladaptive health behaviors
Cognitive processes
Cognitive impairment (e.g., major or mild neurocognitive disorder, delirium)
Perception of stress
Social processes
HIV stigma
Role interference
Transdiagnostic processes
Anxiety sensitivity
Distress tolerance
Emotion dysregulation
Avoidant coping
Personality factors

Based on data from Ref. [2]

persons with HIV and AIDS. Anxiety sensitivity has also been implicated in clinically significant outcomes such as suicidality in this population. While this cross-sectional data is limited, the effect of anxiety sensitivity appears to be clinically significant in that it is incremental [2].

Distress tolerance, the perceived ability to withstand negative emotional/physical discomfort or the act of withstanding a distressing internal state elicited by a stressor [21], has interestingly been found to significantly predict depressive symptoms, panic symptoms, and social anxiety symptoms, as measured by the Inventory of Depression and Anxiety Symptoms (IDAS) in persons with HIV and AIDS [22]. This is believed to be mediated by emotion dysregulation, in which subjects have difficulty in the self-regulation of affective states and difficulty with self-control over affect-driven behaviors [23, 24]. Even after adjusting for covariates (e.g., demographics, substance use), emotion dysregulation was significantly related to panic and social anxiety symptoms among persons living with HIV and AIDS [2].

Another transdiagnostic process which has been implicated in anxiety manifestation in persons living with HIV and AIDS is avoidant coping [2]. Coping reflects conscious, voluntary attempts to manage internal or external stressors that an individual perceives as exceeding psychological-based resources [25]. Several studies have shown that avoidant coping was significantly related to increased anxiety symptoms [26, 27].

In regard to personality factors, neuroticism was significantly related to anxiety symptoms, whereas openness and conscientiousness were significantly negatively related to anxiety symptoms [28], meriting further investigation into the role personality may play in anxiety psychopathology among persons living with HIV and AIDS. It is worth noting that while much of the data in the literature on these topics is limited due to the cross-sectional nature of many of the studies, the findings

described above are still of clinical relevance. Further research into the causative mechanisms of anxiety in HIV subjects is warranted, as this topic is difficult to research given the multiple biopsychosocial factors as well as transdiagnostic domains described above interplaying in a complex manner and manifesting as anxiety in this population (Table 9.5).

Case Vignette 9.2: Etiology

Mr. B was a 34-year-old male with HIV who was new to your clinic and presented complaining of 2 months of episodes consisting of a "racing heart," numbness in his hands, and feeling "like he cannot breathe." These episodes occurred a couple times each week. He said he otherwise had been feeling well besides mild difficulty with memory during daily tasks, which he says it was not of concern to him. He recently started a new medication when he last saw his provider, but cannot remember the name of it. Upon further discussion, he stated that he actually had not been seen since his original diagnosis, claiming he could manage this on his own and did not want the diagnosis to interfere with his schedule and more importantly did not want others to know he had HIV. He requested a refill of whatever the previous provider had him on.

What potential etiology(s) of anxiety in this HIV patient are present?

(a) Medication side effect
(b) Underlying HIV infection and chronic inflammation
(c) Multiple transdiagnostic domains (i.e., anxiety sensitivity)
(d) All of the above

Correct answer: (d)

What is the next best step in working up the etiology of his symptoms?

(a) Dismiss the patient's concerns, as it is likely nothing, and tell him to follow up in 3 months if symptoms do not resolve.
(b) Determine what HIV medication(s) the patient was on, and if known to cause symptoms of anxiety (e.g., efavirenz), switch to an alternative pharmacologic therapy.
(c) Order additional labs and testing (e.g., thyroid panel) to first rule out other pathologies that may be causing the patient's symptoms.
(d) Order a CT chest/abdomen/pelvis to evaluate for pheochromocytoma.

Correct answer: (c)

Impact of Anxiety on HIV

Sexual Transmission

Although most research examining the relationship between mental health and sexual transmission risk behaviors in people living with HIV is focused on depressive disorders and substance use, some research gives attention to the anxiety disorders. A review by Brandt et al. [2] yielded nine studies examining this relationship; of those, five reported a positive association between anxiety symptoms and sexual risk-taking behaviors, two reported no association, and two reported a negative association. Overall, the number of available studies on this topic is very limited, particularly when considered within the context of the broad spectrum of symptoms that the anxiety disorders encompass, ranging from specific phobias to generalized anxiety, from predominantly somatic features to symptoms that are largely cognitive.

The number of distinct anxiety disorders suggests that there could be multiple anxiety-specific pathways that affect sexual risk-taking behaviors in people living with HIV. Various models have been suggested to explain this relationship [29]. These include the idea that increased sexual activity could be a coping strategy to avoid intolerable feelings of stress or that anxiety itself could negatively impact decision-making. Substance use can further moderate this relationship. Another posited model, based on existing theories of social anxiety, suggests that people with HIV and high social anxiety could avoid negotiating conversations around condom use, as a result of their preoccupation with being negatively evaluated by others. Avoidance of negotiation about condom use may increase the risk of unprotected sexual behavior and result in negative long-term consequences. For example, two cross-sectional studies by Hart et al. [30, 31], involving MSM living with HIV, demonstrated an association between social anxiety and increased unprotected insertive anal intercourse with partners who were not known to have HIV. However, a later cross-sectional study by O'Cleirigh et al. [32] demonstrated no association between sexual transmission risk behavior and social anxiety, as well as panic disorder.

Additional limitations to existing research on the impact of anxiety on HIV sexual transmission risk factors include the lack of prospective studies and the lack of studies on the effect of interventions, which could improve clinical practice in the future. Finally, there is also a dearth of qualitative data, such as interviews, that could reveal insights of people living with both HIV and anxiety disorders on how their symptoms of anxiety affect their perspective on sexual risk-taking.

Quality of Life

Among the general population, many studies have investigated the effect of anxiety disorders on quality of life. There is a substantial body of literature demonstrating that among medically healthy individuals as well as specific groups of people living with chronic medical illness, different anxiety disorders are associated with dysfunction in quality of life [33, 34] and in specific domains of health-related quality of life [35].

No studies have been reported to examine the effect of anxiety disorders on quality of life among people living with HIV. One recent meta-analysis identified five studies that commented on this relationship; all five studies seemed to suggest that the presence of anxiety symptoms was associated with lower quality of life among this population [2]. However, these were all cross-sectional studies, and examinations of the relationship between anxiety and quality of life were performed via secondary analysis. Future studies are necessary to clarify the nature of this relationship and to identify useful interventions to guide clinical practice.

Case Vignette 9.3: Quality of Life

Mr. C was a 45-year-old man who worked full time as a nurse in a hospital and was a single parent of two young children. He was diagnosed with HIV 8 months previously and had since been experiencing new symptoms of uncontrollable worry, restlessness, irritability, and muscle tension. He ruminated over whether and when to disclose his HIV diagnosis to his children, who were unaware. Mr. C feared that he will one day become very ill and unable to care for his children. He also worried that his coworkers at the hospital will learn about his HIV diagnosis and look down upon him and that it would put his job at risk. He felt tired and worn out and noticed more physical pain throughout the day. He had less time and energy for spending time with his children and friends. He felt distracted and unable to accomplish his usual tasks at work.

For individuals such as Mr. C, being diagnosed with HIV and experiencing symptoms of anxiety is related to lower health-related quality of life. How is health-related quality of life defined in this context?

(a) How a person's HIV diagnosis and anxiety symptoms impact functioning and perceived well-being in multiple domains of life (physical, mental, and social)
(b) How well a person is able to cope with their new diagnosis
(c) How much time a person is able to spend on meditation, exercise, and other wellness activities
(d) How highly a person rates their satisfaction with their health

Correct answer: (a)

Suicidal Thoughts

Suicide is a serious global public health concern, which, in many countries, has been shown to disproportionately affect people living with HIV, even *after* the advent of effective antiretroviral therapy [36]. Various studies have sought to identify risk factors for suicidal thoughts and behaviors in persons living with HIV and AIDS. There is limited research consisting of three cross-sectional studies and one retrospective cohort study that examines the relationship between anxiety disorders and suicidal thoughts and behaviors among people living with HIV [2]. While this initial data would suggest that symptoms of anxiety are associated with thoughts and behaviors related to suicide, these associations were examined via secondary analysis, and the four studies used different measures to screen for and identify anxiety.

The currently available research and clinical knowledge are too limited to ascertain whether anxiety disorders are a risk factor for suicidal thoughts and behaviors among people living with HIV. Among the general population, anxiety disorders have been more extensively examined as potential risk factors for suicide, and most recent meta-analyses have indicated that anxiety disorders in themselves are very weak predictors of suicide over time [37]. Future research is necessary to clarify if this weak association between anxiety and suicidal thoughts is applicable to people living with HIV and to better understand the role of anxiety disorders in assessing suicide risk in this population. There is a notable absence of any prospective data, which would be an important area for future study. Please see Chap. 13 for a detailed discussion on suicide and suicidality in persons with HIV and AIDS.

Cognitive Impairment

HIV-associated neurocognitive disorders remain globally highly prevalent and contribute significantly to morbidity from HIV infection, in spite of the many advances in HIV care and treatment with antiretroviral medications. While the relationship between anxiety and neurocognitive disorders has been more extensively described in the general population, the role of anxiety in moderating cognitive impairment is less well understood among people living with HIV. There are only four studies examining this association [2]. Three of the four studies used a cross-sectional design that examined the relationship between anxiety and cognitive impairment via secondary analysis; they used self-report of cognitive symptoms rather than a battery of neuropsychiatric tests. There was only one prospective study, and it utilized the Wechsler Adult Intelligence Scale as a measure of cognitive performance over time [38].

From the existing data, it is unclear if the anxiety itself causes cognitive function to worsen, or if anxiety and cognitive impairment are *both* symptomatic of the same HIV-related brain involvement. Further research, including more prospective

studies, and more standardized and rigorous methods of evaluating cognitive performance, is needed to more accurately understand the nature of the relationship between anxiety symptoms and cognitive impairment.

Case Vignette 9.4: Adherence to ARV Treatment
Mr. D was a 32-year-old male with a long history of anxiety, which worsened significantly after he was diagnosed with HIV 1 year previously. About 9 months previously, he established care at an HIV specialty clinic. On his first appointment, he felt flooded by the barrage of information he received about his diagnosis, and he had difficulty retaining any information. He also worried that a friend or a coworker would see him walking into the clinic and that this would place him at risk of being rejected by his friends or losing his job. Since his first appointment at the HIV specialty clinic, Mr. D missed more than half of his follow-up appointments. He took his ARV medication sometimes but experienced significant physical symptoms of anxiety when taking his medication, as they reminded him of his illness. He continued to have detectable levels on his viral load tests.

Among individuals diagnosed with HIV, persons with symptoms of GAD experience the following in comparison to persons without symptoms of GAD:

(a) Lower ART prescription
(b) Lower ART adherence
(c) Lower viral suppression
(d) All of the above

Correct answer: (d)

Case Vignette 9.5: Risk Behavior
Mr. E is a 28-year-old male with a history of social anxiety and HIV, which was diagnosed a year and a half ago. After a brief hiatus, Mr. E decided that he was ready to start dating again. He had already noticed that some of his friends who were aware of his HIV diagnosis had been acting differently around him and sometimes avoid physical touch with him. He worried about how he will disclose his HIV status to potential partners and how they will react to it. He wondered if potential partners will react negatively and be less interested in him if he asks them to use condoms during sex. He also worried if he will have more difficulty performing sexually while using a condom. He felt overwhelmed when he thought about how he might navigate some of these difficult conversations, and he sometimes felt it would be easiest to avoid those conversations altogether.

What is the proposed mechanism for how symptoms of anxiety lead to increased high-risk sexual behaviors in individuals diagnosed with HIV?

(a) Internalized self-stigma leading to decreased condom use
(b) Fear of being negatively evaluated by a sexual partner leading to decreased condom use
(c) Increased use of recreational drugs to attenuate social anxiety
(d) All of the above theories have been suggested but need to be explored further in future research

Correct answer: (d)

Case Vignette 9.6: Illness Progression

Ms. F is a 45-year-old female who was diagnosed with HIV 3 years ago. Her diagnosis came as a very unexpected surprise, and since then, she has continued to feel overwhelmed by her diagnosis of HIV, which she views as unpredictable and frightening. Several years prior, she lost a close friend to an AIDS-related complication. For the past 3 years, she has experienced frequent and uncontrollable worry that a protracted and severe course of illness is in her future as was the case for her friend. She fears that she will become too ill to work or to spend time with her loved ones. As a result of these worries, she has difficulty sleeping at night, and during the day, she is often tired, irritable, and unable to focus. Throughout most of this time, she has engaged fairly consistently with her HIV care, consistently taking ARV medication.

Recently, Ms. F started to attend individual therapy sessions with an embedded mental health practitioner in her HIV care clinic. In therapy, she engaged in cognitive restructuring exercises which helped her realize that her illness had not progressed in the 3 years since her diagnosis and had actually remained very stable. This has helped to decrease her symptoms of anxiety and improve her overall quality of life.

How is anxiety related to HIV disease severity and progression?

(a) Anxiety protects against disease progression by promoting increased bodily vigilance and engagement with HIV care.
(b) Anxiety hastens disease progression via the anxiety state's impact on the immune system response.
(c) There have been a few studies examining the relationship between anxiety and disease progression, and their results have not consistently established any clear relationship.
(d) After controlling for prescription and adherence to ART, there is still a positive relationship between anxiety and disease progression.

Correct answer: (c)

Therapy

Pharmacological Treatment

Benzodiazepines (BZPs) comprise two-thirds of the cases where medications are prescribed for anxiety among HIV-infected individuals [39]. Patients with HIV infection are particularly sensitive to the side effects of BZPs, especially excessive sedation. However, studies examining the efficacy of BZPs for the treatment of anxiety in HIV-infected individuals are lacking [39]. In a survey done to a group of mental health clinicians (mostly psychiatrists) and medical students who provide care for persons with HIV and AIDS in the United States and other areas in the world, clonazepam and lorazepam were considered benzodiazepines of choice for the first treatment of syndromal anxiety disorders (e.g., panic disorder) in HIV patients [40]. Clonazepam and lorazepam do not have active metabolites and are safe in terms of drug-drug interactions with antiretroviral treatment [40]. Non-BZP hypnotic agents (e.g., zopiclone, zolpidem, zaleplon) should also be used with caution in patients with antiretroviral treatment. Other therapeutic options for anxiety include SSRI, buspirone, and pregabalin. In the survey by Freudenreich et al., escitalopram and citalopram were considered first-choice treatment for depression [40]. They also could be considered as non-BZP first-choice treatment of anxiety disorders. Please see Chap. 17 for more detailed information about the use of psychopharmacologic agents and antiretrovirals as well as drug-drug and drug-illness interactions in persons living with HIV and AIDS.

Non-pharmacological Interventions for Anxiety Symptoms and Disorders in Persons with HIV and AIDS

Results of research studying non-pharmacological interventions for anxiety symptoms in HIV patients range from showing little to no significant effect to notable reduction in anxiety symptoms by certain interventions. In a systematic review of 39 studies including 50 treatments, Clucas et al. [41] found that non-pharmacological interventions were generally more successful in reducing symptoms than pharmacological approaches. Intervention methods that were studied were psychological, psychosocial, physical, or nutritional supplementation; 48% of these were shown to be effective and included cognitive behavioral stress management (CBSM), cognitive behavioral therapy, art therapy, peer support counseling, relaxation training, and therapeutic touch. Another study consisting of a randomized controlled trial by Jones et al. [42] also found that CBSM decreased anxiety more than individual information sessions teaching stress management.

Other interventions that were proven to be effective focused on mindfulness techniques. In a randomized controlled trial by González-García et al. [43], a

Table 9.6 Evidence-based non-pharmacological therapeutic options for HIV patients with anxiety

Cognitive behavioral therapy
Cognitive behavioral stress management
Mindfulness-based cognitive therapy
Peer support counseling

mindfulness-based cognitive therapy program resulted in reduction of anxiety symptoms with a large effect size from baseline to 8 weeks in addition to improving subjective quality of life, overall emotional state, and immunity status over 3 months. Another study [44] showed that a mindfulness-based stress reduction program (MBSR) could even be associated with decline in the CD4+ T lymphocyte count. There is some evidence that group therapy may be helpful for people living with HIV for adapting to the diagnosis or recovering from anxiety in relation to this [45]. The most used non-pharmacological interventions are summarized in Table 9.6.

Conclusions

All clinicians caring for persons living with HIV and AIDS can benefit from familiarity with the high prevalence of both anxiety symptoms and anxiety disorders in their patients across the life span. Indeed, estimated rates of anxiety disorders among persons with HIV and AIDS are much higher than those among the general population, with rates about 23% in some studies. Although the etiology of anxiety is poorly understood and likely due to the complex biopsychosociocultural interactions that manifest in a variety of presentations, the impact of anxiety on quality of life and general function on persons living with HIV and AIDS is very clear. However, compared with the efforts to improve diagnosis and treatment for depressive disorders, anxiety disorders are sometimes regarded as the neglected condition in psychiatric care of persons with HIV. Screening for anxiety disorders is indicated on a regular basis, not only by psychiatrists and other mental health clinicians, but are also indicated as part of routine evaluations by other professionals caring for persons living with HIV and AIDS. There is little evidence of the efficacy of psychopharmacological treatment for anxiety disorders in HIV; however, non-pharmacological strategies such as cognitive behavioral therapy, cognitive behavioral stress management, mindfulness-based cognitive therapy, and peer support counseling seem to give greater benefit. HIV clinicians should recommend these non-pharmacological strategies or, at least, relaxation techniques to prevent or address anxiety in their patients.

Disclosure The opinions and assertions expressed herein are those of the author(s) and do not necessarily reflect the official policy or position of the Uniformed Services University or the Department of Defense.

Multiple-Choice Questions

1. According to the critical review by Brandt et al. (2017) [2], what is the approximate mean value of anxiety disorders prevalence among PLWHA, based on diagnostic interviews?

   (a) 50%
   (b) 40%
   (c) 30%
   (d) 10%

   Correct answer: (c)
2. When examining specific anxiety disorders individually, which has a *similar* rate of prevalence in PLWHA compared to in the general population?

   (a) Generalized anxiety disorder
   (b) Panic disorder
   (c) Specific phobia
   (d) Social anxiety

   Correct answer: (c) (Brandt et al. 2017 [2]).
3. Which of the following statements about anxiety sensitivity in PLWHA is not true?

   (a) Anxiety sensitivity is defined as the extent to which individuals believe anxiety and its related sensations to be harmless.
   (b) Anxiety sensitivity is related to anxiety and related negative mood symptoms.
   (c) Anxiety sensitivity is related to HIV symptoms.
   (d) Anxiety sensitivity is related to poorer medication adherence among PLWHA.

   Correct answer: (a) (McNally, 2002 [19]; Reiss 1985 [20]).
4. Among the following, which psychometric tool to screen persons with HIV for anxiety may be considered most suitable?

   (a) Hospital Anxiety and Depression Scale
   (b) Beck Depression Inventory
   (c) Hamilton Depression Rating Scale
   (d) Patient Health Questionnaire-9

   Correct answer (a) (Zigmond and Snaith 1983 [15])
5. In relation to the pharmacological treatment of anxiety in PLWHA, which is the incorrect answer?

   (a) A high percentage of medications prescribed for anxiety among HIV-infected individuals are benzodiazepines (BDZ).
   (b) Patients with HIV infection are particularly sensitive to the side effects of BZPs, especially excessive sedation.
   (c) Alprazolam was considered benzodiazepine of choice for the treatment of syndromal anxiety disorders.

(d) Non-pharmacological interventions were generally more successful in reducing anxious symptoms than pharmacological approaches.

Correct answer: (c) (Freudenreich 2010 [40])

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Chapter 10
HIV-Associated Neurocognitive Disorders and Delirium

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Part 1. HIV-Associated Neurocognitive Disorder

Introduction and Epidemiology

Case 10.1
Mr. J was a 61-year-old man admitted through the emergency department following a fall and left intertrochanteric hip fracture after tripping over his cat. He was referred for a preoperative medical evaluation. He had a long mustache and stubble on his chin and was wearing stained boxer shorts under his hospital gown. His manner was friendly, but his affect was flat. He stated that his health was "fair" and he had no medical complaints other than pain in his left hip. His past medical history was noteworthy for long-standing human immunodeficiency virus (HIV) first diagnosed in 1994, for which he was followed by an infectious disease specialist in

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addition to his general internist. He stated that his viral load had been undetectable for "about 3 years." He also had a history of hypertension, "high cholesterol," and diabetes mellitus and a history of a small abdominal aortic aneurysm last measured by ultrasound 6 months previously. On review of systems, he had had two other ground-level falls in the previous month, once while bending over to pick up a fork on the kitchen floor and once when he tripped in the backyard, causing significant abrasions that necessitated a visit to the emergency department. He had intermittent stabbing pain in his feet that was helped by a "nerve pill." The patient admitted that he could not name his specific medications because his "very solicitous" husband organized his medicines in a multi-compartment pill box, but he knew that he took two different pills for his blood pressure, a cholesterol pill, a "nerve pill," a diabetes medication, and a pill for his HIV. He had not taken his medications on day of presentation. Per the chart, the patient was taking a combination antiretroviral consisting of abacavir, dolutegravir, and lamivudine once daily, olmesartan 40 mg daily, hydrochlorothiazide 25 mg daily, gabapentin 600 mg twice daily, metformin 850 mg twice daily, atorvastatin 40 mg at bedtime, and acetaminophen (paracetamol) 325 mg with 5 mg of hydrocodone up to 4 times per day as needed for neuropathic pain. On social history, Mr. J stated that he left his job running an antique shop 2 years previously because it was becoming "too stressful." He drank a glass of wine with dinner on most nights and smoked marijuana recreationally once or twice a week, but denied use of any other street drugs. On physical examination, Mr. J was mildly obese with a body mass index of 31.5 kg/m^2. His blood pressure was 162/100 mm Hg with a regular heart rate of 88 bpm. Examination of his chest revealed clear lungs were, but he had a soft systolic murmur at the lower left sternal border. On neurological exam, he correctly named the date and day of the week but was off by one on the year. He had decreased vibration sensation to the knees and slightly slowed rapid alternating movements in both hands. Laboratory examination was notable for a slightly elevated creatinine of 1.24 mg/dL (109.6 μmol/L) and a random blood glucose of 198 mg/dL (10.99 mmol/L). HIV RNA was below detectable limits, and his CD4+ T cell count was 560 cells/mm^3 (within normal limits). His chest roentgenogram was unremarkable, except for calcification in the aortic knob, and his electrocardiogram showed T-wave inversion in lead III. Recommendations were made for treatment of his hypertension, resumption of his outpatient medications except for olmesartan and metformin, control of his blood sugar, and fluid and electrolyte management. There were no contraindications to proceeding with surgery following implementation of the recommendations.

Mr. J manifested several features of long-standing HIV. He had signs of premature aging with early atherosclerosis. He had probable osteoporosis, which may be a consequence of HIV, antiretroviral therapy, and/or chronic inflammation [1]. Although his mildly impaired cognition could in part reflect the opioids given for his pain and/or the gabapentinoid for his peripheral neuropathy, his responses and past history should raise concern about mild neurocognitive disorder (MND).

In many respects, Mr. J is representative of persons from developed countries in 2021 who live with human immunodeficiency virus (HIV) and receive antiretroviral therapy. He had been living with HIV for 26 years, having been diagnosed and

started on treatment prior to HAART, which has transformed HIV from a near-uniformly fatal infection to a chronic illness. Persons living with HIV (PLWH) now have age- and gender-adjusted life expectancies that approach those of persons without HIV. Like Mr. J, the majority of HIV-positive individuals in developed countries are over age 50 [2]. With the introduction of HAART, the prevalence of HIV-associated dementia (HAD; formerly known as HIV encephalitis and AIDS dementia complex) has declined from approximately 20% to under 5%. Yet, the overall prevalence of HIV-associated neurocognitive disorder (HAND) remains largely unchanged in developed countries, ranging between 20% and 50%, depending on the study. HAND now consists primarily of asymptomatic and milder forms of cognitive impairment that may persist despite normalization of the CD4 count and suppression of viremia [3, 4] (Fig. 10.1).

Mr. J appeared to have responded well to antiretroviral therapy and to be in sustained remission from the infection. His medical records did not document cognitive impairment, and on casual conversation he appeared cognitively intact. However, he did not know any of the names of his medications, apparently required help to take them, and missed the year on questions of orientation. To complain of significant stress while running an antique shop may raise suspicion about executive impairment. The routine use of screening tests could have led to earlier identification of symptoms of neurocognitive impairment. As discussed later, although there is some controversy about the routine use of screening tools for identifying milder forms of HAND, they have the potential to identify cognitive deficits in patients who may otherwise appear cognitively unimpaired during a routine clinical interview. Furthermore, with the patient's permission, his

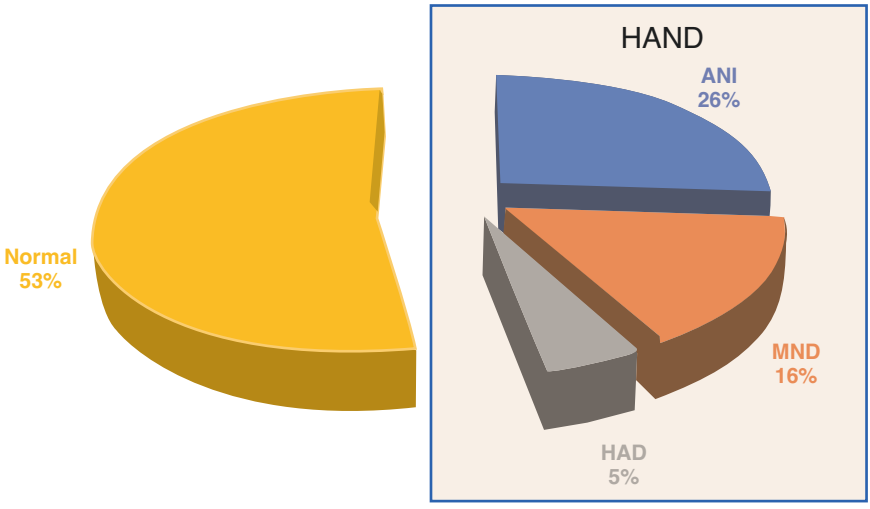

Fig. 10.1 Approximate distribution of cognitive function in persons living with HIV. HAND HIV-associated neurocognitive disorder, ANI asymptomatic neurocognitive impairment, MND mild neurocognitive disorder, HAD HIV-associated dementia. (Based on data from Ref. [1])

spouse could have been interviewed regarding his perceptions of changes in Mr. J's memory, executive function, and functional status. Mr. J needed formal mental status (including cognitive) testing, and HAND should be considered in the differential diagnosis of suspected cognitive impairment. It should be noted that the prevalence of HAND has been derived from cohort studies of volunteer participants that are not population-based, and therefore may not represent the HIV-positive community at large. The true percentage of PLWH with unrecognized, milder forms of HAND is unknown. Depending on their community of residence, many persons with HAND are marginalized by society, lack longitudinal primary care or even health insurance, and may not have access to HIV specialists.

Mr. J illustrates another feature of older adults living with HIV as a chronic illness: premature aging. Although he had never used tobacco, he exhibited signs of significant atherosclerosis at age 61. He may also have had osteoporosis, given the hip fracture. The causes of premature aging and its relation to HAND will be discussed in more detail in this chapter under the following topics: premature aging, geriatric syndromes, and HAND. Additionally, Mr. J exhibited polypharmacy (five or more prescribed medications) with the potential for adverse reactions and drug interactions. In the United States, approximately 15% of individuals over the age of 45 regularly take eight or more medications [5].

Classification and Natural History of HAND

Case 10.2

Ms. S was a 49-year-old woman who was domiciled and in a monogamous relationship with her partner for 5 years. Prior to moving to California from the Midwest in 2010, Ms. S had short-term, covert relationships with a series of women because she did not want her law-firm partners or parents to know she was a lesbian. She was diagnosed with HIV in 2011, but because she was busy getting established with a new law firm, she abstained from sex and deferred antiretroviral therapy until late 2012. She met her partner, who was HIV negative, in 2014. From 2012 to 2013, Ms. S's HIV was partially resistant to antiretroviral therapy, and although her CD4+ T cell count rose from 286 cells/ mm^3 to 386 cells/mm^3, her viral load never went below 150 RNA copies/mL until her regimen was changed. After 5 months on the new regimen, her CD4+ count rose to 494 cells/mm^3, and her viral load became undetectable (below 50 RNA copies/mL). She had generally felt well and never had an AIDS-defining illness. In 2018, Ms. S, a litigation attorney, felt she that was having more difficulties cross-examining witnesses and opted to switch her focus to contracts and trusts. Her HIV specialist was concerned about possible HAND and referred her for neuropsychological testing. Although she graduated in the top third of her law school class at a prestigious institution, her IQ was estimated only to be in the average range. However, she continued to be productive at the law firm and

remained independent in all her instrumental activities of daily living. Consequently, she was given the diagnosis of asymptomatic neurocognitive impairment (ANI).

Case 10.3
Ms. G-F was a 37-year-old homeless woman and a frequent user of intravenous methamphetamine and heroin. She was admitted for an abscess and cellulitis in her left upper extremity. Because of agitation and aggressive behavior toward staff, she was seen on hospital day 2 by the consultation-liaison psychiatry service. She was known to be HIV-1 positive but had been non-adherent to her medications while keeping only one of her last four appointments at the HIV clinic. Because of her non-adherence, antiretroviral therapy had not been offered due to the potential for developing HIV-1 drug resistance. In addition to HIV-1, she had been diagnosed with hypertension, type 2 diabetes mellitus, hepatitis C, and heart failure with a reduced ejection fraction of 40%. On presentation, she was tachycardic and hypertensive, but by hospital day 2, her pulse and blood pressure had normalized. She was overweight and unkempt and had her upper front teeth missing. She is alert and appropriate (Richmond Agitation and Sedation Scale = 0) but scored 16/30 on the Mini-Mental State Examination (consistent with moderate cognitive impairment). She failed the attention screening component of the Confusion Assessment Method-ICU. Her viral load was 155,000 RNA copies/mL (high). Magnetic resonance imaging of the brain showed increased cortical atrophy for her age and substantial periventricular white matter disease. The previous evening, she was given a total of 2 mg of risperidone for severe agitation and became rigid. Neurological examination revealed persistent cogwheel rigidity in her arms and a mask-like face. Although she manifested subclinical delirium, her overall history and clinical exam supported the diagnosis of underlying HIV-associated dementia (HAD).

Prior to 2005, the American Academy of Neurology (AAN) recognized two categories of HIV-associated neurocognitive impairment: *HIV-associated dementia* (HAD) synonymous with HIV encephalitis, HIV dementia, and AIDS dementia complex and the less severe *minor cognitive motor disorder* (MCMD). The diagnosis of HAD required the presence of motor and/or behavioral and psychosocial symptoms that substantially impaired performance of daily activities. In addition to a cognitive disturbance that caused mild impairment in work or daily activities, MCMD included mild personality changes, slowed movements, and other motor abnormalities [2]. As milder forms of cognitive dysfunction began to predominate with the introduction of HAART and more effective antiretroviral medications, the older AAN criteria failed to capture individuals with more subtle neurocognitive impairment without functional decline. A similar shortcoming characterized the 5-point Memorial Sloan Kettering (MSK) clinical staging of the AIDS dementia complex [3]. Older classification systems from the pre-HAART era that emphasized AIDS indicator conditions or common symptoms, like the Centers for Disease Control A, B, C staging, likewise are insensitive for classifying milder forms of HAND. To update criteria for HIV-related cognitive impairment, the National Institute of Mental Health sponsored a 2005 conference in Frascati, Italy, which

culminated in the so-called "Frascati criteria" [2]. The Frascati criteria, summarized in Table 10.1, represent the currently accepted staging criteria used for HIV-associated neurocognitive disorder (HAND) and consist of three categories: *asymptomatic neurocognitive impairment* (*ANI*), *mild neurocognitive disorder* (*MND*), and *HIV-associated dementia* (*HAD*). In contrast to the pre-HAART era, HAD now makes up less than 5% of HAND in HIV-positive cohort studies, whereas ANI comprises up to 70% [4]. Delirium is included in Table 10.1 because it represents another cause of neurocognitive impairment that at times may be difficult to differentiate from HAND. The hallmark of delirium is that its severity fluctuates over time, often within the day or even within hours. Delirium can be acute and transient, or may run a more indolent course, as might be the case in a patient experiencing neurocognitive side effects from an anticholinergic medication like the bladder antispasmodic oxybutynin or antihistaminic medications such as diphenhydramine.

Table 10.1 Diagnostic criteria for HIV-associated neurocognitive disorders

	Asymptomatic neurocognitive impairment ANI	Mild neurocognitive disorder MND	HIV-associated dementia HAD	Delirium
Cognitive impairment (domains)	2 or more	2 or more	2 or more	Attention/ orientation ± others
Cognitive impairment (severity)	Mild Performance ≥1 SD below mean for age and education-adjusted norms on ≥2 cognitive domains* Does not interfere with everyday functioning	Mild to moderate Performance ≥1 SD below mean for age and education-adjusted norms At least mild interference in daily functioning	Moderate to severe Deficits in learning new information Slowed information processing Deficits in attention and concentration Marked interference in everyday functioning	Variable Acute onset or fluctuating course PLUS Inattention PLUS Disorganized thinking *or* altered level of consciousness
Functional impairment on ADLs	No obvious impact	Mild (instrumental ADLs)	Moderate to severe	Variable
Onset	Insidious	Insidious	Gradual	Acute
Clinical course	Variable	Progressive decline	Progressive decline (± Episodic crises)	Fluctuates

Based on data from Ref. [2]

Natural History

In persons living with HIV (PLWH), neurocognitive impairment has been shown to independently predict mortality over 13 years of follow-up when compared to neurocognitively intact HIV-positive individuals, after adjusting for demographic factors, baseline viral load, and CD4+ count [5]. However, the analytic sample used to derive these data had a mean viral load of >4000 RNA copies/mL, and neurocognitive impairment was based on the 5-item HIV Dementia Scale [6], which was developed to identify AIDS dementia in the pre-HAART era. The results therefore are more germane to HAD patients on HAART but not to the majority of HAND patients with milder ANI and MND. In a cohort of 436 patients enrolled in the CNS HIV Anti-Retroviral Therapy Effects Research (CHARTER) study, low viral load in univariate analysis was significantly associated with cognitive stability or improvement over an average of 35 months of follow-up. In multivariable modeling, higher IQ and no history of a major depressive disorder, in addition to a lower total protein and a lower liver transaminase – but not viral load or CD4+ T cell count – predicted cognitive stability or improvement. Conversely, greater comorbidity, being off antiretroviral therapy (ART), a history of major depressive disorder, methamphetamine use, and Latino ethnicity, in addition to several physiological parameters, predicted cognitive decline [7]. Other research has shown cognitive improvement with ART over the course of up to 27 months, including in older individuals, in those with a longer duration of HIV infection, and in those with less education [8]. Conflicting results reflect, in part, the diversity of the sample cohorts. Some characteristics appear consistently associated with a worse prognosis: the historical low nadir of CD4+ cell counts, a history of depression, as well as an AIDS defining illness [7, 8]. Both Mr. J and Ms. S have achieved viral suppression, yet both appear to have developed the milder forms of HAND. Mr. J's therapy for HIV began in the era of a single-agent nucleoside reverse transcriptase inhibitor, while Ms. S deferred ART for 2 years in order to establish her career in California while she was asymptomatic with HIV-1. Both had persistently low CD4+ cell counts until their current ART regimens. Their nadir CD4+ cell counts likely contributed to their neurocognitive decline, and these cases exemplify the importance of early treatment for HIV infection in order to restore immune function (Fig. 10.2).

The likely correlation of variables like education, depression, and non-adherence to ART with the CD4+ count and HIV viral load may have caused these HIV-related variables to be mathematically dropped from the multivariable models in the CHARTER study [7]. Consequently, these models can best be interpreted as showing risk factors for, but not causality of, progression. Psychosocial factors strongly influence the prognosis of HAND. They do so directly by impacting access and adherence to therapy and indirectly by increasing the probability of having worse HIV status at presentation and a greater burden of comorbidity. Among aging HIV+ patients, the concurrence of comorbidities like metabolic syndrome, cardiovascular disease, and other systemic illness may act synergistically with or independently of HIV to contribute to the development and progression of HAND [9, 10]. HIV+ individuals experience chronic inflammation and metabolic derangements as a

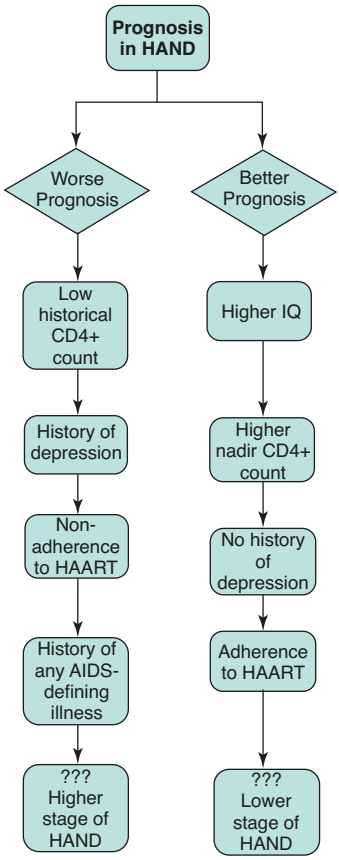

Fig. 10.2 Prognostic factors in HIV-associated neurocognitive disorder (HAND). Uncertainty remains because of the biased nature of observational studies, as well as the confounding effects of comorbid conditions

result of the HIV infection itself, coinfections, immune activation, and certain classes of antiretrovirals. These factors contribute to metabolic and cardiovascular changes that have been linked to the premature aging seen in many HIV+ patients, including those who are virally suppressed [11].

In the CHARTER study, 226 participants who were not neurocognitively impaired and 121 participants with ANI at baseline received neurocognitive assessments every 6 months for a median of 45.2 months (interquartile range 28.7–63.7 months). Based on the combination of self-report and performance-based measures, the relative risk that asymptomatic neurocognitive impairment would progress to symptomatic neurocognitive impairment, compared to progression in persons with no cognitive impairment, was 3.02 (95% CI 2.08–44.2). Notably, among the 55 ANI and 85 neurocognitively non-impaired participants with HIV-1 suppression at baseline ($\leq$ 50 RNA copies per mL), the relative risk was unchanged (3.01, 95% CI: 1.7–5.7) [12]. These findings support the observation that neurocognitive decline will occur in some patients regardless of efficacious antiretroviral therapy and suppression of HIV-1.

Pathophysiology of HAND: Why Is There Neurocognitive Decline Despite Effective Viral Suppression? (Fig. 10.3)

The unchanged prevalence of HAND since the introduction of HAART can be attributed in part to survival bias. Persons living with HIV (PLWH) are surviving into their 60s and beyond, when competing risk factors for neurocognitive impairment develop. These risk factors, however, disproportionately affect PLWH and contribute to the "premature aging" seen in this population. Other factors that may contribute to neurocognitive decline despite viral suppression include chronic neuroinflammation with neuronal damage, inadequate penetration of ART into the central nervous system (CNS), neurotoxicity of antiretroviral therapy, and neuronal damage from HIV of long duration, i.e., acquired pre-HAART.

Neuroinflammation

The virus enters the CNS within days to weeks after the primary infection and damages the blood-brain barrier by infecting microvascular endothelial cells and perivascular macrophages. The latter release proinflammatory cytokines and matrix metalloproteinases that disrupt the tight junctions between endothelial cells and permit invasion of infected CD4+ T cells and monocytes as well as free virus particles. The HIV-1 releases proteins such as the transactivator of transcription (Tat), which also stimulates proinflammatory molecules [13]. Virus that has entered the CNS may replicate inside brain macrophages and cause the chronic activation of

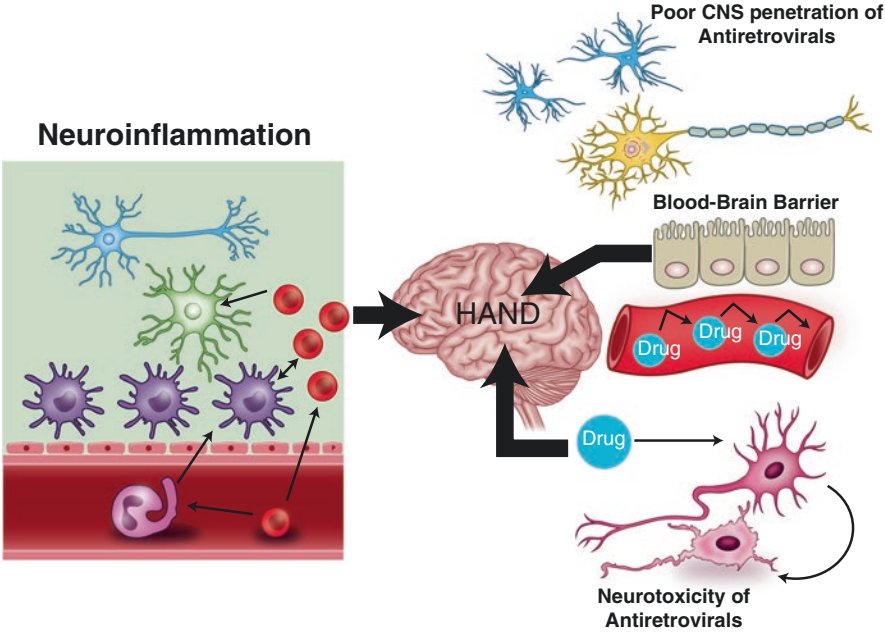

Fig. 10.3 Proposed causes of HIV-associated neurocognitive disorder (HAND)

microglia and astrocytes, which release proinflammatory cytokines and other molecules that damage neurons [14, 15]. HIV primarily reproduces in microglia and brain macrophages, but can also infect astrocytes, the most abundant cells in the CNS. Although HIV in astrocytes cannot replicate into a viable virion, viral synthetic activity continues, with production of HIV proteins like Tat envelope protein gp120. Astrocytes detoxify excitatory amino acids like glutamate, but when infected with HIV, reuptake of glutamate is impaired, causing excitotoxicity of neurons. Glutamate excitotoxicity has been implicated in neurodegenerative conditions like Alzheimer's disease (AD) [16] and may contribute to HAND. Although astrocytes normally play a critical role in neuronal support and survival, injured astrocytes induce apoptosis of neurons [17]. HIV, as an intact virion or as a partial virion within an astrocyte, produces Tat and envelope protein gp120, which adversely affects the structure and function of microtubules and the neuronal cytoskeleton, leading to the degeneration of axons and dendrites and affecting intercellular communication [18]. Metabolically stressed neurons, as occurs after the release of pro-inflammatory cytokines like TNF-α, produce the mixed-lineage kinase 3 (MLK3), which has been implicated in neuronal apoptosis [19]. There are three postulated mechanisms that exist independently or in combination in neuro-HIV to cause the cognitive decline that affects nearly one-half of HIV-infected men and women despite peripheral viral suppression: [1] a reservoir of HIV within the CNS, possibly sequestered within tissue macrophages or microglia and resistant to ART, [2] a self-perpetuating neuroinflammatory crosstalk among microglia and astrocytes that was initiated by the original HIV infection, and [3] ongoing release of HIV neurotoxic proteins from inside of infected astrocytes despite ineffective replication of the virus.

The existence of a reservoir (or compartmentalization) of CNS HIV-1 is supported by the phenomenon of "viral escape," which describes the appearance of HIV-1 in the cerebrospinal fluid (CSF) despite peripheral viral suppression [9, 20]. Viral escape may affect up to 25% of PLWH [9]. Using dynamic contrast-enhanced perfusion MRI, Chaganti et al. found that disruption of the blood-brain barrier occurs even in the setting of suppressed viral loads [21]. Whether this is caused by ongoing neuroinflammation or is the consequence of persistent subclinical HIV infection (i.e., < 50 RNA copies/mL of virus) that damages endothelial tight junctions remains unclear, but loss of integrity of the blood-brain barrier (sometimes referred to as the neurovascular unit) permits entry of monocytes and lymphocytes which may lead to the release of inflammatory mediators culminating in neuronal injury. The role of early infection of CNS by HIV, chronic inflammation, and immune activation causing neurotoxicity underscores the importance of an early start of antiretrovirals in order to potentially prevent the development or progression of neurocognitive impairment in this population.

Inadequate Penetration of Antiretrovirals into the CNS

Failure of ART to eradicate HIV-1 compartmentalized in the CNS could contribute to the development of HAND. In its original schema, the CNS Penetration Effectiveness Ranking System (CPE) correlated with the CSF viral load [22]. The CPE ranking was revised in 2010 to rank antiretroviral drugs from 1 to 4, in which 4 represents better penetration or effectiveness in the CNS and a stronger association with lower CSF viral loads [23]. The scores of individual drugs are added to yield a regimen's total CPE score. In cross-sectional analysis, multivariable modeling of 417 HIV-positive individuals on ≥3 antiretrovirals for at least 90 days found that the total CPE score was independently and inversely associated with overall cognitive impairment (global deterioration scale ≥0.5), with an odds ratio of 0.84, but the confidence interval approached 1 (OR = 0.84, 95% CI 0.71–0.99). Results show an inconsistent association of CPE with neurocognitive outcomes [24, 25]. Inconsistencies of the CPE score with cognitive decline may depend, in part, on the accuracy of pharmacodynamic and pharmacokinetic data used to formulate the drug CPE, as well as the existence of known and unknown pharmacogenetic associations of antiretroviral drugs with CNS exposure, resulting in patient-to-patient variation in CPE [26]. Despite uncertainty over the overall effectiveness of high-CPE ART, especially in ANI, its use should be considered in patients with a low CD4+ nadir, higher plasma HIV RNA, and the presence of new neurological symptoms with detectable CSF HIV RNA [27, 28] despite peripheral viral suppression. Of note, a randomized controlled trial with the goal of assessing the effects of intensification of ART regimens with maraviroc and dolutegravir on neurocognitive performance is underway (NCT02519777) (Table 10.2).

Neurotoxicity of Antiretroviral Drugs

Current antiretroviral therapy may be associated with neurotoxicity, including neurocognitive and neuropsychological complications that may be difficult to distinguish from other contributing factors [29]. It is beyond the scope of this chapter to discuss the specific neurological side effects of each medication, but each class of antiretroviral can be associated with adverse reactions that may directly or indirectly contribute to cognitive decline.

Nucleoside reverse transcriptase inhibitors (NRTIs), which prevent the formation of functional complimentary DNA (cDNA) that can be incorporated into the host cell genome, were the first class of antiretroviral to be developed in the 1980s and are exemplified by zidovudine (azidothymidine), didanosine, abacavir, and lamivudine. NRTIs have been associated with a painful peripheral neuropathy due to mitochondrial toxicity that may persist after discontinuing the drug [30]. In Case 10.1, Mr. J, whose HIV treatment began in in 1994, may have been exposed to NRTIs. Although not directly causing neurocognitive decline, the experience of serious adverse reactions may make patients reluctant to faithfully adhere to their antiretroviral regimens. Mr. J's dependence on opioids and a gabapentinoid for

Table 10.2 Concentration/penetration effectiveness score (CPE)

Class	Drug	CPE Score	Potential neurotoxicity	Contribution to cardiovascular risk
NRTI	Zidovudine	4	+	–
	Abacavir	3	+	++
	Emtricitabine	3	–	–
	Lamivudine	2	–	–
	Tenofovir	1	–	–
NNRTI	Nevirapine	4	+	–
	Efavirenz	3	++	–
	Etravirine	2	+	–
	Rilpivirine	n/a	+	–
PI	Lopinavir-rit	3	+	++
	Darunavir-rit	3	–	+
	Atazanavir-rit	2	+	–
	Atazanavir	2	+	–
II	Raltegravir	3	+	–
	Dolutegravir	n/a	?	–
	Elvitegravir-rit	n/a	+	–
EI	Maraviroc	3	–	–
	Enfuvirtide	1	–	–

Based on data from Ref. [28]

pain control could lead both to impaired cognition and to increased vulnerability to the effects of HAND. There may be direct effects on the CNS. Abacavir may stress the endoplasmic reticulum of astrocytes, whose support role for neurons has been discussed. Didanosine has been linked to the depletion of brain mitochondria [29].

Non-nucleoside reverse transcriptase inhibitors (NNRTIs), such as nevirapine and efavirenz, also impair the synthesis of cDNA. Although generally better tolerated than NRTIs, NNRTIs may cause CNS symptoms. Nevirapine has been associated with persecutory delusions, visual hallucinations, depression, and sleep disturbances [31], which may affect drug adherence. Efavirenz was among the most commonly prescribed NNRTIs but may cause neuropsychological symptoms in approximately 50% of patients, including hallucinations, mania, and depression, while also being linked to the induction of proinflammatory cytokines [32]. Neuropsychological symptoms may begin in as few as 2–4 weeks, and efavirenz has been associated with memory loss and multi-domain cognitive impairment [29, 31]. *As a consequence, efavirenz is relatively contraindicated in patients diagnosed with HAND.*

Protease inhibitors (PIs), like ritonavir, lopinavir, and indinavir, block the cleavage of HIV protein precursors into mature viral proteins. Based on in vitro and clinical studies, their toxicities vary by individual PI. Ritonavir may cause dizziness, circumoral paresthesias, and nausea [29]. In vitro studies suggest that the PI indinavir may inhibit nicotinic acetylcholine receptors [33], potentially contributing to

cognitive dysfunction. From a clinical perspective, PIs are strong inhibitors of the cytochrome P450 enzyme CYP3A4, resulting in potential drug-drug interactions with macrolide antibiotics, calcium channel-blocking agents, and other commonly prescribed medications [34]. Integrase inhibitors, such as raltegravir and dolutegravir, block the integration of viral cDNA into the host cell's DNA. Neuropsychological symptoms have been reported, but, to date, interference with cellular mechanisms implicated in cognitive function has not been seen [29, 31, 32].

Section Summary

Despite the marked benefits of ART for prolonging life and preventing the more severe forms of HIV dementia, HAND still affects approximately half of PLWH. In many individuals with HAND, cognitive decline continues at a slow rate despite effective viral suppression. As outlined above, this decline is likely multifactorial. As evidenced by the occurrence of detectable CSF HIV RNA despite undetectable serum HIV RNA, HIV may become compartmentalized within the CNS, which contributes to an increase in neuroinflammation that may also become self-perpetuated. HIV sequestered within the CNS may be resistant to a variety of antiretrovirals due to inadequate CNS penetration. Finally, individual antiretrovirals have their own idiosyncratic neurotoxicities, which may also contribute to neuronal dysfunction and cognitive decline in selected cases. Early initiation of effective antiretroviral regimens has the potential to prevent the progression of HIV-associated cognitive impairment.

Premature Aging, Geriatric Syndromes, and HAND

Much of the immunosenescence that accompanies aging is replicated in chronic HIV infection. As PLWH get older, the twin insults on the immune system of HIV and aging promote a hyper-inflammatory state that contributes to diseases associated with aging, such as coronary heart disease (CHD), certain cancers, osteoporosis, frailty, and major neurocognitive disorders [11, 35]. CD4+ cells principally reside in the gut and are rapidly depleted during acute HIV infection. This leads to damage to gut epithelium and translocation of bacterial products from the gut microbiome, setting off an inflammatory cascade with production of TNF-α and interleukin (IL)-6, as well as the activation of clotting factors [11, 36]. Even with effective ART, markers of chronic inflammation still persist. Alterations in the composition, diversity, and function of the gut microbiome bear a similarity to what occurs in aging, with disruption of the mucosal barrier and low-level translocation of gut bacteria, leading to persistent immune activation [37]. In an analysis of individuals aged 45–76, virally suppressed HIV participants of the Strategies for Management of Antiretroviral Therapy (SMART; viral load ≤400 copies/mL) were compared to participants of the population-based Multi-Ethnic Study of Aging

(MESA). SMART participants on average had a 37.8% higher C-reactive protein, 60.1% higher IL-6, and a 49.1% higher level of D-dimer (all $p < 0.001$) [38], underscoring the persistence of chronic inflammation.

Age-associated changes in innate and adaptive immunity ("immunosenescence") are accompanied by an imbalance between pro- and anti-inflammatory states, resulting in subclinical, low-grade inflammation dubbed "inflammaging." This increase in inflammation is believed to contribute to the development of atherosclerosis [39], potentially resulting in coronary heart disease and vascular cognitive impairment. Many of the T cell abnormalities seen in HIV infection resemble age-associated immunosenescence: increased inflammatory markers like IL-6, low proliferative potential for T cells, a low naive to memory cell ratio, and a lower CD4+ to CD8+ ratio [40].

PLWH have higher rates of myocardial infarction and other forms of cardiovascular disease (CVD) when compared to age-matched uninfected individuals [10, 41], and the age of onset often occurs earlier in middle age [10]. Observational studies in the United States and Europe found that persons living with HIV had a risk of CHD that was approximately 1.5–2 times greater than the control population, even after controlling for traditional risk factors [36, 42]. PLWH, now on average over age 50 in most developed countries, have a high prevalence of non-calcified coronary plaque. The increased macrophage-associated inflammation in HIV may therefore contribute to the accumulation of pro-inflammatory macrophages in non-calcified, "soft" plaques and add to atheromatous inflammation [43]. Carotid intima-media thickness (CIMT) measurements, used in epidemiologic cohort studies as a marker for atherosclerotic cardiovascular disease, indicate that earlier atherosclerosis may occur in middle-aged PLWH receiving HAART [10]. During the HAART era, CVD mortality in PLWH has risen steadily, despite declining CVD mortality in the general population. HIV patients still have an increased risk of ischemic stroke compared to the uninfected population [44].

Vascular cognitive impairment (VCI) refers to a diverse group of pathological processes which cause ischemic changes in the brain that culminate in cognitive impairment. The most common cause is atherosclerotic vascular disease. In 2017, the Vascular Impairment of Cognition Classification Consensus Study agreed on two forms of VCI, *mild* and *major*, with mild causing impairment in at least one cognitive domain without any impairment in activities of daily living. Major VCI, also known as vascular dementia, produces clinically significant deficits in ≥ 1 cognitive domain as well as severe disruption of activities of daily living not attributable to motor or sensory deficits [45]. Mild VCI may present with clinically silent small vessel disease causing microinfarcts not visualized on standard MRI. As mild VCI progresses to major VCI, lacunar and larger-sized infarcts become apparent, and white matter changes become more prominent. The definitions of mild and major VCI overlap with the ANI and HAD definitions in HAND, respectively, and both share multiple radiographic and pathologic features [46]. MRI and CSF analyses were performed on 94 HIV volunteers without CNS infection or tumor. Although the sample had a mean age of only 45 years, 89 (95%) of

the patients had multifocal or diffuse white matter changes. Fifty-five (59%) had at least mild periventricular white matter disease, and 30 (32%) showed mild-severe white matter changes within the basal ganglia. Patients with higher-grade white matter changes had higher levels of total tau in the CSF, a measure of neurodegeneration [47].

Inflammation outside of and within the brain can occur as a result of other disorders prevalent in older age, including in PLWH. As PLWH age, the prevalence of conventional CVD risk factors – diabetes mellitus, metabolic syndrome, hypertension, hyperlipidemia, and central obesity – has increased commensurately, compounding HIV-mediated atherosclerosis and contributing to VCI. Conventional ASCVD risk factors in HIV patients are amenable to interventions like statins and blood pressure control but may not eliminate HIV-associated risk of inflammation and atherosclerosis.

Based on the Fried criteria, frailty can be defined as unintentional weight loss, poor strength (measured by grip strength), slow gait, feeling exhausted, and low levels of activity [35]. One to two frailty criteria define a pre-frail state, and 3 or more criteria fulfill the definition of the full frailty state. Frailty and its individual components have been associated with higher levels of inflammatory markers such as IL-6 [48]. Geriatric syndromes are conditions of multifactorial etiology that are prevalent in old age and include falls, urinary incontinence, impaired mobility, depression, cognitive impairment, as well as frailty, and they have been linked to elevated inflammatory markers [48]. In a research cohort of 94 predominantly male patients with HIV (median age 57 years, interquartile range 54–62), 56.1% were pre-frail, 25.8% reported falls, 21.9% had impaired mobility, 46.5% had difficulty with at least 1 instrumental activity of daily living, and 9% were fully frail. Notably, 46.5% had cognitive impairment based on the Montreal Cognitive Assessment [49]. Using the Rockwood frailty index in an older cohort of 103 PLWH who were functionally independent with undetectable viral loads (mean age and SD 56.4 ± 6.1), the presence of cognitive impairment on one or more of three neuropsychological tests was associated with a significantly higher frailty index than in individuals without subjective or objective cognitive impairment [50]. Frailty, closely associated with chronic inflammation, is an independent risk factor for cognitive impairment in PLWH.

Section Summary

The chronic inflammation from HIV (*HIV-flammation*) shares features with the inflammation resulting from aging of the immune system (*inflammaging*). These two sources of inflammation interact additively, if not synergistically, to culminate in the premature aging seen in PLWH. In PLWH, the atherosclerosis resulting from this inflammation may lead to vascular changes in the brain that resemble white matter changes seen in older HIV-free individuals. These HIV-associated vascular changes may progress to HAND, which bears a resemblance to vascular cognitive impairment. The frequent co-occurrence of geriatric syndromes like frailty,

sarcopenia, impaired mobility, and neurocognitive impairment at a comparatively younger age in PLWH suggests that the management of HAND requires a "geriatric" approach that addresses the simultaneous impact of these "geriatric syndromes" and related comorbidities on the patient's functional status and quality of life.

Neurocognitive Screening for HAND

Introduction

The gradual onset of neurocognitive deficits is often overlooked during the longitudinal care of patients. In contrast to acute conditions or easily recognized laboratory abnormalities, gradual, often subtle neurocognitive changes may not elicit complaints from the patient or be clinically recognized unless actively suspected and systematically investigated by the treatment team. This represents one of the key barriers to the early identification and treatment of HAND. The diagnosis of any neurocognitive disorder is clinical and supported by neuropsychological tests. "Soft signs," such as the ones observed in the case of Ms. S (Case 10.2), may already indicate the insidious development of HAND in the form of asymptomatic neurocognitive impairment (ANI). Unless actively asked about and screened for, the early manifestations of ANI may be missed. Systematic cognitive assessments remain the cornerstone of diagnosis and longitudinal monitoring, for which additional laboratory and neuroimaging investigations may provide additional information. Ideally, cognitive monitoring should be done by a highly cohesive multidisciplinary team "that knows the patient."

As HIV has evolved from a progressive, nearly universally fatal illness to a chronic illness with which PLWH may age into their seventh decade and beyond, more sensitive cognitive screening is now required to identify the incidence and prevalence of neurocognitive decline in this population. In clinical practice, a panoply of comorbid conditions shape HAND into unique presentations depending on underlying aging-related comorbidities (e.g., kidney and cardiovascular diseases), co-infections (e.g., hepatitis C, syphilis), and the development of neurodegenerative disorders like Alzheimer's disease. Furthermore, predisposing factors for cognitive vulnerability, such as a formal diagnosis of intellectual disability, traumatic brain injury, or a co-occurring mood or psychotic disorder, may further fuel the risk for the development and aggravation of HAND manifestations.

From a syndromic perspective, depression and apathy are the most observed comorbidities in chronic HAND, with depression occurring about twice as commonly as apathy. Over 40% of PLWH may develop major depressive disorder (MDD) throughout their lives, and about 1 in 4 may be currently experiencing a major depressive episode: eight times more likely than in the general population [51]. MDD can affect cognitive performance and thus confound neurocognitive screening. Consequently, depression should be treated prior to a formal diagnosis of HAND (especially ANI and MND subtypes), and screening for depression should be performed routinely in PLWH.

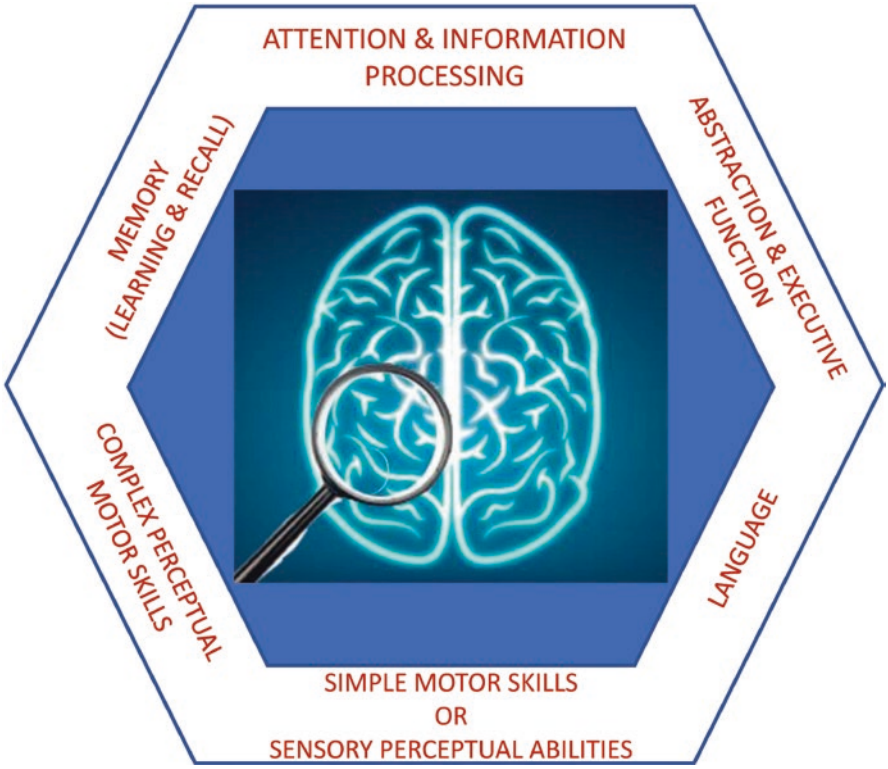

Fig. 10.4 Core neurocognitive domains recommended in the Frascati criteria for the assessment of HIV-associated neurocognitive impairment (HAND). (Based on data from Ref. [2]; brain logo courtesy of freepik.com)

Selecting the Right Approach for Your Patient Population and Clinical Setting

The neuropsychological spectrum of HAND ranges from asymptomatic neurocognitive impairment to a mild neurocognitive disorder to HIV-associated dementia (Table 10.1 and Fig. 10.4).

Using screening questions: The Frascati criteria for HAND are predicated on neuropsychological testing of at least five of six neurocognitive domains: attention-information processing, abstraction-executive function, language, complex perceptual motor skills, memory (learning plus recall) and simple motor skills, or sensory perceptual abilities [2]. Formal neuropsychological testing remains the gold standard for assessing cognition in HAND but is expensive, time-consuming (averaging about 2 hours or more), and not always available to clinicians or their patients. Consequently, alternative, more time-efficient but valid cognitive screens have been sought. Although not sufficient to rule out HAND, querying about cognitive functioning and functional status can identify patients who would benefit from more in-depth assess-

ment and should be integrated into the regular clinical follow-up of PLWH. Simioni and colleagues developed three simple questions to identify patients with cognitive complaints but undetectable levels of HIV-1 (mean age = 47 years). Please see Table 10.3 for the Simioni questions. HIV patients with complaints were 15 times more likely than non-complaining HIV patients to be diagnosed with MND or HAD [52]. The guidelines of the European AIDS Clinical Society (EACS) recommend using the Simioni questions as a means to screen for neurocognitive impairment at the time of diagnosis and periodically after the initiation of treatment, depending on patient's symptoms. If the patient answers "yes, definitely" to any of these questions, clinicians are advised to first rule out depressive disorders and then refer for neuropsychiatric assessment. The guidelines also provide a useful algorithm for the diagnosis of HAND in PLWH without obvious confounding comorbidities [53].

Functional status and performance of social roles add an important dimension to screening by providing insight into the personal impact of HIV. The Medical Outcomes Study HIV (MOS-HIV) uses a validated, 35-item questionnaire that assesses domains such as pain, physical functioning, quality of life, and social and cognitive functioning and takes roughly 5 minutes to complete [54]. The instrument is accessible to clinicians and researchers at the PROQOLID website [55]. Instrumental activities of daily living correlate well with executive function and include higher activities such as using the telephone, shopping, financial management, and meal preparation. By definition, they are unlikely to be impaired in ANI, although impairments may be reported in MND and HAD. In asymptomatic neurocognitive impairment, alterations in cognition are likely to be subtle and may be manifested by changes in work performance or the ability to carry out previously routine leisure activities like playing games, complex hobbies, handling email, and household repairs. These activities, individualized for the patient, have been referred to as Advanced Activities of Daily Living (AADL). Ms. S in Case 10.3 admitted to increased difficulties interrogating witnesses as an attorney and shifted her work to contracts. This subtle decline in function prompted referral for neuropsychological testing and the diagnosis of asymptomatic neurocognitive impairment. Not all patients with HAND will have evaluable AADL, limiting the utility of this screening tool. An example of AADL that cover a broad range of activities can be found in the questions used by De Vriendt and colleagues [56] to explore subtle changes in performance quality as well as frequency of activities that

Table 10.3 Simioni questions

Question	Never	Hardly ever	Yes, definitely
Do you experience frequent memory loss (e.g., do you forget the occurrence of special events, even more recent ones, appointments, etc.)?	☐	☐	☐
Do you feel that you are slower when reasoning, planning activities, or solving problems?	☐	☐	☐
Do you have difficulties paying attention (e.g., to a conversation, a book, or a movie)?	☐	☐	☐

Based on data from Ref. [52]

Table 10.4 Instrumental activities of daily living (self-report version)

	Activity	Score
1.	*Can you use the telephone*	
	Without help	3
	With some help	2
	Are you completely unable to use the telephone?	1
2.	*Can you get to places out of walking distance*	
	Without help	3
	With some help	2
	Are you completely unable to travel unless special arrangements are made?	1
3.	*Can you go shopping for groceries*	
	Without help (or don't do this but could without help)	3
	With some help (or would need some help)	2
	Are you completely unable to do any shopping?	1
4.	*Can you prepare your own meals*	
	Without help (or don't do this but could without help)	3
	With some help (or would need some help)	2
	Are you completely unable to prepare any meals?	1
5.	*Can you do your own housework*	
	Without help (or don't do this but could without help)	3
	With some help (or would need some help)	2
	Are you completely unable to do any housework?	1
6.	*Can you do your own handyman work*	
	Without help (or don't do this but could without help)	3
	With some help (or would need some help)	2
	Are you completely unable to use the telephone?	1
7.	*Can you do your own laundry*	
	Without help (or don't do this but could without help)	3
	With some help (or would need some help)	2
	Are you completely unable to do any laundry at all?	1
8a.	*Do you take medicines or use any medications?*	
	Yes → Answer Question 8b	
	No → Answer Question 8c	
8b.	*Do you take your own medicine*	
	Without help (in the right doses at the right time)	3
	With some help (take medicine if someone prepares it for you and/or reminds you to take it)	2
	(Are you/would you be) completely unable to take your own medicine?	1
8c.	*If you had to take medicine, can you do it*	
	Without help (in the right doses at the right time)	3
	With some help (take medicine if someone prepares it for you and/or reminds you to take it)	2
	(Are you/would you be) completely unable to take your own medicine?	1
9.	*Can you manage your own money*	

(continued)

Table 10.4 (continued)

	Activity	Score
	Without help (or don't do this but could without help)	3
	With some help (or would need some help)	2
	Are you completely unable to handle money?	1

For each question, circle the number corresponding to how much help you need (or would need)
Based on data from Lawton and Brody [127]

may reflect early cognitive decline. Driving is nearly ubiquitous and requires the rapid processing of simultaneous sensory inputs. Getting lost while driving to familiar locations, recent traffic violations, or accidents (major or minor) may indicate decline of executive function or motor processing speed that merits further evaluation. Invaluable information about neurocognitive and functional decline often comes from concerned family members and intimate partners, whose input should be sought if the patient consents (Table 10.4).

Using screening instruments: The line between ANI and MND is often indistinct, due to uncertainties regarding what defines dependence versus independence in daily activities. Because of cultural, gender, educational, or social factors, PLWH may not be employed, have hobbies, or perform standard instrumental activities of daily living. Assessment can be facilitated by using validated screening tools when a comprehensive neuropsychological battery is not readily available. The selection of routine screening tools for this proactive cognitive monitoring needs to be tailored according to clinical setting, patient population, and cultural appropriateness. For example, busy primary care clinics with short appointment times require sensitive, time-efficient screening instruments, whereas a specialized clinic for the care of HIV psychiatry patients may seek in-depth screening tools with high specificity to provide a more refined understanding of the cognitive domains involved, enabling individualized treatment strategies to be developed.

HIV-focused neurocognitive screening: Brief neurocognitive screening tests have been developed specifically for HIV. The HIV Dementia Scale (HDS) was developed early in the AIDS pandemic when HIV dementia affected up to 20% of HIV-infected individuals with an annual incidence of 7% [6]. The HDS consists of four timed tests and one recall test but requires training in the measurement of anti-saccadic eye movements. A score of <10 points suggests HIV dementia and is associated with a sensitivity and specificity of 80% and 91%, respectively. However, these pertain to the detection of HIV dementia and not detection of the subtler ANI and MND forms of HAND [6]. In the HAART era, the HDS has yielded a high sensitivity of 96.2% for ruling out HAND, but its sensitivity drops to 54.1% [52], rendering it unsuitable as a stand-alone screening instrument.

The International HIV Dementia Scale (IHDS) tests motor speed, psychomotor speed, and memory recall and can be completed in under 10 minutes, with a cutoff of ≤10 out of 12 suggesting need for further testing. Compared to the HDS, it has

the advantage of not including the difficult-to-administer evaluation of anti-saccadic eye movements. The IHDS has been validated in the United States and Uganda, and thus has transcultural validity, but because it was originally developed to detect HIV dementia (HAD using the Frascati criteria), its utility as a screening tool has been questioned. In its original validation, its good sensitivity of 80% was balanced by a modest specificity of only 55%, limiting its role to screening without the ability to convincingly rule out HIV-related cognitive impairment. In an East African cohort in which 68% were receiving HAART, the sensitivity rose to 68%, but the specificity dropped to 17% using the standard cutoff of ≤10, and no acceptable sensitivity/specificity balance could be found for any cutoff [57]. In the Dutch TREVI cohort study [58], the addition of the IHDS to the three Simioni questions resulted in a sensitivity and specificity of 50% and 73%, respectively. In an evaluation of the psychometrics of HAND screening in Thailand, the IHDS (cutoff ≤10) similarly had poor sensitivity (53%), but when the Trail-Making Test A, a simple, short, and timed paper-and-pencil test that assesses psychomotor speed, was added to the IHDS (using a cutoff of ≤1 standard deviation below the age-related norm), the sensitivity and specificity rose to 86% and 79%, respectively, for *symptomatic* HAND (MND and HAD but excluding ANI) [59]. However, this combination needs to be validated in other populations before being recommended for general use.

There are few data on the use of longitudinal screening, the optimal frequency of screening, the biasing (or practice) effects of repeated testing on scores, or agreement on the extent of baseline impairment that warrants in-depth neuropsychological testing. However, a consensus has developed that effective screening for HAND requires a sensitivity and specificity of ≥70%. "Neuropsychological testing – lite" may be able to yield acceptable sensitivities and specificities while using as few as two neuropsychological tests, such as the Hopkins Verbal Learning Test and the Wechsler Adult Intelligence Scale III, or the paper-and-pencil Trail-Making Test Parts A and B used in combination with letter fluency (e.g., the number of words beginning in "F" that can be named in 60 seconds) [60]. "Neuropsychological testing – lite" may be an acceptable approach that could be adapted to the office setting and performed by staff trained by a neuropsychologist. The 2012 consensus report of the Mind Exchange Program recommends the use of selected screening tools every 6–12 months if the patient is at high risk for cognitive decline, every 12–24 months if the patient is at low risk, and immediately in the case of suspected cognitive deterioration [61].

Montreal Cognitive Assessment: The Montreal Cognitive Assessment (MoCA) was introduced in 2005 as a validated, 10-minute screen for mild cognitive impairment in older adults [62]. Its incorporation of tests of executive function (mini-Trails B, copying a diagram, and clock draw) broadens its potential applicability to ANI and MND. However, when compared to neuropsychological testing, its performance for the diagnosis of HAND has been modest, with variable results based on small, unrepresentative test populations of HIV+ subjects [63–65]. Based on receiver operating characteristics (ROC) curves, two studies found an optimal cutoff

score of <26 out of 30 on the MoCA but identified markedly different sensitivities (56% and 84%) with mediocre specificities (63% and 56%) [63, 64]. In a third study, the optimal cutoff by ROC curve was <25, yielding a sensitivity of 72% and specificity of 67% [65]. Although false-positive screens can be expected, these results suggest that the MoCA has potential as a practical general screening tool for

Table 10.5 Summary of instruments for cognitive assessment in HAND

Instrument	Duration	Cutoff values	Key cognitive domains tested	Strengths	Weaknesses
International HIV Dementia Scale (IHDS)	4 mins	≤11	Psychomotor speed/ processing Short-term memory	Time efficient Average sensitivity High specificity	Evaluates fewer domains Limited utility for screening Suboptimal for screening in lower suspicion cases
Montreal Cognitive Assessment (MOCA)	13 mins	<26 for screening	Executive function, calculation, visuospatial skills, abstraction Attention, concentration, orientation, language, episodic memory	The most sensitive test (ideal for screening) Evaluates various domains	Low specificity for the diagnosis Time-consuming
Mini-Mental State Examination (MMSE)	12 mins	≤24 for diagnosis	Visuospatial skills, language, concentration, orientation, working memory, memory recall	The most specific test (i.e., higher probability of HAND when positive)	Low sensitivity for the diagnosis (i.e., cannot rule-out) Time-consuming, copyrighted
Simioni Symptom Questions (SSQ)	3 mins	≥1 for screening	Not applicable	Minimal time requirement Good sensitivity Focus on symptoms	Low specificity Does not evaluate cognitive domains
Cognitive Assessment Tool Rapid version (CAT-rapid)	7 mins	≤10 for screening	Executive function Short-term memory	Time-efficient Average sensitivity and specificity Has symptom questions	Evaluates fewer domains
Clock Drawing Test	2 mins	Depends on scoring method	Executive function, visuospatial skills, concentration, working memory, abstraction, motor skills	Smallest time requirement	Requires motor skills Evaluates fewer domains

HAND. The MoCA is available in multiple languages, and as a longitudinal screening tool, it also has the advantage of having multiple validated versions in major languages, reducing the risk of prior exposure influencing the score.

Conclusions Regarding Cognitive and Functional Screening

A summary of available screening instruments can be found in Table 10.5. At present time, office-based neurocognitive screening strategies that rely upon a single test may fall below acceptable ranges for sensitivity and/or specificity. The combination of the International HIV Dementia Scale (IHDS) and the Trail-Making Test Part A yields acceptable sensitivities and specificities. Published normative data for the Trails A can be used to identify age-based cutoffs for completion times [66]. Abbreviated neuropsychological testing that utilizes two or three elements of the full neuropsychological test battery ("neuropsychological testing – lite") holds potential but requires further validation as well as training of staff in basic psychometrics. Although imperfect, the Montreal Cognitive Assessment (MoCA) appears to have adequate sensitivity but may falsely identify patients with HAND. The MoCA, IHDS plus Trails A, and "neuropsychological testing – lite" should be supplemented by self-reports from the patient about cognitive and functional status, which can be standardized and incorporated into pre-visit questionnaires. When there is uncertainty over the diagnosis of HAND, especially of ANI, neuropsychological testing should be sought whenever possible.

Role of Neuroimaging and Laboratory Analysis

Neuroimaging as a Biomarker

Magnetic resonance imaging (MRI) and more advanced techniques like magnetic resonance spectroscopy, diffusion tensor imaging, and functional MRI correlate with the severity of HAND [47] and provide insight into HIV neuropathology. However, there currently is insufficient evidence to recommend any of these modalities as a replacement for neuropsychological testing to diagnosis HAND and monitor its clinical progression. With the advent of HAART, the incidence of HIV dementia (HAD) has dramatically decreased, along with a commensurate reduction in the incidence of characteristic subcortical changes on cranial imaging. In the pre-HAART era, computed tomography and MRI were important in identifying space-occupying lesions from opportunistic infections and malignancies. This role still remains relevant in HAD and MND, but neuroimaging may not be necessary in patients with ANI unless there are concomitant abnormalities on neurological examination or the cognitive changes appear subacute.

Neuroimaging can be used to support a diagnosis of HAND and help differentiate it from other causes of major neurocognitive disorders. In younger patients with HIV, MRI scans may show cerebral atrophy or periventricular white matter disease

in excess of normative values for the patient's age, even in individuals with normal cognitive function [67]. As PLWH age, other types of neurocognitive disorders like vascular cognitive impairment, Alzheimer's disease (AD), and mild cognitive impairment may compete with HAND and share many of its morphometric features. Differentiation of HAND-related stages like MND from early AD is suggested by different patterns of cerebral atrophy. In early AD (a cortical dementia), cortical atrophy affects the entorhinal cortex and hippocampus, which may be reduced in volume. By contrast, HAND, particularly the MND and HAD subtypes, causes atrophy in a more subcortical pattern, affecting the cortical motor strip, cerebellum, and the basal ganglia [68]. It should be noted, however, that patients with HAND can simultaneously suffer from vascular cognitive impairment (VCI) and/or a neurodegenerative disorder like AD.

Positron emission tomography (PET) provides complimentary imaging of the molecular mechanisms underlying the pathophysiology of HAND. Abnormalities in fluorodeoxyglucose (^{18}F-FDG) PET imaging have been seen in PLWH without cognitive impairment and showing effective virological suppression with HAART. However, ^{18}F-FDG PET does not correlate well with clinical and cognitive function in the various forms of HAND [69], and the use of PET in 2020 remains largely experimental.

Blood and CSF Markers

Although apolipoprotein E (Apo-E) is a genetic risk factor for AD, it is neither sensitive nor specific, particularly in the very old. Thus, it is not useful for differentiating HAND from AD. Both low vitamin B12 and hypothyroidism are potentially reversible contributors to cognitive impairment, regardless of the etiology, and consequently should be checked.

There is a substantial interest in identifying CSF biomarkers for HAND. However, lumbar punctures (LP) are invasive and uncomfortable and may be technically difficult in older adults. As a consequence, information obtained from a LP should have high sensitivity and specificity as a diagnostic tool, as well as offer a clear benefit in directing therapy.

Neurofilament light (NF-L), found in myelinated axons, serves as a biomarker of neuroaxonal damage and is present in numerous neurodegenerative conditions, including vascular dementia, amyotrophic lateral sclerosis, Huntington disease, frontotemporal dementia, and Alzheimer's disease. HIV researchers have observed the highest levels in HIV-associated dementia, including patients with mild neurocognitive disorder [68, 70]. However, levels of NF-L overlap between conditions, and in HIV, levels must be adjusted for age, gender, and disease severity. Older PLWH may have coexisting conditions like cerebral vascular disease that also elevate NF-L, muddying the interpretation of

levels. As a consequence, CSF NF-L cannot be recommended for screening or monitoring.

Others have investigated the role of CSF Microtubule Associated Protein-2 (MAP2), which rises in brains infected with HIV because of the toxic effects of the HIV protein gp120 on microtubules [71]. Although PLWH with a diagnosis of HAND have higher levels of CSF MAP2, compared to normal controls [71], more research is required to establish norms for other neurodegenerative conditions, and it offers no advantage as a screening tool.

Detecting CSF viral load: Case series have described detection of viral replication in the CSF despite effective suppression of the plasma viral load, a phenomenon known as viral escape. Cases also have been described of the emergence of resistant viral strains in the CSF [20]. In patients on ART who develop new neurological findings or show an acceleration of cognitive decline, concern for viral escape should prompt consideration of a lumbar puncture to obtain a CSF viral load.

Section Summary

Optimal screening for HAND starts with raising awareness and establishing best practices in the identification of soft signs of neurocognitive decline. The decision on what screening instruments to use will largely depend on the setting (primary care vs. specialized clinic), patient population (substance misuse, extremes of age, comorbid psychiatric conditions), and the availability of resources to the treatment team (advanced brain imaging, advanced CSF assays, neuropsychological testing).

Since the advent of HAART, the milder forms of cognitive impairment (asymptomatic neurocognitive decline and mild neurocognitive disorder) dominate HIV-associated neurocognitive decline, rendering HAND a largely silent process with the potential for significant morbidity and negative impact on quality of life. In the office setting, neuropsychological screening of PLWH can be done using simple questionnaires targeting performance of daily activities as well as short cognitive screening instruments, but the gold standard remains formal neuropsychological testing. Neuroimaging plays a limited role in screening but may be helpful in trying to differentiate HAND from other age-associated neurocognitive disorders. Lumbar puncture to analyze cerebrospinal fluid for HIV viral load is indicated principally in PLWH who have effective peripheral viral suppression yet are experiencing progressive cognitive decline.

Basic Principles for the Management of HAND

HAND, Comorbidities, and Functional Decline

As persons living with HIV (PLWH) age, HAND usually occurs in the context of multimorbidity, with an associated impact on physical functioning. Over 45% of a cross-sectional sample of 452 PLWH over age 49 reported 4 or more of 20 non-infectious chronic conditions. Within the entire sample, the investigators observed a mean decline of 34% and 42% from optimal social and physical functioning, respectively; the number of chronic conditions correlated significantly with the degree of functional impairment ($p < 0.001$) [72]. A sample of 3227 veterans with HIV was compared cross-sectionally to 3240 non-infected veterans, and functional scores associated with aging were estimated from the mean values of different age groups. Although the predicted functional score declined from age 45 in both groups, the observed decline was slightly but significantly greater in the HIV-positive group after age 49 [73].

The Importance of a "Geriatric" Approach

Age-associated changes in organ function interact with multimorbidities to produce declines in physical and psychosocial functioning that adversely affect quality of life as individuals progress into old age. Rather than addressing individual medical problems as if independent of one another, geriatric medicine recognizes the interconnectedness of multimorbidities, medications, and physical functioning and centers its approach in the optimization of overall functional status. In recent years, this approach has been formalized into the paradigm of "5 Ms.:" *m*ind, *m*edications, *m*obility and self-maintenance, *m*ulticomplexity, and what *m*atters most to the patient. The 5 Ms. lend themselves to the overall management of HAND and have been proposed as a paradigm for all older PLWH, with the addition of a sixth M for *m*odifiable risk factors [74].

Mind: Persons with HAND or at risk of developing this condition require monitoring of their cognitive status at regular intervals. The optimal frequency of cognitive screening should be determined by initial severity and clinical suspicion. This suspicion, in turn, is raised by regularly inquiring about their instrumental and advanced activities of daily living. What is important is not merely whether or not they are dependent in an activity, but how well they are doing it from a cognitive standpoint compared to historical baseline. "Mind" also refers to mood disorders and other mental illness, discussed elsewhere in this book. Depression bears a complex relationship to HAND. Major depressive disorders (MDD) have been associated with HAND in the literature, but the relationship is confounded by depression-associated non-adherence to antiretrovirals and antidepressants. Some longitudinal cohort studies have shown that although PLWH have a higher incidence of complaints of cognitive impairment, cognitive impairment often is not substantiated on formal

neuropsychological testing [75]. Nevertheless, the co-occurrence of MDD and HAND should prompt careful neuropsychological screening whenever depressive symptoms are detected, and PLWH should be assessed for depressive symptoms as part of their screening for HAND.

Medications: Polypharmacy (by convention, taking ≥5 prescription medications) is a hazard of the comorbidities that accompany aging. PLWH have a high burden of comorbidities even when adjusted for age [72, 76]. In the Multicenter AIDS Cohort Study, 1715 HIV-positive and 1445 HIV-negative participants were followed for up to 12.5 years. Across all study visits, after adjustment for age, race, and medication insurance, participants in the HIV-positive cohort had a 6.6% higher prevalence of polypharmacy than HIV-negative participants (25.3% v 18.7%, $p < 0.0001$) [77]. HIV-positive individuals ≥ age 50 have a high prevalence of non-HIV polypharmacy, and one third show at least 1 potential drug-drug interaction [78]. Polypharmacy has been associated with a 52% increased risk of hospitalization (95% CI 1.49–1.56) and a 43% increased risk of mortality (95% CI 1.36–1.50) that are independent of HIV status [79]. The potential adverse effects of antiretroviral medication have been outlined above. As the number of medications accumulates due to multiple primary care and subspecialty prescribers, clinicians caring for PLWH need to periodically review the medication list of their patients for adverse drug reactions and potential drug-drug interactions, eliminating potentially inappropriate medications whenever possible. Potentially inappropriate medications that should be avoided in older adults are applicable to PLWH and can be found in the Beers criteria [80]. Clinicians should also bear in mind that drug metabolism may be altered due to changes in kidney and liver function that have occurred as a result of HIV itself or chronic diseases like hepatitis C.

Mobility and self-maintenance: Mobility involves all aspects of patient movement, including locomotion, gait speed, self-propulsion (if wheelchair-bound), transferring, and repositioning in bed or chair. Mobility is inextricably linked with balance and coordination and is an important measure of functional independence. Gait speed declines with aging and is an established predictor of functional decline and mortality. Mr. J could not walk due to his hip fracture, but his rapid alternating movements served as a proxy of motor integrity and were noticeably slow. Impaired mobility, slow gait, and cognitive impairment often co-occur in PLWH. In a group of HIV-positive volunteers (median age 57, interquartile range 54–62), 22% reported mobility impairment, and 47% demonstrated cognitive impairment [49]. PLWH appear to experience a more rapid decline in gait speed compared to non-infected individuals. In a cohort of 973 HIV-positive and 1052 HIV-negative men (mean age 50.5 years) followed for 6 years, gait speed (i.e., usual gait at a "normal, comfortable pace") in the HIV-positive group declined an average of 0.025 m/s faster than in HIV-negative men, and HIV-positive men had a 57% higher risk of developing a severely slow gait (defined as <1.0 m/s) [81].

Self-maintenance involves instrumental and advanced activities of daily living (IADL and AADL). Relevant to HAND among IADLs are handling finances and medication management. AADLs address the more nuanced changes in the quality of occupational performance as well as changes in recreational pursuits and how well they are done. In Case 10.1, Mr. J gave up an antiques business for unclear reasons. What produced the stress to which he alluded? Was he losing the ability to multitask or handle the finances? He also did not manage his own medications. Why? Did he forget to take them? There is no information on his recreational activities, but a history should be taken on what recreational pursuits the patient has stopped doing in recent months. For example, if Mr. J had been a Scrabble™ player but gave it up, could that have been caused by a decline in his vocabulary or visual perceptiveness? These subtler changes might warrant more sensitive neuropsychological testing, if available. In Case 10.2, Ms. S gave up litigation work for contracts and trusts at her law firm and as part of neuropsychological testing took an IQ test on which she scored lower than anticipated based on her level of education. Both of these findings raise concern about subtle cognitive decline related to HAND. Ms. S needed formal neuropsychological testing rather than a quicker but less sensitive screen like the Montreal Cognitive Assessment.

The role of medications in the management of HAND: It is beyond the scope of this chapter to discuss specific antiretroviral drug regimens in this rapidly changing field. However, a long-standing concern has been that HAND develops despite low or undetectable peripheral viral loads. Sequestration of HIV-1 within the CNS has been postulated as a contributor to HAND, and consequently, there has been intense interest in improving the CNS penetration of antiretrovirals. In 2008, Letendre et al. validated a CNS penetration effectiveness score (CPE) by showing that drugs with lower CPE scores were associated with higher CSF viral loads after adjusting for the total number of antiretroviral drugs, estimated drug adherence, plasma viral load, the duration and type of drug, and the CD4+ count [22]. Letendre's group revised the CPE in 2010 [23]. As has been discussed above, neurocognitive impairment in HAND commonly resembles vascular cognitive impairment associated with atherosclerosis. Data from the Ontario HIV Treatment Network Cohort Study indicated that higher CPE scores based on the revised methodology of Letendre et al. [23] significantly correlated with a lower prevalence of neurocognitive impairment, although the prevalence of neurocognitive impairment remained relatively stable until the CPE score reached 9 or above [82]. Although identifying regimens with very high CPE remains a holy grail in HAND research, clinical results to date suggest that selecting a very high CPE regimen is likely to confer limited benefit in slowing the progression of HAND. CNS penetrance of an antiretroviral does not necessarily protect the CNS against cognitive decline. For example, efavirenz, a non-nucleoside reverse transcriptase inhibitor (NNRTI) with excellent CNS penetrance [26], has been associated with memory loss and multi-domain cognitive impairment [31]. Nevertheless, the consensus among HIV specialists is to maximize viral suppression as early as possible to mitigate penetration into the CNS and ideally stop the replication of virus that already has crossed the blood-brain barrier.

Current guidelines recommend antiretroviral therapy for all patients with HIV regardless of the CD4+ count [83] and also recommend antiretroviral therapy begin as soon as possible after an HIV diagnosis. Optimizing medication adherence and effecting lifestyle changes may require a multidisciplinary approach emphasizing psychosocial interventions.

Multicomplexity and what matters most: In a large research cohort of 22,969 adults with HIV, multimorbidity (defined as two or more comorbid conditions) significantly increased in prevalence between 2000 and 2009 after adjustment for age.[1] Twelve percent of participants aged 50–59 and 33% of participants over age 59 had three or more chronic conditions [84]. Multicomplexity embraces not only multimorbidity but also the often complex psychosocial and socioeconomic dynamics in which comorbid conditions occur. In Case 10.3, Ms. G-F has an acute cellulitis in addition to HIV-associated dementia as well as diabetes mellitus, hypertension, hepatitis C, and heart failure. Adding to the complexity of treatment were her homelessness, drug-use disorder, and lack of a reliable caregiver. HAND occurs within the context of increasing multicomplexity in the aging HIV population, and its management requires an assessment of the relationships among comorbidities and the interactions and side effects of the medications used to treat them. In PLWH, types of comorbid conditions tend to cluster in predictable and unpredictable ways, with mental health disorders significantly correlating with all identified comorbid clusters [85]. These disease clusters underscore pathophysiologic relationships and help prioritize realistic medical as well as psychosocial interventions like case management and social services. Listening to patient preferences and priorities may improve adherence to interventions by leading to negotiated treatment decisions and a willingness to accept the risk of some outcomes in favor of those that have a direct bearing on perceived quality of life.

Modifiable risk factors: As exemplified by the case of Mr. J and substantiated by the literature, atherosclerosis is highly prevalent in older PLWH and may contribute to HAND with or without reservoirs of HIV-1 that reside within the CNS. HIV-1 itself increases inflammatory mediators that contribute to atherosclerosis. Known non-HIV risk factors for atherosclerosis, such as hypertension, obesity, and diabetes mellitus can be reduced by aggressive treatment of these conditions with commensurate patient education and dietary and lifestyle modifications.

[1] Defined as >1 of the following conditions: hypertension, diabetes mellitus, chronic kidney disease, hyperlipidemia, end-stage liver disease, and non-AIDS-related cancer

Role of Cognitive Enhancers

HAND is a subcortical dementia similar to vascular cognitive impairment, but cognitive enhancers like cholinesterase inhibitors and memantine thus far have not shown statistically significant or meaningful improvement in cognitive function in small clinical trials [86–88]. Whether larger clinical trials will reveal a small but statistically significant benefit in HAND or its subtypes is unknown. As PLWH age into their 70s and 80s, non-HAND forms of neurocognitive impairment such as Alzheimer's disease will increase in frequency. As is currently the case, non-HIV progressive neurocognitive impairment may respond slightly to cognitive enhancers such as memantine and cholinesterase inhibitors. This responsiveness potentially could differentiate non-HIV neurocognitive impairment from HAND in addition to characteristic metabolic patterns seen on positron emission tomography and functional MRI. As of this writing, cognitive enhancers cannot be recommended in HAND despite generally being well tolerated.

Summary

The clinical management of HAND lends itself to a geriatric approach that emphasizes the optimization of the patient's functional status while recognizing the complex interactions of comorbidities, medications, and physical functioning. This approach fits into the paradigm of the "6 Ms": mind, medications, mobility and self-maintenance, multicomplexity, what matters most to the patient, and modifiable risk factors.

- Mind: PLWH require regular monitoring of their cognitive status and mood.
- Medications: Polypharmacy is common among PLWH, and clinicians caring for PLWH need to periodically review the medication list for drugs with potentially adverse drug reactions, drug-drug interactions, and potentially inappropriate medications as determined by validated criteria like the Beers criteria.
- Mobility and self-maintenance: PLWH commonly experience faster declines in gait speed and motor function than persons without HIV, potentially resulting in impairment of advanced and instrumental activities of daily living. As with older patients, mobility and functional status should be reviewed periodically, preferably using standardized instruments.
- Multicomplexity refers to the frequent co-occurrence of multiple comorbidities in the presence of complex psychosocial and socioeconomic problems. The average age of PLWH now exceeds 50 years, resulting in a growing number of comorbidities that need to be managed in the context of HAND.
- What matters most: Setting priorities for the management of the patient's comorbidities, HAND, and functional status depends on the patient's priorities and preferences for their quality of life.
- Modifiable risk factors: The clinical progression of HAND is influenced by comorbid neurocognitive disorders like progressive degenerative dementias and

vascular cognitive impairment, the latter influenced heavily by risk factors for atherosclerosis. Because HIV-1 increases inflammatory mediators that in turn predispose toward atherosclerosis, known risk factors like hypertension, diabetes mellitus, and obesity should be aggressively managed.

Part II. Delirium

Introduction

Delirium must be included in any discussion of the spectrum of neurocognitive impairment seen in HAND. Delirium can be conceptualized as acute brain failure and is usually reversible if a cause can be identified and addressed. Delirium classically refers to an acute disturbance in attention, awareness, and cognition that is a change from a person's baseline. It tends to fluctuate in severity throughout the day (and even within the hour) and is caused by underlying medical conditions that can include infection, sepsis, metabolic or chemical toxicity, and withdrawal states. However, the onset and presence of delirium can be subtle and its course protracted. For example, PLWH may experience sustained but potentially reversible memory loss and multi-domain cognitive impairment as a result of taking the non-nucleoside reverse transcriptase inhibitor (NNRTI) efavirenz for several weeks [29, 31]. An older woman with HIV and urinary incontinence might be prescribed oxybutynin, a potent centrally acting anticholinergic that may cause cognitive slowing or mild confusion. A PLWH given divalproex for bipolar affective disorder may develop hyperammonemia resulting in slowed mentation and confusion that could be misinterpreted as HAND. Depressive disorders, which can affect cognitive function, may occur idiopathically or arise as a toxicity from certain NNRTIs [31, 32] and contribute to neurocognitive dysfunction. The treatment of depressive disorders (or the withdrawal of the responsible drug) may improve cognition.

Delirium increases morbidity and mortality, even upon recovery, and may be associated with lingering functional impairment and/or acceleration of a premorbid cognitive impairment. It is a great imitator and presents differently in each patient, requiring a high index of suspicion, and it currently has eluded disease-specific

Table 10.6 Delirium subtypes

Hyper-active subtype	Disturbance in attention and cognition with mood lability and agitation, sometimes leading to uncooperativeness with medical care
Hypo-active subtype	Disturbance in attention and cognition with sluggishness, lethargy, and sometimes stupor
Mixed subtype	Disturbance in attention and cognition with normal level of psychomotor activity or with a fluctuating level of consciousness

Based on data from Ref. [93]

pharmacologic targets for prevention and definitive, disease-modifying intervention. This section will discuss the clinical features, pathophysiology, epidemiology, impact, and the diagnosis of delirium. The overall aim is to present recommendations on best practices for prevention and treatment based on the most recent evidence-based research, tailored to persons living with HIV (PLWH).

Clinical Features

The *Diagnostic and Statistical Manual of Mental Disorders* (DSM-5) describes delirium as an acute disturbance in attention, awareness, and cognition that is a change from a person's baseline. Classic delirium tends to fluctuate in severity throughout the day and is caused by an underlying medical condition that can include toxicity and withdrawal states. Similar to other organs in the body that fail under profound stress, delirium can be described as "acute brain failure" and should be treated with the same urgency, especially in patients with HIV who have delirium risk factors. The presentation of delirium varies and has been divided into three different motoric subtypes: *hyperactive*, *hypoactive*, and *mixed* level of motor activity. These states are based on the individual's psychomotor agitation and mood lability versus sluggishness and lethargy, whereas the mixed subtype is notable for a rapidly fluctuating presentation (DSM-5). The hypoactive subtype is often missed or misconstrued as "depressive disorder" and thus requires active monitoring and a high level of suspicion (Table 10.6).

Pathophysiology

The clinical presentation of delirium can be thought of as the combined manifestations of a final common pathway of pre-delirium subacute events occurring in a setting of varying degrees of pre-delirium vulnerability. The pathophysiological events leading to delirium are a complex cascade of inflammation, cytokine release, and oxidative stress, leading to multiple neurotransmitter dysregulation and impaired functional neural connectivity that are responsible for the objective signs of delirium.

Inflammatory cell recruitment leads to vasodilation and increased cell permeability. This then allows toxins, "deliriogenic" (or "psychotoxic") medications, and cytokines to enter the neurons and cause further damage through inflammation and apoptosis [89]. Certain cytokines involved in inflammation affect the HPA axis and increase the release of glucocorticoids. High levels of glucocorticoids are known to damage the hippocampus, causing a key feature in delirium: impaired memory [89].

In addition, oxidative stress from inflammation and/or brain hypoperfusion simultaneously *decreases* synthesis of acetylcholine and *increases* release of dopamine and glutamate [89, 90], leading to other key clinical features in delirium:

disturbed attention, arousal and perception, and cognitive impairment. Other neurotransmitters involved in delirium to varying degrees include melatonin, norepinephrine, GABA, 5-HT, and histamine [89]. While primary deficits or excess of various neurotransmitters may all contribute to the clinical manifestations of delirium, in many cases, a condition of simultaneous *dopamine excess* (e.g., leading to psychosis) and *acetylcholine deficiency* (with impairment in arousal, memory, and other cognitive functions) economically describes much of the psychiatric appearance in delirium. This neurotransmitter imbalance model also parsimoniously explains how dopamine and glutamate excess and/or acetylcholine deficiency can *promptly* lead to a delirium presentation, as in drug overdose conditions (e.g., dopaminergics, anticholinergics).

As with other organs, the compensatory and protective changes the body makes in the brain in the short term can lead to a vicious cycle of further inflammation, more oxidative damage, and extensive end organ damage in delirium. While less visible than a hypertrophic heart on an echocardiogram or a cirrhotic liver on computed tomography, delirium can lead to sustained cognitive deficits on validated cognitive testing tools. Two fMRI studies describe impaired neural connectivity throughout the brain thought to cause *acute* delirium symptoms as well as *persistent* cognitive deficits following a delirium episode. One of the studies of delirium neuropathology describes an acute disconnect between the suprachiasmatic nucleus and other regions leading to impaired arousal (posterior cingulate cortex), impaired memory (parahippocampal gyrus), and impaired cognitive processing and coordination (thalamus and cerebellum) [90, 91]. The second study describes an altered connection between the posterior cingulate cortex (responsible for sustaining arousal) and the dorsolateral prefrontal cortex (involved in executive function) that does not quickly resolve after clinical improvement in delirium. This suggests a possible pathway for lingering cognitive impairment post delirium [92].

These neurovascular, immunochemical, and neuroanatomical changes in delirium are broad and lead to many potential actions in prevention and treatment. Currently, there is no evidence to support a different pathway to delirium in patients with HIV per se, though a greater level of delirium vulnerability is plausible, especially in HIV patients with premorbid central nervous system (CNS) impairment such as HAND. Analogous to the increased delirium risk of patients with major neurocognitive disorders, patients with HAND may be at greater risk of developing delirium under conditions of physiologic and/or emotional stress, sleep deprivation, and other delirium-provocative events.

Epidemiology

The risk of delirium as cited in the literature varies widely, depending on the patient population. In the community, the prevalence ranges from 1% to 2% with increasing numbers in the hospitalized population [93]. However, it can be found in outpatient clinics, rehab facilities, and emergency departments. Delirium prevalence at time of

hospital admission ranges from 10% to 31% on medical floors [94] and is higher in elderly, critically ill patients in surgical and medical intensive care units [95]. Similarly, a New York Metropolitan area study showed that delirium is found equally frequently in persons with AIDS, in persons with asymptomatic HIV infection, and in those persons without HIV [96]. While the study found significant differences in other disorders between the three study populations, delirium seems to be an equal opportunity illness, affecting all persons, including those with HIV, by a common pathway.

Morbidity and Mortality

The morbidity and mortality of delirium in the HIV patient population are markedly elevated. One small retrospective chart review of 41 patients in a residential care facility identified delirium in AIDS patients as a marker for decreased survival. Over a median time of 10 days, there was a 100% mortality rate in the patients who were admitted with delirium, compared to a 63% mortality rate in patients admitted without delirium [97]. All patients in this study were Do Not Resuscitate. In a prospective study of 110 patients admitted to an HIV/AIDS unit in a tertiary hospital, those developing delirium tended to have a longer length of stay and a need to be discharged to skilled nursing care [98]. With these adverse outcomes, identifying and preventing delirium in HIV patients is crucial to their survival and quality of life.

Diagnosis

Delirium is a clinical diagnosis. Despite the underlying pathophysiology, there currently is not a sensitive or specific single biomarker for delirium. The diagnosis is made by core clinical features with support from targeted laboratory work, neuroimaging, and a thorough physical and mental status exam. Hospital-administered delirium screening tools (e.g., Confusion Assessment Method (CAM)) in the hands of a well-trained nursing staff can assist in case finding. The psychiatric interview in suspected cases of delirium should routinely include assessment of level of arousal (e.g., with the Richmond Agitation-Sedation Scale [RASS]), severity of symptoms (e.g., with the Delirium Rating Scale [DRS]), and standardized assessment of cognitive function (e.g., Montreal Cognitive Assessment [MoCA] or Mini-Mental State Examination [MMSE]).

An electroencephalogram (EEG) can be used as a supporting tool since generalized slowing in both the delta and theta frequencies ranges can be associated with delirium. The sensitivity and specificity for EEG in a diagnosis of delirium were 83.5% and 67.1%, respectively, in a study of a heterogeneous population, and EEG is reported to have up to 90% sensitivity and specificity in populations without other neuropsychiatric disease [99]. Delirium should not be ruled out as a diagnosis if no slowing is apparent on EEG, but it can be supportive of the diagnosis if there is a

clinical suspicion and other clinical findings consistent with delirium. An EEG does not need to be obtained in the majority of delirium cases but can be useful to differentiate delirium from other psychiatric conditions and non-convulsive epileptic seizures that affect alertness or cognition [100]. There is no current research indicating that EEG patterns would be different in patients with HIV compared to other delirium patients, and thus EEG should be used similarly for support of a delirium diagnosis in patients with HIV.

Outpatient Delirium Prevention

Preventing delirium depends on understanding the risk factors and intervening on ones that can be modified. This is especially important when a patient has multiple fixed risk factors, like age, male gender, poor functional status, sensory impairment, premorbid neurocognitive disorders, and coexisting medical conditions. A patient with HIV is subject to all the risk factors of the general population along with the complicating aspects of HIV and antiretroviral treatment, which carry their own specific risks for delirium. The risks for delirium have been studied mostly in the geriatric population. A meta-analysis of cohort studies showed that dementia (major neurocognitive disorder in DSM-5 terminology) had the highest odds ratio of all risk factors included for incident delirium [101], suggesting, by reasonable inference, that HIV-associated neurocognitive disorder and its three subtypes are significant risk factors for delirium.

Table 10.7 Delirium risk factors

Advanced age
Male gender
Poor functional status
Terminal illness
Preexisting neurocognitive disorders/dementia
Infection
ART
Metabolic disorders
Low vitamin D
Hypertension
Perioperative pain
Polypharmacy
Sleep deprivation
Vision/other sensory impairment
Use of bladder catheter, restraints, and intravenous lines
Malnutrition and dehydration
“Psychotoxic” or “deliriogenic” medications, e.g., anticholinergics, opioids, steroids, dopamine agonists, benzodiazepines

Based on data from Refs. [102, 105]

Infections; certain medications, including corticosteroids, anticholinergics, and opioids; and metabolic derangements are common predisposing factors in a medically ill, geriatric patient population [102] and can also help guide risk assessments in patients with HIV. In older adults, hypovitaminosis D has been independently associated with an increased risk of delirium, although in multivariable modeling it is also linked to a higher burden of chronic disease, which could influence the incidence of delirium [103]. Vitamin D deficiency is highly prevalent among PLWH [104]. Given its prevalence, vitamin D should be routinely checked in adult HIV patients and corrected when deficient or insufficient.

With HIV, high viral load and low CD4 count can affect infection risk. Drug-drug interactions among antiretrovirals and other medications can cause direct neurotoxocity or lead to increased levels of deliriogenic medications. Direct treatment of HIV-related opportunistic infections can cause psychiatric symptoms in and of themselves. Table 10.7 lists common risk factors for delirium that should be considered in patients with HIV during all routine care visits.

Inpatient Delirium Prevention: Non-pharmacologic and Pharmacologic

Once hospitalized, every patient has "earned" an additional risk factor just by being admitted; therefore, delirium prevention becomes even more important. In addition to the full medical evaluation for causative factors in delirium, mobilization of non-pharmacologic measures should be prioritized. This is especially critical in hospitalized patients, and ideally, the hospital could develop widely implemented non-pharmacologic delirium prevention or minimization programs. Items to address include minimization of sleep disruption and promotion of sleep, frequent verbal reorientation, a strategy to avoid or minimize physical restraint, prevention of immobility and/or early mobilization, physical therapy activities, occupational therapy assessment and intervention, provision of adequate hydration, and correction of visual and hearing impairment. Family members can be trained to identify signs of delirium behavior and to orient patients with familiar images. Formal geriatric consultation to minimize deliriogenic medications before additional medication are added may be practical and helpful.

Points of intervention in delirium prevention for patients who are hospitalized for surgery have been studied based on the accepted pathophysiology of delirium. While innovative and intuitive, preventing delirium by decreasing inflammation postoperatively with ketamine only *increased* troublesome hallucinations [106]. Intravenous (IV) acetaminophen for pain control has also been studied postoperatively. While the study reported decreased delirium incidence with IV acetaminophen plus dexmedetomidine or propofol, the study was not representative of a generalized population, as it looked at Caucasian, male cardiac surgery patients who were mostly cognitively intact premorbidly [107]. IV acetaminophen is also expensive, and while this is an area with potential, it needs further research before applying to the HIV population.

Intravenous sedatives are a potentially promising delirium preventative tactic to consider when patients with HIV require surgery. Two 2018 meta-analyses highlighted differences in delirium incidence between the GABA agonist propofol and the alpha-2 agonist dexmedetomidine. While the meta-analyses again focused on postoperative patients and included some low-quality studies, the dexmedetomidine treatment groups had a lower incidence of delirium [108, 109]. If a patient requires surgical intervention with a sedative agent and has other risk factors for delirium, these trials support the preferential use of dexmedetomidine over the GABA-active medications.

Ramelteon, a melatonin agonist and hypnotic agent, is a preventative strategy that requires adding a medication short term to a patient's medication regimen to mitigate delirium risk; however, due its low side-effect profile, it is worth considering for hospitalized patients with delirium risk factors. A small single-blind trial looked at the use of ramelteon and delirium incidence in patients with serious medical conditions over a 1-week observation period. The ramelteon 8 mg per night treatment group had significantly lower incidence of delirium [110]. Although hydroxyzine was also offered to patients if they suffered from insomnia, there was not a significant difference in hydroxyzine use between groups. *It should be noted, however, that hydroxyzine, as a sedating and anticholinergic antihistamine, can itself precipitate delirium and should not be used in patients at risk of delirium.* The lessons learned from this study apply to patients with HAND, as well as to older HIV patients.

If a melatonin agonist is not readily available, the most solid, non-pharmacological, evidence for delirium prevention is the Hospital Elder Life Program (HELP) program, which addresses the sleep-wake cycle and other delirium risk factors in a multimodal prevention program. Now deployed in over 200 hospitals worldwide, the strategy involves patients, caregivers, nurses, geriatricians, and volunteers trained to provide reorientation and reassurance to patients. In hospitals where this program is utilized, patients are enrolled if they screen positive for delirium risk factors. The program is tailored to each patient and can include daily orientation, sensory optimization, early mobilization, fluid and feeding assistance, pain management, constipation management, aspiration pneumonia prevention, hypoxia management, medication screening, and many other therapeutic activities. A meta-analysis looking at the effectiveness of this tailored non-pharmacological approach showed pooled odds ratios favoring the intervention group [111].

Not every hospital will have the HELP program available, but elements of this approach can be easily adopted in clinical care and are applicable for older PLWH and those diagnosed with HAND. For example, physician and nursing rounds can include opening shades in the morning, re-orientation during examinations, and ensuring the patient has eyeglasses and/or hearing aids available to optimize sensory processing and reality testing. A comprehensive medication review by pharmacy targeting deliriogenic medications is recommended to tailor prescribing practices.

Treatment of Delirium

Once a patient has developed syndromal delirium, the focus is simultaneously on limiting harm to the patient and addressing the underlying contributors. Antipsychotics as a sole intervention neither treat nor prevent delirium and should be reserved for the control of severe agitation that does not respond to reorientation or reassurance, which prevents essential care, which places the patient at risk of self-harm, or jeopardizes the safety of caregivers. All restraints may exacerbate agitation in the delirious patient. The use of restraints in delirium is challenged by the fact that restraints (and the patient's struggle against them) can increase delirium incidence. Restraints can be justified in severe agitation when applied to prevent a predictable adverse event (e.g., protecting a vulnerable surgical wound from damage by the patient himself). As many hospitals and other healthcare facilities have eliminated or at least significantly curtailed the use of restraints, the physician must conform to local policies and regulations. When restraints are used for safety, they should be limited to a specific safety concern and should be used conservatively. Mitts may prevent pulling of lines. Newer belt or vest restraints can prevent the patient from getting up from the bed without restricting side-to-side movement. If necessary, wrist and ankle restraints can be applied but limit bed mobility. The need for restraints should be evaluated every shift. In some cases, agitation can be controlled by using specially designed "busy aprons" that preoccupy the patient with simple repetitive tasks like opening and closing strips of Velcro™ or zippers.

Antipsychotics should not be used as a substitute for searching for the underlying cause of causes based on the patient's risk factors. A meta-analysis looking at 12 studies using antipsychotics for delirium treatment showed no significant difference in delirium duration, hospital length of stay, or 30-day mortality [112]. One randomized controlled trial of patients enrolled in palliative care observed worse delirium symptom scores and increased extrapyramidal symptoms (EPS) in patients given antipsychotics versus placebo [113]. Patients with advanced, poorly controlled HIV are sensitive to the motor side effects of antipsychotics, particularly irreversible dopamine blocking agents (e.g., haloperidol, risperidone), so this study supports continued caution in antipsychotic use in PLWH with delirium.

Two trials looked at antipsychotics for delirium specifically in persons with HIV. In 1989, a study treated patients with large doses of haloperidol and lorazepam, which, not surprisingly, caused a high incidence of extrapyramidal symptoms (EPS). Due to the study's unclear goals for treatment, open trial design, and use of a non-validated rating scale, use of antipsychotics cannot be supported by this study [114]. In 1996, a small double-blind trial looked at haloperidol versus chlorpromazine versus placebo in the treatment of delirium. A lorazepam arm was discontinued early due to intolerable side effects related to cognitive impairment, but the study suggested a decrease in delirium scores in the antipsychotic groups over placebo. This study also used low doses of the antipsychotics due the concern that HIV infection affects subcortical basal ganglia structures, making patients sensitive to dopamine blockers [115]. These two studies, conducted before or at the beginning of the HAART era, both cautioned that antipsychotics can cause EPS and so should be

used at the lowest possible dose. Although the latter study suggested that low-dose antipsychotics can decrease severity of delirium symptoms, the results could have been confounded by the sedative effects of the medications. A study looking at haloperidol versus haloperidol plus lorazepam on delirium symptoms suggests that lorazepam with haloperidol is an option for treating delirium; however, the primary outcome of that study was the change in Richmond Agitation-Sedation Scale (RASS); thus, improved RASS scores after treatment with lorazepam and haloperidol may actually have reflected a switch from hyperactive to hypoactive delirium (i.e., sedation), and not a true alleviation of delirium symptoms per se [116].

When prescribing antipsychotics for severe agitation, they should be used strategically, and patients should be monitored for cardiac arrhythmias, rigidity, akathisia, and EPS. Antipsychotics do not treat the underlying mechanism of delirium, but if a patient is agitated to the point of putting their medical care in jeopardy or is having troublesome hallucinations, antipsychotics can be used judiciously to decrease severity of these symptoms. After checking the QTc interval on electrocardiogram, assessing drug allergies and intolerances, and considering other medical comorbidities, the lowest possible dose should be tried and then repeated in 30 minutes if ineffective (Table 10.8). Doses for persons with HIV can be adapted from the palliative care literature [117], with recommendations for even lower starting doses for persons with poorly controlled HIV due to their likely sensitivity to antipsychotics. In those patients with hyperactive delirium, use of more sedating antipsychotics like quetiapine and olanzapine can be considered. Haloperidol is helpful in patients requiring IV administration. Olanzapine and ziprasidone have intramuscular formulations, if an IV line is lost due to agitation.

It is common to continue antipsychotics at discharge for patients who have been treated with them during an episode of delirium, including when discharging a recovered delirium patient to somewhere other than home. Two studies report statistics that 21% to 27% of hospitalized patients given antipsychotics as a new medication for any diagnosis, but most commonly for delirium, were continued on the antipsychotics at discharge [118, 119]. Antipsychotics have not been shown to prevent delirium [112], are associated with adverse side effects, and should not be continued indefinitely at discharge when initiated for a delirium indication. In general, if recommending an antipsychotic during a period of severe agitated delirium, the antipsychotic should be discontinued prior to discharge or a tapering strategy should be provided.

The alpha-2 adrenergic agonist dexmedetomidine is another agent with great promise in delirium management. A 2009 study by Maldonado et al. showed that postoperative sedation with dexmedetomidine was associated with a 3% incidence of postoperative delirium, compared to 50% incidence of delirium with propofol and 50% incidence with midazolam [120]. A 2018 meta-analysis of dexmedetomidine in postoperative patients (118 studies, 3309 patients) found a significant decrease in postoperative delirium associated with dexmedetomidine (OR 0.35) [121]. This agent appears to have significant promise in delirium prevention and management; studies in HIV populations would be welcomed to validate its use in delirium in HIV patients.

Table 10.8 Antipsychotic starting doses

Antipsychotic starting dose	Antipsychotic route	Considerations
Haloperidol 0.25–1.0 mg/day	IV, IM, PO	Monitor QTc interval. EPS risk at higher doses. IV administration available
Risperidone 0.25–1.0 mg/day	PO, disintegrating tablet	EPS at higher doses. Monitor QTc interval
Olanzapine 2.5–5.0 mg/day	IM, PO, disintegrating tablet	Worsens glycemic control and not indicated in diabetic ketoacidosis or uncontrolled diabetes mellitus. Has anticholinergic side effects
Quetiapine 12.5–50 mg/day	PO	Sedating effects can help sleep wake cycle. Least EPS risk for those with parkinsonism or otherwise sensitive. May worsen glycemic control, some anticholinergic side effects, but considered less than with olanzapine. Monitor QTc interval. Alpha-1 blockade may lead to orthostasis
Ziprasidone 10–20 mg/day	PO, IM	Monitor QTc interval

Cognitive Monitoring and Delirium Rating Scales

When a patient is delirious, standardized rating scales for delirium symptoms and cognition should be used to monitor progression or improvement in symptoms and to further guide treatment. There are many rating scales available, and there are advantages and disadvantages to each based on time to complete, who administers the scale, and the cost. To help guide the use of validated, reliable, and accurate rating scales on the severity of delirium, a systematic review of 42 delirium rating scales was completed based on strict selection criteria and resulted in 6 instruments meeting study criteria: the Confusion Assessment Method (CAM), Delirium Rating Scale (DRS), Memorial Delirium Assessment Scale (MDAS), Confusional State Examination, Delirium-O-Meter, and Delirium Observation Scale. The CAM, DRS, and MDAS were the most commonly used scales found in literature [122].

Inpatients with dementia frequently experience superimposed delirium. The literature supports use of the CAM or the CAM-ICU (a standardized version of the CAM) to diagnose delirium in patients with dementia, whereas a revised version of the DRS (the DRS-R-98) can clinically differentiate delirium from dementia but requires the user to have training in psychiatry [123–124]. It is unknown how well the DRS-R-98 performs in patients with milder HIV-related neurocognitive impairment (ANI and MND), which make up greater than 95% of patients with HAND. Because delirium, particularly the hypoactive form, often is missed in hospitalized patients, frequent assessment for delirium is advisable in HIV patients who have been diagnosed with HAND. In the end, use of a consistent scale by the same person every day is more helpful than no monitoring at all (Table 10.9).

Once discharged, cognitive status should also be monitored systematically. Not all delirium will fully resolve by the time of discharge, and some delirium symptoms may persist for days to weeks, especially if not all contributing factors have

been eliminated. The persistence of lingering symptoms of delirium must be distinguished from previously unrecognized dementia. In addition, the relationship between delirium and dementia appears to be bi-directional, with dementia predisposing to delirium and delirium potentially worsening or increasing the risk of dementia due to possible persistent neuronal damage caused by delirium [125]. Approximately one third of cognitively intact older patients with delirium develop dementia after a median of 24 months [126]. Further research is needed to assess the impact of delirium on the clinical progression of HAND, but because many PLWH are entering the geriatric age group, the occurrence of delirium should intensify monitoring for incident HAND as well as its progression. The diagnosis and monitoring of HAND are discussed in the first half of this chapter.

Section Summary

Overall, since delirium is a heterogeneous condition, solid recommendations for specific populations require targeted research. At this time, delirium prevention, management, and monitoring are based on broad population studies and not solely on the HIV population. However, some helpful guidance can be drawn from the work completed. First, preventing delirium remains the most important message, as quick, direct treatment, other than identifying and managing the underlying contributors, is currently unavailable. To prevent delirium in an outpatient setting, monitor drug-drug interactions, limit or do not use drugs that are risk factors for delirium, and control other medical comorbidities to prevent infections, electrolyte imbalances, and hypoxia.

Second, if the patient is hospitalized, the risk of delirium automatically increases as a consequence of the index illness and the act of hospitalization itself. In patients with many risk factors for delirium, employing non-pharmacological interventions like optimizing sleep, ensuring patients have hearing aids and eyeglasses, and frequent orientation currently have the strongest evidence for delirium prevention. Additional non-pharmacologic interventions include physical and occupational

Table 10.9 Delirium screening tools

Confusion Assessment Method (CAM)
Confusion Assessment Method for the Intensive Care Unit (CAM-ICU)
Delirium Rating Scale (DRS)
Delirium Rating Scale, revised version (DRS-R-98)
Delirium Detection Scale (DDS)
Delirium Observation Screening Scale (DOSS)
Digit Span Test (DST)
Nursing Delirium Screening Scale (NuDESC)
Single Question in Delirium (SQiD)
Memorial Delirium Assessment Scale (MDAS)

therapy interventions, involvement of family members, and elimination of unneeded medications. Other considerations for delirium management for hospitalized patients include the use of dexmedetomidine over propofol for sedation (in cases of perioperative management and/or extreme agitation) and use of melatonin or a melatonin agonist to improve sleep.

Third, if a patient has delirium, contributing factors should be systematically identified based on known risk factors (Table 10.7) and addressed. Without current evidence that antipsychotics decrease delirium incidence, duration of hospital stay, or 30-day mortality, antipsychotics should not be used routinely to treat the delirium. This is especially true in patients with advanced or poorly controlled HIV due to their increased sensitivity to extrapyramidal side effects. An antipsychotic may be appropriate to treat severe psychotic symptoms and/or extreme agitation associated with delirium for the safety of the patient and/or healthcare providers when non-pharmacologic approaches are unsuccessful. When used, antipsychotics should be given at the lowest effective dose and routinely stopped upon recovery and prior to discharge. Once the delirium has resolved, cognitive status should be monitored due to the association of incident delirium with subsequent cognitive decline.

Conclusion

The chronic and sometimes progressive HAND and the acute-onset delirium are critical and unique aspects of HIV psychiatry and have been hallmarks of HIV illness since the beginning of the HIV pandemic. Chronic HAND may gradually and progressively impair function over long periods of time. HAND and its cognitive and functional impairments can impact adherence to antiretroviral treatments as well as prevention and thus indirectly compromise survival and functional status in HIV patients and lead to HIV transmission. In addition, HAND can increase the risk of acute delirium due to decreased cognitive reserve, rendering patients acutely delirious following relatively innocuous acute illness. Chronic management of HAND may improve patient function and minimize delirium risk. Comprehensive delirium strategies addressing non-pharmacologic and pharmacologic prevention and mitigation strategies offer the best chance for minimization and mitigation of delirium episodes in HIV patients. Clinical practices that include vigilance for neurocognitive disorders, both chronic and acute, are critical elements of providing comprehensive primary care, specialty medical care, and psychiatric care for patients with HIV.

Questions for HAND and Delirium Chapter

1. A 67-year-old HIV-positive retired art gallery owner, who has a history of urinary retention, peptic ulcer disease, and hypertension, undergoes an elective prostatectomy. That evening, the nurse finds him confused and agitated. He pulls

out his urinary catheter, tries to climb out of bed, and curses the nurse when she attempts to place wrist and ankle restraints. Which of the following statements is true?

(a) All opioid analgesics should be withheld in this patient because they may be associated with delirium.
(b) An antipsychotic like olanzapine should be administered to reduce the severity and duration of the delirium.
(c) The occurrence of delirium in this patient is a risk factor for his development of a major neurocognitive disorder in the next 2–3 years.
(d) All visitors, including the patient's life partner, should be banned from visiting the patient in the hospital because they may exacerbate his delirium.

Answer to 1:

(c) True. In older patients, delirium has been associated with the development of dementia after a median of 24 months, and this risk of dementia likely extends to patients with undiagnosed HIV-associated neurocognitive disorder (HAND), which affects up to 50% of persons living with HIV (PLWH).
Explanations of other responses:

(a) False. Following his surgical procedure, this patient is expected to experience moderate to severe pain. Although non-opioid analgesics like acetaminophen (paracetamol) and nonsteroidal anti-inflammatory drugs (NSAIDs) can reduce the amount of opioid required, NSAIDs are relatively contraindicated in this patient due to his ulcer history. Uncontrolled pain can contribute to delirium, requiring a balance between avoidance of deliriogenic drugs and appropriate analgesia.
(b) False. Antipsychotics have not been shown to prevent or treat delirium. They have a limited role in managing psychotic symptoms or controlling severe agitation that places the patient or caregiver(s) at risk of harm despite reassurance and reorientation. They should be administered at the lowest effective dose and discontinued as soon as possible. Some antipsychotics like olanzapine and quetiapine have anticholinergic properties which can contribute to delirium. Restraints, although sometimes necessary, themselves can exacerbate agitation.
(d) False. The Hospital Elder Life Program and other research have shown than frequent reorientation and reassurance can help prevent and control delirium, and the presence of an intimate partner allows timely notification of the nurse should delirium occur. Intimate partners should be allowed as much access to the patient as possible throughout the day and night if the patient is at risk of delirium.

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2. A 53-year-old bisexual musician is followed by a community psychiatrist for bipolar affective disorder. He has been diagnosed with HIV-1 since 1997 and is prescribed antiretroviral therapy but admits to missing several appointments at

his HIV clinic. He claims his viral load was undetectable a year ago. He continues to work as a clerk in a music store during the day and performs weekends in a local band as its bass guitarist. Which of the following statements is true?

(a) The patient should be screened annually with brain magnetic resonance imaging to look for cerebral atrophy.
(b) The patient should undergo a lumbar puncture to look for HIV replication in the cerebrospinal fluid.
(c) Formal mental status evaluation is unnecessary because the patient's professional career appears stable.
(d) An office-based cognitive assessment, supplemented by an assessment of instrumental and advanced activities of daily living, should be conducted periodically.

Answer to 2:

(d) True. The gold standard for screening for HIV neurocognitive impairment is formal neuropsychological testing that may take hours to complete and is not available to all patients. However, the use of office-based tests like the Montreal Cognitive Assessment or validated scales like the International HIV Dementia Scale in combination with relatively brief timed tests like the Trails A provides good sensitivity and acceptable specificity. Suspicion of subtle cognitive impairment can be gleaned by using standardized tests of instrumental and advanced activities of daily living, supplemented, whenever possible, by information from the patient's partner or close family.
Explanations of other responses:

(a) False. Routine brain imaging is expensive, does not help identify patients with HAND, and has little clinical utility. Patterns of involvement on the MRI can help differentiate Alzheimer's disease from HAND or vascular cognitive impairment, and it can be useful to rule out lesions produced by cerebral infarcts, opportunistic fungal infections, and tumors when there is clinical suspicion based on the history and physical examination.
(b) False. Lumbar puncture is painful, and analysis of the cerebrospinal fluid provides little diagnostic benefit except when subacute clinical deterioration in cognitive function raises concern about HIV proliferation within the CNS despite suppression of the peripheral viral load.
(c) False. "Stability" in the patient's career does not exclude the early stages of HAND such as *asymptomatic neurocognitive disorder* (*ANI*). It is important to explore *how well* the patient is performing in his career and private life (i.e., instrumental and advanced activities of daily living) and to perform neurocognitive screening.

3. B.L. is a 52-year-old HIV-positive man in the mild neurocognitive disorder stage of HAND. He carries the diagnoses of hyperlipidemia, hypertension, coronary heart disease, depression, and HIV, for which he takes 11 different medications

prescribed by his HIV doctor and family physician. The patient complains of fatigue, and on examination, his trousers appear too loose at the waist. He has had a recent undetectable viral load. On the way to the examination room, he walks with a noticeably slowed gait and later has difficulty arising from his chair without pushing off with his hands. His brother has taken control of his finances because he consistently failed to pay his bills on time. The patient was recently laid off from his job as a loan officer at a bank. He remains independent in his basic activities of daily living, as well as in shopping and housework. Which of the following statements is false?

(a) Because the patient is only 52 years old, standard routine medical care is appropriate.
(b) The patient would benefit from a "geriatric" approach to his care that emphasizes the optimization of his functional status and assesses the complex interactions of his medications, physical functioning, and comorbidities.
(c) The patient's slowed gait, along with probable weight loss and fatigue, is consistent with the development of frailty based on the Fried criteria.
(d) The patient's medication list should be reviewed, looking for potentially inappropriate medications – i.e., medications with a high risk of adverse side effects and for which a less harmful substitute is available.

Answer to 3:

(a) False. This 52-year-old man with ANI has a number of attributes of a geriatric patient: multiple comorbidities, polypharmacy, and functional as well as cognitive impairment. Simultaneously addressing his medical, functional, and psychosocial problems represents the optimal approach to his care; this approach characterizes geriatric medicine, which emphasizes the paradigm of 6 Ms.: *mind* (cognition and mood); *medications* (polypharmacy, adverse drug reactions, and drug-drug interactions); *mobility* and self-maintenance (including overall functional status); multicomplexity (both multimorbidity and complex psychosocial issues); what *matters* most (i.e., the patient's personal priorities for quality of life); and *modifiable* risk factors.
Explanations of other responses:

(b) True. See discussion for item a, above.
(c) True. Frailty can be defined as unintentional weight loss, poor strength, slow gait, feeling exhausted, and low levels of activity that cannot be explained by other disease states. One-to-two frailty criteria define pre-frail, and 3 or more criteria define fully frail.
(d) Polypharmacy has been defined as 5 or more prescription medications and has been associated with an increased risk of falls, hospitalization, and mortality and is more common in PLWH than in age-matched controls. When polypharmacy is present, clinicians should evaluate the medications (including over-the-counter preparations) for potential toxicity and drug-drug interactions, as well as for the presence of *potentially inappropriate medications*, defined as drugs with a high potential for adverse reactions

that should be avoided whenever possible, especially when there are safer alternatives.

4. Ms. T is a 47-year-old woman who used IV methamphetamine and heroine when she travelled with a rock band as a young woman. She was diagnosed with HIV when she developed an AIDS-defining illness (*Pneumocystis jiroveci* pneumonia) 12 years ago. Although her CD4+ count has been within normal limits and her peripheral viral load has been undetectable for the last 3 years om HAART, she recently has been demonstrating progressive cognitive decline, scoring 16/30 on the Montreal Cognitive Assessment (consistent with moderately severe dementia). Which of the following statements is *not* a possible cause of her cognitive decline?

   (a) The patient may be showing viral escape, i.e., replication of HIV-1 in the CNS despite peripheral viral suppression by HAART therapy.
   (b) The patient's cognitive deterioration suggests development of a CNS opportunistic infection despite her suppressed HIV-1 viral load.
   (c) The patient may be experiencing chronic neuroinflammation due to the activation of brain microglia and astrocytes that release proinflammatory cytokines and other molecules that damage neurons.
   (d) The patient has been taking efavirenz because it has relatively high penetrance into the CNS.

Answer to 4:

(b) False. An opportunistic infection is unlikely, given the patient's normal CD4+ count as well as undetectable HIV-1 viral load.
Explanations of other responses:

(a) True. HIV-1 that penetrated into the CNS may be sequestered within macrophages and microglia, where they can replicate. Replication is favored by lower penetration of some antiretrovirals into the CNS and may also occur as a result of the development of resistance of the sequestered CNS HIV to the selected antiretroviral therapy.
(c) True. HIV-1 induces a state of chronic neuroinflammation, causing perivascular macrophages to release proinflammatory cytokines and matrix metalloproteinases. The HIV-1 itself releases proteins such as Tat, which also stimulate the production of proinflammatory molecules. Virus that replicates inside brain macrophages and microglia, or invades astrocytes, results in further release of pro-inflammatory proteins as well as inhibition of cytoprotective mechanisms, causing apoptosis of neurons.
(d) True. Efavirenz, a non-nucleoside reverse transcriptase inhibitor (NNRTI), has excellent penetration into the CNS but has been associated with memory loss and multi-domain cognitive impairment.

5. A 57-year-old nurse returns to his primary care physician (PCP) for worsening diarrhea and weight loss. He carries a diagnosis of ulcerative colitis (UC) that historically was mild and managed with rectal budesonide, but in the past several

months, his diarrhea has been refractory to oral steroids, infliximab, and now adalimumab. Recently, he underwent a colonoscopy with biopsy, which demonstrated cytomegalovirus infection. Social history is notable for the recent marriage of the nurse to his male partner of 2 years. In routine premarital screening, the patient's HIV test came back positive, with a viral load of 12,500 RNA copies/mL and a CD4+ count of 192 cells/μL. Which of the following represents the most appropriate action for this patient?

(a) Refer the patient to a gastrointestinal surgeon for possible colectomy.
(b) As part of his overall management, the patient should undergo screening for HAND.
(c) The patient's diarrhea should be treated acutely with high-dose intravenous steroids.
(d) Antiretroviral therapy should be deferred until the patient's ulcerative colitis is better controlled.

Answer to 5:

(b) The patient is at risk for HIV-associated neurocognitive disorder and as part of the management of his AIDS should undergo screening for HAND.
Explanations of other responses:

(a) False. The patient's previously mild inflammatory bowel disease is now complicated by cytomegalovirus (CMV), which may be causing much if not all of the diarrhea. Colectomy should be reserved for patients with truly refractory ulcerative colitis.
(c) False. High-dose steroids may exacerbate the patient's CMV infection and predispose him to life-threatening opportunistic infections and such conditions as CMV retinitis and secondary blindness.
(d) The patient's CD4+ count of 192 cells/μL is an AIDS-defining state. The patient requires aggressive management of his HIV with the goal of eradicating HIV within his CNS.

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Chapter 11
Substance-Related and Addictive Disorders

John A. R. Grimaldi, John Bodnar, Daniel R. Lavin, Michael L. McLaughlin, J. J. Rasimas, and Kenneth Ashley

Introduction

Substance-related and addictive disorders have been associated with HIV since the beginning of the epidemic. Injection drug use (IDU) is a significant risk factor for HIV transmission, and non-injection use of substances such as alcohol and psychostimulants is associated with HIV sexual risk behaviors and increased rates of HIV transmission [1–5].

Active substance use disorders (SUDs) contribute to various systemic medical comorbidities and may negatively affect outcomes across the HIV continuum of care. Studies have linked substance-related and addictive disorders to delayed testing and entry to care, decreased initiation and receipt of prescriptions for antiretroviral therapy (ART), lower rates of adherence and viral suppression, and increased morbidity and mortality related to HIV and other illnesses. Substance use also is

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associated with progression of HIV disease and is a risk factor for HIV-associated neurocognitive disorder (HAND) [6, 7].

The Joint United Nations Programme on HIV/AIDS (UNAIDS) estimated that in 2018 there were 1.7 million new infections and 37.9 million people living with HIV (PLWH) globally [8]. Global HIV incidence fell by 22% for all ages between 2011 and 2017. However, incidence among people who inject drugs (PWID) rose from an estimated 1.2% in 2011 to 1.4% in 2017. Outside sub-Saharan Africa, PWID and their sexual partners constituted approximately one-fourth of new HIV infections. In Eastern Europe, Central Asia, the Middle East, and North Africa, PWID accounted for more than one-third of new infections in 2017 [9]. According to recent global estimates, 2.8 million PWID were living with HIV, accounting for 17.8% of all PWID. HIV prevalence among PWID varied substantially across geographic regions, ranging from 1.1% in Australasia, 3.6% in the Middle East and North Africa, and 4.5% in Western Europe, to 24.7% in Eastern Europe and 35.7% in Latin America; Eastern Europe and Latin America had the largest numbers of PWID living with HIV [10].

In the United States, IDU accounted for 9% of new HIV infections in 2017. Among women, 86% of new infections were related to heterosexual contact and only 14% to IDU. In men, 82% of new infections were due to male-to-male sexual contact, 9% to heterosexual contact, 4% to IDU, and 4% to IDU and male-to-male contact [11].

This chapter reviews the role of substance-related and addictive disorders in HIV. The substances most commonly associated with HIV will be reviewed in detail, including prevalence, role in HIV acquisition, and effect on HIV course of illness and treatment. Assessment and management of substance-related and addictive disorders will also be discussed.

Terminology and Definitions

Accurate diagnosis of substance-related and addictive disorders is essential to provision of effective psychoeducation for persons living with HIV, for treatment planning, and for risk assessment and mitigation. The *Diagnostic and Statistical Manual of Mental Disorders*, fifth edition (DSM-5) [12], divides substance-related and addictive disorders into two categories: substance use disorders and substance-induced disorders. See Table 11.1 for the DSM-5 criteria for substance use disorders.

In DSM-5 the differentiation between abuse and dependence was revised to a single category of substance use disorders (SUDs) with specifiers for level of severity. Tolerance is defined as either the need for increased amounts of the substance to achieve the desired effect or a decrease in the effect with the ongoing use of the same amount of the substance. Withdrawal is manifested by either a substance-specific set of signs and symptoms associated with the abrupt discontinuation, reduction, or antagonistic blockage of a substance or the substance being used to relieve or avoid the signs or symptoms of withdrawal. Additionally, the specifiers

Table 11.1 Substance use disorders: DSM-5 criteria

A problematic pattern of substance use leading to clinically significant impairment or distress as manifested by two (or more) of the following occurring within a 12-month period:
Larger amounts or over a longer period of time than intended
Continued use despite recurrent social or interpersonal problems
Most time spent in addiction (i.e., activities needed to obtain, use, or recover from the substance)
Important social, occupational, or recreational activities given up
Use despite knowledge of persistent or recurrent physical or psychological problems
Craving or strong desire to use
Unsuccessful efforts to decrease/cut down
Failure to meet obligations at work, school, or home
Recurrent use in hazardous situations
Tolerance
Withdrawal

Table 11.2 DSM-5 substance-induced disorders

Intoxication
Withdrawal
Depressive disorder
Bipolar disorder
Psychotic disorder
Anxiety disorder
Sleep disorder
Sexual dysfunction
Delirium
Major or mild neurocognitive disorder

for course and descriptive features have been maintained, although DSM-IV's "on agonist therapy" has been replaced by "on maintenance therapy" in DSM-5. See Table 11.2 for DSM-5 substance-induced disorders.

Assessment of Substance Use Disorders

The high prevalence and medical consequences of unrecognized substance use make obtaining a complete drug use history essential to the comprehensive medical care of persons living with HIV and AIDS. For each substance identified, a detailed history may include elements listed in Table 11.3. Urine toxicology screens may also be obtained with the patient's consent, keeping in mind that depending on the laboratory technology used, screening may not detect the presence of certain substances such as synthetic cannabinoids and other novel psychoactive substances.

Table 11.3 Elements to consider when taking a substance use history

Age when use began
Patterns, frequency, and amount of use
Routes of administration
Longest period of abstinence
Past treatment history and response to treatment
The patient's perspective on the positive and negative effects of use and abstinence
Systemic medical, neurological, and psychiatric consequences of each substance used

Internalized stigma, shame, concerns about confidentiality, and social desirability bias may limit the accuracy of a detailed drug use history which may need to wait until a therapeutic alliance has been established [13–15]. Additionally, adequately training HIV clinicians to address substance use-related problems when they arise and the availability of resources for referral for treatment of patients with more severe disorders should be considered.

Studies of validated, patient-administered screening tools demonstrate the acceptability and feasibility of incorporating this procedure in an HIV clinic setting without unduly compromising staff time and workflow [13, 14]. Screening, Brief Intervention, and Referral for Treatment (SBIRT) is an effective intervention in reducing problem drinking and tobacco use in individuals without HIV [15, 16]. A recent study found that implementation of SBIRT in an HIV ambulatory clinic was well accepted by patients, but well-controlled effectiveness trials are lacking [16, 17]. See Table 11.4 for screening tools and Table 11.5 for a description of SBIRT.

Across all approaches to detection and treatment of substance-related and addictive disorders, a patient-clinician therapeutic relationship is critical to successful engagement and retention in HIV and substance use care. To achieve a mutually trusting relationship, clinicians should consider open acknowledgement of HIV and drug use-related stigma and patient and clinician bias, and foster conditions for a psychologically safe relationship. The principles of trauma-informed care can be a useful guide to establishing a therapeutic alliance. See sections on Trauma-Informed Care and Stigma.

Substance Use Syndemic and Associated Conditions

Among persons living with HIV and AIDS, substance use commonly co-occurs with other psychiatric illnesses and social conditions which in combination may interact to produce poor health outcomes and unequal access to care. Substance use is also associated with HIV sexual risk behaviors, including increased risk for sexual assault, trauma, and stigma. Associated comorbid medical conditions, such as tuberculosis and viral hepatitis, may complicate HIV treatment [55–60].

Table 11.4 Screening tools validated for detection of problematic alcohol, tobacco, and other drugs in HIV and primary care settings

Screening tools			
Screener	Substance(s)	Available at	References
AUDIT and AUDIT-C (AUDIT-Concise)	Hazardous and unhealthy drinkers and/or alcohol use disorders	https://www.integration.samhsa.gov › images › res › tool_auditc (accessed 12/22/19)	[18–21]
Alcohol Use Disorders Identification Test			
CAGE	Alcohol use disorders	www.patient.co.uk/doctor/cage-questionnaire.	[20–23]
Single-Question Alcohol Screening Test	Alcohol	file:///C:/Users/jag22/Downloads/MAP-Screening-Quick-Reference-Guide%20(4).pdf	[20, 21, 24]
		NIDA	
BSTAD	Alcohol	https://www.drugabuse.gov/nidamed-medical-health-professionals/screening-tools-resources/screening-tools-for-adolescent-substance-use (accessed 12/22/19) www.drugabuse.gov	[20, 21, 25]
Brief Screener for Adolescent Alcohol, Tobacco, and Other Drugs	Tobacco		
	Heroin, prescription pain relievers		
	Cocaine, crack, amphetamines, methamphetamine, prescription stimulants		
	Hallucinogens, inhalants		
	Prescription sedatives/hypnotics		
	Over-the-counter medications		
CRAFFT	Alcohol, marijuana, illicit drugs, over-the-counter drugs	https://www.integration.samhsa.gov/clinical-practice/sbirt/CRAFFT_Screening_interview.pdf (accessed 12/22/19)	[20, 21, 26]
Car, Relax, Alone, Forget, Friends, Trouble			

(continued)

Table 11.4 (continued)

Screening tools			
Screener	Substance(s)	Available at	References
DAST-10 Drug Abuse Screening Test – 10 Items	Cannabis (e.g., marijuana, hash), solvents, anxiolytics (e.g., diazepam), barbiturates, cocaine, stimulants (e.g., dexedrine), hallucinogens (e.g., LSD), or opioids (e.g., heroin). Questions do not include alcohol or tobacco	https://med.dartmouth-hitchcock.org/documents/DAST-10-drug-abuse-screening-test.pdf	[27]
ASSIST Alcohol, Smoking and Substance Involvement Screening Tool	Screens for alcohol, tobacco, cannabis, cocaine, amphetamines, inhalants, sedatives or hypnotics, hallucinogens, opioids, and other drugs	https://www.samhsa.gov/sites/default/files/programs_campaigns/samhsa_hrsa/alcohol-smoking-substance-screening-test.pdf	[20, 21, 28]

Table 11.5 Psychosocial interventions

Intervention	Description
Screening, Brief Intervention, and Referral to Treatment (SBIRT)	Evidence-based
	Consists of 1–4, 15–45-min counseling sessions
	Sessions provide psychoeducation regarding safe substance use levels, comparison to other individuals using normative data, consequences of misuse including impact on HIV medication adherence and HIV disease, and strategies to quit or reduce harm
	Also includes an assessment of readiness to change and often integrates tenants of motivational interviewing [29]
	Referral for treatment of more severe at-risk substance-related behaviors or substance use disorders [30]
	Shown to reduce number of drinks, number of binge drinking episodes, and days of hospitalization among alcohol users [31]. Evidence exists for SBIRT's effectiveness in addressing tobacco use; however, little data exist on its use in illicit drug use
Motivational interviewing (MI)	Counseling style designed to enhance motivation by resolving ambivalence toward reducing substance use and invoking patient self-efficacy
	Techniques include reflective listening, expressing empathy, developing discrepancy between present behavior and desired goals, avoiding confrontation, and exploring personal motivations for reductions in substance use. Confidence scales are used to invoke "change talk" and strengthen patient confidence [32]
	Used also for antiretroviral therapy adherence and sexual risk-taking behavior
	Studies suggest benefit in reducing alcohol and cocaine use in patients with HIV. Results are less impressive for use in cannabis use disorder [33, 34]
	Transtheoretical model of change used to assess readiness to change various behaviors, including substance use:
	Stages of change correspond to degree of motivation
	Precontemplation stage: no desire to change, offer to provide education
	Contemplation: willingness to understand the costs and benefits of substance use
	Preparation: consider discrete change options
	Action plan: implemented when an individual is ready to change behaviors

(continued)

Table 11.5 (continued)

Intervention	Description
Peer-support programs	12-step programs such as Alcoholics Anonymous (AA) are effective as cognitive behavioral therapy (CBT) and motivational interviewing in reducing alcohol use [35]
	12-step program chapters may discourage the use of medication-assisted treatment
	Abstinence approach or spiritual aspect of 12-step programs may be unrealistic or alienating
	SMART recovery programs which do not emphasize spirituality, anticipate relapse, and incorporate harm reduction may be more appropriate for some patients
	Social support is a protective factor among patients with triple diagnosis who use alcohol and cocaine [36]. In one study comparing various psychosocial treatments for cocaine use disorder, a combination of individual and group counseling was superior to other modalities [37]
Contingency management (CM)	Offers incentives to learn new behaviors via tangible rewards
	Utilizes operant conditioning principles and non-drug reinforcers to change behavior
	Effective tool in the treatment of benzodiazepines, cocaine, nicotine, alcohol, opiates, marijuana, and methamphetamine.
	Common approach provides vouchers in combination with community reinforcement (drug avoidance skills, and counseling targeting lifestyle changes, relationships, vocation, and mental health) in exchange for drug-free urine tests
	Vouchers for healthy food and healthy recreational activities
	Improve psychosocial functioning and abstinence in cocaine users [38]
	In people living with HIV (PLWH), shown to reduce alcohol use and increase ART compliance [39]
	In men who have sex with men (MSM) with HIV sexual risk behaviors, reduced methamphetamine use [40]
Cognitive behavioral therapy (CBT)	12–24 sessions that emphasize the relationship between maladaptive behaviors and thought patterns
	Common interventions: self-monitor thoughts and emotions, recognize cravings, triggers, and vulnerability factors
	Patients challenge problematic thoughts that lead to substance use
	Behavioral interventions: relaxation skills and partaking in drug-free activities
	In an open trial of young people living with HIV (PLWH) and comorbid alcohol and cannabis use disorders, combined CBT/CM model was associated with a reduction in alcohol and cannabis use, withdrawal and dependence symptoms, high-risk sexual behavior, ART adherence, and mental health symptoms [39]
	CBT designed to enhance self-efficacy in PLWH, improved ART adherence among alcohol users, and lowered viral load [41]
	CBT shown to reduce methamphetamine and cocaine use in gay men and may help a subset of gay in PLWH [40]

Table 11.5 (continued)

Intervention	Description
Dialectical behavioral therapy (DBT)	May benefit patients with triple diagnosis of HIV, SUD, and borderline personality disorder
	Emphasizes mindfulness, as well as improving affective regulation and interpersonal effectiveness skills [42]
Third wave therapies (mindfulness and acceptance and commitment therapy)	Substantial evidence for effectiveness of mindfulness and acceptance and commitment therapy (ACT) in substance use disorders (SUD)
	Data is limited on effectiveness in PLWH [43]
	Mindfulness training in SUD may increase awareness of relapse triggers and improve distress tolerance to avoid substance use as a coping strategy [44]
Harm reduction	Strategies used to mitigate risk of injury or death
	Useful for engaging patients who are ambivalent about their substance use and not ready to commit to abstinence
	Helpful at any stage of addiction
	Reduces risk of alienating patients, encourages patient autonomy, and increases likelihood that patients will be forthcoming regarding problematic behavior or relapse [45, 46]
	Behavioral strategies:
	Scheduling abstinence days
	Limiting settings where drug use takes place
	Buying substances only on day of use
	Using one substance at a time
	Diluting beverages, lower alcohol content drinks
	Drinking at home
	Giving car keys to a friend
	Taking vitamins such as thiamine and folate [47]
	Methamphetamines: use less potent administration methods, e.g., snorting rather than smoking and maintaining adequate hydration and nutrition [48]
	People who inject drugs (PWID):
	Syringe service programs (SSP) [49, 50]
	Supervised injection facilities (SIF): reduce HIV transmission, increase access to primary care and addiction treatment, and reduce risk of overdose [49, 51, 52]
	Naloxone, an opioid antagonist available as injectable or nasal spray and can be obtained without a prescription, effective intervention to reduce death from opioid overdose [53, 54]

(continued)

Trauma

The higher-than-expected exposure to violence among people living with HIV and AIDS who use drugs, especially those socioeconomically disadvantaged and living in urban areas, has given rise to the term "SAVA syndemic" (substance abuse, violence, HIV, and AIDS) to describe this phenomenon [56]. See Chap. 14 for a more detailed discussion of HIV syndemics (synergistic epidemics). Exposure to psychological trauma was overrepresented in both people living with HIV and AIDS (PLWH) as well as people with substance use disorders. In one study of non-HIV-infected and HIV unknown individuals seeking treatment for substance use disorders, approximately half also met criteria for posttraumatic stress disorder (PTSD) [61]. Adverse childhood events were correlated with a tenfold increased risk of co-occurring substance disorders [62, 63].

Trauma shares a bidirectional relationship with substance use disorders. It is a common belief that drug use is a coping strategy for victims of trauma that may lead to substance use disorders [64]. Studies supporting this effect demonstrated that preexisting trauma predicted subsequent substance use [58]. Conversely, substance use disorders may put individuals at risk for further exposure to trauma, especially in the form of sexual assault [58]. The symptoms of each disorder seemed to reinforce each other. Ongoing substance use was predictive of the severity of PTSD [65]. Reciprocally, severity of trauma symptoms was a predictor of relapse in substance use disorders [66] and improvement in trauma symptoms appeared to result in a reduction in substance use [67]. Studies suggested that because of the close association among HIV, trauma, and substance use, integrated treatment, if available, may result in improved outcomes across disorders [58]. See Chap. 7 for a more detailed discussion of trauma and HIV.

Trauma-Informed Care

Exposure to psychological trauma may affect engagement in treatment across the full HIV continuum of care and influence interactions with the healthcare community. Conditioned behavioral responses to reminders of trauma, or triggers, are a core feature of PTSD that is characterized by hyperarousal and subsequent avoidance of triggering situations [68]. Chronic trauma, such as ongoing intimate partner violence, and developmental trauma, such as childhood neglect and abuse, may affect an individual's ability to integrate emotion and cognition into a cohesive whole and lead to unfocused responses to stressful situations [69]. Individuals exposed to repeated trauma may become unusually sensitive to and respond strongly to even small perceived threats [64]. Retraumatization and consequent disruptive behavior in response to events that may be perceived as trivial to others is not unusual in an HIV ambulatory care setting. These responses include not only arousal behaviors such as anger or panic but also avoidance behaviors, such as disassociation, risk taking, substance use, and avoidance of care [68].

Healthcare systems themselves are often sources of retraumatizing events. These retraumatizing events include obvious sources of stress, such as insensitive staff or coercive clinicians, and more subtle sources such as systemic racism and sexism. They may also include perceived threats, such as fear of involvement of child protective services or coerced inpatient psychiatric hospitalization [70]. Unavoidable and less obvious sources of stress may also interfere with treatment. Environmental factors, such as poor lighting or cramped or exposed patient reception areas, may create anxiety in trauma-exposed patients while having no apparent effect on other individuals. Rather than helping those exposed to trauma, healthcare services may unintentionally cause further harm and reinforce avoidance of care [70].

Trauma-informed care recognizes that aspects of the healthcare system may unknowingly threaten patients' sense of trust and safety. An organizational approach that anticipates potential triggers and endeavors to promote patient autonomy and empowerment may foster improved outcomes. Trauma-informed care is generally conceived as a value system as opposed to a precise treatment methodology, although organizations such as the Substance Abuse and Mental Health Services Administration (SAMHSA) have developed sets of recommendations. The SAMHSA defines six principles of a trauma-informed approach, listed in Table 11.6 [70]. Repeated exposure of clinicians to clients with histories of trauma may lead to emotional exhaustion, or what has also been termed compassion fatigue, vicarious trauma, or burnout. Trauma-informed care incorporates organizational interventions to manage clinician self-care, such as opportunities for peer support [71].

Comorbid Psychiatric Disorders

Psychiatric disorders commonly co-occur with substance-related and addictive disorders. Studies estimated that nearly 40% of Americans with an alcohol use disorder also have another psychiatric disorder. Of those with a substance use disorder other than alcohol, half were found to have a comorbid psychiatric disorder, the most common being major depressive and generalized anxiety disorders [72]. Studies also indicated that certain psychiatric disorders are more predictive of a comorbid substance use disorder. Nearly 90% of individuals with antisocial personality disorder and about 50% of those with bipolar disorder and schizophrenia had substance use disorders [73]. The relationship between other psychiatric illness and substance

Table 11.6 Principles of trauma-informed care

Perception of physical and psychological safety within the organization
Trustworthiness and transparency of the staff
Peer support of patients from other individuals with trauma exposure
Collaboration between staff
Client empowerment
Organizational awareness of cultural, historical, and gender issues, biases, and stereotypes

use disorders is likely heterogeneous. Some individuals may develop substance use disorders secondary to psychiatric conditions, in an attempt to "self-medicate." In other individuals, substance use disorders precede psychiatric disorders and trigger their development due to direct effects of the substances, such as with chronic use or withdrawal, or indirectly through changes in environmental and social stress brought on by the substance use [74].

Substance use disorders that co-occur with psychiatric illness are typically more difficult to treat. Co-occurring psychiatric illnesses may be difficult to diagnose when they are overshadowed with behavioral patterns that may be associated with substance-related and addictive disorders. Patients with both disorders demonstrated increased severity of substance use, had a higher rate of relapse, and were more disabled compared to patients with only a substance use disorder [57]. Individuals dually diagnosed with substance use and mental health disorders are also at greater risk for engaging in HIV sexual risk behavior, putting them at greater risk for acquisition and transmission of HIV compared to individuals with substance use disorders alone [57]. Refer to Chaps. 5 through 12 for further information regarding diagnosis and treatment of other multimorbid psychiatric disorders.

Sexualized Drug Use

The interplay between substance use and sexual activity is not a new phenomenon. Sexualized substance use has persisted in different venues and involving different drugs from at least the 1960s. More recently, substance-enhanced sexual activity deserves attention given its close connection with HIV transmission and impulsive HIV sexual risk behavior as well as the sharing of needles and other paraphernalia used to inject drugs.

Sexualized drug use in men who have sex with men (MSM) is colloquially referred to as "PnP" (party and play), "chemsex," and "slamming" (use of injected substances) [75]. More broadly, sexualized drug use is the use of substances before or during sexual activity, to facilitate, prolong, intensify, or enhance the sexual experience [75–78]. Among MSM, chemsex often involves use of one or more drugs. See Table 11.7 for examples of drugs used to enhance sexual activity [75, 76, 79]. These substances may be used in conjunction with other drugs including those for erectile dysfunction and amyl nitrate ("poppers"), which is used to induce

Table 11.7 Drugs used in a sexual setting

3,4-Methylenedioxy-methamphetamine (MDMA)
Mephedrone
Methamphetamine
Gamma-hydroxybutyrate and gamma-butyrolactone (GHB, GBL)
Cocaine
Ketamine

euphoria as well as to facilitate anal sex through relaxation of involuntary muscle [80]. Other perceived benefits of chemsex include lowering inhibitions, enhancing sexual arousal, stamina, and connection with sex partners, and making receptive anal intercourse easier [81]. Chemsex sessions may last up to several days and typically involve more frequent HIV sexual risk behaviors [79, 82]. Several studies found that MSM with a history of chemsex participation had a higher prevalence of unprotected anal intercourse (UAI), also referred to as "barebacking," "fisting" or placing a hand or arm in the rectum, prolonged sex, sharing of sex toys, injection of drugs, or sex with multiple partners [75–77]. Protracted sex may result in rectal trauma or penile abrasions, which could increase the risk of HIV transmission [83]. Chemsex participation may have psychosocial consequences such as loss of social supports, decline in functioning, psychological distress, and loss of employment [81].

Detailed epidemiologic information is limited though chemsex has been found to be prevalent in Europe and the United States. A 2019 meta-analysis found prevalence rates among men who have sex with men ranging from 3% to 29% depending on the sample used. Higher prevalence was found among MSM attending sexual health clinics and users of a particular geo-social dating app [75]. Higher prevalence was also noted among participants with known HIV disease [75, 79]. MSM living with HIV are more likely than MSM without HIV to use substances, perhaps to counteract the effects of HIV and antiretroviral treatment on sexual function [84].

Of particular concern with chemsex in people living with HIV and AIDS is an association with reduced adherence to antiretroviral therapy and higher detectable viral loads [76]. A study conducted in the United Kingdom found that participation in chemsex was associated with a fivefold increase in the odds of being newly diagnosed with HIV though other studies have been inconclusive [77]. It is worth noting that chemsex participants have a higher number of potential sources of HIV exposure including sexual activity, shared sex items, and shared drug paraphernalia compared to individuals with either HIV sexual risk behavior or problematic substance use alone. Clearly, participation in chemsex has the potential for syndemic association with HIV.

Partnering for men who have sex with men has historically been associated with physical locations such as adult bookstores, public restrooms, bathhouses, and parks, typically with anonymous partners [85]. With the proliferation of smartphones, dating-oriented apps, and sexually oriented websites, adults in general and MSM in particular are able to more efficiently find partners for sexual activity. Notably, many sexually oriented dating websites and smartphone dating apps cater to specific niches, usually allowing users to more efficiently search for partners on the basis of common interests or geographic proximity. In some cases, the expectation of participation or availability of chemsex is directly advertised. Multiple studies have found an association between the use of the Internet to find sexual partners and higher incidence of unprotected anal intercourse, anonymous sex partners, and higher average number of sexual partners in the previous 6 months [85]. A study in New York found a greater proportion of users of the gay dating app Grindr had never been tested for HIV compared to a population-based sample of MSM [85].

Substance use treatment planning in men who have sex with men or people living with HIV can be complicated by co-existing compulsive sexual behaviors, as occurs with sexualized substance use. While "sex addiction" is not recognized in the DSM-5, it stands to reason that sexual activity that fulfills the same criteria used to define substance-related and addictive disorders would need to be addressed. For example, compulsive sexual behavior may cause severe distress and lead to significant impairment in an individual's ability to fulfill major role obligations at home, work, or school. Similar to substance use, individuals may repeatedly fail to limit or stop sexual behaviors despite associated social and interpersonal problems that are as damaging as substance use may be to their lives [12]. Fully evaluating a patient's pattern of sexual and drug use activities may help identify the primary problematic behaviors and guide the initial focus of treatment. It is worth noting that sex and substance use are both strong motivators of behavior and there is likely to be overlap.

Stigma Related to Substance Use

There is substantial evidence that healthcare professionals carry negative attitudes and beliefs about patients with substance-related and addictive disorders [86]. Despite a better understanding of the genetic and neurobiological basis of addiction, substance users may not only be perceived as responsible for their illness but also labeled as violent, manipulative, or lacking motivation to get better [87]. Clinician bias may manifest as less time spent with patients, diminished rapport between patient and clinician, and misattribution of physical symptoms to substance use [88]. Stigma by medical professionals toward patients with substance-related and addictive disorders may result in reluctance by patients to access healthcare and may diminish patient self-esteem and self-efficacy leading to poor treatment outcomes [88, 89]. Substance users often feel rejected by providers and this feeling intensifies with repeated exposure to the healthcare system [88]. People who inject drugs, when compared to non-injection drug users, perceive stigma from providers more often and are more likely to cope by withholding information from providers [88].

Self-stigma involves the internalization of negative thoughts and feelings due to identification with a marginalized group. Internalized substance use stigma is associated with worse psychiatric outcomes and less engagement in treatment [90]. It can manifest in many ways, including shame and self-devaluation, labeling oneself as morally corrupt or evil, as well as reluctance to disclose substance use [91]. Reluctance to identify as someone suffering from a substance use disorder may discourage patients from participating in peer-support programs such as Alcoholics Anonymous or in accessing medications used to treat substance-related and addictive disorders. Reluctance to utilize medications may also stem from stigma related to the belief that taking medications such as buprenorphine means that one is "not sober" [92].

Self-stigma and related psychosocial stressors experienced by people living with HIV, such as discrimination, may increase risk for maladaptive coping styles such

as substance use and negative psychiatric outcomes, including development of substance-related and addictive disorders [93]. Patients with both HIV and substance use disorders are especially vulnerable to provider bias which may negatively affect treatment [94]. A 2005 study found that people who both inject drugs and are living with HIV who were treated by physicians with negative attitudes toward injection drug users were more than 50% less likely to be exposed to antiretroviral therapy [95]. Patients exposed to substance use stigma also had more difficulty with antiretroviral therapy adherence [96]. In another study of patients with HIV risk behaviors, stigma against drug users was associated with higher rates of depression, as well as greater association with other drug users, perhaps due to social rejection from non-users [97]. Discrimination against drug users is associated with the formation of high-risk social ties including an increased number of sexual partners and injection partners, which may lead to HIV transmission [98]. People who inject drugs with internalized stigma and negative feelings toward other users are less likely to access syringe services programs (SSP) [99]. Refer to Chap. 3 for more information on stigma associated with HIV.

Specific Substances

Alcohol

Prevalence and Correlates

Alcohol use is highly prevalent among people living with HIV (PLWH) and is a risk factor for HIV transmission, at-risk sexual behaviors, drug use, psychiatric morbidity, and poor HIV outcomes [100–102]. Lifetime and 30-day prevalence rates of unhealthy or hazardous drinking and alcohol use disorders vary depending on the population studied and definitions used to categorize levels of alcohol use. A nationally representative, population-based study of people living with HIV in the United States, done early in the era of antiretroviral therapy, found an 8% 30-day prevalence rate of heavy drinkers, a rate double that found in the general population [103, 104]. More recent estimates demonstrated rates of hazardous drinking and binge drinking to be as high as 27% and 34%, respectively, among people living with HIV receiving HIV primary care [100–102, 105]. For National Institute on Alcohol Abuse and Alcoholism (NIAAA) definitions of low-risk drinking, binge drinking, heavy alcohol use, and alcohol use disorders, see https://www.niaaa.nih.gov/publications/brochures-and-fact-sheets/alcohol-facts-and-statistics accessed 10/18/20.

Hazardous alcohol use is significantly associated with multiple demographic and clinical factors. Co-occurring conditions may interact synergistically to disproportionately influence HIV outcomes [106, 107]. They also serve as modifiable targets for interventions that may improve overall outcomes. Alcohol use is correlated with smoking tobacco which is highly prevalent in people living with HIV (PLWH), compared to the general population [107]. PLWH with hazardous alcohol use are

also more likely to use marijuana and other drugs especially cocaine and crack cocaine and to be younger in age. Depressive disorders, anxiety disorders, and post-traumatic stress disorder are common in PLWH and are associated with drinking. Studies examining the synergistic effect of these conditions with heavy alcohol use are mixed, although their interaction is at least additive and may result in a magnification of their adverse consequences [108]. In contrast, one study found that depression co-occurring with hazardous alcohol use may confer increased motivation to quit drinking [106]. Since the introduction of antiretroviral treatments, more severe forms of HIV-associated neurocognitive disorders (HAND) are less prevalent, yet overall prevalence of HAND is unchanged. Alcohol's negative impact on the central nervous system in persons without HIV is well-documented but how this interaction may differ in PLWH is less clear. PLWH co-infected with hepatitis C (HCV) and co-occurring alcohol use face additional risks including more rapid progression of liver disease and alcohol-induced cirrhosis. The effect of antiretroviral treatments on hepatic metabolism requires further elucidation [109].

Effect of Alcohol on HIV

Alcohol use may negatively influence outcomes at any point along the HIV continuum of care [110]. It may facilitate HIV transmission by loosening inhibitions, impairing judgment, and increasing the likelihood of engaging in condomless anal intercourse and having a higher number of sexual partners. Alcohol use may serve as a barrier to HIV testing and engagement and retention in care. Many studies have examined alcohol's effect on adherence to antiretroviral medications [111, 112]. While any alcohol use may interfere with adherence, there appears to be a dose-dependent relationship between higher levels of alcohol use and poorer medication adherence. Patients' beliefs about a toxic interaction between antiretroviral medications and alcohol are a factor that may drive medication nonadherence [109, 113]. HIV may accelerate HIV progression indirectly, primarily through medication nonadherence, or directly through biological mechanisms. Both alcohol and HIV may exacerbate microbial translocation, immune activation, disrupted gut microbiome, and systemic inflammation. These processes may partially mediate the higher mortality rate observed among PLWH with heavy alcohol use compared to those with no or moderate use. Prospective observational studies initiated both before and after the introduction of antiretroviral treatment, which examined the relationship between HIV disease progression and alcohol use, have demonstrated inconsistent findings [101, 107, 114–117].

Treatment

There is ample evidence to support routine screening for alcohol use among people living with HIV (PLWH) followed by easily accessible interventions for those with drinking patterns that place them at risk for poor health outcomes or frank alcohol

use disorders. Alcohol use is often not identified and undertreated in HIV primary care settings. In one study only 9% of PLWH with problematic alcohol use were identified by their HIV primary care providers during routine care [118].

The US Preventive Services Task Force (USPSTF) recommends screening for unhealthy alcohol use in adults 18 years or older receiving care in a non-HIV primary care settings. For those who screen positive for at-risk or hazardous drinking, brief behavioral counseling is recommended [119–121]. See Table 11.4 (screening tools) and Table 11.5 (psychosocial interventions).

Studies testing the efficacy of behavioral interventions to improve alcohol use disorder outcomes in people living with HIV (PLWH) are limited. A 2013 systematic review found that the majority of randomized, controlled studies utilized motivational interviewing (MI) and cognitive behavioral therapy (CBT) approaches, both alone and in combination. A synthesis of results from these studies was inconclusive regarding the effectiveness of the intervention condition in reducing alcohol use quantity and frequency compared to the control group [122]. The presence of syndemic conditions such as depressive disorders, anxiety disorders, and posttraumatic stress disorder, as well as social factors may have influenced trial results [123].

There are several approved pharmacologic agents that when combined with psychosocial interventions may significantly improve alcohol-related outcomes: disulfiram, acamprosate, and naltrexone. Disulfiram may increase abstinence by causing aversive physical effects when combined with alcohol. Nausea, vomiting, shortness of breath, sweating, tachycardia, and hypotension occur as a result of disulfiram's inhibition of acetaldehyde dehydrogenase and consequent excessive accumulation of acetaldehyde in the blood. Although acamprosate's mechanism of action is not fully understood, it has inhibitory activity at a metabotropic glutamate receptor and both inhibitory and excitatory effects at N-methyl-D-aspartate (NMDA) receptor sites. Clinical trials have demonstrated that treatment with acamprosate may increase duration and rates of abstinence. Naltrexone is a mu-opioid receptor antagonist that has been shown to reduce heavy drinking and cravings. It is less effective in promoting complete abstinence. Sustained-release intramuscular form of naltrexone may be effective when medication adherence is problematic [124]. See Table 11.8 for drug-drug interactions between antiretroviral medications and disulfiram.

Case Vignette 11.1

M. was a 45-year-old African-American woman with HIV disease diagnosed over 20 years ago shortly following her college graduation. Despite intermittent nonadherence to antiretroviral therapy and episodic viral non-suppression, her CD4 cell count has remained above 500 cells/cubic millimeter, about which she felt proud and which confirmed her belief that she was medically "in great health." She presented with a request for medications for insomnia and "anger attacks." She explained that caring for her disabled grandmother, who raised her, and her adolescent daughter and son consumed all her energy. By bedtime, M. was "too exhausted to turn off her mind and fall asleep."

Table 11.8 Drug-drug interactions: antiretrovirals and methadone, buprenorphine, and disulfiram

Methadone			
Antiretroviral medication	Decreased	Increased	References
Abacavir	Monitor for withdrawal and need to increase dose		[125]
Efavirenz and nevirapine	Monitor for withdrawal and need to increase dose		[126, 127]
Efavirenz-containing regimen is discontinued		Monitor for toxicity and need to reduce dose	
Lopinavir/ritonavir, rilpivirine	Monitor for withdrawal and need to increase dose		[128, 129]
Ritonavir	Consider increase in dose		[130]
Ritonavir-containing regimen is discontinued		Monitor for toxicity and need to reduce dose	
Tipranavir/ritonavir	Monitor for withdrawal and need to increase dose		[131]

Buprenorphine			
Antiretroviral medication	Decreased level of buprenorphine	Increased level of buprenorphine	References
Atazanavir/ritonavir		Monitor for toxicity and need to reduce dose	[132]
Darunavir/cobicistat		Monitor for toxicity	[133]
Ritonavir		No clinically significant pharmacodynamic changes	[134]
Efavirenz, Tipranavir/ritonavir	No evidence for withdrawal and therefore dose adjustment not necessary		[135, 136]

Disulfiram				
Antiretroviral medication	Decreased disulfiram efficacy	Disulfiram-like reactions	Disulfiram inhibits	References
Atazanavir	Decreased likelihood of deterring alcohol use			[137]
Lopinavir and ritonavir oral solutions		Avoid combinations		[138, 139]
Tipranavir capsules				

Table 11.8 (continued)

Disulfiram				
Antiretroviral medication	Decreased disulfiram efficacy	Disulfiram-like reactions	Disulfiram inhibits	References
Fosamprenavir/amprenavir oral suspension containing propylene glycol			May result in propylene glycol toxicity	[138, 139]

Prior to M.'s office visit she completed the AUDIT-C questionnaire and scored 7, indicating that she likely had an alcohol use disorder. In the office, she disclosed without prompting that she "sometimes drank a glass of wine at bedtime to help get herself to sleep." You sensed that she was unaware of the discrepancy between her self-report on the AUDIT-C and her self-report to you. You believed that if you confronted her with this discrepancy, she would feel shamed and accused of lying. You wondered how to introduce alcohol in the conversation in a supportive and caring manner. After reviewing her vital signs and laboratory results, you asked M. if she was interested in reviewing the questionnaires she completed prior to seeing you. With her consent you explained that the questionnaire about alcohol use indicated that there was an opportunity to reduce her risk of potential complications of alcohol. You asked her permission to discuss these risks and then proceeded by briefly discussing the medical, neurologic, and psychiatric problems, including withdrawal, associated with alcohol. You reinforced her experience of feeling listened to by focusing your comments on the relationship between alcohol and sleep, emotional regulation, antiretroviral therapy adherence, and HIV disease progression. You asked M. if she was interested in hearing your thoughts about what she can do to improve sleep and "anger attacks," maintain a healthy immune system, and continue to function well in her role as a mother and granddaughter. M. was interested in discussing a sleep medication only but agreed to return if her anger persisted despite improvement in sleep.

M.'s case illustrates the value of taking a nonjudgmental and supportive approach with a patient unaware of the potential dangers of her alcohol use. Her situation also demonstrates the incorporation of Screening, Brief Intervention, and Referral for Treatment (SBIRT) and motivational interviewing in an office visit with someone in the precontemplative stage of readiness for change. If in the future she is interested in addressing her alcohol use, you may offer a trial of naltrexone to reduce alcohol cravings and consider a serotonin reuptake inhibitor trial to address an underlying anxiety disorder. A motivational interviewing style that emphasizes "change talk" and addresses M.'s ambivalent relationship toward alcohol may strengthen her motivation to reduce drinking to safer levels. See Table 11.5 for a description of Screening, Brief Intervention, and Referral for Treatment (SBIRT) and motivational interviewing (MI), stages of readiness to change.

Tobacco and Nicotine

Cigarettes, chewing tobacco, and e-cigarettes/vaping devices contain nicotine, an agonist of nicotinic acetylcholine receptors. After being absorbed into the bloodstream, nicotine causes dopamine release from the ventral tegmental area which stimulates the reward pathway. Epinephrine is released from the adrenal glands, resulting in activation of the sympathetic nervous system. Nicotine has a half-life of 2 h; however, nicotine metabolites can persist in the bloodstream for much longer [140].

Prevalence and Correlates

People living with HIV (PLWH) are two to three times more likely to smoke cigarettes than people without HIV, with rates estimated to be as high as 70% [141, 142]. As PLWH taking antiretroviral (ARV) medication live longer, smokers with HIV may lose more years of their life to smoking than to AIDS-defining illnesses [143]. Smoking is associated with lower quality of life in multiple dimensions, including general health perception, physical functioning, bodily pain, energy, and cognitive functioning [144, 145]. HIV infection may interact synergistically with smoking to potentiate its harmful effects [145]. Smoking is associated in PLWH with greater vulnerability to various diseases including community-acquired pneumonia and *Pneumocystis jiroveci* pneumonia [146], periodontal disease, oral lesions such as candidiasis [147], coronary artery disease [148], chronic obstructive pulmonary disease [149], and lung cancer [142, 150, 151].

It is unclear which psychosocial factors contribute to elevated rates of smoking in people living with HIV (PLWH). Higher rates of psychiatric illness in PLWH may contribute, as depression has been linked to increased smoking and nicotine dependence [152]. Smoking may also function as a coping style for managing stigma and reduced social support in PLWH [142]. Several studies have found elevated rates of cigarette smoking in sexual and gender minorities, with the highest rates in men who have sex with men [153, 154]. Smoking often co-occurs with alcohol use and illicit drug use [155–157]. In youth living with HIV, rates of daily smoking are higher in those with housing instability or criminal justice involvement [155].

E-cigarette use has increased since 2011, particularly among sexual and gender minorities [158]. In a review of e-cigarette use, four randomized controlled trials showed that e-cigarettes were effective in helping current smokers reduce smoking [159]. E-cigarettes may reduce exposure to tobacco smoke, and some writers have proposed that they could function as a possible harm reduction intervention [160]. However, there is concern that vaping may prolong nicotine use or introduce youth to nicotine products [153, 158, 160, 161]. At the time of this writing a significant number of case reports have linked e-cigarette additives to serious lung injury and death [162]. More research is needed into the public health impact of e-cigarettes before physicians consider their use in harm reduction.

Effect of Tobacco Use on HIV

Although high smoking rates in people living with HIV are the largest contributor to increased COPD and lung cancer risk, there is evidence that HIV is an independent risk factor, likely due to its impact on lung and systemic inflammation and association with recurrent lung infections [145, 150]. Studies investigating the link between smoking and HIV progression have been mixed. Evidence exists that smoking is associated with worse antiretroviral therapy (ART) adherence, impaired immune response, reduced viral suppression [155, 162, 163], and increased morbidity and mortality even among PLWH who are adherent to ART [164].

Treatment

Given the prevalence of smoking, and its association with negative health outcomes and increased mortality in people living with HIV (PLWH), it is vitally important to offer smoking cessation treatment [145]. PLWH may have low readiness to quit, due in part to higher rates of illicit drug use and psychiatric comorbidity [157]. Additionally, HIV providers may be less likely to identify smoking in PLWH and may feel less confident in their ability to influence smoking cessation [165, 166]. Despite obstacles to treatment there is evidence that smoking cessation strategies that benefit the general population may be effective in PLWH [145]. These interventions include brief advice, telephone-based counseling, motivational interviewing, and cognitive behavioral therapy [152, 167].

Psychopharmacological options for smoking cessation include nicotine replacement therapy (NRT), varenicline, and bupropion. While not compared specifically in people living with HIV (PLWH), a large randomized controlled trial found that all three options were effective and that varenicline was the most effective in helping smokers achieve abstinence [168]. Further research is needed to assess the tolerability and effectiveness of smoking cessation aids in PWLH. There were no differences in neuropsychiatric adverse events among the three medications [168]. Bupropion metabolism is inhibited by antiretroviral (ARV) medications such as nelfinavir, ritonavir, and efavirenz in vitro; however, in limited studies no clinically significant interactions were observed [152]. No drug-drug interactions between varenicline and ARV medications have been found [152].

Nicotine is metabolized by hepatic P450 enzymes, mostly CYP2A6, where it is activated into reactive oxygen species. PLWH have enhanced nicotine metabolism, which may result in an increase in compounds that cause oxidative stress and carcinogenesis [169]. Drug-drug interactions between nicotine and antiretroviral (ARV) drugs likely exist, as nicotine increases activity of MDR1, an efflux transporter that may lower the bioavailability of some ARV medications [170]. Theoretically, interaction of nicotine with P450 enzymes may result in subtherapeutic ARV levels, oxidative stress on monocytes, and ultimately increased HIV-1 replication [141, 171].

Opioids

Opioids refer to a group of naturally occurring, semi-synthetic, and synthetic compounds that act as agonists or partial agonists at opioid receptors in the central and peripheral nervous systems. Opioids are primarily used in clinical settings for their analgesic effects. When used for recreational or other nonmedical purposes, opioids comprise a large number of compounds that can be ingested, inhaled as smoke or vapor, or injected intravenously. Agonism of opioid receptors produces analgesia, sedation, euphoria, constipation, and suppression of respiratory drive. Sustained use produces both psychological and physiologic dependence, meaning that discontinuation may result in a withdrawal syndrome [172].

Prevalence and Correlates

Opioids are a leading cause of death in the United States, which may occur as a result of opioid-induced respiratory suppression. Additionally, non-sterile equipment used to inject opioids and other substances may transmit HIV and HCV, as well as bacterial infections, which account for up to 25% of opioid-related deaths [173].

Drug overdoses were the leading accidental cause of death in the United States in 2017. Of those deaths, nearly 70% involved opioids [174]. Like other forms of substance use, opioid use disorder (OUD) is overrepresented in people living with HIV (PLWH). Injection drug use (IDU) is common in OUD and can represent a vector for HIV transmission. However, due to improved prevention strategies, the proportion of new HIV infections from IDU fell from 20% to 6% between 2012 and 2016 [175]. The higher-than-expected prevalence of OUD may reflect higher rates of chronic pain in PLWH. Chronic pain can result from HIV as well as from side effects of antiretroviral (ARV) medications. Consequently, opioids are prescribed to PLWH at a higher rate compared to the general population, increasing exposure and risk for addiction in this population [175–177].

Effect of Opioids on HIV

Opioid use may affect outcomes at multiple points along the HIV continuum of care. Opioid use is associated with delays in HIV diagnosis and initiation of antiretroviral therapy due to reasons ranging from mistrust of healthcare providers to low self-efficacy and limited access to resources, such as medical insurance and food [178]. The association between opioid use and poor antiretroviral (ARV) adherence may lead to virologic non-suppression, immune suppression, and increased development of HIV resistance to antiretroviral medication [178]. Opioid use is also associated with both HIV sexual risk behaviors and substance-related HIV risk behaviors such as poor needle hygiene. These behaviors may not only contribute to HIV transmission but also increase risk of injury, trauma, overdose, or bacterial

infection [57, 176]. Some evidence suggests that nonmedical opioid use may be a risk factor for development of HIV-associated neurocognitive disorder (HAND) [179]. HIV and opioid use may interact synergistically to increase overall mortality [179].

Case Vignette 11.2
B., a 26-year-old male, was recently diagnosed with HIV and hepatitis C in the context of intravenous heroin use. He presented to your psychiatric clinic 1 week after meeting with an infectious disease specialist, whom he was scheduled to see again to receive recommendations for therapy. He was referred to you for help with substance use. He reported that he had been using heroin daily for about 2 years and had tried to stop four times in the past 6 months because of worsening negative effects of substance use on his life. Unfortunately, withdrawal and cravings were unbearable for the patient, and he quickly resumed use. The patient asked if you would help him with "detox" and his infectious disease specialist asked for your advice about whether to start antiretroviral therapy.

Treatment

Opioid withdrawal can be treated either directly with opioid agonists or symptomatically, with medications such as clonidine [180]. Regardless, treatment of withdrawal alone is likely insufficient for B. Although some individuals are able to quit opioids on their own, B. gives several indications that he will require additional interventions. His history indicates that he is physiologically dependent, as he describes withdrawal symptoms during discontinuation. He has also been using heroin through injection and has tried to quit more than three times without success, which are both predictors of high relapse risk [181]. Further history should also be taken regarding psychiatric and trauma comorbidity, which are both predictors of relapse as well as prognosis and could be areas warranting additional pharmacologic or psychotherapeutic intervention [57, 62, 66, 72].

Opioids are notable among abused substances in that strong pharmacological interventions are available to aid in treatment when physiologic dependence is present. There are currently three medications approved for treatment of opioid use disorder in the United States. These include methadone, a full opioid agonist; buprenorphine, an opioid partial agonist; and naltrexone, an opioid antagonist, which may be used in the form of a monthly injection to block additional opioid use. Methadone and buprenorphine have been controversial because patients remain dependent upon an opioid as opposed to maintaining abstinence, but the evidence for their benefits is extensive. Patients who take methadone and buprenorphine are more likely to stay in treatment, decrease illicit opioid use, and have reductions in all-cause mortality compared to patients who do not use these medications [182]. Methadone and buprenorphine treatment are associated with reductions in high-risk

behaviors that can lead to HIV transmission [60, 183] and are associated with better adherence to antiretroviral therapy (ART) [183]. In light of this evidence, you may recommend that B. in the clinical vignette begin ART.

Extended-release naltrexone is also associated with reduced rates of opioid use and increased retention in substance abuse treatment compared to placebo, but there is less evidence supporting its use when compared to methadone and buprenorphine [184], especially in the context of HIV infection. Naltrexone initiation requires that the patient be abstinent from opioids for about 1 week in order to not precipitate withdrawal. If B. wanted to utilize this approach, he should be provided with treatment for symptoms of withdrawal. Naltrexone gives patients a non-opioid pharmacologic option which can have important psychological as well as practical benefits. If B. chose to start buprenorphine or methadone, he should know that discontinuation may result in withdrawal and high rates of opioid relapse [184].

Methadone remains the gold standard for pharmacotherapy of opioid use disorder (OUD). In head-to-head comparison trials with buprenorphine, use of methadone is less likely to result in early discontinuation of treatment [184]. Methadone unfortunately has several drawbacks compared to buprenorphine that limit its use. Methadone can only be administered in a federally regulated treatment program. Patients are also typically required to present daily to these programs to receive doses, at least during the initial phase of treatment. Although buprenorphine may require a federal practitioner waiver, a 30-day supply can be prescribed in an outpatient office setting which offers a significant advantage over methadone. Buprenorphine, as a partial opioid agonist, and naltrexone, as an antagonist, are also relatively safe in overdose, with the caveat that buprenorphine has been implicated in sedation and death when combined with other sedatives. Methadone, as a full opioid agonist, is potentially lethal in overdose [185].

Potential drug-drug interactions are especially pertinent with B., as he is about to start antiviral therapy for both HIV and HCV. See Table 11.8 for drug-drug interactions between antiretroviral medications and medications used to treat opioid use disorder.

Marijuana and Cannabis

Marijuana refers to the dried leaves, flowers, stems, and seeds of the hemp plant, *Cannabis sativa* or Cannabis indica. Routes of use include smoking, drinking, or eating the plant or inhaling vapors produced by heating its concentrates. Marijuana contains delta-9-tetrahydrocannabinol (THC) whose psychoactive properties produce the desired "high." While paranoia, anxiety, and hallucinations may occur, especially at high doses, people living with HIV (PLWH) report using marijuana to self-treat depression, anxiety, sleep, and weight loss. THC's effect on the brain is mediated through the endocannabinoid system whose activity extends to the hippocampus, orbitofrontal cortex, cerebellum, basal ganglia, and the brain's reward

system [186]. THC-containing e-cigarette or vaping products have been linked to a recent, large multi-state outbreak of severe lung injury and deaths. Although the responsible ingredient has not been definitively identified, the Centers for Disease Control and Prevention (CDC) has recommended against the use of THC-containing e-cigarette or vaping products [187].

Marijuana has been used by people living with HIV (PLWH) since early in the epidemic, both for recreational purposes and to relieve HIV-related symptoms stemming from AIDS wasting syndrome, intractable pain due to peripheral neuropathy, and nausea and vomiting induced by early antiretroviral (ARV) medications. Recent trends in the legalization of recreational marijuana and growing accessibility of medical marijuana have complicated the identification and assessment of marijuana use among PLWH in a clinical care setting. The indistinct boundary between nonmedical and medical uses of marijuana and the lack of evidence-based guidelines to assist with assessment have further complicated clinical decision making. These factors underscore the importance of understanding the scope of problematic marijuana use, its correlates and common comorbidities, its impact on HIV outcomes, and how to enhance possible benefits while mitigating harms.

Prevalence and Correlates

Most epidemiologic research of cannabis use in people living with HIV (PLWH) has relied on clinical samples of persons receiving medical care. A recent study used data from the 2005–2015 National Survey on Drug Use and Health, a US nationally representative sample, to estimate prevalence and correlates of different levels of marijuana use and medical marijuana use among PLWH. Prevalence of past-year cannabis use was nearly 3 times greater than that found in the general US population, 34.9% versus 13.3%. Daily cannabis use and cannabis use disorders were also overrepresented among PLWH. The prevalence of medical cannabis use was 1.5 times greater than the general population. Compared to recreational users, medical cannabis users were more likely to be White, married, and less likely to have used alcohol in the past year. Tobacco smokers were more likely to use cannabis including daily cannabis. Similarly, having a lifetime major depressive episode was associated with greater likelihood of daily cannabis use. Additionally, data suggest a dose-response relationship between level of cannabis use and risk of developing depression and intensity of tobacco use [188]. Other studies using nationally representative samples to estimate prevalence of drug use in HIV-infected individuals found similarly elevated rates of cannabis use compared to prevalence rates in HIV-uninfected individuals [189, 190]. Youthful age and male gender were the strongest predictors of being at risk for developing cannabis use disorder in an analysis of a large US multiregional cohort of PLWH in medical care, the Centers for AIDS Research (CFAR) Network of Integrated Clinical Systems (CNICS) cohort [189, 190]. These findings suggested the need for interventions that target all conditions in an integrated care setting [191].

Effect of Marijuana on HIV

Studies that have examined the relationship between cannabis use and HIV outcomes have found mixed results likely related to heterogeneity of study design, sampling methods, and measurements used. A large single-site longitudinal study found no adverse effect of cannabis use on CD4 cell count. Similar to the Women's Interagency HIV Study (WIHS) and other studies, the use of any marijuana increased the likelihood of having a detectable viral load [6, 192, 193]. Among participants in the Veterans Aging Cohort Study (VACS), marijuana use was not associated with increased mortality, while psychostimulant use did confer additional risk [194]. In an analysis of CNICS participants, having a marijuana use disorder significantly negatively affected retention in care, particularly in young adults, relative to having other substance use disorders or having no substance use disorder [195]. Results from other studies suggested a dose-response relationship between marijuana use and antiretroviral adherence and number of missed clinic visits with frequent or daily use being associated with poorest retention in care and adherence [196, 197].

Cannabis and Opioid Use and Misuse for Pain

Studies examining marijuana as a possible adjunct to opioids prescribed for pain have yielded mixed results. While some studies demonstrated an association between marijuana use and decreased odds of prescribed opioids for pain in people living with HIV (PLWH) [198], others did not. One study found no association between recreational marijuana use and opioid misuse, opioid dose, or pain severity among PLWH attending an HIV ambulatory care clinic. Additionally, current marijuana users were three times as likely to have a detectable viral load compared to participants with no use. These finding are not consistent with claims that marijuana use is associated with a reduction in opioid requirements for the treatment of chronic pain [199].

Treatment

Several psychotherapeutic modalities have been studied in clinical trials. Evidence supports the effectiveness of cognitive behavioral therapy (CBT), motivational enhancement therapy (MET), and contingency management (CM) with a combination of CBT, MET, and CM producing the best outcomes. Screening, Brief Intervention, and Referral for Treatment (SBIRT) for marijuana use in HIV settings has not been well studied [16, 200].

There are no approved medications for treatment of cannabis use disorder or cannabis withdrawal. Evidence suggests the benefits of gabapentin to mitigate withdrawal symptoms and prevent relapse and mirtazapine for sleep disturbance, poor appetite, and weight loss associated with withdrawal [201, 202].

Clinically significant drug-drug interactions between delta-9-tetrahydrocannabinol (THC) and antiretroviral medications have not been clearly delineated. THC undergoes hepatic metabolism utilizing the cytochrome P450 (CYP) enzyme system and may potentially inhibit or induce CYP3A, CYP1A, CYP2C9, CYP2B6, and CYP2A6 isoforms. Studies that have examined the effect of marijuana on CD4 cell count and viral suppression in the context of antiretroviral treatment are inconclusive. Some studies suggest that marijuana may increase antiretroviral side effects and decrease plasma levels of protease inhibitors [203]. However, a randomized placebo-controlled trial of smoked marijuana and dronabinol showed no significant changes in plasma levels of either nelfinavir or indinavir [204].

Cocaine and Crack Cocaine

Cocaine is an alkaloid extracted from the leaf of the Erythroxylum coca bush native to South America. The hydrochloride salt consists of a fine, white, crystal powder, is water soluble, and can be administered orally, intravenously, or nasally by insufflation. When sold as an illicit drug, cocaine may be mixed with fentanyl which increases the lethality of overdose. The free-base form of cocaine, known as crack cocaine, can be heated and smoked. Crack cocaine's quick onset of action, 3–5 s, peak effect in 1 min, and the intense euphoria it produces make it the most addictive form of the drug. Cocaine is a powerful sympathomimetic agent whose physiologic and psychoactive effects are mediated by blocking presynaptic reuptake of dopamine and norepinephrine, resulting in an excess of these neurotransmitters at postsynaptic receptors and altered neurotransmission. Cocaine acts on the brain's limbic system circuitry where its influence on regulation of pleasure and motivation leads to dependence and addiction [205–207].

Prevalence and Correlates

Cocaine and crack cocaine use are highly prevalent among people living with HIV (PLHW) compared to the general population [208] and are associated with risk for HIV transmission, at-risk sexual behaviors [209], and poorer HIV outcomes [210]. Cocaine use confers additional risk for other drug use [211], psychiatric comorbidity [212, 213], and intimate partner violence [214]. A US national study of a population of heroin users found that frequency of crack cocaine use was associated with use of heroin, other forms of cocaine, and at-risk behaviors such as having a larger number of sexual partners and sharing needles [215]. A study of PLWH 50 years and older found that 10.5% had used cocaine or crack cocaine which was second to the 32.6% who had used marijuana in the past 12 months [216]. Among a group of homeless, chemically addicted mentally ill patients studied, cocaine users were 3.4 times more likely to have shared needles compared to users of other drugs [217] and 42% named cocaine as their primary drug of abuse.

A 2017 systematic review and meta-analyses of health outcomes associated with crack cocaine use found an elevated risk of posttraumatic stress disorder (PTSD) and attention-deficit/hyperactivity disorder (ADHD) compared to the general population. The evidence has been mixed regarding crack cocaine and an increased risk of other mental disorders such as major depressive disorder, anxiety disorders, bipolar disorder with mania, and psychotic disorders [206]. Cocaine may induce psychiatric symptoms such as anxiety, depression, mania, insomnia, loss of appetite, and paranoia which do not meet full DSM-5 criteria for a frank cocaine use disorder and which may last up to several weeks.

Effect of Cocaine on HIV

Cocaine and crack cocaine affect clinical outcomes at each point along the HIV continuum of care. A 2009 30-month longitudinal study of actively drug using people living with HIV (PLWH) found that participants who used crack cocaine were more likely to show an acceleration in decline of CD4 cell count to an AIDS-defining level and elevated viral load compared to non-users. This effect occurred independent of antiretroviral therapy (ART) and was not found among those who used powder cocaine, alcohol, marijuana, or heroin. This finding suggested that crack cocaine may have a direct effect on HIV disease that interacts with antiretroviral adherence to accelerate disease progression [218]. A 2008 study of the Women's Interagency HIV Study (WIHS) cohort found similar results. Crack cocaine users were significantly more likely than non-users to develop or die of an AIDS-related illness, and to show greater CD4 cell loss and higher viral load after controlling for antiretroviral (ARV) adherence, age, race, income, education, problem drinking, and illness duration [219]. Like these studies, a study of Black women found that crack cocaine users were significantly less likely to report adherence to antiretroviral medications [220].

Treatment

A 2015 comprehensive narrative overview of intervention studies testing psychosocial therapies for crack cocaine use disorders found the strongest evidence for treatment that incorporated cognitive behavioral (CBT) and contingency management components [221]. A study examining the effect of Screening, Brief Intervention, and Referral for Treatment (SBIRT) in an HIV primary care urban setting found a higher-than-expected prevalence of cocaine use and a significant reduction in cocaine use at 6 months post-intervention [16].

There are no US FDA-approved medications for treatment of cocaine or crack cocaine use disorder or withdrawal. Several pharmacologic agents have been studied but none was found to be either effective or tested in randomized controlled trials. A vaccine designed to stimulate production of IgG anticocaine antibodies was unsuccessful [222]. N-Acetyl cysteine is well tolerated and may attenuate

withdrawal symptoms and craving in cocaine use disorders [223]. Case reports suggested that gabapentin may be effective in reducing cocaine cravings [224], trazodone may reduce cocaine-induced compulsive behaviors [225], carbamazepine may reduce frequency of use [226], and injectable flupenthixol decanoate may reduce cravings [227].

A systematic review and meta-analysis of randomized controlled trials of topiramate did not find sufficient evidence to support its use for cocaine dependence [228]. Similarly, a randomized, double-blind, placebo-controlled trial of quetiapine did not show an effect for cocaine use disorder [229]. A 2017 systematic review and meta-analysis of modafinil treatment of cocaine dependence did not find evidence to support its effectiveness; however, subgroup analyses suggested that larger trials may show more promising results [230].

Cocaine is metabolized primarily by hydrolysis by cholinesterase, and only a small percentage undergoes N-demethylation to norcocaine by hepatic isoenzyme CYP 450 3A4. Theoretically, a strong inducer of CYP 3A4 such as efavirenz may cause a shift toward hepatic CYP metabolism resulting in an excess of norcaine, a known hepatotoxic metabolite. Reports of significant interactions among cocaine, crack cocaine, and antiretroviral medications are uncommon [203, 204, 231].

Methamphetamine

N-Methylamphetamine, or "methamphetamine" (MA), is a synthetic psychoactive central nervous system stimulant available in crystalline, powder, and liquid forms [232]. Although MA may be injected, swallowed, or inhaled [232], smoking is the most common route of administration and, aside from injection, has the highest bioavailability of the drug at an estimated 90% [232]. MA is metabolized in the liver into several active metabolites which are eventually excreted by the kidney [232]. At the synaptic level, methamphetamine causes the release of dopamine, norepinephrine, and serotonin from presynaptic vesicles. It also inhibits monoamine oxidase, which prolongs the availability of these neurotransmitters in the synapse [232]. Frequent use results in depletion of presynaptic monoamines and downregulation of target receptors. MA is also neurotoxic and structural brain lesions have consistently been found among users [232].

Acute effects of methamphetamine include euphoria, increased level of arousal, and behavioral disinhibition [232]. Additionally, tachycardia, stereotypy (characterized by repetitive, non-goal-directed motor activity), hypertension, appetite suppression, and mydriasis may be seen following use [232]. The period of intoxication varies depending on route of administration, though it is typically much longer than that of other stimulants, ranging from 8 to 24 h [233–236]. Associated systemic medical complications include myocardial infarction, cerebrovascular events, and rhabdomyolysis [237]. MA-induced psychiatric conditions may also arise and involve anxiety disorders and psychotic disorders characterized by hallucinations, delusional ideation, and paranoia that may extend months beyond the period of

intoxication [238]. In two small studies, the rate of persistent psychotic symptoms in users at 1 and 3 months following the last use was 16% and 17%, respectively [238]. Withdrawal from methamphetamine intoxication commonly results in depressive disorders, sometimes lasting weeks following abstinence [232].

Prevalence and Correlates

Methamphetamine (MA) in the US general population is low but use among subpopulations can be significantly elevated [232]. For example, survey data in Los Angeles and San Francisco estimated prevalence at 11% and 13%, respectively, among gay and bisexual men [232]. While small-scale domestic manufacture of the drug exists, the overwhelming majority of methamphetamine in the United States is made elsewhere, with criminal organizations in Mexico being at the forefront [233]. Well-meaning interventions to combat availability and use of the drug such as restriction on precursor chemicals and limitations on pseudoephedrine availability have resulted in reduced domestic production of MA, but net availability has remained essentially unchanged. The trend away from domestic manufacture has amplified medical risks to users, since the chemical purity and potency of imported MA is much higher [233].

Prevalence of methamphetamine use disorder using DSM-IV criteria was estimated at 0.2%, or approximately 535,000 individuals in the United States in 2012 [232]. Data from the Treatment Episode Data Set (TEDS), which provided information regarding primary indication for admission to substance abuse treatment facilities in the United States, showed an overall increase, with methamphetamine-related admissions increasing from 78,248 in 2001 to 239,852 in 2017, or 11.5% of all admissions [232, 239].

Methamphetamine use, in particular among men who have sex with men (MSM), is significantly associated with HIV infection [232]. In addition to the risks associated with shared drug paraphernalia, and the drug's association with HIV sexual risk practices, emerging data demonstrated impaired CD4 cell function and upregulation of HIV entry co-receptors CXCR4 and CCR5 on macrophages following use of MA [240]. These immunologic effects correlated with higher viral infection rates of macrophages, higher rates of viral replication, and overall higher viral loads seen in MA users [240].

Treatment

There is modest evidence to support the use of psychosocial treatments, namely, cognitive- behavioral therapy (CBT), in the treatment of methamphetamine (MA) dependence. CBT-based therapies may be limited by poor treatment adherence and exclusion of patients with impaired executive functioning [232].

There are no approved medications for the treatment of MA or amphetamine use disorders [235, 241]. However, a variety of agents have been examined. A study

examining the use of naltrexone found that it may be helpful in attenuating the subjective effect of dextroamphetamine in dependent patients, though later studies have failed to demonstrate efficacy in reducing use [234, 235, 242]. Bupropion has been associated with reduction in methamphetamine use among light users though this effect was not seen with heavy use [232, 243]. More recently, a 2021 study demonstrated that a combination of extended-release, injectable naltrexone combined with bupropion was significantly more effective than placebo in reducing MA use measured by urine drug screening [244]. Another study combining mirtazapine with CBT also found a significant reduction in MA use [232].

Metabolism of methamphetamine (MA) utilizes primarily the CYP2D6 and to a lesser extent CYP3A4 isoenzymes. Ritonavir and cobicistat are strong CYP3A4 inhibitors that theoretically may interact to increase MA blood levels and prolong exposure to MA. Similarly, bupropion, some serotonin reuptake inhibitors (SSRIs), and ritonavir may interfere with MA metabolism through CYP2D6 inhibition [244–246]. Although these interactions have not been examined in pharmacokinetic studies, there were case reports of deaths of people living with HIV (PLWH) in the setting of MA use [247]. See Table 11.9 for drug-drug interactions with antiretroviral medications.

Club Drugs: Lysergic Acid Diethylamide (LSD), Ketamine, Gamma-Hydroxybutyrate (GHB), 3,4-Methylenedioxy-Methamphetamine (MDMA, Ecstasy)

Electronic dance music (EDM) parties and dance festivals have grown in popularity in recent years and are often associated with the use of club drugs, including psychostimulants, LSD, ketamine, GHB, and MDMA [248, 249]. EDM is also popular at circuit parties, which are weekend long events attended by gay men, and associated with drug use and unprotected anal sex [250]. Common reasons for using club drugs at EDM parties include achieving a sense of connection or "oneness" with other partygoers or to intensify the party experience [249].

Club drug use is associated with systemic medical and neuropsychiatric sequelae. MDMA use can result in adverse cardiac effects, serotonin syndrome, seizures, hepatic failure, and death [251, 252]. MDMA is associated with serotonergic neural injury and

Table 11.9 Antiretroviral-substance interaction

Ritonavir and cobicistat CYP450-mediated interaction may result in substance toxicity [202, 203, 247]
Methamphetamine
3,4-Methyl-enedioxy-methamphetamine, MDMA (Ecstasy)
Mephedrone (bath salt)
Gamma-hydroxybutyrate (GHB)
Ketamine

5HT transporter depletion in the brain. This may explain why prolonged use is associated with depressive disorders, anxiety disorders, insomnia, and impaired cognition [251, 252]. GHB intoxication can result in nausea, vomiting, unconsciousness, and coma [253]. Its sedating properties have also been implicated in sexual assault cases [253]. Frequent GHB use can lead to addiction and a withdrawal syndrome characterized by sleep disturbance, anxiety symptoms, psychosis characterized by agitation, hallucinations, and paranoia, and delirium [253, 254]. People with comorbid psychiatric disorders such as anxiety disorders, depressive disorders, and borderline personality disorder are especially vulnerable to GHB use disorder [253]. Overuse of ketamine can cause dissociation, adverse cardiac and neurological effects, and respiratory depression [253]. Patients may develop dependence and tolerance to ketamine [253]. LSD use may lead to dangerous impulsive behavior resulting in injury or death [255].

Prevalence and Correlates

Men, Hispanic individuals, residents of large metropolitan areas, and people with higher incomes are more likely to attend electronic dance music (EDM) events. One study of EDM party attendees in the United States found that within a year, 41.1% used MDMA, 21% used LSD, 16.1% used ketamine, and 4.6% used GHB. Approximately one-third of EDM partygoers experienced an adverse effect from a drug, particularly when combined with alcohol [248]. The number of drug-related deaths at EDM dance festivals is on the rise [249].

The majority of research into use of club drugs in people living with HIV (PLWH) has focused on men who have sex with men (MSM), with limited research into their use in heterosexuals [253, 255, 256]. The use of club drugs in PLWH is associated with increased sexual risk taking and has recently been implicated in the expansion of the HIV epidemic [248]. The popularity of specific club drugs changes quickly and is often location specific. With that caveat in mind, in a survey of 2248 HIV-positive MSM in the United Kingdom, half of all participants reported use of recreational drugs in the past 3 months. Of those, 13% used ketamine, 12% used MDMA, and 10% used GHB. Nearly a quarter of MSM living with HIV combined three or more drugs. Polydrug use was associated with condomless sex, including condomless sex with serodiscordant partners [257]. Rates of club drug use among MSM who participated in EDM culture were even higher. In a US study of gay and bisexual men at a New York City dance club, one-third of attendees used MDMA. MDMA use was associated with condomless anal sex [258]. In studies of MSM who attended circuit parties, 25% of attendees used GHB, and 43% used ketamine [253].

Treatment

There is limited research into effective psychosocial interventions for club drug use. It is unclear whether interventions such as harm reduction, motivational interviewing, cognitive behavioral therapy, or contingency management could be effective

[253]. Drug checking is a public health strategy in which individuals or healthcare providers can test drugs for purity and evidence of adulteration. This allows individuals to make less risky choices, e.g., decreasing the use of a substance, disposing of contaminated drugs, and changing drug dealers. Drug checking also enables public health officials to gather information regarding the current drug supply and educate the public on potential risks. Several studies have demonstrated the effectiveness of on-site drug testing services in changing behavior, with participants more likely to not use a drug, dispose of a drug, or warn others after receiving a contaminated test result [259]. Additional harm reduction measures for club drug users might include encouraging hydration, discouraging mixing club drugs with alcohol, safer-sex counseling, HIV pre-exposure prophylaxis, and promotion of the use of condoms [253].

There are currently no approved medical treatments for club drug use disorders [253]. GHB-dependent patients may require detoxification with benzodiazepine taper. According to one study in the Netherlands, nearly 60% of GHB-dependent patients relapsed following detox. Treatment of ketamine intoxication includes hydration, supportive management, and benzodiazepines for acute agitation [253].

Drug-drug interactions between club drugs and ARVs may occur via inhibition or induction of CYP450 enzymes, glucuronidation, and cellular transporter proteins. Nonnucleoside reverse transcriptase inhibitors (NNRTIs), protease inhibitors boosted with ritonavir or cobicistat, and elvitegravir/cobicistat may interfere with drug metabolism [247].

MDMA is primarily metabolized by CYP2D6 and CYP1A2. There have been at least two deaths reported in patients taking ritonavir with MDMA, as well as cases of cardiotoxicity associated with ritonavir-boosted protease inhibitors [247].

Ketamine (vitamin K, special K) is administered orally, via insufflation, intravenously, or intramuscularly. It is an NMDA-receptor antagonist, is generally not associated with chemsex, and is less popular with men who have sex with men (MSM). Ketamine is metabolized primarily by CYP3A4. Interactions with antiretroviral (ARV) medications have not been studied; however, coadministration with ritonavir or cobicistat (CYPR3A4 inhibitors) could theoretically result in ketamine toxicity [247].

Lysergic acid diethylamide (LSD, acid, Lucy) may induce psychotic-like effects by acting as a 5HT2A receptor partial agonist and 5HT1A receptor agonist in the dorsal raphe and stimulating D2 and 5HT2A receptors in the ventral tegmental area. LSD is thought to be metabolized by the liver; however, details of its metabolism and drug-drug interactions remain unclear [260, 261].

Case Vignette 11.3

P. was a 23-year-old Latino gay man with a history of HIV, intermittent antiretroviral therapy (ART) nonadherence, and social anxiety disorder treated with sertraline 100 mg daily. Once or twice a month, P. attended nightclubs where he drank 3–4 mixed alcoholic beverages and "rolled on Molly (MDMA)." He reported that MDMA enhanced his enjoyment of the music,

allowed him to dance more confidently, and made it easier to connect to people around him. He frequently had sex with one or more partners after leaving the club and intermittently used condoms. P. felt shame after his sexual encounters, which he associated with his religious upbringing, and had difficulty getting out of bed or taking antiretroviral medications in the days following MDMA use. P. was diagnosed with HIV at age 19 and has told only one of his sisters about his diagnosis. His family and friends, with whom he generally feels close, did not know about his sexual orientation or HIV status. He has never had a serious boyfriend, explaining that he has difficulty disclosing his HIV diagnosis. He interacted with members of the gay community primarily in the night club setting. Although P. did not want to stop using MDMA because it was vital to his social and sexual life, he understood that it came at a price to his health.

P.'s case illustrates the dilemma faced by a patient who is in the very early contemplative stage of change. Going to night clubs without using MDMA feels unrealistic, as the combination of alcohol and MDMA allows him to overcome his social anxiety and connect with gay men socially and sexually. P.'s life appears to be highly compartmentalized between his family life "in the closet" and his "out" life at night clubs, where he may feel his most liberated and authentic self, despite being altered on various substances. In treating P., it is critical to take a nonjudgmental approach, in which the provider "rolls with resistance" and avoids overly directive language. Motivational interviewing (MI) can be used to slowly move the patient toward change, by focusing on what is important to him. For instance, if maintaining an undetectable HIV viral load is important to the patient, an initial approach may be to ask the patient what gets in the way of his antiretroviral medication compliance.

While continuing to look for openings to engage the patient in "change talk," a harm reduction approach should be taken. Harm reduction in the case of P. might include encouraging him to hydrate before taking MDMA and encouraging him to keep condoms with him when going to clubs [262]. "Coping ahead," by anticipating the "comedown" from MDMA, for instance by having his antiretroviral medications (ARV) and water by his bed, may help improve antiretroviral therapy compliance. In addition to motivational interviewing and harm reduction, P. may benefit from supportive psychotherapy in which he can safely discuss the shame and internalized and external stigma related to his HIV status and sexual identity. These painful issues may be interfering in his ability to disclose his HIV status to potential romantic partners and to engage with the gay community in less risky settings. Destigmatizing language, positive regard, curiosity, and open discussions about his identity may, over time, help him create new ways of relating to himself and others in the gay community.

Novel Psychoactive Substances

Cathinones

Synthetic cathinones belong to a class of novel psychoactive substances that are related to naturally occurring cathinone, the psychoactive component of the leaves of the Khat plant (*Catha edulis*) found in the Horn of Africa and the Arabian Peninsula [263]. These substances have psychostimulant properties and usually contain several psychoactive constituents, the most common being mephedrone, methylone, and methylenedioxypyrovalerone (MDPV) [263]. The product is sold for recreational use and consists of a white or brown crystalline powder, sometimes in tablet, capsule, or liquid form, and is administered by ingestion, inhalation, or injection. Names of various preparations include bath salts, flakka, ivory white, vanilla sky, and white lightning [264, 265]. Because these preparations are more potent and less expensive than other psychostimulant drugs, they may be used as unidentified substitutes in street methamphetamine, Ecstasy, and Molly (MDMA) [265]. The mechanism of action of these compounds is similar to methamphetamine and involves both inhibition of reuptake and release of dopamine and norepinephrine in the synaptic cleft [266].

The desired effects of synthetic cathinones are euphoria, sociability, and increased sex drive. Associated adverse cardiac and other physiologic effects similar to those seen with psychostimulants may occur. Associated psychiatric effects include impulsivity, violent behavior, suicidal behavior, and depressive disorder, psychotic disorder, and panic disorder. Repeated use may result in prolonged psychotic disorder [267]. In a 2018 survey of drug use among electronic dance music (EDM) party attendees in New York City, adverse events associated with synthetic cathinone use were most likely to result in a hospital visit, compared to other drugs [249]. Other studies examining the use of novel psychoactive substances found that synthetic cathinones were most commonly associated with poisoning compared to other novel drugs [268, 269]. Cases of hyperthermia, coma, and death have been reported [270].

Prevalence and Correlates

Prevalence estimates of synthetic cathinone use are limited. A 2018 cross-sectional survey of over 1000 people living with HIV (PLWH) attending an HIV clinic in France found that 2.7% of participants had used synthetic cathinones in the past 3 months. Overall psychoactive substance use and synthetic cathinone use were significantly greater among men who have sex with men (MSM) compared to non-MSM [271]. A 2016 survey of drug use among individuals attending an electronic dance music (EDM) venue in New York City found that 6.9% had ever used synthetic cathinones, a lower prevalence compared to synthetic cannabinoids and psychedelic phenethylamines and greater than opioids and benzodiazepines [272]. A

nationally representative US survey, the National Survey on Drug Use and Health (2009–2013), found the prevalence of synthetic cathinones to be lower than most of the other novel substances such as tryptamines, psychedelic phenethylamine, and synthetic cannabinoids [269]. A US online survey of "bath salt" users showed they were more often young, White, and male with some college education. Use was also associated with increased sexual desire and HIV sexual risk behavior. Repeated use on the same occasion was observed [264, 273].

Effect of Cathinones on HIV

The effect of cathinone-related drugs on HIV progression is unknown. Due to a mechanism of action similar to that of cocaine and methamphetamine, it has been hypothesized that these novel compounds may also interact synergistically to potentiate HIV's glial and neuronal toxicity [266].

Treatment

Evidence-based psychosocial or medication treatments for problematic cathinone use are lacking. Reports on interactions among cathinone derivatives and psychiatric and antiretroviral medications are limited. However, synthetic cathinones are metabolized by the liver and some may utilize hepatic cytochrome P450 2D6 and to a lesser extent CYP 2B6, CYP 1A2, and CYP 2C19 enzymes. Due to cathinones' weak to moderate inhibition of CYP 2B6 and CYP 2D6, the metabolism of drugs that primarily use these CYP enzymes may be affected [274].

Synthetic Cannabinoids

Synthetic cannabinoids are a diffuse group of novel psychoactive substances containing various synthetic compounds chemically related to THC (delta-tetrahydrocannabinol), the psychoactive agent found in marijuana. These compounds are either sprayed on dried herbal plants and then sold so they can be smoked, brewed as tea, or sold as liquids that can be vaporized and inhaled ("vaping") through e-cigarettes. Common street names include Spice, K2, and synthetic marijuana. These psychoactive compounds bind to endogenous cannabinoid receptors in the brain, where they are more potent than THC and may have unpredictable, dangerous, and potentially life-threatening effects. In addition to the euphoric effects experienced with marijuana use, more severe psychiatric symptoms such as delusional and paranoid ideation, hallucinations, suicidality, and violent behavior may

occur. Physiological effects include hypertension, tachycardia, renal and cardiac injury, seizures, and death [275].

Prevalence and Correlates

The prevalence of synthetic cannabinoid use in people living with HIV (PLWH) is not well studied. Existing data suggest that use of novel psychoactive substances is more common among individuals who attend electronic dance music (EDM) venues and festivals compared to the general population [272]. A 2018 study of EDM party attendees in New York City found an overall past-year prevalence of synthetic cannabinoid use of 3.6% [276]. In a related 2016 study of EDM attendees in New York City, use of synthetic cannabinoids was more prevalent than any other novel psychoactive substance [272]. A 2017 study conducted by the Centers for Disease Control and Prevention (CDC), using data from the Youth Risk Behavior Survey, found a prevalence of ever having used synthetic cannabinoids of 9.4% among youth in grades 9–12 across the United States. A large majority of synthetic cannabinoid users had also used marijuana, while only 22.8% of marijuana users had ever used synthetic cannabinoids. Users of marijuana only as well as users of synthetic cannabinoids were more likely to use all other substances surveyed, such as inhalants, cocaine, heroin, methamphetamine, Ecstasy, and hallucinogens, compared to those who had never used marijuana or synthetic cannabinoids. Similarly, these groups were at greater risk for violence and injury, mental health problems, and HIV sexual risk behaviors compared to those who never used marijuana or synthetic cannabinoids [277]. In a US nationally representative sample of high school seniors, 10% reported synthetic cannabinoid use [278].

Effect of Synthetic Cannabinoids on HIV

There is limited research on the effect of synthetic cannabinoids on HIV progression, the interaction between synthetic cannabinoids and HIV in the central nervous system, and drug-drug interactions between synthetic cannabinoids and antiretroviral medications. As of 2015, 134 synthetic cannabinoid compounds had been identified in Europe. The inability for users to identify which compound(s) they are using and the widely varying adverse health effects of the different compounds complicates this area of research [279].

Treatment

Research on psychosocial therapies is limited and there are no approved medications for problematic use of synthetic cannabinoids.

Summary of Psychosocial Treatments

Treatment of substance use disorders has benefits that extend beyond reducing the direct harmful effect of drugs and associated behaviors. Even in the presence of ongoing drug use, people living with HIV (PLWH) in substance use treatment may be more risk averse, less likely to share needles and inject drugs in favor of non-injection delivery methods, more likely to use clean needles and condoms, and reduce number of sexual partners, and even increased condom use [60]. Indirect benefits of substance use treatment include improved antiretroviral therapy (ART) adherence and virologic suppression [63].

There are a wide variety of interventions available to effectively treat substance use disorders in patients living with HIV including screening tools, counseling styles, harm reduction tools, peer-support groups, and behavioral therapies. Evidence shows that treatment for substance-related and addictive disorders is equally as effective as treatment for other chronic illnesses; however, it is often difficult for patients living with HIV to access substance-related care [44, 280]. For patients with the triple diagnosis of HIV, substance use disorder, and other psychiatric disorder (10–28% of PLWH), the integrated care model is preferred by most patients and can help with patient retention, monitoring, and care coordination [43, 281, 282]. Integrated care lends itself to a more contextualized understanding of the patient and how the patient's various identities intersect. See Table 11.5 for a description of psychosocial interventions.

Conclusions

The proportion of new HIV infections transmitted through injection drug use (IDU) has decreased substantially since the beginning of the epidemic, yet non-injection substance use continues to have a major effect across the HIV continuum of care. Recent research has deepened understanding of substance use as a syndemic condition whose impact is amplified by its interaction with other psychiatric and psychosocial factors. Treatment as prevention and pre-exposure prophylaxis can only be successful if they reach subpopulations marginalized by stigma, exposure to violence and trauma, and social maladies such as racism and poverty. Overcoming barriers to full implementation of the US national strategy to end HIV will depend on collaboration among people living with HIV (PLWH), local medical communities and social services organizations, and state and federal government agencies.

Multiple Choice Questions

QUESTION 1: STEM
Recent US epidemiologic data suggest that:

Question 1 Key (correct answer)
9% of new HIV infections were acquired through IDU

Question 1: First distractor
Among men, the proportion of new HIV infections acquired through IDU and male-to-male sexual contact was greater than male-to-male sexual contact alone

Question 1: Second distractor
Among women, the proportion of new HIV infections acquired through IDU will likely exceed HIV acquisition by heterosexual contact in the coming year

Question 1: Third distractor
Syringe Services Programs have not significantly influenced HIV incidence rates

QUESTION 2: STEM
A trauma-informed approach to substance use treatment involves principles of:

Question 2 Key (correct answer)
Client empowerment, perception of safety within the organization, peer support

Question 2: First distractor
Client empowerment, perception of safety within the organization, counseling involving reviewing traumatic events

Question 2: Second distractor
Perception of safety within the organization, counseling involving reviewing traumatic events, organizational awareness of biases

Question 2: Third distractor
Client empowerment, peer support, counseling involving reviewing traumatic events

QUESTION 3: STEM
Sexualized drug use is:

Question 3 Key (correct answer)
Colloquially referred to as chemsex

Question 3: First distractor
Most commonly practiced by MSM who inject drugs

Question 3: Second distractor
Recognized in the DSM-5 as “sex addiction”

Question 3: Third distractor
Is not typically associated with loss of social supports or employment

QUESTION 4: STEM
Highly prevalent drug use in PLWH includes:

Question 4 Key (correct answer)
Alcohol, tobacco, marijuana

Question 4: First distractor
Marijuana, cocaine, cathinone-related substances

Question 4: Second distractor
Synthetic cannabinoids, alcohol, tobacco

Question 4: Third distractor
Methamphetamine, marijuana, amyl nitrate

QUESTION 5: STEM
Motivational interviewing:

Question 5 Key (correct answer)
May be combined with Screening, Brief Intervention, and Referral for Treatment (SBIRT)

Question 5: First distractor
Is an evidence-based psychotherapy for cocaine use disorders

Question 5: Second distractor
Is effective for PLWH in the preparation stage of drug use change but not in those contemplating reducing drug use

Question 5: Third distractor
Should not be combined with trauma-informed care

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Chapter 12
HIV and Serious Mental Illness

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Introduction

People with serious mental illness have higher rates of HIV infection than the general population in the United States and elsewhere [1]. The term *serious mental illness* (SMI) often is used to refer to people who have schizophrenia, schizoaffective disorder, other psychotic disorders, bipolar disorder, and major depressive disorder with psychotic features. Although the diagnosis of major depressive disorder *without* psychotic features is common among people with HIV (see Chap. 6), this chapter is focused on the population with psychotic disorders, bipolar disorder, and major depressive disorder *with* psychotic features, for which there is a separate body of research.

These disorders are defined in the Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition (DSM-5), and are characterized by a number of symptoms

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and timeframes of duration of symptoms (more details are available at https://www.psychiatry.org/patients-families/):

- Schizophrenia has several hallmark symptoms including delusions, hallucinations, disorganized speech and behavior, and other symptoms that create difficulties for individuals in terms of their social or occupational functioning.
- Schizoaffective disorder is a combination of mood (major depression and/or mania) and schizophrenia symptoms experienced at the same time.
- Psychosis refers to a set of thoughts and perceptions that create difficulty understanding what is real and what is not.
- Bipolar disorder is a group of disorders that cause extreme oscillations in a person's mood, energy, and ability to function.
- Major depressive disorder affects feeling, thinking, and behaving, with persistent feelings of sadness and lost interest in activities that previously brought enjoyment.

Psychiatrists have had a special role in treating people with serious mental illnesses, particularly when they are chronic and/or recurrent and associated with high service utilization including emergency room visits, psychiatric hospitalization, care for multiple medical and alcohol/substance use comorbidities, and ongoing psychotropic medication, other somatic therapies, and psychosocial supports. Ending the HIV epidemic requires a comprehensive public health approach to prevention and care that must include people with SMI: ongoing testing for HIV infection, prevention of infection among HIV-negative individuals with effective risk-reduction interventions and prescriptions of pre-exposure prophylaxis, and antiretroviral treatment for individuals who are HIV-positive until viral suppression is achieved (treatment as prevention) to decrease forward transmission [2]. These points of contact with the HIV system of care are referred to as the HIV Care Continuum. Evidence is scarce about whether or how well people with SMI navigate this HIV Care Continuum, as well as HIV health service use, antiretroviral adherence, and treatment for other comorbidities like substance use disorders that affect adherence to care.

Case Vignette 12.1

Mr. V was a 27-year-old Latino man with schizophrenia when, in 1986, he was diagnosed with AIDS. He was in comprehensive psychiatric care in a local community service program but did not consistently take his psychotropic medications. When actively psychotic, Mr. V often denied having HIV infection and engaged in unsafe sexual behavior. In the absence of effective antiretroviral treatment (AZT became widely available in 1987), he was also becoming increasingly medically ill, and at the time, lifespan for people in this condition was typically measured in months.

Mr. V's outpatient psychiatric treatment team hospitalized him after he attended a clinic appointment in an agitated state, fled the clinic, and encountered a truck driver unloading his cargo in front of the clinic, at which point he

began spitting at the driver while shouting "I have AIDS, now you have it too." Although superficial contact with saliva was not capable of transmitting HIV, the team decided that Mr. V was acutely psychotic and putting himself at risk for retaliatory attacks by others. When he was hospitalized and treated with his antipsychotic medication, he became clinically stable, and he did not exhibit psychotic or neurocognitive symptoms and had no neurocognitive findings on clinical examinations. The treatment team recognized that Mr. V's overall health was deteriorating and that the time had come for end-of-life residential care. Not a single long-term psychiatric setting would accept Mr. V, likely because of their own worries about staff or other patients acquiring HIV infection from Mr. V. Eventually, Mr. V was accepted to an HIV residential program that did its best to respond to his psychiatric needs and where he spent the final months of his life receiving respectful and compassionate care.

Mr. V's case illustrates the stigma that surrounded HIV infection in the early years of the HIV epidemic, how this affected long-term psychiatric care options for people with both conditions, and the migration out of the system of mental health-care set up for people with SMI into the general system of care for people with HIV infection. People with SMI typically receive short-term psychiatric care in specialized psychiatric hospitals and longer-term care in community-based outpatient psychiatric settings designed to meet their high-intensity psychiatric but not medical needs. This case also highlights the compassion demonstrated by care teams in HIV settings since the beginning of the HIV epidemic and the need to treat people with SMI with dignity when they need medical care.

Fortunately, HIV infection is now both preventable and treatable for persons who have access to services. A near-normal lifespan is possible for people with HIV, though this may not apply to HIV patients with SMI. People with SMI, whether they have HIV or not, have a life expectancy 15–25 years shorter than that of the general population [3, 4]. We need to improve outcomes for persons with SMI in relation to many medical conditions, including HIV infection, yet we are far from creating a seamless system of care for people with SMI who may be affected by HIV.

How Common Are HIV Infection and Risk Behaviors Among People with SMI?

The prevalence of HIV in the general US population is 0.5%; a disproportionately high number of people with SMI are living with HIV. Please see Table 12.1 for details.

Estimates of HIV infection among people with SMI vary based on geography, study sample and sample size, and whether rates were obtained from patient records, through testing of blood or saliva or by self-report. The elevated HIV prevalence

Table 12.1 Rates of HIV infection among people with SMI

HIV among people with SMI [1, 5, 6]
Rates of HIV infection found in over 30 US studies in peer-reviewed literature
Range of published HIV rates: 0–29%
Recent meta-analyses—median HIV prevalence: 1.8–6%

Table 12.2 Behaviors related to HIV transmission prevalent among people with SMI

Sexually active (previous 3 months): 32–65%
Sex without condoms (previous 3 months): 43–78%
Multiple sex partners (previous 3 months): 13–46%
Sex with partners with risk or living with HIV (previous 3–12 months): 2–58%
Sex in exchange for food, shelter, money, and/or drugs (previous 3 months): 5–38%
Injection drug use (IDU): 25% ever; 4% previous year

among people with SMI is not likely a biological vulnerability to HIV but instead is associated with relatively high rates of behaviors related to HIV transmission.

People with SMI report higher rates of condomless sex, injection drug use, and substance use in the context of sexual activity than people in the general population, as well as a greater likelihood of encountering sexual partners who are living with HIV [7].

See Table 12.2 for HIV risk behaviors in persons with SMI.

People with SMI and HIV also have high rates of adverse childhood events and often are incarcerated, rather than treated adequately with mental healthcare; there are ten times more individuals with SMI in prisons and jails than there are in US state psychiatric hospitals, and incarceration of people with SMI is a major public health issue [8, 9].

Chapters 7 and 14 address the syndemic nature of multiple chronic health conditions and the role of trauma in patient outcomes. Substance use, incarceration, and adverse experiences in childhood and later in life intersected with the chronological trajectory that people described about how HIV and their mental illness diagnoses were related [10].

Overview of Approaches to the Care of People with Comorbid SMI and HIV

There are currently no internationally agreed-upon guidelines to support the management of people who have both HIV infection and SMI [11]. In the absence of such guidelines, a wide variety of approaches have emerged based on local leadership, individual practitioners, and setting characteristics and circumstances. These approaches achieve highly variable degrees of care integration.

Some HIV care programs can offer an initial psychiatric evaluation to every patient entering care. These well-resourced HIV care programs have mental health teams that can provide psychotropic medications and a variety of supportive services and psychotherapies. Some programs were developed early in the HIV epidemic and received philanthropic funding to provide psychiatric care. Other programs were able to navigate complex systems to learn how to obtain enough grant money and insurance reimbursement to offer expanded services. Even so, specialized services for people with SMI, such as supervised housing, supported employment, and psychiatric outreach, usually require referral to other agencies. Clinical programs that achieve the greatest degree of integration are those that have a full range of services for both SMI and HIV infection, share a single common medical record, and involve the entire treatment team in creating and implementing a single treatment plan. This degree of integration is currently quite difficult to achieve, and most programs struggle to ensure that their patients receive all the services that they need.

Setting A Vignette
This program began as a nursing home during the time that only palliative care was available for HIV. As people began to live longer, as treatments became more effective and easier to adhere to, over a decade the program took a series of steps toward becoming, first, a federally qualified health center (FQHC) look-alike, then a FQHC for homeless populations, and, finally, a (FQHC) serving all economically disadvantaged populations. Because this program remained committed to its original mission of serving people with HIV, this FQHC also obtained separate licenses to provide the full range of mental health and substance use services. Additionally, Ryan White funding also was obtained to provide services not covered by Medicaid or by Medicare. At that point, people with both HIV and SMI could be comprehensively served for all their healthcare needs, although it remained necessary to refer out for such services as residential care and supported employment programs.

Setting B Vignette
Setting B was a primary care program with underserved patients living with HIV. The program had a full-time social worker and a part-time psychiatrist who was present one day a week. The psychiatrist had a full caseload and could not accept new patients. The social worker tried to refer patients who needed psychiatric care and psychotropic medication to other settings without much success. A consultant suggested implementing the collaborative care model to achieve care integration, but this was not realistic because the infectious disease physicians at setting A did not agree to prescribe psychotropic medication. Moreover, the collaborative care model is not optimized to

address people with SMI, but instead typically focuses on mild-to-moderate common mental illnesses like depressive disorders and anxiety disorders for which small-to-medium effect sizes for short- and long-term outcomes have been established [12]. Setting B is fortunate to have a part-time psychiatrist given that many comparable primary HIV care programs have no psychiatric prescriber [13].

Setting C Vignette
Setting C was a state-funded mental health program specializing in the care of people with SMI. It was only two blocks from a general medical hospital with a specialty HIV clinic. The patients in setting C received excellent psychiatric care, and those who had HIV infection could receive excellent HIV care at the general hospital's HIV clinic, which took a compassionate approach to people with SMI. Nonetheless, the psychiatric program and the general hospital were independent entities and did not share common medical records or common treatment plans. Coordination depended on informal communication between care teams as necessary. Moreover, not every patient with HIV and SMI had been able to stay consistently in either their HIV care or their psychiatric care. Some fell completely out of both care systems, and neither the psychiatric program nor the general hospital had the resources to investigate the whereabouts of these patients.

Setting C is fortunate to have an excellent HIV program to send patients to, but true integration is not a possibility due to structural factors. Those patients who, for whatever reason, cannot negotiate or remain within a fragmented system of services are at risk of dying of progressive illness. It is important to recognize that the HIV Care Continuum does not track mortality, and those who are most disadvantaged can fall off the care continuum without ever being noticed. The loss of long-term care and even asylum from the array of available services to people with chronic mental health conditions also has contributed to the catastrophic growth of unstably housed and homeless populations.

Psychiatric programs for people with SMI vary widely in how closely they are linked to HIV medical services that can care for their patients with HIV infection. We can see from a recent survey of outpatient mental health clinics statewide in New York [14] that mental health settings are far from offering integrated HIV care. Rates of service provision in these programs were better for some services than for others. See Table 12.3 for specific details.

Table 12.3 HIV services provided in outpatient mental healthcare programs throughout New York

HIV educational materials: 60%
Risk-reduction interventions: 47%
Condoms distributed: 61%
Offering HIV testing to clients: 35%
HIV test counseling: 28%
PrEP education: 32%
PrEP prescriptions: 20%
Patient care coordinators for clients with HIV: 28%
Support groups for clients with HIV: 21%
Onsite HIV medical services: 20%
HIV clients on ART:
None: 6%
Unable to estimate: 50%
Primary barrier to addressing HIV-related client needs
Lack of training: 39%

HIV educational interventions are based on the rationale that knowledge about HIV can motivate people to change behavior [15]. Such interventions have relied on presentation of information on HIV transmission, myths and misconceptions, viral epidemiology, strategies for risk reduction, and HIV testing. However, it is clear from three decades of HIV prevention and care experience that information is essential but not adequate to change health behaviors.

HIV Risk Assessment

The general categories of risk behavior are well known [16]. However, the specific acts responsible for HIV transmission often are not discussed in mental healthcare settings. A thorough risk behavior assessment should cover the activities shown below; these sexual and other risk behaviors should be assessed periodically, keeping in mind that risk profiles may change over time, with symptoms, or due to living conditions and opportunities for establishing relationships. See Table 12.4 for further details on risk assessment.

HIV Testing

Recently, there has been an increased emphasis on having both inpatient and outpatient mental health settings offer routine, opt-out HIV testing to improve case finding among persons with mental illness and promoting their linkage to infectious disease care [17]. In fact current CDC testing guidelines recommend routine opt-out

Table 12.4 Assessment of risk behavior

1. Frequency of sexual intercourse (including vaginal, anal, oral)
2. Number, gender, and known HIV risks of sex partners
3. Whether the patient has traded sex (e.g., for money, drugs, a place to stay, cigarettes)
4. Past history and current symptoms of sexually transmitted infections
5. Use of condoms, other infection-prevention methods, and other contraceptive methods
6. Use of drugs, particularly those that are injected or sniffed
7. Sharing of needles, syringes, or other injection equipment

Table 12.5 HIV testing rates in people with SMI

HIV testing rates among people with SMI
Recent HIV test: 7–49%
Lifetime HIV test: 11–89%

Table 12.6 Range of service needs for people with both SMI and HIV

Inpatient medical hospitalization, especially for those with IDU
Multiple service use with higher associated costs
Problems with HIV-related medical care
If mental health centers are to serve as "medical homes" for persons with mental illnesses, they need to embrace the need to provide comprehensive screening and referral for HIV and other STIs

Based on data from Ref. [17]

testing in healthcare settings [18]. Routine HIV testing in mental healthcare settings would ensure that people with HIV who are receiving mental health services are identified and referred to timely infectious disease care. However, HIV testing rates among people with SMI are low [19], and testing does not appear to be done routinely or often enough to allow those with SMI to benefit from appropriate treatment. See Table 12.5 for HIV testing rates in persons with SMI.

The wide ranges found in studies of HIV testing rates reflect the difficulty of examining medical care received by people with SMI because of the segregation of primary care and behavioral healthcare that is characteristic of the US public healthcare system [20].

HIV Medical Services

People with SMI receiving good quality HIV care can achieve adherence rates comparable to those without mental illness [21]. Beyond adherence to their HIV regimens, service utilization studies show a range of needs when people are living with both SMI and HIV (Table 12.6).

People living with HIV may develop a spectrum of cognitive, motor, and/or mood problems collectively known as HIV-Associated Neurocognitive Disorder

(HAND). Typical symptoms include difficulties with attention, concentration, and memory; loss of motivation; irritability; depression; and slowed movements.

Cognitive symptoms may be a component of SMI itself, which can make identifying the neuropsychiatric manifestations of HIV more complex in people with both conditions. Moreover, this complexity may be further complicated by other causes of cognitive changes, such as those associated with substance use and aging. Neuropsychological testing can aid in trying to differentiate the underlying causes of cognitive alterations in this population. Please see Chap. 10 for further details about HAND.

PrEP

Pre-exposure prophylaxis (PrEP) is one of the primary tools by which state and local government health departments hope to reduce new HIV infections and end the HIV epidemic.

PrEP is an ongoing treatment with antiretrovirals for persons who are HIV-negative but at risk of acquiring HIV. This risk may be related to having partners who are HIV-positive or are injecting drugs and/or having multiple partners of unknown HIV status. The extent to which PrEP is offered to SMI patients in their psychiatric care settings is virtually unknown. A recent survey [14] found that 31% of outpatient program directors say that they use their state's PrEP guidelines regularly in practice and that if clients reveal HIV risk, staff inform clients about PrEP in 48% of these settings. However, only 27% report that there are no barriers to offering PrEP in outpatient mental healthcare.

PEP

Post-exposure prophylaxis (PEP) is defined as offering or prescribing specific antiretroviral medications within 72 hours (3 days) after an HIV-negative individual experiences a possible exposure to HIV to prevent HIV infection. The sooner PEP is started after a possible HIV exposure, the better. PEP is meant to be used only in emergency situations and must be taken every day for 28 days following an exposure. It is not meant for regular use by people who may be exposed to HIV on an ongoing basis and is not intended to replace regular use of other HIV prevention methods, such as consistent use of condoms during sex or PrEP.

Little documentation is available about how accessible PEP is to people in their outpatient mental health clinics. The New York state survey previously described found that nearly half (46%) of outpatient directors reported that their programs educate clients who report a very recent possible exposure to HIV about PEP. One-quarter (25%) of directors said that lack information about PEP is the main barrier to offering it to clients.

Table 12.7 Studies suggest that critical elements of risk-reduction include

Knowledge of HIV transmission-related behaviors
Perceived personal vulnerability to HIV
Intent or commitment to risk behavior change
Belief that one can change one's own behavior and reduce personal risk (self-efficacy)
Acquisition of behavioral skills needed to implement change (assertiveness or refusal of risky practices; safer sex negotiation; managing antecedents or triggers of risky behavior; use of condoms and/or PrEP)
Support and reinforcement of efforts to change behavior (self, peer, partner positive responses to change)

Please see Chap. 2 for more details on the role of routine testing, PrEP, and PEP.

HIV Risk-Reduction Interventions

Cognitive-behavioral approaches to HIV behavior change are the most commonly used HIV risk-reduction strategies across populations. Cognitive-behavioral approaches are based on the premise that gaining the behavioral skills needed to effectively handle situations they are likely to confront precedes motivating people to do so [15].

Efficacious Interventions and Their Active Ingredients (Table 12.7)

Risky Situations for People with SMI

Situational determinants and "triggers" for sexual risk behavior may be particular to people who have spent or continue to spend a good deal of their time in psychiatric settings. Opportunities for meeting new people may be restricted, and an individual's activities may be monitored to a degree that impinges upon privacy and sexual expression. Sex trading, sometimes referred to as survival sex, may be a regular form of barter economy for people whose work lives have been impeded due to multiple hospitalizations; studies show higher rates of this risk among people with SMI than in the general population. Each person must understand their own triggers: people, places, and things that create greater likelihood of risky behavior, whether it is alcohol use, a neighbor who is always willing to trade cigarettes for sex, or a peer pressure situation among people one sees every day.

Care team members working with people with both HIV and SMI will need to navigate the strengths and weaknesses of the care system in which their work takes place. Being familiar with the entire range of services clients might need and how

to find or develop them is critical to providing comprehensive prevention, care, and referral services to people with SMI.

This level of healthcare complexity is common among people with both HIV infection and SMI, as are multiple psychosocial challenges. Meeting the full spectrum of needs in this population requires an integrated team approach in which everyone has a role in engaging and retaining the client in evidence-based and judgment-free care.

Case Vignette 12.2

Ms. S had a long psychiatric history of bipolar disorder, posttraumatic stress disorder, and substance use disorder (alcohol, cocaine, and marijuana) in remission for the previous 5 years. She had been living with HIV infection for 4 years, and her viral load was undetectable at her last test. Ms. S had been in weekly psychotherapy and was treated with a mood stabilizer as well as antiretrovirals. She lived with her teenage son and her boyfriend.

At her most recent visit, Ms. S told the psychiatrist that she had been experiencing depressive symptoms for several weeks which she described as her "most severe depressive episode." She reported many recent psychosocial stressors including an increasingly troubled relationship with her son, loss of her job, financial strain, and unstable housing. She started using cocaine and alcohol again "as a way to cope with the stress."

The psychiatrist noted that Ms. S had active suicidal ideation and admitted her to a psychiatric inpatient unit where Ms. S told her inpatient doctors that she had stopped taking her mood stabilizer and her antiretroviral medications 1 month prior to admission. She reported that she tried to avoid thinking about her HIV status, as she feared she might suffer the same fate as her brother, who died of AIDS many years ago. She reported that taking her antiretroviral medications was a daily reminder of her brother's death. Laboratory tests revealed that Ms. S's CD4 cell count had decreased and her viral load was no longer undetectable. The inpatient team reminded Ms. S of the importance of safer sex practices given her detectable viral load. Ms. S informed a team member that her partner was not aware of her HIV status, but that she was not ready to disclose her status to him and did not want the team to do so either, despite the team's offer to assist her. She stated that she would work on getting up the courage after discharge. Based on the laws in their state which did not require them to do so, team members decided not to inform her partner, but encouraged Ms. S to discuss disclosure in her outpatient therapy after hospital discharge. Ms. S was restarted on antiretroviral medication while still on the inpatient unit and agreed that the inpatient team could share her difficulty with partner disclosure and her inpatient records with her outpatient care team. The outpatient team acknowledged receipt of this information and indicated that they would work with Ms. S on the unresolved issue of partner disclosure.

Stigma

People living with HIV and SMI often deal with stigma related to both conditions. Mental illness stigma has been associated with discrimination in multiple systems (e.g., education, housing, work force, health, mental health, judicial) [22]. Stigma operates through an individual's social environment and through social-psychological processes, both of which affect the stigmatized person's sense of who they are. Expectations of rejection can lead to reduced confidence, constricted social networks, depression, and low self-esteem [23] as well as poor health outcomes [24]. The degree to which stigma influences the sexuality and sexual behaviors of people with psychiatric disorders is an important but often overlooked aspect of achieving a person's full potential for recovery. Though mental illness stigma has been described as a contributor to social and sexual isolation, recent evidence suggests that it also may increase sexual risk behaviors [25]. Please refer to Chap. 3 for further discussion of HIV stigma (Table 12.8).

Training

Training HIV care team members about SMI and training behavioral health specialists, including psychiatrists, about HIV infection has been important since the beginning of the HIV epidemic. Initially, much of the training was focused on addressing fear, stigma, discrimination, routes of HIV transmission, universal precautions, and palliative care. Once effective antiretroviral treatment (ART) became available, training largely focused on the pipeline of new HIV medications, their efficacy and side effects, how to select and monitor a regimen, how to improve adherence to ART, and how these medications interacted with psychotropic medications. Today, both HIV infection and SMI are chronic and treatable conditions with well-described care continuums. But since the systems of care for HIV and SMI are often not well integrated, there is a continuous need to train HIV care teams about SMI and SMI care teams about HIV. Of urgent

Table 12.8 Stigma and its effects on sexuality among people with SMI

People with SMI diagnoses report significantly greater stigma experiences than those with non-SMI diagnoses
Most respondents with SMI (66–97%) report supportive attitudes toward their sexuality and romantic relationships from both care team members and family members
49–81% shared beliefs that most people do not show romantic/sexual interest in those with mental illness and think that people with mental illness would not be good partners for people without mental illness
Low attractiveness was endorsed by 41–57% of respondents, with just over one-half of participants saying that mental illness had a negative impact on their opportunities for sexual relationships
One-quarter of all respondents agreed with the statement "in order to be sexually active, you always do whatever people ask of you"

Based on data from Ref. [26]

importance is training to enable delivery of the following services in any venue caring for this population with both chronic illnesses: risk-reduction interventions, condom use skills development and access to condoms and PrEP, patient care coordination, and co-management of ART and psychotropic medications. Of note, part F of the Ryan White Care Act includes funds for training all health providers at no cost through a group of regional and national AIDS Education and Training Centers (aidsetc.org).

Many useful materials and phone consultation lines are available to assist care team members in the treatment and management of patients with both HIV and SMI, including helpful videos produced by the American Psychiatric Association's Office of HIV Psychiatry (https://www.psychiatry.org/psychiatrists/practice/professional-interests/hiv-psychiatry/training-and-education/). Psychiatrists remain essential to the ongoing treatment and management of people with SMI and HIV. Training for psychiatrists can enable them to promote antiretroviral medication adherence, assure secondary prevention, and improve patients' quality of life. Topics of relevance include use of PrEP for patients with behavioral health disorders; HIV-associated neurocognitive disorders; mood, anxiety, sleep, and psychotic disorders and HIV; the use of PEP for HIV-negative patients who are exposed to HIV; and managing opioid use disorders in patients with HIV.

HIV Care System and People with SMI

There is a lack of evidence-based strategies to engage people with SMI in HIV testing and care [27]. This renders individuals with SMI and comorbid HIV disproportionately vulnerable to late HIV diagnosis, undertreatment of HIV, and related morbidity and mortality [28].

Patients with SMI move through levels of psychiatric care in accordance with the severity of their mental illness. Many clinicians working in acute psychiatric inpatient units and psychiatric emergency departments may view efforts to provide HIV testing and linkage with HIV care as outside of their purview. At the least restrictive level, outpatient care is considered suitable for individuals with SMI who are not gravely disabled or an immediate danger to self or others, but due to the siloed systems of care, people with SMI face multiple challenges to accessing the HIV-related services they need unless they are provided in their ongoing psychiatric care setting. This complexity of perceived limitations but also opportunities is shown in Fig. 12.1; arrows indicate possible directions of patient movement between levels of care.

Recovery Approach to Sexual Health

Recovery guidelines include integration of physical health and mental healthcare, but uptake of prevention and intervention strategies for HIV, HBV, and HCV has been scarce in real-world mental health settings [29]. Community mental health

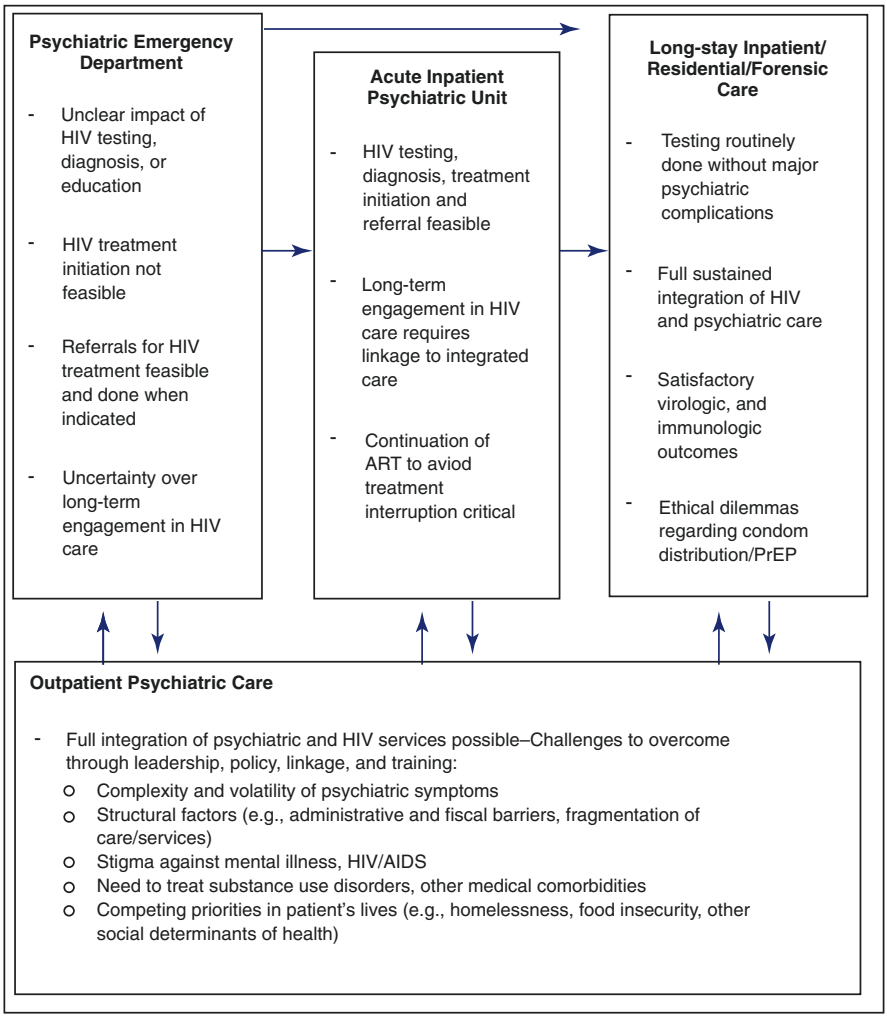

Fig. 12.1 Factors influencing the delivery of HIV-related services to people with SMI. (Based on data from Ref. [27])

services should routinely include programs that explore sexuality and positive adjustment among consumers of all sexual orientations and provide information and referral to other community services [17].

The sexual health of people with SMI is commonly overlooked, neglected, or inadequately addressed in mental healthcare, despite evidence showing that they are more vulnerable to sexually transmitted infections (including HIV), sexual side effects from prescribed medications, and sexual dysfunction than the general population. A recent examination of 186 medical records showed that less than 40% of patients with SMI were provided with sexual health screening during their first 12 weeks of case management [30]. The study also found that screening for sexual

side effects and issues of fertility, sexual self-esteem, safer sexual practices, and sexual dysfunction were rarely carried out. Poor sexual health screening has implications for the safety and quality of care and for the sexual health outcomes of a vulnerable population.

Talking About Sex

Beyond the sexual risk history, few mental healthcare team members are trained to talk with their clients about sex. Persistent or recurrent SMI is usually treated in a continuum of inpatient and outpatient services that afford clinicians the opportunity for long-term contact with a group of people who may enjoy talking in a direct and specific manner about their sex lives or their desires for sexual and other intimacy. Patients and care team members alike bring many concerns, fears, and needs to conversations about sexual relationships (Table 12.9).

Understanding Sexual Side Effects of Psychiatric Medications

Sexual side effects are common when taking medication for psychiatric disorders. It is important for clinicians to inquire about the patient's frequency of sex and changes in sexual activity, including if the patient is experiencing any sexual side effects of medication as this may reduce quality of life and adherence to treatment [31]. Clinicians should ask about frequency of sex, impairments in sexual interest (libido), arousal (vaginal lubrication in women and erection in men), and orgasm (delay or

Table 12.9 Essential skills needed by clinicians

Comfort using sexual language is essential
Modeling comfort will put patients at ease
Understanding patients' cultural frame of reference for sex; their sexual experiences or lack thereof; their religious beliefs about sex; and whether the patient comes from a family, community, or wider culture that associates sex with shame is essential to these conversations
Patients may need "permission" to speak candidly
Appreciation that for many patients, normative psychosexual development may have been interrupted. Sexual relationships may be characterized by naivete, abuse, or interpersonal exploitation
Offering educational groups that address sexual functioning, anatomy, physiology, contraception, pregnancy, parenting, and the effects of psychotropic drugs on sexual intimacy are one way to open deeper conversations about recovery as well as to reinforce healthy sexual norms
Setting ground rules to address comfort and discomfort in these conversations is imperative, given the extent to which many care team members feel reluctant to raise sexuality as a topic of conversation out of concern for potential adverse patient reactions or fears that talking about sex will encourage sexual behavior. These fears are understandable but not well-founded in studies about sexual health and sexual risk-reduction groups

Based on data from Ref. [16]

decline) as any of these factors can be affected by medication for psychiatric disorders. Other medications can cause sexual dysfunction as well, so a clinician should take a careful history of all medications and review for causes of sexual side effects.

Strategies to treat sexual dysfunction include behavioral therapy and medication strategies such as switching to a different medication within the same class with a lower frequency of sexual side effects, switching to a medication of a different class such as bupropion rather than SSRI antidepressants because it has fewer sexual side effects, and adding an adjunctive medication such as those used for erectile dysfunction [31, 32].

Strengths-Based Supports for Preserving and Maintaining Family Relationships

There is strong evidence that individuals with SMI want their families engaged in care, and evidence-based family psychoeducation results in improvement in treatment adherence and clinical symptoms and functioning, with a resultant reduction in relapse rates [33]. While at various times during their lives individuals with SMI may have strained relationships with their nuclear families, they may have others involved in their care. Clinicians should inquire about the patient's desires regarding involvement of collaterals or others in the treatment and get consent for their involvement. It is important to consider a range of significant people in the patient's life including friends, family, and romantic partners. Using a strengths-based approach to working with patients and families can help to build engagement.

Housing to Reduce Risk and Promote Adherence to Care

Lack of adequate housing has been identified as a significant barrier to consistent treatment of chronic health conditions such as HIV and SMI [34]. This is not only limited to those who are homeless, but also includes those who have unstable housing. Homelessness and unstable housing are associated with poor access to medical care and poor adherence [34, 35]. Housing First is a best practice housing intervention prioritizing rapid re-housing for homeless or unstably housed individuals [34]. Public funds used for housing interventions for people with HIV and/or SMI are cost-effective due to reductions in avoidable healthcare costs [34, 35].

Psychiatric inpatient and outpatient facilities are logical settings for implementation of testing, prevention, and treatment of HIV tailored to individuals with SMI. Caring and supportive providers already engaged in therapeutic relationships with their patients can address barriers, alleviate concerns, and facilitate comprehensive prevention and care. Barriers to provision of prevention, testing, and care to people with SMI include insufficient training of mental health staff in evidence-based interventions; inadequate funds, including little money for condoms; the

siloed separation of psychiatric and other medical services; care team members' discomfort addressing patients' intimate relationships, sexual needs, and psychotropic medication side effects; and patients' multiple competing psychosocial and medical needs. Delivery of HIV-related services to individuals with SMI is influenced by a combination of care team, patient, and structural factors and the stigma that affects all these factors. However, there is a growing body of evidence that the HIV care continuum—from prevention and screening to sustained engagement in care and viral load suppression—must be made available to persons with SMI because the prevalence of SMI is higher in persons with HIV and access to services in any care system (e.g., mental health, HIV, primary care) is lower in persons with SMI. Deliberate and well-planned integration of medical and psychiatric care requires skilled behavioral health practice from both specialists and nonspecialists, and psychiatrists and other behavioral healthcare specialists providing direct care or consultation to a care team must be prepared to provide expertise and leadership across the continuum.

Conclusions

Beyond the considerable clinical challenges represented by patients with both HIV and comorbid psychiatric illnesses, HIV patients with comorbid serious mental illnesses are a particularly vulnerable population. They experience two major, lifelong illnesses, where each potentially exacerbates the other. Their medication regimens for both HIV and SMI can be complex, have potential for adherence challenges, and increase the risk of drug-drug interactions and medication-related complications. In addition, HIV patients with SMI are subject to significant social, cultural, and systems barriers as they navigate care for both chronic illnesses. The psychiatrists and other care team members caring for people with serious mental illness and HIV must coordinate between psychiatric and medical interventions and between clinical and social interventions. Their patients tangibly illustrate the application of the biopsychosociocultural model of both illness experience and clinical care. Advocacy for their patients' needs in various spheres is essential to assist them to access and actively participate in care and lead their best lives. The comprehensive care models, best practices, and strategies described in this chapter can be successfully mobilized to optimize patient outcomes for both HIV and SMI.

Multiple Choice Questions

1. Rates of HIV among people with serious mental illness are:
   (a) higher than those in the general population
   (b) the same as those in the general population but on the rise

(c) lower than those in the general population
(d) too understudied to know

Answer: (a)

2. A recent survey of outpatient mental health programs in New York showed that HIV testing is offered by:

(a) almost all programs in accordance with CDC guidelines
(b) about half of programs
(c) about one-third of programs
(d) about one in five programs

Answer: (c)

3. When carrying out HIV risk assessment, which of the following is *not* on the list of behaviors to assess periodically?

(a) history of sexually transmitted infections
(b) sniffing of drugs
(c) trading sex for a place to stay
(d) sexual orientation

Answer: (d)

4. Which of the following is *not* essential for talking to patients about sex, sexual health, and sexual risk?

(a) comfort with sexual language
(b) formal training about sexual anatomy
(c) understanding patients' cultural frame of reference about sex
(d) all of these are essential

Answer: (b)

5. Any program caring for people with both SMI and HIV should receive training to provide which of the following services:

(a) HIV genotyping
(b) co-management of ART and psychotropic medications
(c) differential diagnosis between schizophrenia and schizoaffective disorders
(d) all of the above

Answer: (b)

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Chapter 13
Suicide in HIV

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Introduction

Living with HIV infection can become intolerable and be associated with suicidal behavior. People living with HIV have a nearly sixfold increased risk of suicide [1]. Factors that help individuals navigate the vicissitudes of complex multi-morbidities associated with suicide in HIV include a favorable response to treatment, developing adaptive skills, and building psychosocial support. Effective antiretroviral treatments are costly and access to expert medical care is limited in low- and middle-income countries, as well as for unemployed/uninsured/underinsured patients in higher-income countries. Barriers to care exist in areas where treatments are needed the most. Stigma and discrimination compound psychosocial stressors, and the distress experienced by persons with HIV infection negatively impacts quality of life and survival.

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Suicide is always multifactorial and requires a multidimensional, biopsychosocial, and culturally sensitive approach for its prevention. Suicide is often preventable, even when cognitive and affective states such as hopelessness, shame, guilt, and overwhelming sadness interfere with adaptive coping. By identifying the treatable predisposing psychosocial factors, reducing distress, and capitalizing on protective factors including service enhancement, access to care, and sensible healthcare policy changes, clinicians will be able to help identify reasons to live and anchor the ambivalent suicidal patient preventing premature death by suicide [1].

In this chapter we review determinants of HIV infection as an independent risk factor for suicide and describe how suicidality can be present at any point throughout the course of illness, requiring prevention and coordinated care. Psychiatric diagnoses and medical multi-morbidities associated with loss of function, distressing symptoms, and disfigurement heighten suicide risk. The social oppression that results from stigma and discrimination often precipitates suicidal emergencies. Suicidal behavior in the medically ill, a psychiatric emergency, is one of the most common reasons for psychiatric consultation in ambulatory, emergency, and inpatient general care settings and demands great clinical expertise for its management.

Epidemiology

The epidemiology of suicide and HIV infection is complex. Prevalence estimates of suicidal behavior vary depending on study population and methodology. Suicides are underreported due to differences in the way causes of death are classified [2]. Because suicide is stigmatized in certain parts of the world, it is often recorded as "accidental" death [3, 4]. Drug overdose, the most common method of completed suicide among HIV-infected persons, is particularly commonly misclassified as accidental death [5]. Consequently, actual suicide rates are probably higher than reported.

HIV infection is an independent risk factor for suicide. Around the onset of the HIV epidemic, clinical and case reports suggested an association between HIV and suicide [6, 7]. Autopsy studies have since confirmed this association [8]. People living with HIV are more likely to have suicidal ideation [9]. A 2011 systematic review found that suicide accounted for 9.4% of deaths in persons with HIV [8]. This same study found that 26.9% of persons with HIV had suicidal ideation and 22.2% had a suicide plan [8]. Clinical reviews similarly provide compelling evidence for high rates of suicidal behavior in persons with HIV infection across urban, rural, primary care, and general hospital settings [1].

The introduction of antiretroviral therapy (ART) substantially reduced HIV-related morbidity and mortality. HIV infection is now experienced as a chronic medical condition rather than a rapidly progressing terminal illness. While suicide rates correspondingly decreased since the advent of ART, they remain about three

times higher than in the general population [10, 11]. Suicidal behavior in HIV continues to be a major clinical concern in countries with poor access to care and/or where HIV infection carries great social stigma. Studies over the past decade continue to demonstrate an increased risk of suicide in persons with HIV in countries in all continents, including Switzerland [11], France [12], Estonia [13], Denmark [14], Portugal [15], Nigeria [5], Uganda [16], Ethiopia [17], South Africa [18], Kenya [19], Brazil [20], Canada [21], United States [22], South Korea [23], and China [24].

Predisposing Factors

A practical approach to suicide prevention utilizes the biopsychosocial paradigm. Clinicians using this paradigm consider predisposing and protective factors in clinical decision-making, bearing in mind how the individual exists in harmony with the environment and society. Biological vulnerabilities, epigenetic changes during the critical period of CNS development in early childhood, and allostatic overload caused by psychosocial stressors throughout the lifespan may impact onset and course of illness, predisposing individuals to suicide. HIV infection, referred to by Cohen et al. as the "great magnifier of maladies" [25], acts synergistically and independently to increase suicide risk. In this section we will describe predisposing factors associated with suicide in persons with HIV infection and AIDS.

The demographic characteristics of persons with HIV infection who die by suicide may differ from the general population. In the general population, death by suicide among men is three times higher than among women [26]. Among persons with HIV infection, women are at a significantly higher risk for suicidal behavior, including death by suicide [5, 27, 28]. Persons with HIV infection may attempt suicide at any time from diagnosis to end-stage illness [28]. In Europe, Asia, America, and Africa, suicidality in HIV has a bimodal distribution, with peaks at the time of diagnosis with initial HIV seropositivity or infection and at end-stage illness with AIDS [14, 29].

Tables 13.1, 13.2, 13.3, 13.4 and 13.5 describe psychological and social factors, affective states, medical and psychiatric multi-morbidities, and iatrogenic predisposing factors associated with suicide in persons with HIV infection [1, 13, 23, 24, 30–39].

It is noteworthy that a high suicide rate occurs with comorbid major depressive disorder and posttraumatic stress disorder [40, 41], common coexisting conditions in persons with HIV infection [42]. While affective states of depression, guilt, anger, fear, and shame are commonly present and increase suicide risk in persons with HIV, hopelessness has the strongest association with suicide [28]. In areas of the world where people with HIV remain highly stigmatized, affective states of guilt and shame may compound hopelessness to trigger suicidal crises. The following

Table 13.1 Suicide in HIV – predisposing psychological and social factors

Poor or restricted social support
Decreased social integration
Poor family relations
Unemployment
Unstable housing
Being burdened by caregiving
Poverty
HIV stigma
Previous suicide attempts
Highly lethal planning
Family history of suicide attempts
Family history of death by suicide
Adverse childhood events
Stressful or traumatic events in adulthood
Bereavement and anniversary reactions
Impulsivity
Disclosing seropositive status
Not disclosing seropositive status
Having an HIV seropositive spouse or children
Learning of seropositive status
Onset of opportunistic infection
Learning about fluctuations of immune function (e.g., drop in CD4 cell count and increase in viral load)
Awareness of cognitive decline
Sense of foreshortened future
Access to means (firearms, pesticides, medications)

Table 13.2 Suicide in HIV – predisposing affective states

Hopelessness
Helplessness
Worthlessness
Loneliness
Guilt
Shame
Sadness
Anxiety
Anger

Table 13.3 Suicide in HIV – predisposing medical multi-morbidities

Nociceptive and neuropathic pain
Pruritus
Intractable hiccups
Insomnia
Dyspnea
Nausea
Emesis
Wasting
Vision loss
Motor deficits
Paresis
Reduced serotonin function
Opportunistic infections
HIV-associated cancers

Table 13.4 Suicide in HIV – predisposing psychiatric multi-morbidities

Alcohol use disorder
Stimulant use disorder
Cocaine use disorder
Opioid use disorder
Tobacco use disorder
Alcohol-induced depressive disorder
Stimulant-induced depressive disorder
Cocaine-induced depressive disorder
Opioid-induced depressive disorder
Opioid withdrawal
Alcohol withdrawal
Cocaine withdrawal
Depressive disorders
Posttraumatic stress disorder
Schizophrenia and other psychotic disorder
Personality disorders
Adjustment disorders
Major neurocognitive disorder (dementia)
Delirium

Table 13.5 Suicide in HIV – predisposing iatrogenic factors

Akathisia from first- and second-generation antipsychotics
Dysphoria from alpha interferon
Negative affective states and suicidality from efavirenz
Depression and suicidality from treatment with dolutegravir
Depression and suicidality from treatment with raltegravir
Depression and suicidality from treatment with rilpivirine
Behavioral disinhibition from antidepressants when anergia lifts before sadness
Lipodystrophy from ARV medications causing disfigurement

vignettes illustrate multidimensional aspects to be considered when assessing for predisposing factors.

Case Vignette 13.1
M., a 20-year-old man living in Jakarta, Indonesia, learned that he became infected with HIV as an adolescent after sharing needles when injecting heroin. M. was an only child of hardworking parents who rarely spent time at home. No one in his family knew about his addiction. A medical workup for intractable diarrhea requiring hospitalization led to diagnoses of a gastrointestinal opportunistic infection and HIV seropositivity. A psychiatric consultation and encouragement from other medical providers led to successful recovery from opioid dependence with sustained abstinence. A greater challenge was to inform his girlfriend of his medical condition. Their relationship of 3 years was approved by both families, and they planned a wedding in the near future. M.'s girlfriend knew of his substance use disorder and had tried to help him for years. After hard work building up courage to disclose his HIV status to her, she surprisingly reacted to the news in a loving and supportive way. But when she tested HIV seropositive, M.'s guilt and incapacitating shame for likely infecting her intensified, resulting in isolation, depressive symptoms, and paranoid thoughts. Thoughts of death and a suicide plan to jump from a building after weeks of isolating himself in his room resulted in a brief psychiatric admission. He was stabilized with a selective serotonin reuptake inhibitor and supportive psychotherapy. While his depressive symptoms lifted, sporadic suicidal ruminations persisted, mostly linked to unresolved affective states of guilt and shame.

Case Vignette 13.2
P. was a 26-year-old, married, and well-educated woman from northern Tanzania who found out that she was HIV infected when she was 6 months pregnant. She developed symptoms of major depressive disorder including

pervasive low mood, insomnia, weight loss, crying outbursts, and feelings of worthlessness and guilt in anticipation of giving birth to an HIV seropositive child. She was fearful of sharing her HIV status with loved ones. She attempted suicide twice during her third trimester by poisoning with pesticides. After giving birth, she disclosed her seropositive status to her family, who as she predicted became enraged and alienating. During the early phase of psychiatric outpatient treatment, on one night, she laid down with her baby on a highway and phoned her therapist to say goodbye. She was rescued from this suicide/infanticide attempt. She was treated with antidepressant medication and psychotherapy. In view of her inconsistent adherence to treatment and a tentative therapeutic alliance with her psychiatrist, her prognosis remained guarded.

The case of M. demonstrates how guilt regarding infecting partners and perceived stigma can increase suicide risk but also how the social support of loved ones and medication treatments of comorbid depression can mitigate that risk. The case of P. illustrates how societal attitudes, guilt, and alienation from family may compound depressed mood and other symptoms of depressive disorder to increase suicide risk, in spite of apparently adequate psychiatric treatment.

Serotonergic dysfunction is a common finding described in the neurobiology of suicide in most populations. Persons with HIV infection have decreased levels of cerebrospinal fluid (CSF) 5-HT and 5-HIAA, suggesting that the virus may interfere with serotonin production in the brain [43]. Recent data suggest that certain serotonin transporter gene polymorphisms may be associated with suicidality in HIV [44].

While identifying predisposing factors is vital for determining suicide risk, awareness of protective factors is essential for designing suicide prevention algorithms that will inform psychotherapeutic, public health, and psychosocial interventions.

Protective Factors

While the clinical valence of suicide protective factors may vary in diverse populations, understanding the totality of protective factors that may diminish risk is critical for adequate prevention and effective psychotherapeutic interventions. Table 13.6 describes research-validated protective factors proven to diminish suicide risk in persons with HIV infection [1, 39, 45].

Table 13.6 Suicide in HIV – protective factors

Positive reappraisal coping skills
"Taking-charge" attitude
Adequate understanding of illness
Using denial and isolation of affect without compromising treatment adherence
Treatment adherence
Increasing social support
Optimism
Feelings of responsibility toward family
Fear of social disapproval
Fear of suicide
Having reasons for living
Religious engagement
High levels of hope
Low levels of distress
Higher emotional expression
Higher depth processing
Experiential involvement
Self-esteem enhancement
Adaptive shift in coping strategies
Secure attachments
Meaning and purpose

The following vignette illustrates suicide protective factors in a person who has been HIV infected for decades who benefited from intensive psychotherapy and skillfully adapted to adverse life events, finding meaning in life even when threatened with overwhelming stressors.

Case Vignette 13.3
J. was a 60-year-old gay man in New York, USA, who was tested and learned of his HIV status 30 years previously. He was tested following the death of a romantic partner and the loss of many friends to complications of AIDS during the early years of the HIV pandemic. J. developed disabling cytomegalovirus (CMV) retinitis followed by immune recovery uveitis. Vision loss, complicated bereavement, alienation from most of his family because of his being gay, loss of employment as an editor in a mainstream publishing company, and oppressive poverty resulted in major depressive disorder. He was treated with intensive psychotherapy, but no psychotropic medication, as all antidepressant medications worsened his already compromised visual acuity. At the beginning of psychotherapy, he ambivalently related suicidal plans to jump in front of a moving train or overdose on antiretroviral medications. Psychotherapy treatment focused on symptomatic relief and maximizing

life's potentials. With encouragement, he allowed the therapist to help bridge connections with those family members who were less judgmental of his lifestyle and choices. He became active in NGOs helping older men living with HIV, learned computer programs to assist persons with low vision, and was referred to social services consultations with links to NGOs to find adequate housing and support services. He attended musical performances, listened to audio books, and developed a vibrant and consistently supportive social network. He continued psychotherapy (individual and or group modalities) for 25 years.

Suicide is never "random" and always meaningful. Psychodynamic explorations can be helpful to understand what motivates behavior that may result in death by suicide. Psychodynamic formulations are case-specific and need to consider the individual's social context, present and past, in order to adequately inform suicide prevention efforts.

Psychodynamics and Cultural Context

Recent advances in epigenetics validate what psychodynamic psychiatrists observed over time: early adversity alters neurobiology and gene expression, predisposing individuals to various psychiatric disorders [46] and suicidal behavior [47]. Psychodynamic formulations help clinicians to understand present stressors within the social context and throughout the lifespan. Early adversity, re-traumatization later in life, and intolerable affective states such as hopelessness, helplessness, loneliness, sadness, guilt, rage, anxiety, and shame, following experiences of loss, a sense of alienation, social oppression, and expendability, are common dynamic factors present in suicidal crises.

A basic psychoanalytic concept that merits discussion is meaningfulness, originally formulated as psychic determinism. Clinicians explore behavior as always being potentially meaningful and purposeful, rather than random. Attentiveness and empathic attunement to ambivalence in suicidal persons, the oscillation between extremes of wanting to live and wanting to die, is of essence to establish a therapeutic alliance. Freud and Abraham emphasized that loss is a precursor of depression, and internalized anger turned against the self may explain suicide. Rage and sadness coexist following loss of loved ones or loss of function and suicide may be cathartic while symbolically attempting to recapture what has been lost [48–50].

Overwhelmingly negative affects can lead to near-psychotic states where reality testing is compromised. Litman referred to this as a constriction of cognition resulting in the distorted view that suicide serves as the only way to alleviate suffering and distress [51]. Unbearable psychic angst interferes with creative thinking and makes it difficult to effectively access problem-solving skills and adaptive coping.

Table 13.7 Psychodynamics of suicide in HIV

Early adversity followed by re-traumatization and loss
Early trauma and re-traumatization creating a sense of foreshortened future
Anger/sadness turned against the self
Constriction of cognition – suicide as an illusory means to achieve control
Conflicts over relinquishing autonomy and intolerable dependency
Valuing autonomy over life itself
Inability to trust and accept help from significant others magnifying distress
A core sense of expendability that stems from alienation and loneliness
Insecure attachments with disturbance of self-esteem leading to poor self-care

Table 13.8 HIV, suicide, and social dynamics

AIDSism, HIV stigma, and discrimination
Addictophobia
Homophobia and heterosexism
Misogyny
Social disintegration and deregulation
Social endorsement of extreme individualism
Socioeconomic inequities
Recent immigration with poor acculturation
Epidemic of intimate partner violence
Dogmatic and inflexible religious attitudes

Countertransference avoidance may compound hopelessness and helplessness interfering with the collaborative and co-creative work necessary for suicide prevention.

Table 13.7 summarizes relevant suicide psychodynamics in HIV. The systematic study of suicide began in the discipline of sociology [52]. Social dynamics are particularly relevant to suicide in HIV [1]. These are summarized in Table 13.8.

Identifying predisposing factors and understanding individual psychodynamics and social dynamics are key to capitalizing on protective factors through collaborative work and comprehensive preventive efforts.

Prevention

There are many strategies clinicians can use to prevent suicide in people living with HIV, ranging from individual interventions to advocacy work for a larger population. On an individual level, data suggest that a high-risk period for suicide in persons living with HIV is immediately after diagnosis, when many patients are feeling intensely overwhelmed, isolated, stigmatized, and unsure of their prognosis [38]. Being aware of such a phenomenon, screening and closely monitoring patients with

new diagnoses, providing psychoeducation on resources, and bolstering their social supports may help prevent a suicidal crisis.

Suicide prevention starts with taking a suicide history of every patient with HIV. Clinicians need to inquire about suicide in detail and with comfort and must develop awareness of countertransference avoidance to avoid failure of therapeutic empathy. Negative affective states, through projective identification and enactments, may paralyze the clinician's ability to infuse hope and help the patient find alternatives to suicide. Allowing the patient to put difficult feelings into words, especially verbalizing affects of guilt, shame, rage, sadness, and despair, may prevent aggressive acting out and circumvent turning the negative emotions against the self. As a narrative discourse evolves amidst either unexpressed or torrential affects, a broader perspective may ensue, and suicidal impulses may dissipate once unendurable emotions are verbalized.

An adequate suicide history of an individual includes an assessment of past and current suicidal ideation, methods, plans, and intent as well as past suicide attempts and their severity and non-suicidal self-injurious behavior. The clinician obtains this history by asking both open-ended questions, e.g., "Tell me about your suicidal thoughts," and closed-ended questions, e.g., "Have you ever made a plan to end your life?" in a calm, caring, and non-judgmental manner [1]. A suicide history also systematically examines all predisposing and protective factors, some of which can be modifiable. Potentially modifiable factors include depressive, anxiety, and substance use disorders as well as untreated pain or other physical symptoms, co-infection with HCV, homelessness, and social isolation [31]. Depending on the level of suicide risk, some patients may require an inpatient hospitalization, while others can be safely managed in the outpatient setting. Table 13.9 lists important questions that the clinician needs to ask a patient in order to assess suicidality.

Identifying psychiatric symptoms and disorders in patients with HIV can lead to prompt and effective treatment, preventing suicide. A number of studies internationally have shown that depressive, anxiety, and substance use disorders are more common in patients with HIV and contribute to significantly increased risk for suicide [12, 13, 23, 32, 34, 38]. After conducting a thorough evaluation and making a diagnosis, cautious prescribing of antidepressants, anti-anxiety medications, and/or medication-assisted treatment for substance use disorders, while considering drug-drug interactions with antiretrovirals, can help to treat psychiatric disorders and mitigate risk. A clinician might also consider, if possible, avoiding efavirenz, which can be a highly effective antiretroviral treatment, but can also cause neuropsychiatric side effects including anxiety, mood changes, psychosis, and suicidal ideation in an estimated 40% of patients [33].

The clinician should be aware that in depressive disorders, anhedonia and psychomotor retardation often improve first, and hopelessness, dysphoria, and suicidal behavior take longer to improve [53]. Individual and group psychotherapy treatments aimed toward the patient's diagnosis can reduce symptomatic distress, promote conflict resolution, increase networking, and improve quality of life. Psychotherapy modalities that can help suicidal patients include interpersonal, cognitive-behavioral, motivational, dialectic-behavioral, psychodynamic, and

Table 13.9 Sample questions for evaluation of suicidality[a]

1. Do you wish you were dead?
2. Do you feel that your family/friends/partner/spouse/children would be better off if you were dead?
3. Do you have fleeting thoughts of suicide? Follow up with: What prevents you from acting on these suicidal thoughts?
4. Have you attempted suicide in the past?
5. Do you entertain ways of killing yourself?
6. Are you feeling suicidal right now?
7. Has anyone in your family died by suicide? If answer is no, reframe question: Has anyone in your family died in mysterious ways?
8. Do you feel sad?
9. Do you feel hopeless?
10. Do you have little interest or pleasure in doing things?
11. Do you use alcohol or other substances to escape/self-medicate/ease your distress?
12. Do you experience intense shame?
13. Do you experience intense guilt?
14. Were you abused as a child? Describe adverse life events you experienced as a child (may follow up with specific questions about emotional, physical, and sexual abuse)
15. Are you lonely?
16. Do you feel discriminated against?

[a]Follow up all Yes/No answers with: Could you describe/elaborate/tell me more about this?

supportive [1]. Undertreated chronic pain and physical symptoms may increase distress and precipitate suicidal ideation and behavior. Providing symptomatic relief and palliation of nociceptive and neuropathic pain, pruritus, diarrhea, nausea, emesis, and anorexia can avert a suicidal crisis in persons with HIV infection [9]. Furthermore, some data also suggest that co-infection with HCV raises suicide risk [31]. When possible, offering treatment for HCV, which can now be curative, can help to lower suicide risk.

Adverse childhood events (ACEs) are linked to poor health outcomes, reduced educational and occupational functioning, and high-risk behaviors. Preventing ACEs decreases leading causes of death, *including suicide* [54]. Interventions aimed at reducing ACEs during the sensitive period of development prevent suicide later in life. These include improving access to care and social and economic support, enhancing connections of children at risk to caring adults, and linking adults to family-centered addiction treatments and parenting interventions [54].

Multiple studies demonstrate the crucial role of perceived social support in mitigating risk of suicide in people living with HIV [32]. An individual clinician might effectively decrease isolation and alienation by allowing the patient in crisis to borrow ego strength. However, it is also critical to help mobilize the patient's family and friends to offer the suicidal person comfort and protection. Encouraging the patient to reach out to and confide in any available loved ones and engaging in joint problem solving to address how to involve social supports in the patient's care can be lifesaving. In some cases, when trusted significant others are unavailable or

nonexistent, suicidal patients are at higher risk and may need to be hospitalized until the crisis resolves and networking that builds on protective factors is in place. Homelessness is also a known risk factor for suicide in persons with HIV [31, 37]. Assisting a patient in connecting to any social or housing services available or to live with a friend or family member may help mitigate risk.

On a population level, promoting legislation and activism that protects vulnerable individuals from discrimination, stigma, and social oppression can make a major difference in the lives of individuals with HIV. Experiences of discrimination among people living with HIV including verbal, physical, and sexual violence, social exclusion, and workplace discrimination have be linked to increased suicide risk [31, 36]. To prevent suicide on a population level, clinicians should support public education about HIV, anti-bullying initiatives, equal rights for women and sexual minorities, and access to treatment for substance use disorders. Community-level suicide prevention activities may be necessary before national strategies are developed, especially in low- and middle-income nations. Restoring hope, developing goals and prospective thinking, making nurturing and reciprocal connections, addressing interpersonal conflicts, and finding meaning in life may repair the constriction of cognition that commonly increases risk in suicidal persons. Equally important to avert suicidal behavior are palliative care, reduction of distress, and having access to adequate medical treatments. Clinicians can act on many levels from the individual, to the family system, to a larger population to help decrease the risk of suicide in distressed people living with HIV.

Multiple Choice Questions

1. Adverse Childhood Experiences (ACEs):

   A. Do not affect development of anxiety disorders in adulthood
   B. Do not affect the development of depressive disorders in adulthood
   C. Lower the risk of suicide later in life
   D. Have a minimal impact on the global burden of disease
   E. Are associated with the intergenerational transmission of trauma

2. Research-validated protective factors proven to diminish suicide risk in persons with HIV infection include:

   A. Low levels of hope
   B. High levels of distress
   C. Having a sense of meaning and purpose
   D. Feeling detached from family
   E. Living in a middle-income country

3. Social dynamics that increase suicide risk in persons with HIV include:

   A. HIV stigma and discrimination

B. Internalized heterosexism
C. Having access to affordable healthcare
D. Recent immigration with adequate acculturation
E. Being part of a supportive community

4. Psychodynamic factors associated with suicide in HIV include:

A. Traumatic life events creating a sense of foreshortened future
B. Developing an erotic transference
C. Using defense mechanisms such as humor, altruism, and anticipation
D. Using defense mechanisms such as rationalization, sublimation, and reaction formation
E. Having an anxious attachment style

5. Iatrogenic factors associated with suicide in HIV include:

A. Akathisia from treatment with clonazepam
B. Depression and impulsivity from treatment with efavirenz
C. Impulsivity caused by low-dose nortriptyline
D. Impulsivity caused by low-dose lithium
E. Lowering of the seizure threshold cause by bupropion

Correct answers:
1. E; 2. C; 3. A; 4. A; 5. B

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Chapter 14
HIV Syndemics

Mariam Abdurrahman, Luis F. Pereira, and Mark V. Bradley

Abbreviations

SAVA	Substance abuse violence and HIV/AIDS
STI	Sexually transmitted infection
TB	Tuberculosis
VIDDA	Violence, immigration, depression, type 2 diabetes mellitus, and abuse

The Evolution of HIV/AIDS and Syndemic Theory

The underlying subtext of the "wages of sin" and other negative social constructs about HIV/AIDS detracted from early recognition of the important role of contextual factors [1]. Singer argued that the failure to recognize the social underpinnings of the disease and failure to analyze HIV/AIDS in context have largely been driven by the dominant conceptual model of disease: a biomedical model of discrete conditions. While a biomedical model accounts for associations and comorbidity, it lacks an avenue for understanding HIV/AIDS disparities and the synergy with contextual factors [1, 2]. Although the biopsychosocial approach extends the biomedical concept to include psychological and social determinants, it is not nearly as broad or inclusive as the syndemic approach to HIV/AIDS. The syndemic concept has significant public health implications.

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Singer observed that urban minority populations experience disproportionately elevated rates of substance use disorders, tuberculosis, HIV, and other chronic diseases like asthma, diabetes mellitus, and hypertension [1]. He observed that these conditions are strongly influenced by sociopolitical and economic factors (see Table 14.1) which interact synergistically at multiple levels to collectively generate poor health status and excess disease among the urban poor. Based on these observations, in the early 1990s Singer coined the term "syndemics" to describe a set of health or social epidemics that mutually reinforce each other to account for the disparities seen in HIV/AIDS outcomes in urban black and Latino populations [1].

Among black and Latino families in New York, Singer observed that poverty, inadequate nutrition, compromised access to healthcare, chronic stress, and living in neighborhoods with higher prevalence of IV drug use and STIs all represented mutually supporting conditions that increased the likelihood of HIV transmission and susceptibility to AIDS. Singer also noted that while conventional thinking around HIV transmission had focused on individual acts of choice around sexual behavior and drug use as the focus for prevention, which tended to support a victim-blaming point of view, a syndemic perspective emphasized the role of structural and social forces in determining HIV risk behavior [1]. Singer proposed the term syndemic to describe these observations which were reported as a cluster of epidemics of substance abuse, violence, and AIDS (SAVA) that disproportionately affected impoverished racialized urban residents in American cities [1].

Table 14.1 Contextual factors in HIV syndemics among the urban poor [1, 3–7]

Person/population
Ethnicity
Gender
Race
Sexual identity
Sexual orientation
Place
Housing
Ecological health
Social infrastructure
Social network
Time
Hegemony and ethnocultural discourses of the time
Political climate
Social support program climate
Vectors and pathways
Conflict and war: Communal violence, gang wars, civic unrest
Global warming
Stigma
Structural violence
Urban decay and migration: Urban desertification, "planned shrinkage"

Components of SAVA were noted to be interactive and mutually accelerating, with the entwinement resulting in an excess burden of illness relative to the impact of each component by itself, thus constituting a syndemic. This mutually propulsive interaction forms the crux of syndemic theory [1]. Singer went on to describe the component epidemics of the SAVA syndemic as being "reciprocally influenced and sustained by the larger risk environment and the broader set of power relations shaped by class, ethnicity and gender" [1]. To this end, the syndemic framework has particular utility as HIV/AIDS is *not* a homogeneous illness but is, rather, a *constellation* of symptoms, conditions, and infections shaped by the broader ecological, sociocultural, and geopolitical climate in which they occur [1–9]. The syndemic approach has both theoretical and practical applications, as it illustrates the influence of macro-level social factors on illness burden at the *population* level while also illustrating the impact of such factors on morbidity at the *individual* level [6].

The diffusion of the syndemic concept from medical anthropology to other health-related disciplines has been relatively slow but is now garnering increasing discourse [8], with somewhat varied viewpoints as to the nature of a syndemic orientation. The lexicon presented in Table 14.2 is an aid to a shared understanding of syndemic conceptualization relative to conventional epidemiology.

This chapter examines the application of a syndemic framework to HIV/AIDS, the challenges inherent with a shift toward a syndemic orientation, and the potential merits of adopting this perspective. While the conventional biomedical model has added a wealth of knowledge about the HIV virus, pathophysiology of the infection, and antiretroviral drugs, it has *not* been able to account for the structural pathology that drives the infection within populations, nor has it generated a comprehensive understanding of excess illness burden in populations with high prevalence rates.

Table 14.2 A brief epidemiological lexicon [1, 6–8, 10, 11]

Epidemiology: The distribution (frequency, pattern) and determinants (causes, risk factors) of health-related states and events in specified populations
Endemic: The constant presence and/or usual prevalence of a disease or infectious agent in a population within a geographic area. Hyperendemic describes an elevated number of cases beyond the background prevalence rate expected
Epidemic: An increase, often sudden, in the number of cases of a disease above what is normally expected in that population in that area
Syndemic: The disproportionate occurrence of two or more health conditions clustered within a given population, with the health conditions occurring in excess as a result of synergistic interaction between noxious social forces and biological disease processes in a vulnerable populace
Syndemic orientation: Recognition that upstream social, political, and structural determinants can contribute more to health inequities than biological factors or personal choices
Syndemic risk factor: Social, political, economic, and environmental factors that increase the risk for the clustering of two or more diseases. These factors interact with biological disease processes in a multiplicative (rather than solely cumulative) manner to generate clusters of disease. Syndemic risk factors are typically more proximal in the chain of conditions that subsequently give rise to a disease or negative health outcome
Syndemogenesis: The evolution of a syndemic through multiple dynamic biosocial processes, pathways, and stages of interaction

Syndemic Theory and Relevance to HIV/AIDS

The syndemic framework was introduced as a means to examine the way AIDS affects vulnerable communities. Following the recognition of the first SAVA syndemic in the early 1990s, many other HIV-related syndemics have been recognized, including the syndemic of HIV, tuberculosis, crowded housing, and poverty [1, 8, 12–14]; syndemics of HIV, substance use disorders, and other psychiatric illness [15, 16]; syndemics of type 2 diabetes mellitus, HIV/AIDS, tuberculosis, and depressive disorders [7]; syndemics of syringes, substance use, and infectious diseases [17]; and syndemics of intimate partner violence and HIV [18–22]. Research on these syndemics has examined how social and structural forces conspire with synergistic systemic medical and psychiatric illness to mutually reinforce one another, with resultant recommendations for structural changes to help reduce HIV transmission, such as decriminalization of currently illegal drugs, or policy changes that increase the empowerment of women [23].

Syndemics are not uniform across populations, in spite of shared component conditions, chiefly because of the variability in context from one population to the next. As Singer [4] noted, there are *multiple* SAVA syndemics, each driven by its own dynamic configuration of social conditions and relationships. The syndemic framework shifts the lens from discrete disease entities to disease linkage, interaction, and fluctuation within a biosocial framework of three key facets: *populations of interest, social contexts shaping disease, and biological interactions that are synergistic* [4, 5, 24, 25] (see Fig. 14.1; see section "Syndemics: What Are the Components and How Do They Interact?").

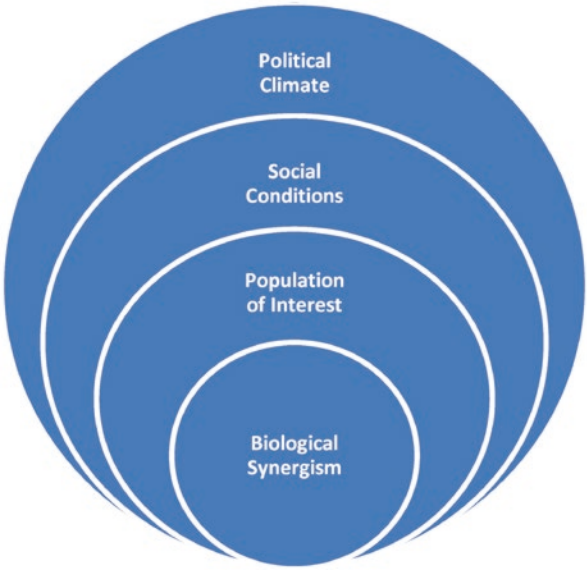

Fig. 14.1 The biosocial framework of population and contextual factors with biological synergy

The course of HIV/AIDS is conventionally understood as an exclusively biological mechanism, with limited recognition of the role of contextual factors [1, 24–27]. This view fails to explain the excess burden of illness that is increasingly noted among the most marginalized groups, added to which it has been difficult to address the reasons for relatively limited uptake of conventional public health interventions in the most vulnerable populations. Although the HIV virus is a biological entity with an existence independent of social factors, its presence and activity within populations is shaped by social factors. Most notably, the ability of individuals and communities to adopt HIV/AIDS prevention and management strategies is largely psychologically and socially determined [1].

Syndemics: What Are the Components and How Do They Interact?

As noted above, there are three core elements of a syndemic conceptualization: populations of interest, social contexts shaping disease, and biological interaction that are synergistic (Fig. 14.1). Just as epidemics are about *person*, place, and time, syndemics are also about *population*, place (physical and structural context), and time (temporal interaction of syndemic components within the body at opportune time; sociopolitical climate of the time).

Core Elements of Syndemics: Population

At the population level, syndemics are characterized by a disproportionately elevated level of cases in a given population [8, 28]. The cases cluster by population, place, and/or time, but the underlying etiology for clustering is usually multilayered and dynamic, in keeping with the geographic, social, political, and economic context in which the population dwells. These social forces are embodied pathologically at both the individual and population levels as exemplified in HIV-TB syndemics (see section: "Core Elements of Syndemics: Biological Interaction").

Most of the reported syndemics occur within marginalized populations [1, 3–9, 11, 25, 26, 29–38], reflecting particular syndemic vulnerability in populations with pervasive social disadvantage. Psychosocial stress from adverse social conditions is transmitted biologically and thus is embodied within individuals and populations, which in turn perpetuates further vulnerability [1]. Notably, the psychological effects of poverty, internalized stigma, and violence interact within populations to generate psychiatric and other systemic physical health states that in turn influence behavior, health choices, and the health status of populations. Based on syndemic theory, transient reductions in any of the component epidemics in a syndemic will not result in a sustained or appreciable impact on the affected population in the absence of eliminating or controlling the forces that tie the diseases together [39].

Thus, preventing a syndemic requires knowledge of the forces that tie the syndemic conditions within a given population [1, 5, 39].

Core Elements of Syndemics: Social Context

Social conditions present an essential syndemic factor and may include sociopolitical, economic, and environmental factors that increase the likelihood of disease clustering (Table 14.2). HIV/AIDS-related syndemics have been reported predominantly in marginalized populations, thus underscoring the essential role of structural adversity, social transmission of illness, and oppressive social relations in marginalized populations [1]. The embodied pathology of social forces is perhaps most notable in HIV-TB syndemics within prisons, overcrowded low-income dwellings, and homeless populations [5]. The marked patterned occurrence of the HIV-TB syndemic cannot be explained by the virulence of the individual syndemic components alone, as the prevalence of HIV and TB in these populations well exceeds that expected for either infection alone [5, 8]. The social conditions that characterize each setting contribute to disease burden through multiple social-biological, psycho-biological, and social-psychological interactions as subsequently described.

Core Elements of Syndemics: Biological Interaction

Synergism is the key feature of the biological interactions in syndemics. The HIV-TB syndemic is perhaps one of the best-studied HIV-related syndemics to date. Multiple synergistic interactions have been identified as contributing factors in the HIV-TB syndemic, including the synergistic effect of HIV-related immune impairment and TB activation as a result, stress-mediated alterations in immunity, and malnutrition-induced impairment in the immune system [5, 12–14, 40, 41].

Granulomas are present in persons with intact immunity who have had exposure to TB, but absent or poorly formed in persons with poor immune responses [42]. In the HIV-negative individual, *Mycobacterium tuberculosis* exposure quickly results in the pathogen being walled off and suppressed in a granuloma, with very limited ability to replicate [42, 43]. However, HIV/AIDS accelerates and enhances the virulence of TB by dampening the immune response sufficiently to avert granuloma formation and allow *M. tuberculosis* to replicate freely [8, 14, 40, 44]. Similarly, the chronic stress of impoverishment, associated malnutrition, overcrowding, and inadequate accommodation is transmitted from a socio-psychological level to a biological level in the form of impaired immune function, impaired homeostasis, and chronic hypothalamic-pituitary-adrenal axis stimulation, with high cortisol states begetting further health impairment. Psychological stress has been associated with more rapid HIV disease progression [5, 45]. As such, structural conditions come to be embodied at the biological level and foster further synergistic interactions that drive the burden of disease.

No Health Without Mental Health [46]: The Syndemogenic Effect of Psychiatric Illness

People living with HIV/AIDS experience an excess burden of psychiatric illness and psychological distress, concomitant with missed screening opportunities during clinical encounters, and significant disparity in access to mental health services relative to the general population [46–50]. Higher rates of substance use disorders, depressive disorders, posttraumatic stress disorder, dyssomnia, and psychotic disorders have been reported in people living with HIV/AIDS [50]. In addition, the rates of psychological distress and psychiatric illness are higher among people vulnerable to acquiring HIV [49]. Psychiatric illness also increases the risk for HIV acquisition and transmission, stemming in part from the impact of psychiatric illness on risk exposure [47, 49]. Most concerning, psychiatric illness also increases the risk for negative health outcomes at each step along the HIV care continuum, leading to elevated viral load, decreased CD4 levels, and increased risk of opportunistic illnesses [49]. HIV/AIDS independently confers increased risk for psychiatric comorbidity, which further exacerbates negative outcomes in HIV/AIDS. Specifically, untreated comorbid psychiatric conditions interfere with health-seeking behavior, complicate treatment, and contribute to poor outcomes in other health and social domains [50]. In persons living with HIV/AIDS, unmet mental health needs constitute an emergency given the mutually enhancing adverse effects on health [48, 50, 51].

The mechanisms underlying the complex bidirectional relationships between HIV/AIDS and mental health are yet to be well understood, but are thought to stem from neuroendocrine, immune-inflammatory, and neuro-inflammatory processes [48–52]. In spite of the significant bidirectional relationships described above and the substantial syndemogenic interaction of HIV/AIDS and psychiatric illness, primary care clinicians often do not address psychological distress or adequately diagnose and treat comorbid psychiatric conditions in patients infected with HIV, thus limiting the effectiveness of care [47, 49]. Furthermore, the adverse psychosocial environments that facilitate and enhance interactions between HIV/AIDS and psychiatric illness contribute to complex multisystem illness, further exacerbating vulnerability as psychiatric illness also adversely influences adherence with treatment for concurrent nonpsychiatric illness [50].

Significant multisystem morbidity has been observed in syndemics of HIV/AIDS, substance use disorders, other psychiatric illness, and noxious biopsychosocial conditions. Depressive and stressor-related disorders (acute stress disorder, posttraumatic stress disorder) are the most prevalent psychiatric illnesses in people living with HIV/AIDS [48–51]. Multiple studies have reported an inverse correlation between these conditions and HIV prognosis as measured by treatment adherence, behavioral modifications, CD4 count, disease progression, and other HIV-related outcomes [48–50, 53]. Syndemics of HIV/AIDS and psychiatric illness are not circumscribed; they strongly influence the health status and wellbeing of vulnerable populations, further underscoring the need to eliminate the anachronistic

mind-body dichotomy that endures in medicine. Like HIV/AIDS, psychiatric illness is a systemic illness and one that is quite prevalent; thus, mental healthcare should form a core component of holistic care for people living with HIV/AIDS.

The syndemic interaction of psychiatric illness and HIV and the grave implications for prognosis are increasingly being recognized and should inform policymakers and frontline workers in the care of people living with HIV/AIDS. Healthcare providers should consider the possibility that the diagnosis of HIV may be experienced as a defining traumatic event, particularly in individuals with multiple prior traumatic exposures. Practically speaking, the high degree of psychiatric comorbidity persons living with HIV indicates that healthcare professionals should routinely screen for psychiatric illness, given the evidence for a predictive role in HIV-related outcomes and overall health status [48–50, 53]. Similarly, clinicians should consider routinely using a model of psychological stewardship and trauma-informed care in the treatment of seropositive and vulnerable seronegative patients. Subsequent exploration of the role of childhood adversity and HIV-related outcomes will underscore the substantial role of trauma in this vulnerable population. Although the components of a syndemic HIV/AIDS care platform continue to be debated, the uniform inclusion of mental health screening in current clinical practice is indeed a matter of urgency and patient-centered care. Beyond identifying and treating psychiatric illness, promoting the wellbeing and resilience of people living with HIV/AIDS necessitates active mental health promotion.

Syndemics of HIV/AIDS and psychiatric illness are emblematic of the problematic mind-body dichotomy in medicine. This dichotomy persists but has no place in achieving the goal of comprehensive care for people living with HIV/AIDS. Prince et al. issued a rousing call for "no health without mental health" well over a decade ago [46]. They observed that the relative alienation of mental health from mainstream efforts to improve health and reduce poverty is entrenched in conventional methods of measuring the contributions of mental and physical disorders to disability and mortality [46]. This historical alienation from conventional salutogenic approaches is problematic in light of the pervasive interactions of psychiatric illness with HIV/AIDS, particularly in impoverished settings.

From a policy standpoint, tackling the problem requires simultaneous micro- and macro-level prioritization. Macro-level policy should aim to disrupt syndemogenic milieus, particularly those associated with poverty, while micro-level policy should address the localized structural conditions that favor syndemic interactions. Oldenburg and colleagues note that the association between co-occurring syndemic factors and incident HIV infection is magnified in the setting of poverty and recommend that mental health interventions should be considered as a means of reducing HIV transmission, particularly in socioeconomically disadvantaged areas [53].

The cumulative stress load that shapes and maintains vulnerability in HIV/AIDS syndemics translates to a significant burden of illness, which is unlikely to subside with *downstream* measures given the *upstream* inception of the syndemogenic milieu. To this end, a syndemic orientation is proposed as a means of reformulating public health thinking and consequent responses to syndemic events [5]. Reframing the public health approach to HIV/AIDS will necessitate a shift on multiple levels

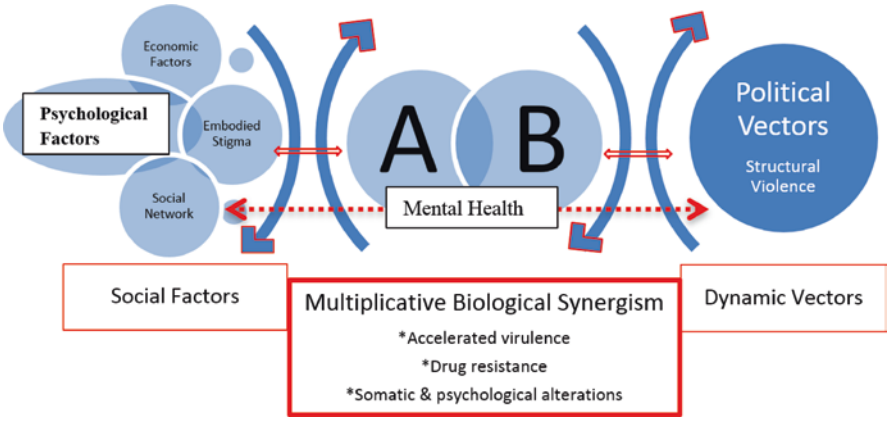

Fig. 14.2 The syndemic orientation: multiple domains of biosocial interaction generating excess cases of HIV and other health conditions (illustrated as A and B), with mental health as a potent mediator

to effect the adoption of a more "upstream" orientation. The syndemic orientation (Fig. 14.2) suggests that healthcare in its current form is not adequate for the health needs of people living with HIV/AID, as the dominant paradigm is reductive relative to the context in which HIV/AIDS evolves.

Key Syndemics Associated with HIV

Although the relationship among the three component epidemics in SAVA is still not fully understood, Singer proposed some mechanisms. The relationship between substance use and HIV infection/AIDS may be explained by shared injection equipment, transactional sex in order to obtain money or drugs, and overall higher rates of unsafe behavior, including disinhibition [1, 54]. In fact, chemsex, the sexualized use of substances, is a key factor in HIV/AIDS syndemics in communities of gay, bisexual, and other men who have sex with men [55, 56]. The use of drugs may also lead to an increase in violent behaviors, as intoxication and withdrawal states may lead to agitation, confusion, and impulsivity. Furthermore, drug dealers often use violence to ensure payments and/or to protect markets. Several drugs have been associated with violence and HIV transmission risk, including cannabis, alcohol, PCP, heroin, cocaine, and amphetamines [15, 29, 54–56]. Finally, violence, predominantly physical but also structural, increases the risk of HIV transmission [1, 54].

The VIDDA syndemic of violence, immigration, depression, type 2 diabetes mellitus, and abuse was described by medical anthropologist, Mendenhall, and underlines how poverty, abuse, and longing for family may contribute to an increased burden of depressive disorders and diabetes mellitus [7]. The increased frequency in

diabetes mellitus diagnoses in low-income populations is thought to be related to increased social stress, poor access to preventive primary and secondary healthcare, and comorbidity with depressive disorders [1]. Similarly, HIV infection seems to cluster with diabetes mellitus in aging populations as a result of metabolic complications of antiretroviral medications and age itself, which are likely enhanced by poverty and limited access to healthcare.

The syndemic congregation of HIV infection, substance use disorders, other psychiatric illnesses, and sexually transmitted infections (STIs) has been extensively reported in the literature. Psychiatric illnesses, particularly substance use disorders, are associated with increased risk for HIV infection and other STIs, likely related to an increased risk of unprotected sex [30]. This has been described in more detail in gay and bisexual populations and underlines the need to concomitantly address high-risk behaviors and psychiatric illnesses [30, 31]. In a prospective study involving 450 young men who have sex with men, Mustanski et al. found that the syndemic of substance use, violence, and internalizing mental health factors (such as depression, anxiety, and suicidal ideation/attempts) predicted the number of condomless partners [32]. This association was stronger in white participants and less significant among black and Latino men who have sex with men [32].

Case Vignette 14.1

Mr. F. was a 43-year-old male who presented to the clinic endorsing anxiety and poor sleep. He emigrated from Ecuador 3 years previously. He fled Ecuador due to gang violence that was endemic in his hometown and had killed many of his close friends and family members. Although he felt safer in the USA, he often felt overwhelmed by the fear of being deported and the longing for family members. He was haunted by recurrent thoughts of past violence he witnessed. Mr. F. identified as gay and reported internalized stigma which had led to depressive symptoms. He often used cannabis and methamphetamines to cope with his distressing thoughts and admitted to unprotected sex with multiple sexual partners, often while intoxicated. Mr. F. feared that he may have been infected with HIV and requested a rapid HIV test. He confided that he feared a positive test result would increase discrimination from his friends in the USA.

Which of the following choices is correct regarding the above clinical vignette?

(a) Mr. F.'s high-risk sexual behaviors and drug use should be addressed independently as they are clearly not related.
(b) Mr. F. felt safer since he migrated to the USA and therefore if the HIV test is negative, no further interventions are indicated.
(c) Mr. F.'s description underlines the complexities of syndemic factors that contribute to significant burden of disease in vulnerable populations.
(d) Assessment of social support is not indicated because Mr. F. felt supported by his community.

Answer Guide

The correct answer is option C. Mr. F's life on the margins as an undocumented immigrant mirrors the experiences of vulnerable immigrants trapped in an environment of plenty but unable to access or utilize resources that may potentially moderate their syndemogenic milieu. The social reality of an undocumented immigrant with past exposure to traumatic violence and concurrent use of recreational drugs to cope is complicated by the stigma of homosexuality and untreated psychiatric illness. These tightly intertwined conditions cannot be addressed independently. Although Mr. F felt supported by his community, fear and internalized rejection limit the extent of support he can draw on, which further exacerbate risk behaviors within a highly syndemogenic context. Mr. F's drug use was in part sexualized and in part a means of managing negative feelings like his internalized stigma in a broader environment of homophobia.

Mr. F's reality highlights the oft-described syndemic congregation of HIV infection, substance use, and other psychiatric illness and STIs, added to which this case also mirrors a number of elements observed in syndemics of violence, immigration, depressive disorder, type 2 diabetes mellitus, and abuse. Such syndemics may in fact serve as a harbinger for other syndemics among immigrant populations because of the current uncertainty around American immigration policy [33]. Although syndemic theory was developed with a view toward understanding population health patterns, the application of a syndemic approach can also be quite valuable in the clinical setting for expanding the focus beyond reasons for poor patient outcomes to examining other contributory factors, and thus better understanding the patient in context [33].

HIV syndemics reflect a complex fabric of biopsychosocial and cultural factors, with social capital exerting a modulating effect. In a cross-sectional study which analyzed survey data from the 2016 Behavioral Risk Factor Surveillance System in four US states (Louisiana, Michigan, Rhode Island, and Tennessee), the odds of participating in behaviors that increase the risk for HIV infection increased with increasing mental health needs and decreased with the perceived level of social support [34]. The multiple biopsychosocial drivers of the complex syndemic comprising of substance use disorders and other psychiatric illness, HIV infection, other STIs, violence, and sexual abuse in gay, bisexual, and men who have sex with men populations have been well described by Halkitis et al. [30, 31]. As depicted in Fig. 14.3, the complex interactions between these five syndemic health problems are strongly and dynamically influenced by multiple biological, behavioral, psychosocial, and structural factors [31].

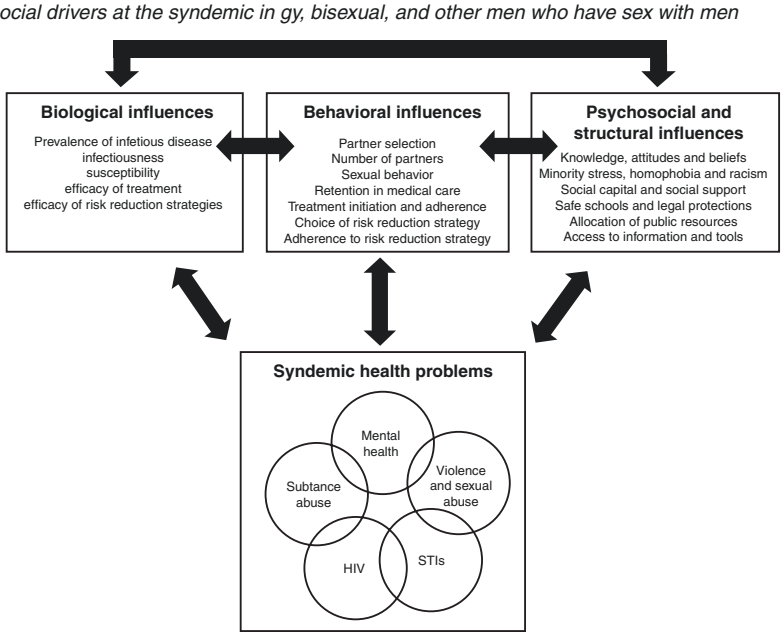

Fig. 14.3 Syndemic drivers of HIV/AIDS in men who have sex with men. (Reprinted from Halkitis et al. [31]. Copyright © 2013, American Psychological Association)

A Syndemic Approach to HIV/AIDS Prevention: Future Directions

Conventional public health approaches have contributed much to the reduction in incidence, prevalence, and longevity of people living with HIV/AIDS. In industrialized nations, the "graying of HIV/AIDS" has changed the face of illness to one of chronicity, with fewer and fewer infected persons dying of AIDS. However, HIV/AIDS remains a notable source of morbidity, mortality, and global burden of illness. Furthermore, the preponderance of HIV/AIDS syndemics in the most dispossessed has established that HIV/AIDS is not solely a component condition in syndemics but is itself also a syndemic generator; thus, a syndemic approach to primary prevention serves a critical role [8]. Primary prevention aims to reduce the incidence of HIV transmission, whereas secondary prevention aims to reduce the severity of the infection through early detection and prompt intervention, thus reducing the progression from HIV to AIDS and optimizing the quality of life of those living with HIV [10, 35]. Using a syndemic framework, there are multiple potential avenues to shape existing prevention strategies.

In terms of primary prevention, the chief challenge is to shift orientation to as proximal or upstream a level as possible, thus necessitating a major shift in the current organization and delivery of clinical medicine, public health, and social service fields [8, 27]. Current primary prevention models focus on education to reduce exposure by reducing risk behavior. Adopting a syndemic orientation to primary

prevention calls for policy and program development designed to target the adverse social conditions that drive risk behavior and enhance the interaction of biosocial factors [1, 5, 8, 25, 27]. Primary prevention should simultaneously target key syndemogenic vectors, particularly in children and youth as social and structural conditions contribute to the risk of exposure to early life adversity [36, 37]. Early life adversity in turn exacerbates inequities in social, economic, and health outcomes including HIV acquisition, transmission, and morbidity in later years [36, 37].

Early adversity is associated with leading causes of adult morbidity and mortality [36, 37]. Merrick et al. examined the impact of childhood trauma, described as adverse childhood experiences, on the health of adults living in the USA [36]. Almost two-thirds of over 200,000 adults surveyed across 23 states reported a history of 1 adverse childhood event, while almost a quarter reported 3 or more events. The study reinforced that early childhood and later trauma can have pervasive and persistent effects on health, wellbeing, life opportunities, and self-actualization [36].

The effects of childhood trauma are systemic at both a biological and structural level. At a biological level, trauma can disrupt healthy brain development and social development and can compromise immune systems [37]. At a structural level, exposure to adverse childhood experiences can exacerbate inequities in health, opportunity, social outcomes, and economic outcomes, with persisting intergenerational effects [36, 37]. The evidence confirms that traumatic exposures increase the risks of chronic diseases and sexually transmitted infections, including HIV [36, 37]. As trauma is also associated with poor HIV outcomes and interferes with the self-efficacy required to successfully navigate health and social systems, it suggests a key role for the use of the Adverse Childhood Experiences (ACE) instrument as a screening tool in HIV care [38]. The ACE instrument may enhance the understanding of the psychosocial and cultural roots of limited clinical care engagement and poor HIV suppression [38]. These findings underscore the importance of upstream prevention strategies as the antecedents of a syndemic are already underway well before syndemics are subsequently recognized.

HIV/AIDS is one of many illnesses that are now being recognized as having significant biopsychosocial and cultural determinants. Since the concept of syndemics was first introduced, a number of researchers have adopted this framework to examine social determinants of HIV risk, in the hopes of understanding new interventions for HIV prevention. This work focuses on different populations in order to identify the concurrent patterns of health and illness that work together to increase HIV infection within specific vulnerable groups. For example, syndemic research in men who have sex with men has strongly emphasized mental health factors, including alcohol and other substance use, childhood sexual abuse, stress, and depression [57]. Some authors have drawn on the concept of the *minority stress model* developed by Meyer in order to describe the role of stigma within a syndemic framework [58]. This work has posited the operation of syndemics within a developmental trajectory, such that early adverse experiences by men who have sex with men interact with later factors to produce synergistic and mutually supporting problems around substance use, shame, and HIV risk behavior, leading to increased HIV transmission [59].

The recognition of syndemics may be enhanced through surveillance, a core function of public health. “Heat maps” of various types are in use with the goal of

detecting sentinel events in order to prevent further disease incidence. Surveillance methods can be adapted to identify and interrupt syndemogenesis. Vulnerable populations are well recognized in spite of the relative dearth of syndemic risk factor mapping. With the implementation of syndemic mapping, further information about the unique syndemic factors in vulnerable populations can be elucidated and, in turn, used to identify "hot zones" for more immediate upstream prevention strategies. Heat maps can also be used to target secondary prevention tactics. In populations with identified HIV/AIDS-associated syndemics, the heat map may identify additional syndemic conditions. Public health planners may also be able to utilize heat maps with modeling applications in a predictive fashion and as such plan targeted programs concurrent with ongoing policy change to address disparity.

Secondary prevention is essential, particularly as HIV/AIDS-related syndemics have been identified to reduce treatment adherence, increase risk behavior, and generate cascades of negative health outcomes. Secondary prevention could also involve devising a *syndemic care system* that addresses needs in a less reductive fashion, relative to conventional healthcare. In some low and middle-income settings, attempts to address this gap have implemented care platforms that "bundle" health and social services in order to optimize uptake [6, 7].

Challenges and Limitations of the Syndemic Approach

It is evident that syndemic interactions are of considerable importance in the health status and prognosis of people living with HIV/AIDS [8]. Although there is increasing information about the types of structural and social factors that tend to give rise to syndemics, the precise mechanisms of deleterious biosocial enhancement are yet to be characterized in most of the syndemics recognized to date. Specifically, the mechanisms of social-biological, social-psychological, and bio-psychological interplay remain largely opaque, although there is good evidence for the nature of biological-biological interplay. Syndemics remain understudied; as such, the emergence of syndemics and the factors that produce specific health configurations in populations continue to be pressing lines of inquiry [5].

Concern has been raised about the misconception that a syndemic approach requires complex, resource-intensive multicomponent interventions that target all component health conditions in a given syndemic [26, 28]. However, depending on the nature of the biosocial interactions at play, appropriate intervention may only require that *one* component epidemic be targeted [26, 28]. In synergistically interacting epidemics that are *not* mutually causal, *single-component interventions* may serve as a cost-effective alternative, which is particularly important in low-resource settings [28].

Multiple stakeholders are involved with HIV/AIDS management; however, the role of current stakeholders across the health-related disciplines is unclear with respect to the adoption of a syndemic framework. At the clinical level, what is the role of clinicians in a syndemic framework? Is health and social service integration the first step toward a syndemic platform? While there are potential synergies from

combined care platforms, it is unclear which services to integrate, at what level of the healthcare and social service systems to do so, and how integrated care should be delivered [27]. It remains unclear what "syndemic care" would look like and who should deliver it. Many practical considerations are required in a shift toward a syndemic perspective; however, the dialogue is underway, and the momentum needs to be sustained in order to advance this novel orientation further.

Case Vignette 14.2

Joe Brown was a 46-year-old married man with a history of opioid use disorder, asthma, type 2 diabetes mellitus, and chronic pain. His opioid use disorder developed in the context of prescription opioid analgesia when he injured his lower back and feet at a factory job 10 years previously. His worker's compensation was terminated 4 years after the injury, and he was no longer able to afford his prescribed opioids.

Joe's family had always lived at the poverty margin and became more destitute after Joe's injuries limited further employment. Financial constraints and lack of health benefits forced him to turn to illicit avenues for ongoing opioid analgesia and eventually resulted in legal charges. He was recently incarcerated for 5 years for possession with intent to traffic narcotics and was released 2 months ago, at which time he returned home to his wife and two young adult children. The family resided in subsiseds housing and subsisted on disability support payments issued to Joe, with added income from sporadic sex work by his wife.

While incarcerated, Joe continued to use injection opioids but was largely able to avoid sharing needles and sharps with other inmates. He had difficulty obtaining supplies as with his limited income he was not able to buy commissary products to barter for opioids. He had to become creative to ensure ongoing access to opioids. During his last month of incarceration, he began experiencing respiratory symptoms and intermittent night sweats. He was advised that given his history of asthma he was likely reacting to the air quality in his damp cell block. This explanation appeared reasonable to Joe whose asthma was stable for years before he was incarcerated. As with similarly affected inmates in his block, he was treated with a combination of oral and inhaled corticosteroids, which he discontinued on being released. His symptoms worsened over the 2 months since he returned home. The family was initially not concerned as Joe had asthma, was a heavy smoker, and a number of people in their high-rise building appeared to have similar symptoms which were assumed to stem from poor air quality in the building. Joe began to lose weight and eventually sought medical attention. Based on the history provided so far, what is the potential etiology of Joe's symptoms?

Joe is suddenly quarantined by regional health authorities who announce an epidemic of tuberculosis (TB) that is traced to the cell block Joe was incarcerated in. Further alarm is raised when it was determined that the cell block

is in fact the focus of three hyperendemic diseases in the prison population: TB, HIV, and HCV. Investigations further revealed that among the affected residents of the cell block, there was an unusually high prevalence of type 2 diabetes mellitus, aspergillosis, and fungal skin conditions. Reports documented a decaying building infrastructure with high airborne *Aspergillus* spore counts, high relative humidity, and overall unsanitary conditions.

Many of those affected had fulminant cases of pulmonary aspergillosis, with chest X-rays being notable for the presence of both granulomas and aspergillomas. Furthermore, it was determined that although screening tests were conducted as required on entry to the prison, prisoners who subsequently became symptomatic were not appropriately screened as a result of a fraudulent health service vendor. The cohort of affected prisoners had remained in quarantine where they were treated for TB. The disparity between the affected cell block relative to others was striking for racialization and the degree of social adversity pre-incarceration.

Utilizing the syndemic lens, what biosocial interactions hypothetically contributed to this syndemic? Based on the above scenario, would you be concerned about any parallel syndemogenesis? Given the vulnerabilities of prison populations, what might a syndemic care platform entail for this population?

Answer Guide

Joe's symptoms are suggestive of multiple etiologies which are subsequently identified in the epidemiological investigations recounted above. Joe's cough was likely a manifestation of aspergillosis and TB, both of which also trigger inflammatory changes that would likely exacerbate his underlying asthma. Joe also tested positive for HIV and HCV, which he may have acquired from injection drug use. Although he largely avoided sharing needles and sharps, he did so on one or two occasions while intoxicated, added to which unbeknownst to him two of his cellmates used his sharps on a few occasions.

Joe had to become creative to procure an ongoing supply of opioids, so he may have had to trade sexual favors. Joe's wife also engaged in sporadic sex work and may potentially have exposed him to HIV. Joe's financial constraints prevented him from engaging in a cleaner trade by barter with commissary supplies. The constellation of nutrition inadequacy in prison, type 2 diabetes mellitus, chronic inflammatory effects of asthma, and aspergillosis infection would have created a ripe biological setting for TB to become activated and subsequently disseminated in the presence of HIV-mediated immune impairment. The combined effects of these synergistic biological interactions would have been further exacerbated by the geopolitical interactions of substandard prison healthcare and environmental degradation of the prison block.

Violence is another vector endemic to prison life and constitutes an important syndemogenic factor in this setting. Although not clearly elucidated yet, as discussed previously violence is a notable factor in multiple syndemics as exemplified in the multiple SAVA syndemics reported to date. In Joe's case, the reactivation of his asthma may have stemmed from a combination of both the poor air quality in his cell block and the toxic stress (i.e., prolonged activation of the stress-response system) [37] of living with the violence endemic to prison settings.

The excess cases noted in the investigation do not identify any one causal factor or mechanism to account for the unusually high incidence and prevalence of the multiple diseases and adverse conditions identified. Nor is a cumulative sum of risks able to explain the observed excess of cases, thus suggesting a complex syndemic pathway. This aspect of syndemics remains the key challenge in that the biosocial conditions identified in this case have been repeatedly observed and reported, and there is increasing understanding of proliferative biological mechanisms of interaction; however, the nature of the biosocial interactions that result in excess cases in these settings is yet to be illuminated. To this end, it is challenging to conclusively justify the appropriate components and location of a syndemic care platform in the incarcerated population.

Syndemic approaches ideally address more upstream factors in order to minimize downstream disparities. In this scenario where much of the upstream syndemic factors are already well underway and more distal factors are unfolding in the prison setting, an ad hoc care platform is required to stem the syndemic while further work is done to address more upstream factors. As noted by Douglas-Vail [25], waiting to develop a syndemic care system is not an option while new cases continue to occur. In this case, an ad hoc syndemic care platform should ideally span the pre-entry to post-release stages of incarceration. Given the well-studied biological synergies in incarcerated populations, the pre-entry screening process should focus on identifying and managing priority diseases and conditions, particularly psychiatric illness, concurrent with enhanced protection of prison surveillance systems in order to prevent health vendor malfeasance and identify incident priority conditions quickly.

At the post-release phase, it would be important to optimize reintegration factors including health status for more successful reintegration into communities. Mendenhall et al. suggest that community health workers may prove an avenue to providing long-term syndemic care that addresses social and medical problems concurrently by facilitating access to a bundled care platform [6, 7]. This avenue may have averted a secondary syndemic from originating in the community, as Joe would have accessed medical care on release from

prison. Joe's community at large is a highly concerning secondary location for an HIV-TB syndemic. Joe has been home and symptomatic of TB for 2 months, thus exposing residents of the subsidized housing complex who also share Joe's biosocial vulnerabilities. Similarly, Joe may have infected his wife with HIV, which would continue to be transmitted to his wife's clients in the course of her sporadic sex work. As such, concerns about syndemogenesis are not confined to the cell block but extend well into the community by virtue of a failed custodial system and pervasive sociopolitical adversity that interact synergistically with HIV.

Conclusion

HIV/AIDS is a socially bound epidemic [1, 4–8]. Although the role of social conditions in illness patterns has long been recognized, conventional public health approaches have typically focused on downstream social determinants of health, risk groups, and risky behavior and to a lesser extent on the structural relationships and social contexts that transmute risk [25]. This has resulted in a relatively compartmentalized approach to HIV/AIDS, thus generating inefficiencies, reductive approaches to care, and less-than-optimal approaches to HIV/AIDS prevention and treatment [8, 9, 27].

In contrast, the syndemic framework has introduced a means to examine the way HIV/AIDS affects vulnerable communities and redirects the focus from the narrower and more downstream scope of individual risk factors to population health patterns and clusters of disease. Conventional thinking around HIV transmission has focused on individual acts of choice and risk as the focus for prevention, but this has been problematic in that it supports a victim-blaming point of view. In contrast, a syndemic perspective emphasizes the role of structural and social forces in determining HIV risk behavior and as such holds promise for a fuller understanding of excess disease in disproportionately affected populations.

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Chapter 15
HIV in Specific Populations

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Introduction

The HIV epidemic has impacted various individuals, populations, and communities in different ways. This chapter reviews issues related to HIV in populations that have unique characteristics that are important to factor in when engaging and caring for persons at risk for, affected by, or infected with HIV. Clinical issues relevant throughout the life cycle are discussed, beginning with children, adolescents, and their families and ending with older HIV-infected men who have sex with men (MSM). The impact of HIV in the lives of women will be reviewed, including issues related to the roles of women in society, work, and relationships as well as family, pregnancy, labor, delivery, menopause, and mental health. We explore the disparities in the rates of HIV among Black Americans and MSM and some of the underlying causes. Additionally, we review the care, the incidence, and prevalence of HIV in transgender populations and an overview of transgender HIV care. There we

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present the structural barriers to care, the need for culturally appropriate care, and the importance of diversifying the healthcare field**.**

HIV and AIDS

Acquired immune deficiency syndrome (AIDS) was first recognized as a new illness in 1981 when clusters of young MSM were diagnosed with unusual opportunistic infections (such as *Pneumocystis carinii* pneumonia) and rare malignancies (such as Kaposi's sarcoma). HIV, a retrovirus, was subsequently identified as the cause and source of one the most devastating pandemics in recent history [1]. HIV is known to be transmitted through sexual, percutaneous, or perinatal routes, but because 80% of HIV acquisition in adults is due to exposure of mucosal surfaces, it is primarily considered a sexually transmitted disease.

AIDS, caused by two lentiviruses (HIV type 1 and HIV type 2), is the result of cross-species transmissions of a simian immunodeficiency virus (SIV) naturally infecting Central and West African primates. Although various subgroups of the virus resulted in viruses that spread in humans to only a limited extent, the global pandemic had its origins in the emergence of one specific strain—HIV-1 subgroup M—from chimpanzees in southeastern Cameroon [2].

Although isolated incidents of infection can be traced back to 1966, the first case of HIV is thought to have arrived in New York City from Haiti around 1971 and spread to San Francisco in 1976. HIV-1 is believed to have arrived in Haiti from Central Africa around 1967 by an individual or individuals in the Democratic Republic of the Congo [2].

Since it was first discovered, HIV has infected at least 75.7 million people and caused more than 32.7 million deaths [3]. Developing countries, particularly countries in sub-Saharan Africa, have experienced the greatest HIV/AIDS morbidity and mortality, and although ART has reduced the number of AIDS- related deaths, access to therapy is not universal [1]. Thus, HIV continues to pose a significant public health threat.

In the United States, data from the Centers for Disease Control and Prevention (CDC) show that gay, bisexual, and other men who have sex with men are the most affected by HIV, making up to 69% of the 37,968 new HIV diagnoses. Out of the estimated 1.2 million people living with HIV, approximately 740,400 were MSM. Studies have also shown that 1 in 6 gay and bisexual men with HIV are unaware of their status [4].

Biosafety regulations and blood screening techniques for HIV have made risk by transfusion negligible. Vertical transmission (mother to fetus) determined by delivery type, severity of HIV disease, and the availability of preventive ART [5] have demonstrated a decreased risk, leaving the MSM community disproportionately affected by high seroprevalence.

Children and Adolescents

In meeting with HIV-positive children, adolescents, and their families, developmental and contextual considerations are key factors. The HIV/AIDS epidemic in the United States occurs in the context of a syndemic of discrimination against sexual, racial, and ethnic minorities, mass incarceration, poverty, and geography, with new infections greatest among African American adolescent young men who have sex with men in the geographical South [6–8]. On the other hand, maternal to child transmission has almost been eliminated, thanks in part to efforts to destigmatize HIV infection, making it easier for women living with HIV to plan for pregnancy or, if already pregnant, to receive care without fear of judgment [9].

Defining HIV as an immune disorder, rather than a moral failing deserving of punishment and shame, has facilitated access to and provision of high-quality care in urban areas, although less so in rural areas [8]. Many people living with HIV are religious and their beliefs influence their treatment outcomes. Negative religious coping, such as the belief that HIV is a punishment from God, can lead to poor quality of life outcomes [10, 11]. On the other hand, positive religious coping, the belief that God is a loving God who wants all his children to be happy, has been repeatedly shown to improve not just quality of life but to decrease morbidity and mortality [12]. Thus, it is important in working with families of children and adolescents living with HIV and the children and adolescents themselves to elicit their beliefs and provide referrals to hospital-based chaplaincy programs or religious community resources supportive of HIV persons of all races and sexual orientations and identity.

Modeling a nonjudgmental/medical approach to HIV helps to decrease stigma, as does upholding one's professional ethics which include the principles of autonomy, respect for persons, and justice. When this therapeutic stance is challenged by difficult circumstances or ethical dilemmas, it is important for the practitioner to seek consultation. Hospital and institutional ethics committees are excellent resources for consultation. In this context of complex care, interdisciplinary HIV-specialty hospital-based outpatient clinics provide the ideal setting for treatment, when available. For those practitioners in rural areas, it is especially important to find consultative support through professional organizations, as the depth of these services may simply not be available. In these circumstances, advocacy at institutional or political level becomes an important role for the practitioner.

Epidemiology

Despite medical advances, adolescents living with HIV/AIDS still have mortality rates 6–12 times greater than the general United States population [6–8]. Globally, AIDS is the second leading cause of adolescent deaths and the leading cause of adolescent deaths in Africa [13]. On the other hand, mother-to-child, or perinatal,

transmission of HIV has all but been eliminated in the United States. In 2017, only 73 children under the age of 13 received a diagnosis of perinatally acquired HIV in the United States and dependent areas [9]. In the US and dependent areas at the end of 2016, 1814 children were living with diagnosed perinatal HIV. Of these, 1139 (63%) were Black/African American, 269 (15%) were Hispanic/Latino, and 195 (11%) were White [9]. In 2014, the last year for which worldwide data are available, there were 170 new infections among children. Eight out of 10 pregnant women living with HIV were receiving ART, and transmission through pregnancy was 18% in contrast to the US rate of 1% [14]. Thus, HIV remains a serious illness with risk of morbidity and mortality.

HIV Diagnostic Disclosure for Children

Wiener et al. have developed a disclosure protocol that most HIV-specialty clinics in the United States have adopted [15]. An important finding of their research was parents who were pressured to disclose to their child the child's HIV diagnosis when the parent was not ready had children with poorer psychosocial outcomes. Guidelines for disclosure are briefly reproduced here:

Step One—Preparation

- Have a meeting with the parent/caregivers involved in the decision-making process. Staff members who the family trusts should be present.
- Address the importance of disclosure and ascertain whether the family has a plan in mind. Respect the intensity of feelings about the issue. Obtain feedback on the child's anticipated response. Explore the child's level of knowledge and understanding as well as his or her emotional stability and maturity.
- If the family is ready to disclose, provide guidance as to various ways of approaching disclosure.
- If the family is not ready, encourage them to begin using words they can build on later, such as immune problems, virus, or infection. Provide books and pamphlets about viruses for the family to read with the child. Strengthen the family through education and support and schedule a follow-up meeting. Strongly encourage the family not to lie to the child, if the child asks direct questions about why they are taking medications, seeing the doctor so often, or the name of their disease, as this breaks the trust that is so important to their relationship.

Step Two—Disclosure

- In advance, have the family think through or write out how they want the conversation to go. Encourage the family to begin with "Do you remember" to include information about the child's life, medications, and/or procedures so the child is reminded of past events before introducing new facts.
- Have the family choose a place where the child will be most comfortable to talk openly. This can include the HIV clinic or doctor's office.
- Provide the family with questions the child may ask so they are prepared with answers. Such questions include: "How long have you known this?"; "Who else has the virus?"; "Will I die?"; "Can I ever have children?"; "Who can I tell?"; "Why me?"; "Who else knows?"; "Where did I get the virus?"; and "How did I get it?"

- Encourage having present only the people with whom the child is most comfortable. The healthcare provider may offer to facilitate the meeting.
- Keep medical facts to a minimum.
- If the child is asked to keep it a secret, give them names of people to talk to.
- Provide the child with a journal or diary to record questions, thoughts, and feelings.
- Schedule a follow-up meeting.

Step Three—After Disclosure

- Provide child and family follow-up meetings 2 weeks after the disclosure and again every 2–4 weeks for the first 6 months to assess the impact of disclosure, to answer questions, and to help foster support between the child and family.
- Ask the child to tell you what he or she has learned about the virus.
- Assess changes in emotional well-being and provide the family with information about symptoms that could indicate the need for more intensive interventions.
- Support the parents and/or other family members for having disclosed the diagnosis and, if they are interested, refer to a parent support group. Encourage them to think about the emotional needs of other children in the family.
- Remind parents that disclosure is not a one-time event. Ask what supports they would find helpful. Provide information about HIV camp programs for HIV-infected and affected children and youth.

Disclosure of HIV diagnosis by newly diagnosed adolescents to their families and sexual partners should be supported by the healthcare team. The healthcare clinician may offer to facilitate the meeting, which provides a measure of safety and the opportunity to provide the affected persons support with accurate education and support. The clinician should be aware of local laws that may criminalize sexual behavior by HIV-positive persons when counseling patients. The clinician should also be aware of local laws the mandate that parents have the right to NOT disclose to an HIV diagnosis to their sexually active minor child, even if that child is sexually active and engaging in sexual behaviors that put the partners at risk of HIV infection.

Neurodevelopmental Considerations

All HIV-positive persons should receive a baseline psychosocial assessment by an appropriately trained clinician such as a psychologist, which includes a screening for neurodevelopmental issues. The HIV Dementia Scale has been tested with HIV-positive adolescents and found to be sensitive and specific [16]. Specialty referrals for neurological assessment should be provided to all adolescents who fail screening on the HIV Dementia Scale to rule out HIV-Associated Neurological Disorder (HAND). Comprehensive psychosocial assessments should be standard of care for all newly diagnosed HIV-positive children and adolescents. These assessments provide the opportunity to identify and treat previously unidentified learning disabilities, attention-deficit/hyperactivity disorder, substance use disorder, and other psychiatric disorders.

Health Behaviors

Adherence

Adherence with treatment recommendations for adolescents, including being in care, being retained in care, and achieving viral suppression, is lower than that for any other age group living with HIV (See Fig. 15.1).

In a review of published literature from Africa and Asia, more than 70% of HIV-positive adolescent and young adult populations receiving ART were adherent to therapy, while lower rates of adherence were shown in Europe and North America at 50–60% [18]. The reviewers suggest that global differences in ART adherence rates discrepancy are probably multifactorial reflecting differences between focused and generalized epidemics, access to healthcare, and funding.

Adherence is a challenge for all individuals across chronic illnesses and healthcare systems. A recent review of successful adherence interventions concludes that adherence can be assessed and improved within the context of usual clinical care, but more intensive and costly interventions that have demonstrated success will require additional investments by health systems [19]. Randomized clinical trials of adolescent specific treatment interventions are ongoing [20]. The only evidence-based adherence study on the CDC website is an NIH-funded text messaging intervention to improve antiretroviral adherence among HIV-positive youth with a mean age of 24 years (range 16–29 years). Investigators found good evidence for increases in self-reported adherence, which was sustained at 12 months post-intervention, but no significant positive intervention effect on viral load [21]. The CDC-funded

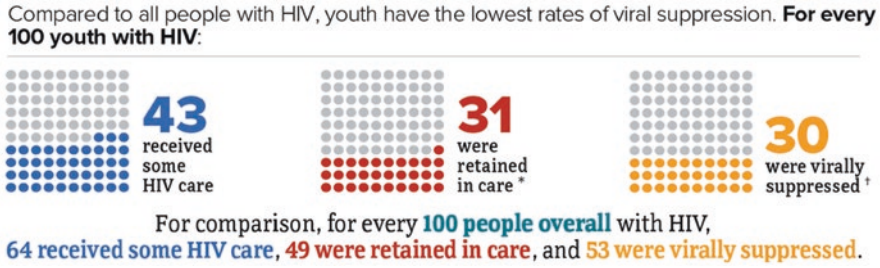

Fig. 15.1 HIV treatment adherence for adolescents vs. overall population. *Had two viral load or CD4 tests at least 3 months apart in a year. †Based on most recent viral load test. (Based on data from Ref. [17])

5-year, multisite, adolescent impact adherence intervention [22], which combined group support and individual counseling for adolescents with HIV, had null results with respect to ART adherence (unpublished). A recent review of adherence interventions for HIV-positive adolescents concluded few studies were high quality and no single intervention strategy stood out as definitively warranting adaptation for adolescents, based on adult studies [23]. Factors associated with unsuppressed viral load include socioeconomic status of youth, feelings of isolation, substance abuse, stigma, and misrepresentation around HIV [24, https://www.cdc.gov/hiv/group/age/youth/].

It is noteworthy that the above strategies excluded families, despite evidence that family engagement is an important factor for adolescents' keeping their medical appointments and for managing medication adherence, especially as they begin a transition to independent living or college [25]. A good example is a patient we will call Carla, who attended a small college in the South and called her mother daily using her smartphone, so her mother could watch her taking her medications, an acceptable form of directly observed therapy. Working with families, although complex and challenging, should be integrated into future research with the aim of engaging adolescents more fully in the continuum of care.

Sex

Half of HIV-positive adolescents who are or who were not infected perinatally have a history of sexual abuse with no differences by gender [26]. All HIV-positive youth should be provided with an assessment for trauma. All adolescents should receive *comprehensive sex education*, as opposed to *abstinence until marriage-based sex education* [27]. However, political will remains conflicted and unfortunately geography again plays a role with abstinence until marriage education being more likely in the states that have the highest rates of HIV in the United States [28]. Political advocacy is necessary here.

Some families of adolescents who are HIV positive also often believe that their adolescent should be abstinent for life because of their infection. Here medical providers can provide guidance individually or through psychoeducational programs targeted at family caregivers to provide them with support as they help their adolescent learn to "love with care" or develop "sex positive" messages that are safe for them and their current or future partners. Families and adolescents should receive education about the very low risk of transmission to either sex partners or future children if their viral load remains undetectable.

Facilitating Transition to Adult Care

Facilitating transition to adult healthcare remains a challenge for adolescents living with a chronic illness worldwide. This transition involves many systems. There are successful hospital-based system-based models for adolescents based in Canada, called the *Good2Go Transition Program* [29]. Similar models are in the process of being adapted to the United States pediatric hospital systems [30]. Recommendations are that a transition plan begin at age 18 years (at the latest) and that handoffs to new adult clinicians be provided face to face, whenever feasible. However, insurance issues remain a barrier, as does the desire of the adolescent/young adult to be "normal," as well as the process of grieving the loss of medical caregivers to whom they had become attached over the many years of their treatment. The challenge of transitioning HIV healthcare from a pediatric to adult clinic setting can have a disastrous impact, leading to illness progression and mortality in young persons. Providing rituals to mark this transition and to strengthen social supports during this critical period might facilitate this process and prevent interruptions in HIV medical care.

Women

In this section we focus on how differences in sex relate to the natural history of HIV infection and antiretroviral treatment. We then discuss gender-based violence and its presence in and impact on women at risk for and infected with HIV. We also explore issues relating to reproductive medicine and HIV, including conception, pregnancy, and menopause. Clinicians treating women with HIV must be aware of the how biopsychosocial factors can affect them differently from their male counterparts. Knowledge of these factors will help clinicians better direct treatment and counseling.

Epidemiology

Globally, HIV risk can vary depending on the region. For example, in sub-Saharan Africa, young women and adolescents account for about 1 in 4 new HIV cases despite making up only 10% of the population. In eastern and southern Africa, they account for 30% of new infections [31].

According to the CDC's HIV Surveillance Report, more than 7000 women received an HIV diagnosis in the United States and its dependent areas in 2018. An estimated 85% of HIV infections were attributed to heterosexual contact. Trends of HIV diagnoses varied among different populations of women, with Black and African American women being disproportionately affected, accounting for 58% of

HIV diagnoses despite making up only 13% of the population. They also accounted for the largest percentage of HIV infection attributed to heterosexual contact among women. Transmission attributed to injection drug use was largest among American Indian/Alaska Native women [4, 32].

Illness Progression

Women are at a higher risk of HIV seroconversion when engaging in heterosexual sexual behavior than men. This may be in part due to inflammation at the cervico-vaginal mucosa lowering the barrier to HIV infection [33]. Although in *early* infection, women seem to have slightly *lower* viral loads, disease progression is comparable in men and women. Women, however, tend to be more susceptible to ART adverse events including nausea and vomiting, protease inhibitor-associated allergic reactions, nucleoside/nucleotide reverse transcriptase-associated hepatotoxicity, changes in body habitus, and metabolic abnormalities [34, 35].

Treatment Issues

Though antiretroviral therapy has reduced morbidity and mortality in individuals with HIV, treatment experiences differ between men and women [35]. Psychosocial factors, such as stigma and fear of disclosure, inter-partner violence, access to transportation, childcare concerns, work constraints, cultural barriers, and finances, can have a negative impact on access to care, treatment, and adherence to ART [35–37]. Even with access to treatment, depression, PTSD, substance use, emotional distress, stigma, and negative impacts of poor social relationships can also detrimentally affect ART adherence, negatively affecting disease progression [36, 38, 39].

Gender-Based Violence

Gender-based violence (GBV) is an established risk factor for HIV transmission [40], and evidence suggests that this risk is bidirectional as women with HIV are also at increased risk for experiencing violence [40, 41]. Gender-based violence can increase the risk of depression and PTSD which can in turn increase the risk of substance use and subsequently increase the likelihood of engaging in risky behaviors and acquiring HIV [39].

Sexual trauma in women has been associated with substance use, depression, and risky sexual behaviors. GBV or fear of violence can also limit a woman's ability to negotiate safer sex practices, access HIV, and sexual/reproductive health services. At the same time, a history of sexual trauma in individuals with HIV can be associated with treatment failure that can result in poorer health outcomes [41, 42].

Conception and Pregnancy

A woman's reproductive desire, HIV testing in pregnancy, risk of vertical transmission, and pregnancy outcomes are important factors to consider, as most women become infected with HIV during their reproductive years. The use of antiretroviral-driven prevention strategies can reduce the risk of HIV transmission for those patients who seek to become pregnant [43]. These therapies can also help reduce the risk of vertical transmission but can be associated with adverse birth outcomes. An observational birth outcome surveillance study comparing live and stillbirths in Botswana by Zash et al. published in 2017 found that occurrence of adverse birth outcomes was higher among HIV-exposed infants. Among HIV-exposed infants, those exposed to ARTs from conception were often small for gestational age and had more neonatal deaths than those exposed to antiretroviral therapy initiated after conception. Infants who were exposed to HIV, but not antiretroviral therapy, had worse outcomes [44].

There are differing standards with regard to breastfeeding in HIV-positive mothers across the world. In the United States, the CDC recommends that women with HIV avoid breastfeeding their infants regardless of viral load and antiretroviral therapy. They do note that in mothers experiencing cultural or social pressure to breast feed, providers should offer ongoing guidance and support. Alternatively, in other areas where resources might be limited the World Health Organization recommends that mothers breastfeed exclusively for the first 6 months of life, regardless of seropositive status. These mothers should be offered antiretroviral therapy to decrease the risk of transmission through breastfeeding [45]. Women with HIV who do not desire pregnancy should be counseled on contraception as part of routine care.

Menopause

Menopause symptoms are common and can have a negative impact on a woman's perceived health, quality of life, and performance at work and within relationships. Data on symptomatology is mixed in women with HIV, with some studies showing no association between HIV status and menopausal symptoms and others showing an association with increased hot flashes and mood changes. Data on the association between HIV and earlier age at menopause is also conflicting [46]. Although estrogen has immunomodulatory effects, there is limited data available on the effect of estrogen deficiency on CD4 count or response to ART [46]. Ageing,

menopause, and HIV can contribute to low bone mineral density and osteoporosis [47]. Initiation of antiretrovirals can be associated with a decrease in bone mineral density in the first few years of use after initiation, but this stabilizes over time [46].

Black Americans

Epidemiology

In the United States Blacks account for a higher proportion of new HIV diagnoses and people with HIV, compared to other races/ethnicities. In 2018 in the United States, Blacks accounted for 13% of the general population but 42% of the 37,832 new HIV diagnoses. In all categories (women, heterosexual men, and gay and bisexual men/MSM), Black Americans have higher incidence rates of HIV [48]. It should be noted, however, that from 2010 to 2017 rates of HIV diagnoses among Blacks in the United States fell in all categories except gay and bisexual men 25–34 years old, who had rates increase by 42% and gay and bisexual men over 55 years old where rates remained stable [49].

Regionally, the South accounts for both the majority of Blacks newly diagnosed with HIV (63% in 2018) and the majority living with an HIV diagnosis at the end of 2017 (58%) [48, 49]. This is related to the proportion of Blacks living in the South, but also likely a result of structural issues, especially the lack of Medicaid expansion in many southern states, leaving increased numbers of people without insurance, thereby limiting access to healthcare [50].

Although data early in the HIV epidemic revealed the disproportionate rates of HIV infection in Blacks, it was not until 1993 that this disparity was given significant attention [51]. This allowed HIV to spread in a community that was unaware of the increased risk of acquiring HIV. There was also an absence of HIV-related programs specifically targeting the Black community for many years. Once this health disparity was widely revealed, culturally appropriate interventions were developed and implemented.

Black Gay and Bisexual Men/Men Who Have Sex with Men (MSM)

Although Black MSM have higher rates of new HIV diagnoses, they engage in fewer risky behaviors than White MSM. However, issues related to structural racism (less educational achievement, higher rates of unemployment, lower incomes, and decreased rates of health insurance) result in decreased access to care. Relative to White MSM, Black MSM are less likely to engage in medical care, more likely to have challenges with adherence to ART, and less likely to be virally suppressed [52, 53]. Due to various social issues, Black MSM are more likely to engage in sexual activity with other Black MSM. Given the increased prevalence of HIV

Table 15.1 Issues limiting the use of PrEP by Black MSM

Lack of awareness
Stigma associated with PrEP
Structural barriers/racist policies (e.g., lack of insurance, distance to healthcare facilities, inadequate public transportation)
Reluctance to discuss sexual health with clinician
Clinician racism/racial bias
Clinician anti-homosexual bias/homophobia/homonegativity
Medical mistrust

among Black MSM, this results in increased risk of exposure to HIV [53]. There are also higher rates of STIs among Black MSM and there is an association between STIs and increased risk of HIV infection [54].

Black MSM dealing with HIV-related stigma and anti-homosexual bias/homophobia from the Black community, churches, and family are less likely to engage in HIV-related care. Anti-Black racism within the majority culture, as well as the anticipation of racism in the White gay community, can cause feelings of devaluation and decreased concern about HIV-risk reduction [55, 56]. It is important that programs are developed to support Black MSM cope with HIV stigma, racism, and anti-homosexual bias/homophobia. Such interventions can help create a supportive community that will allow Black MSM to engage in medical care, as well as help provide a sense of pride and improved psychological well-being [55].

Pre-exposure prophylaxis (PrEP) is efficacious in reducing HIV infections. However, there are a host of issues limiting its use by Black MSM; see Table 15.1.

While there has been a focus on increasing PrEP awareness, increased awareness per se is not associated with increased uptake [57].

Research has shown that one of the most significant barriers to PrEP uptake is related to limited engagement in care related to negative past experiences with the healthcare system or the expectation of a negative experience [58]. There needs to be a focus on addressing provider biases, enhancing culturally appropriate medical care based on sexual orientation, gender identity, and race/ethnicity. Additionally, there must be creative, broad-based, intention-driven programs to create a more diverse healthcare workforce. Many patients feel like they would receive better care from healthcare clinicians who share various aspects of lived experience: race/ethnicity, sexual orientation, and gender identity [59].

Black Women

In the United States Black women have higher rates of HIV incidence than any other racial/ethnic group, making up 57% on new HIV diagnoses in 2018 [6]. Racist policies are instrumental in creating these health disparities, as it results in higher rates of poverty, lower educational achievement, higher rates of unemployment, structural barriers to accessing healthcare, and higher rates of incarceration [52].

The high rates of incarceration of Black men reduce the number of men in Black communities, thereby limiting the available partners for heterosexual black women. Combined with racial segregation, this contributes to the creation of limited sexual networks with overlapping, concurrent partners. Studies indicate that this results in the increased risk of transmission/acquisition of HIV [60, 61].

As previously noted, issues with patient-clinician communication and healthcare clinician stigma can result in negative clinical encounters causing barriers to care. As such, improving training of healthcare workers to provide culturally appropriate care is paramount, as is diversifying the community of healthcare clinicians [62].

Medical Mistrust

Black Americans are disproportionately affected by HIV and show high levels of medical mistrust, including HIV conspiracy beliefs regarding the origin of HIV (e.g., a belief that HIV was a manmade virus to deliberately infect people) and treatment (there is a cure, there is superior ART that is only available to the wealthy) [63]. Given the ongoing issues of institutional racism and the historical legacy of race/class-based nonconsensual medical experimentation and abuse, these findings should be expected. It is important to recognize that these concerns typically do not extend to the healthcare clinicians and individuals are able to recognize their need for medical care [64].

Justice Involved/Incarceration

Racist policies have resulted in the disproportionate incarceration of Black Americans. This plays a role in racial HIV disparities. The role of the high rates of incarceration of Black men increasing the risk of HIV in Black women has already been noted. Additionally, as noted by Shrage in 2016, a host of other issues increases risk of HIV via incarceration: (1) individuals with increased risk behaviors (e.g., substance abuse, sex workers) end up in jail and prisons resulting in HIV prevalence 3–5x that of the general population; (2) there are few harm reduction protocols (condoms, clean needles, medication-assisted treatment of addictions) in many US correctional facilities, in spite of risky behaviors; and (3) incarceration can limit or interrupt HIV treatment [60].

Once released, linkage to care is vital for HIV-infected individuals to maintain viral suppression, thereby decreasing their risk of infecting sexual partners. Additionally, a history of incarceration can result in limited social and employment opportunities, as well as stigmatization via policies prohibiting offenders from various entitlements (e.g., public housing) [61]. As a result, a Black person with a history of incarceration will face increased risks of unstable housing/homelessness, unemployment, and poverty. For someone with HIV this causes a heightened risk of decreased access to healthcare and medication nonadherence. These structural disparities can also put someone at increased risk for HIV infection.

Religion and Spirituality

In the United States the Black church is foundational and centering for the Black community, providing a refuge from the pervasive anti-Black racism in the United States. Black American churches have been front and center in the struggle for Black civil rights. However, the non-affirming attitudes of some Black churches on sexuality and homosexuality have complicated their role in ending HIV epidemic [65, 66].

Systemic literature reviews have shown that religious involvement and spirituality were more often associated with better HIV clinical outcomes based on biomarkers, morbidity, and mortality. However, some studies found negative associations [67, 68].

Studies in Black Americans have also shown positive religious coping significantly predicted medication adherence [69]. Studies have also shown mixed results with Black MSM regarding the role of religion and spirituality in HIV prevention and outcomes, with both positive and negative effects [70, 71]. Further research is needed to elucidate what aspects of religion and spirituality are effective in improving HIV prevention and outcomes.

Rates of HIV/AIDS among Black Americans are epidemic because of institutional racism and bias. The same issues have resulted in a long history of a host of health disparities, most recently evidenced by the COVID-19 pandemic. Addressing these health disparities will require a multi-pronged approach addressing issues of anti-Black racism, poverty, segregation, education and employment inequities, anti-gay bias/homophobia, anti-trans bias/transphobia, clinician bias, and the lack of diversity among healthcare clinicians. Although this seems like an overwhelming task, we have seen a decrease in rates of new HIV infections for many categories of Black Americans by creating culturally appropriate programs and empowering members of the community to develop interventions consistent with their beliefs and needs.

Men Who Have Sex with Men (MSM)

Human immunodeficiency virus (HIV) infection and other sexually transmitted infections (STIs) disproportionately affect men who have sex with men (MSM) [72]. Since the HIV epidemic began in the early 1980s, it has been evident that specific risk behaviors and psychiatric conditions play a central role in HIV transmission. Because of this, HIV has become a condition of mostly vulnerable populations. We will review the risk factors, barriers, and preventive measures in the MSM HIV population, including how psychiatric conditions can affect the course of the disease, primarily through poor adherence to antiretroviral treatment (ART).

Risk Factors and Demographics

Risk factors for HIV infection in the MSM community may include number of sex partners, self-reported condom use, and rates of substance or party-and-play drug use. While informative, they are insufficient to explain the disproportionate rates of

HIV spread in the community. Investigations involving molecular epidemiology of HIV have proven to be more informative of the different dynamics of transmission. Essential biological factors include the high transmission efficiency of receptive anal intercourse—*at an estimated 1.4% per act probability (95% CI 0.2–2.5%) and the very high per partner probability of 40.4% (95% CI 6.0–74.9), roughly 18-fold higher than for vaginal intercourse* [73]—and that men can be both receptive (high risk for acquisition) and insertive (high risk for transmission) partners in anal sex with other men [73].

HIV disproportionately affects specific communities within the MSM population, and the CDC has created a surveillance system to monitor spread within different demographics, age ranges, and geographical areas. The latest results have shown that among MSM with new HIV diagnosis, 35% were black and 19% were Hispanic. When looking at age range between 13 and 29, the number of new HIV infections in Blacks was 1.6 times the number in Whites and 2.3 times the number in Hispanics [74]. Black MSM are disproportionately affected by HIV, and prevalence has been found to be as high as 46% in some cities in the United States [74]. Factors that influence higher rates of transmission within the black MSM community include higher prevalence of STIs and lower knowledge of HIV status. Persons who have been previously diagnosed with HIV were less likely to be on ART and more likely to have partners of the same race [75, 76]. Other hypotheses have been disproven as a reason for these trends, including that black MSM have higher numbers of sex partners and prevalence of unprotected anal intercourse [77]. Although HIV diagnosis and treatment can suppress HIV transmission at the interpersonal and population level, black MSM are least likely to be diagnosed with HIV or to be in care compared with other MSM [73].

Finally, stigma targeting MSM, which occurs when individuals possess a socially devalued identity, has been shown to affect provision of HIV prevention, treatment, and care services. It can operate at several levels affecting health, including internalized (e.g., negative self-view), interpersonal (e.g., discrimination), and structural (e.g., legislation) [78, 79]. Stigma can restrict MSM's public visibility and keep them hidden from prevention efforts due to fear of discrimination. It can also correlate with individual behaviors, placing MSM at heightened risk of infection [73].

Psychiatric Disorders in MSM Living with HIV

To understand the relationship between psychiatric disorders and the MSM population living with HIV, a biopsychosocial approach is highly recommended. Psychiatric disorders in this population, such as depressive disorders, PTSD, and anxiety disorders, are associated with decreased quality of life, decreased adherence to care, faster disease progression, and increased mortality [80]. Studies suggest that psychiatric comorbidities and multimorbidities may affect up to 50% [81] of the MSM population living with HIV. The etiology of this relation is multifactorial and complicated by the direct neurological effects of HIV causing psychiatric manifestations, underlying psychiatric illnesses placing those at risk of HIV acquisition,

transmission and disease progression, the psychosocial burden and stigma of living with HIV in marginalized groups (e.g., MSM, prisoners, patients with severe psychiatric illnesses, and racial/ethnic minorities) leading to trauma, or simply the psychiatric side effects of ARTs [82].

Psychiatric disorders should be viewed as vectors of HIV infections on account of their effects on high risk-taking and self-destructive behavior. As vectors for HIV, active psychiatric symptoms can lead to difficulties in negotiating safer behaviors (e.g., use of condoms), cause the increased use of substances (including injection drugs) to ameliorate psychological distress, and decrease treatment adherence leading to disease progression. Additionally, HIV infection can cause direct damage to subcortical brain areas and chronic stress leading to persistent inflammatory states which have been linked to major depressive disorder, general anxiety disorder, fatigue, insomnia, and suicide [5, 80–82].

This cyclical relation between psychiatric disorders and the MSM population living with HIV can be interrupted by the intervention of mental health clinicians addressing the need for improvement in psychosocial support networks and by the assessment and treatment of psychiatric disorders through psychotherapy (e.g., cognitive behavioral therapy, psychodynamic psychotherapy) or psychopharmacology, both of which have been linked to improved adherence to ART [5].

"Party-and-Play" Drugs in the MSM Community

The use of "party-and-play" (PNP) drugs in MSM, and the wider LGBT community, has become widely spread as part of the nightlife scene. PNP drugs, party drugs, "chemsex" or "chemfun," and "High & Horny" (H&H) are terms that describe a phenomenon, mostly associated with the MSM community which involves the use of drugs to enhance a social or sexual experience. The drugs commonly associated with PNP are crystal methamphetamine, cathinones (mephedrone, 3MMC, 4MMC), and gamma-hydroxybutyrate/gamma-butyrolactone (also known as GHB/GBL, G or Gina), but other drugs are often involved, such as sildenafil, alcohol, ketamine, cocaine, and amyl/alkyl nitrates (poppers).

Studies comparing party-and-play drug users versus non-users reported benefits in social connectedness and community building. Persons using were also likely to score higher levels of resilience and lower levels of perceived HIV-related stigma [83]. Nonetheless, the physical and mental health risks that users face are paramount. The use of PNP drugs has been linked to higher rates of HIV and STIs, accidental overdoses, and the development of substance use disorders [84]. Although not all individuals who use PNP drugs develop issues with abuse or dependence, there are health disparities and other risks noted in MSM with HIV—see Table 15.2.

Studies have also shown that in the MSM community several factors/disparities can lead to the increased use of mood-altering drugs to address these disparities setting up a cycle of depression, anxiety, and ultimately, substance use disorders—see Table 15.3.

Table 15.2 Health disparities and other risk of MSM living with HIV

Substance use disorders	Isolation
STIs	Rejection
Cancer	Anxiety
Cardiovascular disease	Depression
Obesity	Suicide
Bullying	

Based on data from Ref. [85]

Table 15.3 Factors/disparities in the MSM community which may lead to use of mood-altering drugs

Discrimination
Bullying
Trauma
Ostracism
Violence
Internalized homophobia

Based on data from Ref. [86]

Preventive Measures: Pre-exposure Prophylaxis (PrEP)

Pre-exposure prophylaxis (PrEP), a biomedical prevention (emtricitabine/tenofovir disoproxil fumarate), was approved by the Food and Drug Administration (FDA) in 2012 for prevention of HIV in high-risk individuals [87–89], demonstrating that it can reduce the risk of HIV infection by as much as 92% [90], but only about 3% of the targeted population have used this prevention method [91]. Emtricitabine/tenofovir alafenamide was approved by the FDA in 2019 for PrEP with similar efficacy [92]. The uptake of PrEP has been low and could be explained by several factors, including a lack of awareness, low perceived risk of HIV acquisition, cost of medication, and shame associated with perceived violations of accepted codes of sexual conduct.

MSM are globally more likely to acquire HIV than the general population, a phenomenon due to biological, behavioral, social, and cultural factors. It is evident that availability of treatment and prevention strategies has decreased the rates of HIV transmission and progression to AIDS, but further efforts must be placed in order to destigmatize, educate, and provide access to medical care in the community. General medical and mental health clinicians caring for MSM must become familiar with the health disparities, sociocultural pressures, behavioral trends, psychological underpinnings, and sequelae noted in the community to develop comprehensive formulations that address the community's health needs.

Transgender Individuals

Transgender medicine has developed a deep lexicon adopted from transgender individuals as well as from scholars of gender and queer studies. It is important to be versed in speaking about aspects of gender when treating transgender patients to best understand their needs and get better insight into their internal life and mental health. Listed below in Table 15.4 are a few commonly used definitions that are far from exhaustive, and terminology is always evolving. As with any patient, if a transgender patient expresses a term you do not understand or uses one you do in a new way, it is always best to clarify with them to avoid misunderstanding.

Table 15.4 Gender definitions

Sex assigned/ registered at birth, sometimes abbreviated to sex	A person's sex, male or female, registered at the time of birth usually based on assessment of a newborn's primary sex characteristics. "Biological sex" is sometimes used but is not preferred as it incorrectly links "biology" to a male or female exclusive binary
Gender identity	Ones' internal sense of one's own gender. Some transgender people identify as male, female, or as mixture of the two (nonbinary). Others identify as a third gender or as an indigenous gender role such as two-spirit, kathoey, hijra, eunuch, or other roles [93, 94]
Gender expression	Ones' external manifestation of gender. This can have masculine, feminine, or neutral aspects
Gender role	The expectations a society places on someone of a given gender. Transgender people often face rejection or discrimination when they do not conform to the gender role they are assigned at birth
Transgender or trans	A broad term encompassing many people whose gender identity does not match their sex registered at birth
Cisgender or cis	Someone whose gender identity matches their sex registered at birth
Gender transition or transition	Taking steps to makes ones' gender expression more closely match ones' gender identity. Social transition is taking steps to change ones' gender expression in social situations such as using a different name or changing the way one dresses. Medical transition is gender transition with addition of hormones and/or surgery
Sexual orientation	The gender of the persons one is physically and/or romantically attracted to. It is not the same as gender identity
Gender incongruence	Feelings of incongruence between ones' gender identity and their sex assigned at birth. This is sometimes broken into two parts: Social incongruence is between ones' gender identity and how others in their culture treat them based on their sex assigned at birth. Physical incongruence is between a person's gender identity and their primary or secondary sex characteristics
Gender dysphoria	The distress one feels about their gender incongruence. The distress should not be automatically equated with the DSM-5/ICD diagnosis of gender dysphoria, which is a much narrower and specific term

Demographics and Introduction to HIV in the Transgender Population

There are an estimated one million transgender individuals in the United States, though some estimates put the number as high as ~1.4 million [95, 96]. Unfortunately, transgender individuals bear an outsized burden of HIV infection compared to the general population. From 2009 to 2014 an estimated 2351 transgender people had a confirmed diagnosis with HIV in the United States, through data tracked by the National HIV Surveillance System and reported to the CDC. Of those, 84% were transgender women, 15% were transgender men, and <1% identified as nonbinary. These numbers are likely an underestimate due to difficulties accurately recording gender identity vs. sex in public health records. Another meta-analysis examining HIV transmission from 2006 to 2017 by Becasen et al. [97] estimated that 14% of transgender women were living with HIV. When broken down by race, an estimated 44% of Black trans woman, 26% of Latinx/Hispanic trans women, and 7% of White trans women were living with HIV. While there is much less information on trans men living with HIV, limited data suggest a higher rate than the general population, with Becasen et al. [97] placing the rate at about 3%.

The reasons for an increased prevalence and incidence of HIV transmission in transgender persons are manifold. Transgender people are often marginalized in society, and so are at increased risk to receive less support from family, face housing and workplace discrimination, and be the targets of transphobic harassment and violence [98]. Thus, they do not have access to the same housing, work opportunity, or medical care that cisgender people do. This further leads to increased rates of homelessness, unemployment, psychological distress, and financial hardship. This then predisposes transgender individuals into more high-risk circumstances for contracting HIV such as substance use, mental illness, avoidance of medical care, and engaging in sex work or survival sex. This compounding of negative risk factors leading to an increase in morbidity and mortality in marginalized populations is referred to as the stigma-sickness slope [99]. It helps to explain the basis for higher prevalence of HIV in transgender individuals and why those with intersecting marginalized identities (such as Black trans women) bear an even higher HIV burden.

Traditionally, the institution of medicine has been a hostile environment for transgender people to exist in, creating further barriers to access care. Basic issues such as medical professionals using the incorrect name and pronouns to refer to a patient can plague just about any interaction with the medical system. Additionally, insurance companies and individual healthcare providers routinely deny care related to a transgender people due to their gender. The 2015 US Transgender Survey (USTS) surveyed 27,715 transgender respondents covering all 50 states, Washington DC, and all US territories [98] and found that 25% of respondents had a problem with medical coverage in the last year. The 2015 US Transgender Survey (USTS) surveyed 27,715 transgender respondents covering all 50 states, Washington DC, and all US territories [98] and found that 25% of respondents had at least one problem with medical coverage in the last year (Table 15.5).

Table 15.5 USTS respondents' negative issues with medical coverage

Negative action or policy	% of respondents who made such a request of their insurer
Denied coverage for transition-related surgery	55%
Covered only some of the surgical care needed for transition; thus, respondent could not get the coverage for the treatment they needed	42%
Denied coverage for transition-related hormone therapy	25%
Covered surgery related to transition, but had no providers in network	21%
Refused to change records to list current name and gender	17%
Denied coverage of care considered "gender specific" because of transgender status	13%
Denied routine healthcare because of transgender status	7%

Table 15.6 USTS respondents' negative experiences with a healthcare provider

Negative experience	% of those who had seen provider in the past year
They had to teach their healthcare provider about transgender people to get appropriate care	24%
A healthcare provider asked them unnecessary or invasive questions about their transgender status that were not related to their reason for visit	15%
A healthcare provider refused to give them transition-related care	8%
They were verbally harassed in a healthcare setting (such as a hospital, office, or clinic)	6%
A healthcare provider used harsh or abusive language when treating them	5%
A healthcare provider refused to give them care not related to transition (such as a physical or care for flu or diabetes)	3%
A healthcare provider was physically rough or abusive when treating them	2%
They were physically attacked by someone during their visit in a healthcare setting (such as a hospital, office, or clinic)	1%
They were sexually assaulted[a] in a healthcare setting (such as a hospital, office, or clinic)	1%

[a]defined as experiencing "unwanted sexual contact (such as fondling, sexual assault, or rape)"

In addition, 33% of respondents had at least one negative experience with an individual healthcare provider within the last year (Table 15.6).

Lack of therapeutic medical settings forces transgender people to go to further lengths to get adequate care, with only 45% able to receive transition-related care within 10 miles of their home and 6% having to travel more than 100 miles to receive care. The obstacles to care and worry of mistreatment lead 23% of respondents to not seek medical care at least once in the last year when they needed to.

From these experiences we can see the barriers transgender people face to access medical care including HIV treatment and prevention. Despite the high rate of HIV

transmission, the Behavioral Risk Factor Surveillance System, the CDC's online health survey system, reported that two-thirds of transgender men and women have never received an HIV test. When care for treatment and prevention of HIV is available, it is rarely designed with transgender people in mind. Only a single early efficacy study of HIV pre-exposure prophylaxis (PrEP) included trans women [100], and subgroup efficacy analysis among trans women was not deemed feasible due to low enrollment and poor adherence [101]. While PrEP enrollment is generally low, at about 5% of those eligible according to a 2018 CDC report [102], the rate of trans women accessing PrEP appears to be even lower [103], and its effectiveness may not be equal to studies done in gay-identified cisgender men. Additionally, interactions between hormone therapy and PrEP have never been ruled out as a reason for its seemingly lower effectiveness in trans women [104].

Barriers to PrEP access for trans people are multifactorial and still understudied as most data from this trans persons remains at survey level. Medical mistrust including actual and perceived transphobia in healthcare settings plays a significant factor in trans people accessing HIV prevention care [105], as do psychosocial factors such as lack of access to health insurance and homelessness. Prioritization of accessing hormone treatment over HIV prevention may also be a factor [105, 106]. Lack of information on PrEP specifically for trans woman and healthcare providers not offering or being not knowledgeable about PrEP is another major barrier, particularly for younger trans women who appear more knowledgeable about PrEP than their older trans women [105–107]. When given information from knowledgeable medical providers, trans women's attitudes toward PrEP were more positive and their likelihood to consider taking it increased [105, 106].

Mental Health in Transgender Persons

Psychiatry has not been traditionally appropriately fully accepting of transgender people. The mainstream psychiatric and psychoanalytic community in the United States for most of the twentieth century enforced a worldview hostile to gay and transgender people. That has taken both subtle and brutal forms: gender and sexual orientation conversion therapy, forced institutionalization of gay and trans people, and support of anti-gay and anti-trans legislation [108]. Earlier versions of the DSM [109, 110] conceptualized transgender identity as a paraphilia or abnormal gender pathology. The DSM-5 only recently reframed the emphasis of pathology to the feelings of gender dysphoria, not the gender identification itself [111]. The ICD 11 plans to go further and move the diagnoses associated with gender dysphoria from the mental health chapter to a new "conditions related to sexual health" chapter [112].

Though mainstream psychiatry has made significant strides in this area, anti-trans psychiatric and religious-based conversion therapy is still practiced in the United States, despite no evidence of effect on changing gender or sexuality [113] and strong evidence of psychological harm [114, 115]. Of the 2015 US Transgender

Survey (USTS) respondents [98] who discussed their gender with a professional counselor, 18% reported a professional at one time tried to stop them from gender transition. Respondents who had a professional try and "stop them from being transgender" were more likely to have, in their lifetime, attempted suicide, run away from home as a youth, experienced homelessness, had experience doing sex work, and were more likely to be in severe psychological distress at the time of the survey.

The USTS [98] assessed psychological distress in all respondents and found that 39% were currently experiencing severe psychological distress, compared to 5% of the US general population. Understanding the stigma-sickness slope as well as the fraught history between psychiatry and the trans community is important to keep in mind when discussing mental healthcare and statistics around transgender people. The higher prevalence of psychiatric disorders stems from psychosocial factors, untreated gender dysphoria, and lack of access to trans-affirming mental health treatment, not from transgender identity.

There is a relative paucity of research into the prevalence of psychiatric disorders in transgender persons. The studies that exist are often inadequately powered and there is frequent selection bias as most only survey transgender individuals accessing medical or mental healthcare. This can make drawing firm conclusions problematic. There does however appear to be consistent evidence that transgender people suffer from higher rates of bipolar disorders, depressive disorders, anxiety disorders, autism spectrum disorder, posttraumatic stress disorder, and substance use disorders [116–119] than the general population. Data for rates of schizophrenia, attention-deficit/hyperactivity disorders, and personality disorders has been mixed or too weak to draw conclusions from.

With large multi-center electronic medical record data bases and better recording of gender identity and expression, larger cohorts can be captured. An observational retrospective cohort study of de-identified electronic medical records from hospital sites in all 50 states examined 10,270 transgender individuals and 53,449,400 control individuals [120]. It found statistically higher lifetime prevalence of any DSM-5 diagnosis (58% vs. 13%) as well as all diagnostic groups and individual psychiatric diagnoses queried covering most DSM-5 diagnoses and including psychotic disorders, eating disorders, ADHD, and all clusters of personality disorder. The most commonly diagnosed psychiatric disorders in the transgender individuals were major depressive disorder (31%) and generalized anxiety disorder (12%). The authors acknowledge the results are likely an overestimate due to over-surveillance of transgender people accessing medical care who frequently require assessment by a psychiatrist or mental health professional before accessing hormone therapy and/or surgery. However, it affirms a need for mental health services of all kinds to be open and available to meet transgender individuals' needs.

The ultimate treatment for gender dysphoria is gender transition. Gender transition, including hormone therapy and surgery, not only improves symptoms of dysphoria but also improves psychiatric symptoms and quality of life [121–123]. There is also evidence that gender transition reduces mental healthcare utilization [124]. There are no psychotropic medications indicated to treat gender dysphoria, and withholding or delaying transition can increase risk for prolonging dysphoria and

psychiatric symptoms. The rates of surgical regret are very low [125–127]. Reasons for regret are most commonly related to poor functional outcome of the surgery, loss of romantic partner, or loss of family support following surgery. Rates of suicide fell from 29.3% to 5.1% following gender-affirming genital surgery [128], though it remained much higher than the general population, 0.15%. Elevated rate of suicide has been a consistent finding across population studies of transgender people [98, 129].

In addition to transition, supportive family can be critical to reducing mental health burden in transgender people. A study by Olsen et al. [130] looking at socially transitioned transgender teens found they had rates of depression and anxiety approaching cis gender teens when their transition was supported by their families, regardless of hormone treatment.

Gender Dysphoria Treatment

Gender transition has many facets and will vary from individual to individual; this section will provide an overview of "medical transition" which includes both hormone therapy and surgery [131]. Knowledge of what medical transition options are available for transgender patients will allow the psychiatric provider to help guide the patient through transition and set expectations when it comes to hormones and surgery.

The World Professional Association for Transgender Health Standards of Care, Version 7 (WPATH SoC7), are the most wildly accepted guidelines for treatment with hormone therapy and surgery [132]. Other professional organizations also provide guidelines largely in line with the WPATH SoC7 [133]. Past models of treatment involved a set pathway which required transgender people to undergo psychiatric evaluation before induction of hormone treatment and a set period of time on hormone therapy before surgery consideration. This made mental health professionals the de facto "gatekeepers" to transgender care. Newer models of hormone prescribing, including the WPATH SoC7, require psychiatric evaluation only if the prescribing clinician feels it necessary after assessment. Other models of presurgical assessment have also been created for surgical evaluation, which emphasize preparedness for surgery and postoperative recovery over determination of DSM5 diagnosis of gender dysphoria and a length of time on hormone therapy as the primary criteria [134, 135].

Patients interested in medical transition should be referred to the appropriate clinicians: surgeons, endocrinologists, or knowledgeable primary care physicians for treatment. Not all patients will seek all medical interventions, and some may seek none. Transgender individuals with HIV should have an undetectable viral load and CD4 count >200 copies/mL prior to surgery to reduce risk of transmission during surgery and to ensure an adequate recovery with minimal complications [136]. Working with HIV-positive patients with mental health and/or substance use issues on HIV medication adherence may be an essential step in preparing them for gender-affirming surgery.

Hormone Therapy

Gender-affirming hormone replacement therapy (HRT) includes medications that modify levels of sex hormones. In feminizing HRT, estrogen is used in combination with an anti-androgen, typically spironolactone (an anti-androgenic potassium-sparing diuretic) in the United States and cyproterone acetate (an anti-androgenic progestin) outside the United States. Estradiol is typically used in oral, transdermal, or weekly subcutaneous injection formulations. Progesterone is not typically used in feminizing HRT and there is a lack of evidence showing improved feminization; however, some transgender women report improved mood, breast growth, and more rapid feminization with the addition of progesterone.

Masculinizing HRT involves the addition of testosterone; no anti-estrogens are needed, and a patient may continue on hormone-based contraceptives while taking testosterone. Testosterone is typically used in daily transdermal patch or gel, every 2 weekly intramuscular injection or every 3- to 4-month implant formulations.

It is important to discuss the goals of hormone therapy with patients to set reasonable expectations for what can be accomplished with HRT. The tables below (Tables 15.7 and 15.8) show typical effects and timelines [137].

While 78% of respondents in the USTS wanted HRT, only 49% were able to receive it [98]. Not being able to access adequate care and medical oversight for prescribing may force patients to get medication outside of medical oversite. This can include using anabolic steroids purchased on the street or mail-order hormones from other countries which may not be safe or well regulated. As an example, ethinyl estradiol is often present in these mail-order estrogen supplements and has a much higher incidence of blood clotting, compared to oral estradiol [138]. As with other types of needle sharing, needle sharing for hormone injection likely increases

Table 15.7 Feminizing hormone therapy

Effect	Expected onset	Expected maximum effect
Body fat redistribution	3–6 months	2–5 years
Decreased muscle mass/strength	3–6 months	1–2 years
Softening of skin, decreased oiliness	3–6 months	Unknown
Decreased libido	1–3 months	1–2 years
Decreased spontaneous erection	1–3 months	3–6 months
Male sexual dysfunction	Variable	Variable
Breast growth	3–6 months	2–3 years
Decreased testicular volume	3–6 months	2–3 years
Decreased sperm production	Variable	Variable
Thinning and slowed facial hair growth	6–12 months	>3 years
Male pattern baldness	No regrowth, loss stops 1–3 months	1–2 years

Table 15.8 Masculinizing hormone therapy

Effect	Expected onset	Expected maximum effect
Body fat redistribution	3–6 months	2–5 years
Increased muscle mass/strength	6–12 months	2–5 years
Skin oiliness/acne	1–6 months	1–2 years
Cessation of menses	2–6 months	n/a
Clitoral enlargement	3–6 months	1–2 years
Vaginal atrophy	3–6 months	1–2 years
Deepened voice	3–12 months	1–2 years
Facial/body hair growth	3–6 months	3–5 years
Scalp hair loss	>12 months	Variable

risk for HIV, though there is little data on these behaviors and their risk for contracting HIV.

Hormone Therapy and ART

Continuing ART with well-controlled HIV and suppressed viral load improves quality of life and general health and reduces HIV transmission to sexual partners in transgender individuals [139]. Many transgender people prioritize HRT over HIV treatment [140, 141]. Studies on attitudes toward HIV care show that trans women have worries about how HIV medications will interact with their HRT regimens [140, 142]. Braun et al. found that 40% of trans women surveyed at a community health clinic in Los Angeles were not taking ART as prescribed due to concerns over drug-drug interactions between HRT and ART [142]. This concern is not unfounded as many HIV medications do have significant drug-drug interactions with HRT.

The following is far from an exhaustive list but will cover groups of medications and their effect on HRT [139]. Elvitegravir-cobicistat and boosted protease inhibitors may increase the levels of testosterone and dose adjustments may be needed. Protease inhibitors boosted with ritonavir as well as non-nucleoside reverse transcriptase inhibitors efavirenz, etravirine, and nevirapine may reduce estrogen levels needing dose adjustment. Non-nucleoside reverse transcriptase inhibitors efavirenz, etravirine, and nevirapine may also reduce testosterone levels needing dose adjustment. Protease inhibitors amprenavir and fosamprenavir should not be used with estrogen-based HRT, or contraception, as estrogen may lower these drugs' blood levels by 20% resulting in loss of viral suppression. Addressing medication concerns directly with transgender patients and keeping open lines of communication between the patient and mental health and HIV providers can allay fears, allow for adequate hormone and HIV monitoring, and ultimately improve health and quality of life.

Feminizing Surgeries

Feminizing gender-affirming surgeries involve increasing the prevalence of feminine primary or secondary sexual characteristics (such as with breast construction or augmentation) and decreasing masculine characteristics (such as reducing the size of a prominent thyroid cartilage with chondrolaryngoplasty).

Current World Professional Association for Transgender Health (WPATH) standards of care require an evaluation and letter of support from a mental health professional (no qualifications are given; however, most insurance companies will only accept letters from licensed master's level or more highly trained clinicians) or letters from two professionals in the case of sterilizing surgeries. See Table 15.9 for the required elements in the letter.

Vaginoplasty is a procedure by which existing masculine genitalia are converted into a neo-vagina. The most common techniques use the penile skin to form the vaginal canal in inversion vaginoplasty or using a piece of intestinal graft in intestinal/sigmoid vaginoplasty. The head of the penis becomes the clitoris and the skin from the scrotum is used to make labia. The testicles are removed as part of the procedure. An orchiectomy may also be done alone and does not preclude someone from seeking vaginoplasty later on. Breast surgery is done using implants or lipofilling.

Facial feminization surgeries aim to reduce masculine facial characteristics and make more feminine facial characteristics more pronounced. They include rhinoplasty; brow, chin, and jaw recontouring; hairline advancement; and thyroid cartilage reduction, among others. These surgeries are not "cosmetic" and show significant effect in improving quality of life and reducing dysphoria and other psychiatric symptoms [143]. There is no standard of care for facial feminization surgeries set by WPATH standards of care, though most insurance policies and surgeons will still require a letter of support from a mental health provider before surgery. A letter of support and results of a decisional capacity assessment should be done, as with breast surgery.

Vocal surgery or glottoplasty may be done to change the pitch and range of the speaking voice which can cause significant distress especially being misgendered in telephone conversation. It is typically done in conjunction with vocal feminization

Table 15.9 WPATH requirements for a letter from a mental health professional supporting feminizing surgeries

1. Persistent well-documented gender dysphoria. In the United States, this requires a diagnosis of gender dysphoria in accordance with the DSM-5
2. Decisional capacity to consent to the sought procedure(s)
3. Age of maturity in the given country
4. If any medical or mental health "concerns" are present, they are "reasonably well controlled"
5. A period of public, full-time social transition for >1 year
6. A length of time >1 year on hormone therapy in the case of vaginoplasty or orchiectomy and a recommended >1 year (though not requirement) in the case of breast surgery

therapy to address speech patterns [144]. As with facial feminization there is no standard of care set by WPATH. A letter of support and decisional capacity assessment should be done as with breast surgery.

As with hormone therapy, access to adequate surgical care is often difficult to come by [USTS]. In the absence of surgical care, some transgender women use industrial silicone as a subcutaneous filler to achieve fuller lips, cheek, breast, and/or body shape [145]. These injections are often administered by non-trained or minimally medically trained individuals. Many complications can arise from this type of body modification, including infection, autoimmune response, calcification/granuloma formation, silicone migration, lung embolus, and chronic pain and dysfunction. In addition, free silicone can contribute to wound dehiscence when attempts are made to remove it or to preform additional surgeries. This type of procedure is not recommended.

Masculinizing Surgeries

Masculinizing gender-affirming surgeries involve increasing the appearance of masculine primary or secondary sexual characteristics (such as the phallus) and decreasing feminine characteristics (such as with breast reduction surgery). As with feminizing surgeries, current WPATH standards of care require an evaluation and letter of support from a mental health professional or letters from two professionals in the case of sterilizing surgeries. See Table 15.10 for required elements for the letter supporting masculinizing surgeries.

Chest masculinization surgery is the most commonly preformed of masculinizing procedures [98]. It is more complex than a simple mastectomy and involves a bilateral mastectomy, nipple grafting, scar placement, and chest wall reconstruction to achieve a more masculine appearing chest.

Masculinizing genital surgeries are more varied than feminizing surgeries, most generally involving a vaginectomy and hysterectomy. Phalloplasty is a multistage procedure to create phallus from skin graft tissue harvested from the radial forearm, anterolateral thigh, abdomen, or other donor site. The graft is attached above the

Table 15.10 WPATH requirements for a letter from a mental health professional supporting masculinizing surgeries

1. Persistent well-documented gender dysphoria. In the United States, this requires a diagnosis of gender dysphoria in accordance with the DSM-5
2. Decisional capacity to consent to the sought procedure(s)
3. Age of maturity in the given country
4. If any medical or mental health "concerns" are present, they are "reasonably well controlled"
5. A period of public, full-time social transition for >1 year
6. A length of time >1 year on hormone therapy in the case of phalloplasty, metoidioplasty, or hysterectomy
7. There is no hormone therapy recommendation in the case of chest masculinization

clitoris. A urethra is created from skin graft through the phallus and surgically connected to the existing urethra. The labia are formed into a scrotum and testicular implants may be placed. Later procedures are needed to shape the phallus and tattoo a more natural skin texture and coloration. After healing, this allows for one to stand while urinating and to have inserted intercourse, although no erection will take place as the phallus is without erectile tissue. An erectile device may be implanted after the surgery has fully healed.

After testosterone therapy, the clitoris generally enlarges into a phallus of 1–2 inches. Metoidioplasty is a procedure to sever the suspensory ligament of the clitoris which allows the phallus to extend farther. The urethra can also be advanced to the tip of this phallus which may allow one to stand to urinate after the procedure, and testicular implants may also be placed. Insertive intercourse is generally still not possible after metoidioplasty. Metoidioplasty may be done alone or as the first stage of a phalloplasty. Hysterectomy with or without oophorectomy or vaginectomy may also be done alone. Facial masculinization procedures are rarely done in the United States. If sought, a letter of support and capacity assessment should be done as with chest masculinization surgery.

Psychotropic Medications and Hormone Therapy Considerations

The data for pharmacologic interactions in transgender people taking HRT remains understudied. As stated above the treatment of gender dysphoria with hormone therapy typically results in improved psychiatric outcomes. There are some considerations when prescribing psychiatric medications to transgender patients taking HRT that we can infer from studies in other populations.

Luckily, there are few consequential drug-drug interactions between HRT and common psychotropic medications. Regular testosterone and estrogen blood levels as part of routine care allow adjustments to be made relatively quickly should a DDI interaction occur. Estradiol is metabolized hepatically primarily by CYP1A2 and 3A4; however, there are many other CYP enzymes (2C9, 2C19, 2C8, 1A2, and 1B1) involved in further breakdown of active metabolites [146, 147]. Testosterone cypionate is metabolized hepatically as well, primarily by CYP3A4. Spironolactone is metabolized rapidly by the liver by non-cytochrome enzymes into several active metabolites. These metabolites are then further metabolized by several cytochrome enzymes, predominantly 3A4 [148].

Testosterone and Mood Stability

Most patients will report emotional changes when starting on hormone replacement therapy, but as shown above they are greatly outweighed by the emotional benefits of HRT in treating gender dysphoria. There is a persistent myth that

testosterone-based hormone replacement therapy can destabilize bipolar disorder or induce mania and aggression in transgender men. There are inadequate studies in transgender men and nonbinary individuals taking testosterone to draw any conclusions at this time. Most assumptions are derived from animal studies or cisgender women abusing testosterone for body building purposes [149]. Cisgender men with hypogonadism represent a much better studied group of people taking testosterone and would have a more consistent testosterone level to a transgender man on HRT than a cisgender woman abusing anabolic steroids. A blinded prospective study of 705 cisgender men with testosterone deficiency showed no episodes of mania [150]. Neither the Endocrine Society in the United States of America nor the British Society for Sexual Medicine mentions bipolar disorder as a risk factor for prescribing testosterone in cisgender men with low testosterone [151, 152]. As with the addition of any new medication to a regimen in someone with bipolar disorder, closer monitoring of mood should be continued when starting HRT. However, the presence of bipolar disorder or concern for mood destabilization should not be a reason to decline hormone therapy to transgender individuals seeking HRT.

Mood Stabilizers That May Increase Testosterone Production

Valproate and oxcarbazepine are anticonvulsant agents most commonly prescribed in psychiatry to treat bipolar disorder. It has long been known that valproate increases rates of polycystic ovarian syndrome in cisgender women and both of these agents carry a risk for increasing testosterone levels in both cisgender men and cisgender women [153, 154]. Not enough research has been done to determine how HRT impacts these rates in transgender individuals, but it can be reasonably assumed that a similar increase in testosterone would be present. Valproate and oxcarbazepine may have detrimental effects to transgender women and nonbinary individuals attempting to feminize with estrogen-based HRT. Of additional concern is dose-dependent hair loss with valproate [155]. These side effects may lead to reduced medication adherence if not adequately addressed by the clinician.

Lithium and Spironolactone

Lithium is a mood stabilizer prescribed most frequently in bipolar disorder. There may be some concern for increased blood lithium levels in transgender women taking spironolactone for androgen suppression. Studies have shown small increases in blood lithium concentration with co-administration of spironolactone; however, this may not rise to clinical significance [156]. Alopecia is common among long-term lithium users with 12–19% reporting this [155]. Medication-induced alopecia should be screened for and addressed by clinicians, as its presence may contribute to medication nonadherence.

Anti-epileptic Mood Stabilizers and Estrogen

Carbamazepine, oxcarbazepine, and topiramate are anticonvulsant mood stabilizers known to induce CYP3A4 and through that mechanism may reduce serum levels of oral contraceptives [157]. There are no studies examining how these agents may affect HRT in transgender individuals. Care should be taken in co-administering these medications in transgender individuals taking estrogen which can include trans women, nonbinary individuals taking estrogen as part of HRT, or transgender men and nonbinary individual taking oral contraception for purposes of birth control.

Lamotrigine is an anticonvulsant mood stabilizer whose major route of elimination is by conjugation with glucuronic acid. Oral estrogen-based contraceptives induce glucuronidation and can reduce lamotrigine serum levels by up to 50% [157]. Again, there are no studies examining how these agents may affect HRT in transgender individuals. When prescribing lamotrigine to an individual taking estrogen-based HRT, dose adjustments may be needed.

Antipsychotics and Prolactin

Hyperprolactinemia is a well-documented side effect of dopamine blocking antipsychotic medications, most notably risperidone and paliperidone among second-generation agents, as well as high-potency first-generation antipsychotics such as haloperidol [158]. This can cause distressing galactorrhea or breast tenderness which can make chest binding difficulty in transgender men. Hyperprolactinemia can also cause unwanted breast tissue growth following chest masculinization surgery where some breast tissue may remain, unlike in a radical mastectomy for breast cancer.

Older HIV-Positive MSM

MSM continue to constitute a significant population of older adults becoming infected or living with HIV, accounting for 66% of new HIV infections in adults 50 years of age or older [159]. From a psychiatric perspective, MSM share many of the concerns of older adults living with HIV, but face additional challenges related to sexual orientation stigmatization, ageism within gay male communities, and the devastating effects of the AIDS epidemic on social networks. They are also a diverse population of adults differing by race ethnicity, socioeconomic status, access to healthcare, medical comorbidities, and time of initial infection relative to the introduction of ART.

This is a population at significant risk for psychiatric illness. Rates of depressive disorder, PTSD, substance use, and suicidal behavior are elevated in older

HIV-positive gay men compared with older HIV-negative gay men [160, 161]. For older HIV-positive MSM, several factors increase the risk of psychological distress, including salience of identity around HIV status, personal history of discrimination from medical clinicians around HIV status, internalized homophobia, and time since initial HIV infection [162–164].

Age among HIV-positive MSM has variable effects on mental health reflecting such factors as availability of social support, the development of coping skills, access to healthcare, and financial security. With respect to advantages that support physical and psychosocial well-being, older compared with younger HIV-positive MSM are more likely to have access to health benefits and to benefit from extant social support in ameliorating loneliness and isolation and are less likely to misuse alcohol and other substances [165–167]. Those who came of age during the early decades of AIDS and were involved in AIDS activism may also benefit from a post-traumatic psychological growth and acquired resiliency independent of lingering sadness, unresolved grief, and loss of perceived life purpose [168].

Older age in HIV-positive MSM, however, is also associated with psychosocial disadvantage. Compared with younger HIV-positive MSM, older MSM have more limited social support networks and heightened concerns about relying on institutional sources of care and related risks of sexual orientation discrimination. They are more likely to contend with social isolation and loneliness arising from multiple losses due to AIDS, a greater likelihood of living alone, and estrangement from social communities comprising young adult gay men [164]. This is of particular public health concern as loneliness in older HIV-positive adults is associated with depressed mood, decreased health-related quality of life, and substance use [169].

Age is a proxy marker for time since initial HIV infection and whether this occurred before or after the introduction of ART; both factors influence mental health in older HIV-positive MSM [164, 170]. Those infected early in the epidemic lived with the trauma of multiple bereavements, the existential threat of their own mortality, toxicities from early HIV medications, emergent comorbid medical conditions, and the derailment of careers and relationships. Hardships that occurred early in the epidemic may be too difficult to overcome despite admonitions to "fight on and relish life" [164]. Although older MSM infected after the introduction of ART are more likely to benefit from an improved HIV prognosis and decreased stigmatization of HIV and homosexuality, they may also at increased risk to experience shame and guilt about their seroconversion with some feeling that they "should have known better" [170].

Older HIV-positive MSM have been challenged by the more recent global health threat of the COVID-19 pandemic. A survey of older HIV-positive adults, predominantly MSM, during the early months of the pandemic found widespread concerns about becoming COVID-19 infected and self-reported increased use of alcohol, marijuana, and other substances; a quarter of respondents had missed a dose of their HIV medication [171]. While COVID-19-related social distancing undermines the mental health of many adults, its effects on an already psychosocially burdened population of isolated older HIV-positive MSM may be accentuated and need further study. With these considerations in mind, clinicians working with older HIV-positive MSM should assess the issues in Table 15.11.

Table 15.11 Clinical issues for assessment with working with older HIV-positive MSM

Developmental history	What are the patient's lifetime experiences of trauma and stigmatization, bullying, and discrimination related to sexual orientation? How have patients been affected by these adversities?
History during early years of HIV pandemic	What losses were experienced? What change in life plans did HIV cause?
Concerns about aging with HIV	What are the patient's concerns about growing older, e.g., availability of caregivers and caregiving resources, financial worries, apprehension about sexual orientation discrimination by care providers or institutions, feelings about current sexuality, and experiences of loneliness?
Social support	What are the opportunities and resources in a patient's life that could expand his social network?

Conclusion

HIV has infected and affected different communities in differing ways. In the process it has exposed the ongoing issues with healthcare disparities brought about by structural bias and institutional racism. The HIV pandemic has also been witness to the resilience and strengths in various communities. Data has shown that when the unique needs of specific communities are considered, treatment outcomes improve, and the rate of new infections can decrease. It is important for psychiatrists and other mental health clinicians to be aware of the biopsychosociocultural context HIV in various communities in order to address the myriad of issues being faced. Providing such culturally appropriate services as well as diversifying the healthcare workforce will also be necessary to attempt to end the HIV pandemic.

Multiple Choice Questions

1. Recommendations for diagnostic disclosure to a child include all of the below, EXCEPT:

   A. Include parent/caregivers at the time of disclosure of diagnosis to an adolescent if safety is not an issue.
   B. If the family of a perinatally infected child is not ready and the adolescent is sexually active, the clinician should disclose to the adolescent their HIV status—KEY.
   C. Provide support to parents and the child/adolescent, reminding them that disclosure is not a one-time event.
   D. Ask the child/adolescent to tell you what he or she has learned about the virus.
   E. Assess changes in emotional well-being after disclosure and provide appropriate interventions.

   Answer: B

2. Older age compared with younger age among HIV-positive MSM is associated with which of the following psychosocial or medical advantage?

   A. Larger social networks
   B. Greater access to health benefits
   C. Greater social acceptance within the gay male community
   D. Decreased likelihood of living alone
   E. Less lifetime trauma

   Answer: B

3. The following can affect medication adherence negatively in women with HIV, except:

   A. Inter-partner violence
   B. Substance use
   C. Fear of exposure
   D. Depression
   E. Acceptance

   Answer: E

4. Transgender people are at higher risk for contracting HIV for which of the following reasons?

   A. Inherent increased rates of mental illness in transgender people
   B. Higher rates of risky sex work
   C. Poor HIV medical literacy and general education
   D. Transgender people are more concentrated in cities
   E. Intersecting factors of stigma

   Answer: E

5. Risks factors that explain why Black MSM are disproportionately affected by HIV infection when compared to the larger MSM community include all of the following except:

   A. Internalized stigma
   B. Higher rates of STIs
   C. High transmission efficiency of receptive anal intercourse
   D. Higher numbers of sex partners
   E. Institutionalized racism

   Answer: D

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Chapter 16
Principles of HIV Treatment

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Introduction

HIV was identified in 1983 [1, 2], but it was not until 1987 that the first drug, azidothymidine (AZT), was approved for the treatment of AIDS. Although AZT showed initial promising results, it quickly became clear that the virus would become resistant to this medication in monotherapy and that illness would still progress. Furthermore, it was poorly tolerated, with significant side effects, including bone marrow suppression (most importantly anemia), nausea, insomnia, and headaches [3]. For the duration of the following decade, the available antiretrovirals were limited to nucleoside/nucleotide reverse transcriptase inhibitors (NRTIs), with limited efficacy.

Treatment was revolutionized in 1995 with the introduction of drugs with different mechanisms of action – protease inhibitors (PIs) and non-nucleoside reverse

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transcriptase inhibitors (NNRTIs) – in association with the report that the combination of three different antiretrovirals led to successful results [4]. These events started the era of highly active antiretroviral therapy (HAART). HAART is comprised of multiple, potent antiretrovirals that allowed for inhibition of viral replication with ensuing immune reconstitution, significantly decreasing HIV-associated mortality and morbidity, and consequently increasing the life expectancy of people living with HIV (PLWH) [5]. However, despite these significant advances, the first medications introduced were poorly tolerated, required multiple daily dosing and a large number of pills, and had significant implications on adherence and quality of life of fragile patients. The following decades focused on developing new ARVs with innovative mechanisms of action, improved pharmacokinetic properties, and better side effect profiles.

Currently, there are seven different classes of antiretrovirals which can be combined to treat HIV infection with the goal of viral suppression. Although still not curable, HIV infection is now a chronic manageable illness. When treatment is initiated as soon as possible after an HIV diagnosis, PLWH have a life expectancy close to that of the general population [6].

HIV Life Cycle

HIV is a retrovirus with a genome comprised of two identical single-stranded RNA molecules [7]. HIV infects cells that have a CD4 receptor on their surface. First, HIV's envelope glycoprotein gp120 attaches to the CD4 cell receptor, allowing for gp120 to also bind to co-receptors (CCR5 and CXCR4). Glycoprotein 41 (gp41) is then inserted into the host cell, with subsequent fusion of the HIV viral envelope with the cell membrane and release of viral content into the cytoplasm. The enzyme *reverse transcriptase* then converts viral RNA into viral DNA, which is transported into the nucleus and inserted into the host DNA by the viral enzyme *integrase*. When the host cell is activated, proviral DNA is transcribed and then translated into viral proteins which are processed by viral *protease*. New virions are then assembled and released, destroying the host cell, and proceeding to infect new CD4+ cells. The HIV life cycle is summarized in Fig. 16.1. Currently available antiretrovirals inhibit several of these steps and are grouped into seven different classes, according to their mechanism of action:

1. Nucleoside/nucleotide reverse transcriptase inhibitors (NRTIs)
2. Non-nucleoside reverse transcriptase inhibitors (NNRTIs)
3. Integrase strand transfer inhibitors (INSTIs)
4. Protease inhibitors (PIs)
5. CCR5 antagonists
6. Post-attachment inhibitors
7. Fusion inhibitors

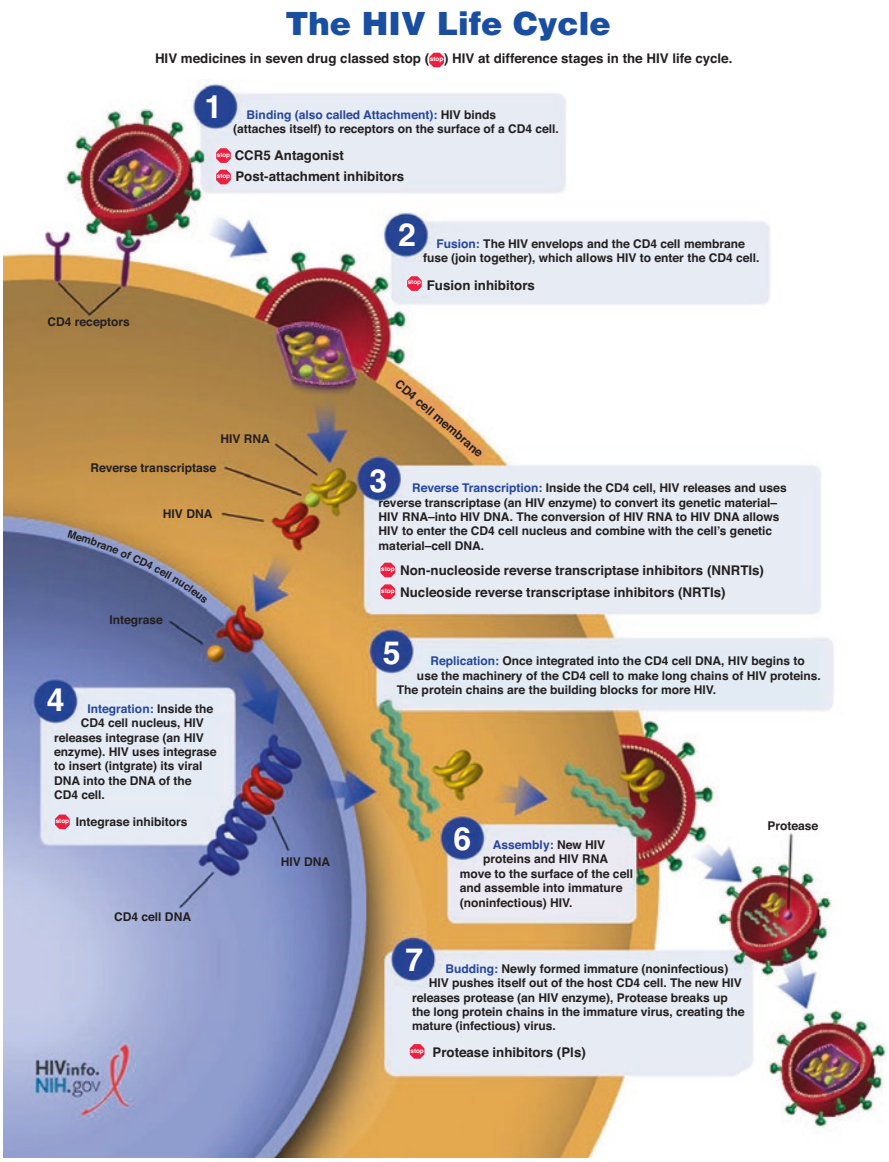

Fig. 16.1 HIV life cycle. (Permission granted by the NIH Office of AIDS Research, HIVinfo.nih.gov)

Considerations of Antiretrovirals

Nucleoside/Nucleotide Reverse Transcriptase Inhibitors (NRTIs)

Nucleoside/nucleotide reverse transcriptase inhibitors, or NRTIs, serve as the backbone for nearly all antiretroviral therapy (ART) regimens. In their active form, NRTIs inhibit reverse transcriptase, terminating DNA chain elongation. They are active against both HIV-1 and HIV-2, and some NRTIs also have activity against hepatitis B virus (HBV). There are relatively few drug-drug interactions with this class. Adverse events usually arise from mitochondrial toxicity and manifest as neuropathy, lipoatrophy, hepatic steatosis, and lactic acidosis. The most commonly used NRTIs include tenofovir disoproxil fumarate (TDF), tenofovir alafenamide (TAF), lamivudine (3TC), emtricitabine (FTC), and abacavir (ABC).

Tenofovir Disoproxil Fumarate

Tenofovir disoproxil fumarate (TDF) was approved for antiretroviral therapy (ART) by the United States (US) Food and Drug Administration (FDA) in 2001 for ART and, when used in combination with emtricitabine, is recommended as part of first-line treatment for patients newly diagnosed with HIV. In plasma, TDF is quickly converted to its active drug form, tenofovir diphosphate (TFV-DP). TDF comes in a fixed-dose combination with emtricitabine, known as TDF/FTC, which is also FDA-approved for use as pre-exposure prophylaxis (PrEP). TDF also comes in a fixed-dose combination with lamivudine, TDF/3TC. Combination therapy with emtricitabine is generally considered as effective as combination therapy with lamivudine; however, TDF/FTC is more commonly used [8]. TDF is also used as standalone treatment for chronic hepatitis B and is a good option for patients with HIV/HBV coinfection. Drug toxicities to monitor for with TDF include kidney injury and loss of bone mineral density. TDF impacts the kidney through a proximal tubulopathy leading to various clinical manifestations, including proteinuria, glycosuria, hypophosphatemia, acute tubular necrosis, Fanconi's syndrome, and nephrogenic diabetes insipidus. Therefore, TDF should be avoided in patients with a creatinine clearance (CrCl) < 60 mL/min [9]. While studies show that TDF decreases bone mineral density, this is thought to stabilize over time [10]. Although research is ongoing to understand the long-term impact of TDF on bone loss, TDF should be avoided in patients with osteoporosis or other preexisting bone disease.

Tenofovir Alafenamide

Tenofovir alafenamide (TAF) was approved by the US FDA in 2016 and is recommended as part of first-line treatment for patients newly diagnosed with HIV infection. TAF is relatively stable in plasma and is converted to TFV-DP intracellularly,

which leads to lower plasma and higher cellular concentrations of the active drug form. Therefore, TAF is given at a much lower dose than TDF. TAF is also an option in patients with HIV/HBV coinfection. Studies have shown that TAF has much less renal and bone toxicity than TDF and has been approved in patients with a CrCl >30 mL/min. However, compared to TDF, studies have shown that patients on TAF have higher LDL cholesterol and triglyceride levels [11]. Some studies suggest greater weight gain in patients on TAF but more evidence is needed to substantiate this finding [12].

Lamivudine and Emtricitabine

Lamivudine (3TC) and emtricitabine (FTC) were approved by the US FDA for ART in 1995 and 2003, respectively, and are considered interchangeable for HIV treatment due to very similar molecular structures. For this same reason, they should never be given together as combination treatment for ART. Along with TDF, TAF, and ABC, either 3TC or FTC make up the NRTI backbone for all first-line ART regimens. More recent studies have shown that 3TC co-formulated with dolutegravir (DTG/3TC) is an effective first-line therapy in certain clinical situations given comparable outcomes when compared to three-drug regimens [13].

Emtricitabine is commonly co-formulated with tenofovir alafenamide (TAF/FTC), tenofovir disoproxil fumarate (TDF/FTC), and other INSTIs. Both lamivudine and emtricitabine have activity against HBV; however, each drug is insufficient as monotherapy and if given alone increases the risk of hepatitis B resistance. If patients with chronic HBV/HIV coinfection on either 3TC or FTC cannot also be treated with tenofovir, another NRTI with activity against hepatitis B should be added. Upon discontinuation of either 3TC or FTC, patients are at risk for severe hepatitis B exacerbation and should be monitored. There is a very low risk of pancreatitis in patients on 3TC and a risk of skin hyperpigmentation of the palms and soles with FTC. However, both are generally very well tolerated.

Abacavir

Abacavir sulfate (ABC) was approved by the US FDA in 1998 for ART and, when used in combination with lamivudine, is recommended as part of first-line treatment for patients newly diagnosed with HIV. Use of abacavir as a fixed-dose combination is contraindicated in patients with chronic hepatitis B and in patients who are HLA-B*5701 positive. HLA-B*5701 is a human leukocyte antigen locus; about half of patients who are HLA-B*5701 positive will have a hypersensitivity reaction to abacavir [14]. Some studies have shown elevated risk of heart disease in patients on abacavir, and there has been a weak association shown with myocardial infarction [15]. Abacavir is relatively contraindicated for persons with an increased cardiovascular risk or known cardiovascular disease.

Zidovudine

Zidovudine (ZDV), also known as azidothymidine (AZT), was the first US FDA-approved treatment for HIV infection, in 1987. Given its inferior potency and many adverse effects including bone marrow suppression, which are much less common with newer NRTIs, AZT is no longer recommended for general use in the USA but can be considered in specific cases where patients are infected with drug-resistant HIV strains.

AZT is still recommended to prevent mother-to-child transmission. It is used intravenously, intrapartum, when mother's HIV viral load is detectable (recommended above 1000 copies/mL and should be considered when VL is between 50 and 999 copies/mL) [16]. It is also used in infants born to mothers with HIV infection, as postexposure prophylaxis, either alone or in combination with other antiretrovirals, depending on the risk of perinatal HIV transmission [16]. Other NRTIs, including *stavudine* (d4T), *didanosine* (ddI), and zalcitabine (ddC), are no longer in use due to toxicity (including headache, malaise, anorexia, nausea, vomiting, severe lactic acidosis, and limb fat loss) and the advancement of newer NRTI treatment options, which are better tolerated (Table 16.1).

Table 16.1 NRTIs

	Dosage (oral)	Most common fixed-dose combination	Adverse effects
Tenofovir disoproxil fumarate (TDF)	300 mg once daily	TDF/FTC	Kidney injury
		TDF/3TC	Loss of bone mineral density
		EFV/TDF/FTC	Lactic acidosis
		RPV/TDF/FTC	
		EVG/c/TDF/FTC	
		DOR/TDF/3TC	
Tenofovir alafenamide (TAF)	25 mg once daily	TAF/FTC	Hyperlipidemia
		BIC/TAF/FTC	
		DRV/c/TAF/FTC	
		EVG/c/TAF/FTC	
		RPV/TAF/FTC	
Lamivudine (3TC)	150 mg twice daily or 300 mg daily	ABC/3TC	Pancreatitis
		DTG/ABC/3TC	
Emtricitabine (FTC)	200 mg daily	TAF/FTC	Skin hyperpigmentation
		TDF/FTC	
Abacavir (ABC)	300 mg twice daily or 600 mg daily	ABC/3TC	Hypersensitivity reaction

Non-nucleoside Reverse Transcriptase Inhibitors (NRTIs)

Non-nucleoside reverse transcriptase inhibitors (NNRTIs) also inhibit reverse transcriptase and prevent the addition of nucleotides to the growing DNA chain with a different target site than NRTIs. They are only active against HIV-1. Currently used first-generation NNRTIs include efavirenz (EFV), while second-generation NNRTIs include rilpivirine (RPV) and doravirine (DOR). Second-generation NNRTIs generally have a higher barrier to resistance than first-generation NNRTIs. Drug-drug interactions can occur with multiple classes of medications, including antidepressants, anxiolytics, opioid dependence treatments, and hormonal therapies. This is especially important given the long half-life of NNRTIs (please see Chap. 17 for more information about drug-drug interactions as well as neuropsychiatric side effects).

Efavirenz

Efavirenz (EFV) is a first-generation NNRTI that was approved by the US FDA in 1998 and is recommended in certain clinical situations when first-line therapy may not be possible. It is beneficial for patients with high pre-treatment viral load and low CD4 counts but has a low barrier to resistance. The main benefit of EFV is once daily dosing. The main adverse effect of EFV is CNS toxicity, which may manifest as vivid dreams, confusion, dizziness, irritability, and suicidal ideation. These can be minimized if EFV is taken without food. Other adverse effects include elevated liver-associated enzymes, QTc prolongation, rash, elevated LDL and TG, and rare ataxia and delirium. Studies have shown that lower dosing of EFV at 400 mg per day instead of 600 mg per day may be associated with fewer discontinuations due to adverse effects [17]. EFV should be avoided in patients with documented psychiatric comorbidities including HIV-associated dementia/major neurocognitive disorder, and/or with moderate to severe liver disease [18]. Prior to initiation of EFV, clinicians must screen for depression and suicidality. It is important to note that the metabolites of EFV can cause a false-positive urine tests for benzodiazepines and cannabinoids.

Rilpivirine

Rilpivirine (RPV) is a second-generation NNRTI which was approved by the US FDA in 2011, and, like EFV, is recommended in certain clinical situations when first-line therapy may not be possible. RPV is only recommended in patients with

baseline HIV RNA < 100,000 copies/mL and CD4 > 200 cells/mm^3, given the higher risk of virologic failure when compared to EFV [19]. It has a higher barrier to resistance than EFV but similar drug-drug interactions. Unlike EFV, it must be taken with food, and its use with protease pump inhibitors is contraindicated. Adverse effects are generally similar to EFV; however, multiple trials have shown that RPV is associated with less dyslipidemia and neuropsychiatric effects than EFV [20, 21].

Doravirine

Doravirine (DOR) is another second-generation NNRTI, approved by the US FDA in 2018. It is also recommended in certain clinical situations when first-line therapy may not be possible and also has higher barrier to resistance than EFV. Studies have shown that DOR is noninferior to EFV- and DRV (darunavir)-based regimens [22, 23]. It also has been shown to have less common neuropsychiatric effects than EFV [24]. DOR is metabolized by the CYP3A system and its use is thus contraindicated with medications that are strong CYP3A inducers.

Other NNRTIs such as nevirapine (NVP) and etravirine (ETR) are generally not recommended for initial treatment. NVP has known risks of serious toxicity, including hepatic necrosis and severe skin reactions like Stevens-Johnson syndrome, and is no longer recommended for use in the USA. ETR is only used in the treatment of drug-resistant virus and should be used with one or two other active drugs. Mild rash is also a known adverse effect of ETR (Table 16.2).

Table 16.2 NNRTIs

	Dosage (oral)	Most common fixed-dose combination	Adverse effects
Efavirenz (EFV)	600 mg daily	EFV/TDF/FTC	Neuropsychiatric effects
		EFV/TDF/3TC	QTc prolongation
			Elevated liver-associated enzymes
			Rash
Rilpivirine (RPV)	25 mg daily	RPV/TAF/FTC	Neuropsychiatric effects
		RPV/TDF/FTC	QTc prolongation
		RPV/DTG	Elevated liver-associated enzymes
Doravirine (DOR)	100 mg daily	DOR/TDF/FTC	Nausea
			Dizziness
			Headache
			Fatigue
			Diarrhea
			Abdominal pain
			Abnormal dreams

Protease Inhibitors (PIs)

In 1995, the US FDA approved the first protease inhibitor (PI), saquinavir, and since then many others have followed. PIs are potent antiretrovirals that have played an important role in the treatment of HIV infection. However, due to substantial side effects and complex drug-drug interactions, their use has decreased over the years. They are no longer considered first-line agents and only a few are used presently, in selected cases. Table 16.3 lists PIs and some selected characteristics, but the majority is described for historic purposes only.

As a class, PIs cause diarrhea, nausea, vomiting, and fatigue, as well as dyslipidemia and lipodystrophy. Insulin resistance is common, as PIs inhibit glucose transporter-4, blocking glucose uptake into adipocytes [34].

Table 16.3 Protease Inhibitors

Protease inhibitor	Dosage (oral)	Selected characteristics
Saquinavir	1000 mg BID, with ritonavir 100 mg BID	The first US FDA-approved PI (1995)
Fosamprenavir	700 mg BID, with ritonavir 100 mg BID	Prodrug of amprenavir; improved pill burden
		Skin rash in up to 33% of patients
Indinavir	800 mg q8H (non-boosted)	May cause nephrolithiasis
Lopinavir	400 mg BID plus ritonavir 100 mg BID or 800 mg plus ritonavir 100 mg daily	Co-formulated with ritonavir
Nelfinavir	1250 mg BID	Must be taken with a meal
		Diarrhea is a frequent side effect
Tipranavir	500 mg BID, with ritonavir 200 mg BID	Approved for treatment-experienced patients who are infected with HIV-1 strains resistant to more than one PI
Ritonavir	600 mg BID, when used as a single antiretroviral	Poorly tolerated when used as an antiretroviral (nausea, diarrhea, vomiting, abdominal pain)
Atazanavir	300 mg daily, with ritonavir 100 mg daily	Minimal effect on insulin resistance or dyslipidemia
		Requires acidic gastric pH for absorption
		Unconjugated hyperbilirubinemia is common, which may cause jaundice or icterus
Darunavir	Once daily regimen: 800/100 mg (with ritonavir) or 800/150 mg (with cobicistat)	First-line PI
	Twice daily regimen: 600/100 mg BID (with ritonavir)	High genetic barrier to resistance
		More favorable metabolic profile
		May cause rash; use with caution in patients with sulfonamide allergy

Based on data from Refs. [25–34]

Some of the limitations of PIs, including poor oral bioavailability, have been overcome with the introduction of pharmacokinetic enhancers. These drugs are potent inhibitors of CYP 3A4 (main isoenzyme responsible for the metabolism of PIs) and P-glycoprotein (P-gp) and can therefore increase serum levels of co-administered PIs by inhibiting their metabolism. They have allowed for lower pill burden, less frequent dosing, as well as reduced impact of food on bioavailability [35].

In the following section, we discuss the two most recently approved PIs (darunavir and atazanavir). For organizational purposes, pharmacokinetic boosters will also be discussed within this section.

Selected Protease Inhibitors

Darunavir (DRV)

DRV was approved by the US FDA in 2006 for use in combination with a pharmacokinetic enhancer (initially ritonavir, but DRV is now also co-formulated with cobicistat). DRV has the advantage of having a high barrier to resistance and a low rate of treatment-emergent drug resistance [36].

Darunavir is active against both HIV-1 and HIV-2, with high potency, and is the first choice when treatment with PIs is indicated. It has an improved metabolic profile when compared with other PIs, but it can cause rash, diarrhea, nasopharyngitis, and nausea [36]. DRV must be taken with food, and no dosage adjustment for patients with renal insufficiency or mild to moderate hepatic impairment is required. It can be taken once daily in treatment-naïve patients and treatment-experienced patients with no DRV resistance mutations.

Atazanavir (ATV)

ATV was approved by the US FDA in 2003 and is a potent drug when combined with a pharmacokinetic enhancer (either ritonavir or cobicistat). ATV has minimal effect on insulin resistance and lipid concentrations but is associated with higher rates of discontinuation compared with DRV, due to gastrointestinal intolerance and jaundice. ATV commonly causes elevation in unconjugated bilirubin due to competitive inhibition of UGT1A1. Although this laboratory finding is benign, even mild jaundice can be stigmatizing for patients and can lead to discontinuation of this drug [37]. ATV requires acidic gastric pH for dissolution, and therefore antacids, H2-blockers, and proton pump inhibitors should be used with caution as they can impair absorption of ATV [37].

Pharmacokinetic Enhancers

As mentioned earlier, these drugs boost the blood concentrations of other antiretrovirals. They can be used with PIs, but also with elvitegravir, an INSTI.

Ritonavir

Ritonavir is a PI and was originally US FDA-approved in 1996 for the treatment of HIV infection at a dosage of 600 mg twice daily. However, because of significant side effects and drug-drug interactions, it later became used solely as a pharmacokinetic enhancer, at 100 mg once or twice a day (as it is better tolerated at lower doses). Ritonavir has complex pharmacokinetic properties; it is a potent inhibitor of CYP P450 3A4, 2D6, 2C19, 2C8, 2C9, and P-gp, but may also induce the isoenzymes 3A4, 2B6, 1A2, and 2C19 at steady state [35]. Therefore, clinicians should be mindful of potential interaction with other drugs (please see Chap. 17 for more information). Ritonavir may cause gastrointestinal side effects (nausea, vomiting, and diarrhea), metabolic disturbances (dyslipidemia, lipodystrophy, and insulin resistance), as well as prolonged PR interval [35, 38]. Ritonavir can be used to boost the following drugs: darunavir, atazanavir, elvitegravir, lopinavir, fosamprenavir, tipranavir, saquinavir, and indinavir. It must be noted that the latter five drugs are rarely used at the present time.

Cobicistat

Cobicistat was approved by the US FDA in 2012 and is used to enhance the pharmacokinetics of darunavir, atazanavir, and elvitegravir. It is a structural analogue of ritonavir but lacks antiviral activity. It is a more specific inhibitor of CYP 3A4, although it is also a weak inhibitor of CYP 2D6, and it does not affect CYP1A2, 2C9, or 2C19 [35]. Cobicistat 150 mg once daily is comparable to ritonavir 100 mg once daily in effectiveness [35].

Cobicistat is generally well tolerated, but can cause nausea, diarrhea, and vomiting. It is less likely to cause lipodystrophy or insulin resistance compared to ritonavir, but it must be noted that cobicistat is a recently introduced drug and, therefore, more time is needed to appreciate its risk of long-term side effects [38].

Integrase Strand Transfer Inhibitors (INSTIs)

Integrase strand transfer inhibitors (INSTIs) prevent the integration of viral DNA into the host genome. They are active against both HIV-1 and HIV-2. INSTI-based regimens are now generally recommended as part of first-line antiretroviral therapy for patients newly diagnosed with HIV [36]. While they are generally well tolerated, side effects include insomnia, headache, dizziness, and (rarely) depression and/or suicidal ideation in patients with preexisting psychiatric disorders. There is also more weight gain associated with INSTI-based regimens compared to PI- or NNRTI-based regimens [39, 40]. Due to decreased kidney tubular secretion caused by INSTIs, there is sometimes a transient elevation in creatinine. Of note, concentrations of INSTIs may be decreased when taken with polyvalent cation-containing

compounds (e.g., aluminum-, magnesium-, or calcium-containing antacids, calcium supplements). The INSTIs include raltegravir (RAL), elvitegravir (EVG), dolutegravir (DTG), and bictegravir (BIC).

Raltegravir

Raltegravir (RAL) was the first INSTI approved by the US FDA, in 2007. It is recommended as part of first-line therapy for patients who are treatment-naïve, as well as for patients who are treatment-experienced [36]. RAL-based regimens were found to be superior compared to EFV-based regimens [41], as well as commonly used protease inhibitor-based regimens, including DRV/r and ATV/r [42]. Dosing depends on whether the patient is treatment-naïve or virally suppressed. It has a lower barrier to resistance than other INSTIs and boosted PIs. Side effects include an elevated CK signifying potential rhabdomyolysis or myositis, as well as neuropsychiatric side effects (e.g., headache, insomnia, depression, suicidal ideation).

Elvitegravir

Elvitegravir (EVG) was approved by the US FDA in 2012. It is recommended in treatment-naïve patients in certain clinical situations, or in treatment-experienced patients in combination with a protease inhibitor [36]. EVG is metabolized by CYP3A4 enzymes, and thus is sensitive to differences in concentration if administered with a CYP3A4 inducer or inhibitor. Similar to RAL, EVG also has a lower barrier to resistance than DTG and BIC [43]. Adverse effects include nausea, diarrhea, headache, and other neuropsychiatric symptoms. It is frequently associated with drug-drug interactions because it is used with a pharmacokinetic booster (ritonavir or cobicistat). EVG is not recommended during pregnancy due to low drug exposure in the second and third trimester, which may increase the risk of virologic failure and mother-to-child transmission [44, 45].

Dolutegravir

Dolutegravir (DTG) was approved by the US FDA in 2013. It is recommended as first-line therapy for treatment-naïve, as well as in treatment-experienced patients [36]. The combination DTG/3TC was recently included as an option for first-line therapy as it was found to be noninferior to DTG/TDF/FTC, excluding cases with elevated viral loads >500,000 copies/mL [36]. It has a higher barrier to resistance than other INSTIs. Important drug-drug interactions include rifampin, and commonly used antiepileptics. DTG has a higher rate of neuropsychiatric side effects compared to other INSTIs. It should be avoided in pregnant women or women of childbearing potential not using contraception, given studies showing increased incidence of neural tube defects in the fetus [46]. However, it must be noted that

some subsequent studies have suggested this risk may be lower than initially thought.

Bictegravir

Bictegravir (BIC) was approved by the US FDA in 2018 for initial therapy for treatment-naïve patients [36]. It confers a higher barrier to resistance compared to other INSTIs, and was found to be noninferior to DTG in clinical studies [47]. It should not be used in conjunction with rifamycin or St. John's wort, given that BIC is a CYP3A4 substrate. Side effects also include nausea, diarrhea, headache, and rare neuropsychiatric side effects. Because of its similarity to DTG in terms of molecular structure, its use is currently not recommended in pregnancy (Table 16.4).

CCR5 Antagonists

CCR5 co-receptor antagonists block viral entry by binding to the CCR5 co-receptors on the surface of the CD4 cells. Maraviroc is the only member of this class, and its use is indicated in cases of virologic failure and resistance to multiple antiretroviral agents. Because it can only be used in CCR5-tropic viruses, it is recommended, prior to initiation, to test all patients for CCR5 tropism [48, 49].

Table 16.4 INSTIs

	Dosage (oral)	Most common fixed-dose combination	Adverse effects
Raltegravir (RAL)	400 mg twice daily or 1200 mg daily	N/A	Weight gain
			CK elevation
			Severe skin reaction
			Neuropsychiatric side effects
Elvitegravir (EVG)	85 mg daily or 150 mg daily	EVG/c/TAF/FTC	Nausea
		EVG/c/TDF/FTC	Diarrhea
			Neuropsychiatric side effects
Dolutegravir (DTG)	50 mg daily	DTG/ABC/3TC	NTD in fetus; avoid in pregnancy
		DTG/3TC	Neuropsychiatric side effects
		DTG/RPV	
Bictegravir (BIC)	50 mg daily	BIC/TAF/FTC	Nausea
			Diarrhea
			Neuropsychiatric side effects

Maraviroc's recommended dose is 300 mg twice per day (BID). However, because it is metabolized by CYP 3A4, its dosage should be decreased to 150 mg BID when strong CYP3A4 inhibitors are co-administered or increased to 600 mg BID in the presence of strong CYP 3A4 inducers [49].

Maraviroc is generally well tolerated. Nausea and diarrhea are the most common side effects. Because it can cause postural hypotension, patients with known cardiovascular comorbidities, risk factors for postural hypotension, or taking other medications known to cause hypotension need additional monitoring. Hepatic toxicity has also been described and liver-associated enzymes should be monitored. Finally, because the CCR5 receptor is located on some immune cells, patients should be monitored closely for signs or symptoms of other infections while receiving maraviroc [48].

Post-attachment Inhibitors

CD4-directed post-attachment inhibitors are the most recent class of antiretrovirals. Ibalizumab-uiyk, which so far is the only member of this class, binds the domain 2 of the CD4 receptor and interferes with the post-attachment steps required for HIV-1 entry. Its use is indicated for the treatment of HIV-1 infection in heavily treatment-experienced patients with multidrug-resistant HIV-1 infection failing their current antiretroviral regimen [50].

Ibalizumab-uiyk is administered intravenously (IV) as a loading dose of 2000 mg, followed by 800 mg IV every 2 weeks [50]. It is overall well tolerated; most common side effects are mild to moderate in severity and include diarrhea, dizziness, nausea, and rash [51]. Laboratory abnormalities have also been reported, including increased creatinine, bilirubin elevation, leukopenia, and neutropenia [50].

Fusion Inhibitors

Fusion inhibitors block entry of HIV-1 into the cell by binding to the gp41 subunit of the viral envelope glycoprotein and preventing the conformational change required for viral fusion [52, 53]. Enfuvirtide (ENF, T-20) is the first and only member of this class, approved by the US FDA in 2003 for the treatment of HIV-1 infection in combination with other antiretroviral agents in treatment-experienced patients with evidence of virologic failure [54]. The recommended dose of ENF is 90 mg injected subcutaneously twice a day [54]. Resistance occurs rapidly in the absence of a fully suppressive antiretroviral regimen [55]. The most common side effects are site injection reactions, diarrhea, nausea, and fatigue, but have also been shown to increase risk of pneumonia, bleeding diathesis, and neuralgia. Enfuvirtide is rarely used currently.

Treatment Recommendations

Treatment Initiation

Current guidelines from the US Centers for Disease Control and Prevention (CDC) recommend routine HIV testing for all persons age 13–64 [56] in the USA. It is also recommended for persons of any age with evidence of either risk behaviors or symptoms suggestive of HIV infection. After a patient is diagnosed with HIV, ART should be initiated as soon as possible regardless of CD4 count, which has been shown to prevent HIV-associated morbidity and mortality [57, 58]. Multiple studies have established both the individual- and population-level benefits of early initiation of ART. Early initiation, even in patients with acute HIV infection, reduces the risk of HIV transmission to seronegative sexual partners when patients remain virologically suppressed, defined as HIV RNA below 200 copies/mL, a concept known as "treatment as prevention" [59]. Furthermore, the US Department of Health and Human Services (DHHS) recommends rapid initiation of ART, defined as same day of diagnosis or as soon as possible thereafter, to shorten time to linkage to care and time to viral load suppression. This approach has also been endorsed by the International Antiviral Society-USA [60].

Immediate, or early, initiation of ART should only be delayed in rare circumstances for medical reasons, e.g., cryptococcal and tuberculosis meningitis, given concern for immune reconstitution inflammatory syndrome (IRIS) [61]. Per guidelines, ART may be initiated 2–10 weeks after antifungal therapy in cases of cryptococcal meningitis, and 8 weeks after antituberculosis therapy for tuberculosis meningitis. Current guidelines do not recommend the delay of ART initiation due to comorbid psychiatric illness, including substance use disorders.

There are multiple treatment goals that should be established with patients living with HIV. Given that HIV cannot be eradicated by ART, lifelong treatment is meant to reduce morbidity and mortality, establish immune reconstitution and CD4 recovery, sustain viral load suppression, reduce HIV transmission to sexual partners and perinatally, and reduce population-level incidence. In the first 6 months of ART for a newly diagnosed patient, sexual partners should use another form of prevention, such as condoms or pre-exposure prophylaxis. If a patient maintains viral load suppression for at least 6 months, there is scientific consensus that it is not possible to sexually transmit the virus. This is commonly referred to as U=U (Undetectable = Untransmittable). Clinicians must assess each patient's motivation for medication adherence to maintain viral load suppression, and also be mindful of the psychological impact of HIV-related stigma. Patients with medication nonadherence are at risk of acquiring viral resistance with treatment interruptions.

The initial assessment of a patient newly diagnosed with HIV includes laboratory testing to identify comorbidities and to assess immunologic status. Important tests at entry into care include CD4 count, HIV RNA, resistance testing, hepatitis B serologies, hepatitis C screen, basic metabolic panel, complete blood count with differential, liver-associated enzymes, random or fasting lipid profile, and random

or fasting glucose. All patients of childbearing potential should have a pregnancy test, and if not pregnant, should be asked about their plans for pregnancy or if they are sexually active and not using effective contraception.

Standard combination ART includes at least three medications from two or more classes, although recent studies have also explored the efficacy of two-drug regimens. Regimen selection is based on a variety of factors, e.g., baseline CD4 count and viral load, HLA-B*5701 status, comorbidities, cost, convenience and potential pill burden, drug-drug interactions and adverse effects, barrier to resistance, and genotypic resistance mutations, which may be transmitted by a sexual partner. Comorbidities that influence initial selection include tuberculosis, hepatitis B, hepatitis C, cardiovascular disease, hyperlipidemia, renal disease, osteopenia, osteoporosis, psychiatric illness, neurologic disease, and substance use especially on opioid replacement therapy.

Viral load suppression below the assay detection limit (< 50 copies/mL) usually occurs between the first 12 and 24 weeks. Important predictors of viral load suppression include low baseline viral load, high potency ARV regimen, regimen tolerability and convenience, and patient adherence. Patients may experience transient viremia, defined as detectable viral loads below 200 copies/mL, which is considered normal variation if patient returns to undetectable.

First-Line Treatment Regimens

With advancement in the number of effective treatment options since the beginning of the epidemic, the US DHHS recommends multiple initial ART regimens for patients who are treatment-naïve. All first-line regimens include two NRTIs, either ABC/3TC, TDF/FTC, or TAF/FTC, plus an INSTI including BIC, DTG, or RAL. Most recent guidelines also allow for a two-drug regimen, DTG/3TC in cases when ABC, TDF, or TAF cannot be used. Potential initial regimens include:

- BIC/TAF/FTC
- DTG/ABC/3TC (if HLAB*5701 negative; if chronic hepatitis B negative)
- DTG/TDF/FTC or DTG/TAF/FTC
- RAL plus TDF or TAF plus FTC or 3TC
- DTG/3TC
  - Not in patients with HIV RNA > 500,000 copies/mL, coinfection with HBV, or prior to genotype testing

Rapid ART can be initiated prior to genotypic resistance testing and HLAB*5701 testing results, and later modified if needed, with the following regimens:

- DTG with TAF or TDF plus FTC or 3TC
- BIC/TAF/FTC
- DRV/r or DRV/c plus TAF or TDF plus 3TC or FTC

(Note: DRV/r – darunavir boosted with ritonavir; DRV/c – darunavir boosted with cobicistat)

Studies have shown that INSTIs are better tolerated than PIs but have a higher risk of weight gain [62, 63]. Boosted PIs and NNRTIs are recommended in certain clinical situations. While some boosted PI regimens, such as DRV/r, have a higher barrier to resistance, they also have more drug-drug interactions, and most have been found to increase cardiovascular risk [42]. ATV/r does not increase cardiovascular risk to the same degree however has a higher rate of discontinuation, compared to DRV/r, which is why DRV/r is preferred among the PIs [64]. NNRTIs have a lower barrier to resistance and varying degrees of effectiveness and adverse effects. EFV is preferred to RPV. RPV is recommended as initial treatment only if HIV RNA < 100,000 copies/mL and CD4 > 200cells/mm^3. DOR is the newest NNRTI option with better adverse effect profile, but it is mostly used only in patients with treatment-resistant virus.

Due to the preponderance of much better-tolerated treatment options, the following medications are no longer recommended per US DHHS guidelines: indinavir, nelfinavir, stavudine, didanosine, and delavirdine.

Special Considerations

Elderly Patients

In elderly patients, the same principles of ART management apply; however, special attention should be paid to drug-drug interactions due to higher rates of comorbidities, mood disorders, and polypharmacy among this population. Patients should also be monitored for HIV-associated neurocognitive disorder, which increases with aging and may negatively impact adherence.

Substance Use Disorders

Patients living with HIV who also have substance use disorder should be offered ART according to the same guidelines as above. Among people living with HIV, substances such as alcohol, cocaine, methamphetamines, cannabinoids, and club drugs may present significant challenges in management, such as increased risk of hepatotoxicity and drug-drug interactions. Patients should be offered a convenient ART regimen (e.g., once-daily dosing, minimal toxicity) and should be treated concomitantly with substance use treatment (e.g., opioid replacement therapy). There are multiple drug-drug interactions to be aware of with alcohol use disorder and opioid use disorder treatment (please see Chap. 17).

Conclusion

Antiretroviral treatment should be initiated as soon after HIV diagnosis as possible and is now recommended regardless of CD4 count, as it has been shown to prevent mortality, morbidity, as well as HIV transmission. Antiretrovirals target different

steps of HIV's life cycle and are distributed among seven classes, according to their mechanism of action: NRTIs, NNRTIs, PIs, CCR5 antagonists, post-attachment inhibitors, and fusion inhibitors. Current guidelines favor the combination of NRTIs and INSTIs because of their favorable side effect profile, although other drugs can be used in selected cases. Currently available ARVs are better tolerated and are now conveniently available in single-pill combinations – a significant advancement since the early ages of ART. However, despite all these advancements, potential side effects and drug-drug interactions still pose significant challenges to the clinician.

Questions

1. Which of the following statements is true regarding initiation of antiretrovirals (ARVs)?

   (a) ARVs should only be started when the CD4 count falls under 200 cells/mm^3.
   (b) Continuous use of antiretroviral treatment (ART) is not advisable because of long-term side effects.
   (c) Initiation of ART should be deferred in patients newly diagnosed with HIV-1 infection who have CD4 counts above 1000 cells/mm^3.
   (d) ART should be started as soon as possible as it has been shown to decrease mortality and prevent viral transmission.

   Answer: (d)

Antiretrovirals should be started as soon as possible after HIV infection is diagnosed, as early treatment has been shown to decrease HIV-associated morbidity and mortality. Treatment should be started despite the CD4 count (in the past, the initiation of antiretrovirals depended on the CD4 count). In selected situations, initiation of ARVs can be delayed such as when the patient does not feel ready to initiate treatment, or when patient is diagnosed with cryptococcal or tuberculosis meningitis, as there is concern for immune reconstitution inflammatory syndrome.

2. What is the advantage of tenofovir alafenamide (TAF) compared to tenofovir disoproxil fumarate (TDF)?

   (a) TAF can be administered once daily, while TDF requires twice daily administration.
   (b) TAF is associated with higher intracellular concentrations of TFV-DP and is associated with fewer renal side effects.
   (c) TDF is more likely to cause dyslipidemia.
   (d) TAF does not cause weight gain.

   Answer: (b)

TAF is converted intracellularly to its active metabolite, TFV-DP, which leads to lower plasma concentrations of this molecule (in contrast, when TDF is

administered, a large proportion of this drug is converted to TFV-DP extracellularly). For this reason, TAF has a lower incidence of renal and bone toxicity when compared to TDF. However, it must be noted that TAF has been associated with increased lipids and possibly weight gain.

3. Which of the following statements is true regarding pharmacokinetic enhancers?

   (a) Pharmacokinetic enhancers boost the blood concentrations of protease inhibitors by inhibition of the CYP 1A2 isoenzyme.
   (b) Both ritonavir and cobicistat have antiretroviral activity.
   (c) Pharmacokinetic enhancers are only FDA-approved to use with protease inhibitors.
   (d) Cobicistat is a more specific inhibitor of CYP 3A4.

   Answer: (d)

Pharmacokinetic enhancers (ritonavir and cobicistat) are used to boost the blood concentrations of other antiretrovirals by inhibition of CYP 3A4. Ritonavir was initially developed as an antiretroviral but is nowadays only used as a pharmacokinetic enhancer; cobicistat does not have antiretroviral activity and is a more specific inhibitor of CYP 3A4. Cobicistat and ritonavir can be used with protease inhibitors as well as with elvitegravir, an INSTI.

4. Please select the correct option regarding integrase strand transfer inhibitors (INSTIs):

   (a) INSTIs are considered first-line options in the treatment of newly diagnosed HIV-1 infection, in combination with other ARVs.
   (b) INSTIs are generally poorly tolerated but rarely cause neuropsychiatric side effects.
   (c) INSTIs should always be combined with two NRTIs (nucleoside/nucleotide reverse transcriptase inhibitors).
   (d) INSTIs are associated with weight loss.

   Answer: (a)

INSTIs are considered first-line options in the treatment of newly diagnosed HIV-1 infection. These drugs are generally very well tolerated but may cause neuropsychiatric side effects as well as weight gain. The two-drug combination of dolutegravir/lamivudine (DTG/3TC), an INSTI and an NRTI, can be used in selected cases as the initial regimen for HIV-1 infection.

5. Which of the following statements is correct regarding protease inhibitors (PIs)?

   (a) PIs are potent ARVs and are frequently used in first-line regimens.
   (b) Whenever PIs are considered, darunavir is the preferred choice.
   (c) Indinavir is a first-line PI because of its favorable side effect profile.
   (d) Currently used PIs must be taken several times per day because of their poor oral bioavailability.

Answer: (b)

Protease inhibitors are potent antiretrovirals, but because of their side effect profile, they are no longer considered first-line treatment for HIV-1 infection. They are still used in selected cases and darunavir is generally the PI of choice. Indinavir is a poorly tolerated PI and is rarely used nowadays. PIs are currently used in combination with a pharmacokinetic enhancer which allows for lower pill burden, less frequent dosing, as well as reduced impact of food on bioavailability.

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Chapter 17
Antiretrovirals and Psychotropics: Drug Interactions and Complications

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Introduction

In this chapter, we start with a brief overview of significant psychopharmacological issues in managing persons with HIV/AIDS (PWHA) and in selecting psychotropics in general. We then introduce our readers to PWHA and comorbid medical and psychiatric conditions with case vignettes. Each disorder meets the DSM-5 criteria for the diagnoses described in the vignette, and the comorbid psychiatric disorder may benefit from psychotropic treatment in addition to the HIV regimen. For each diagnostic and psychotropic category, we take you through the medication decision-making for both a patient newly diagnosed with HIV, and for a patient on long-term antiretroviral therapy (ART) with antiretrovirals (AVRs). These cases highlight important medication prescribing issues for the treatment of PWHA and comorbid psychiatric disorders, for whom there are indications for antidepressants, antipsychotics, mood stabilizers/antiepileptics, and/or anxiolytics/sedative hypnotics.

This chapter also includes detailed medication tables, since the sample cases cannot fully reflect all of the important prescribing considerations for psychotropics in PWHA. The tables also serve as rapid, consolidated references for the reader, and include general information concerning a drug's mechanism of action, common and serious side effects, adverse drug reactions (ADRs), toxicities, and potential drug interactions. It is important to note that the details and considerations about determining a psychiatric diagnosis and addressing broad treatment approaches to PWHA are not addressed in this chapter, but may be found in other chapters in this textbook.

Brief Review of Drug Interaction Principles and Metabolism

We first briefly review the basics of drug metabolism, drug interactions, and common reasons for side effects and adverse drug reactions (ADRs) before delving into case vignettes. Drug interactions are an important consideration in the care of PWHA and comorbid psychiatric conditions. In a recent Australian national cross-sectional study, drug interactions as a result of polypharmacy were found to occur in nearly one-half of PWHA on ART [1]. Psychotropics may be metabolized via the same enzymes or transporters that metabolize HIV medications, and polypharmacy may have serious clinical implications and magnify side effects and toxicities [2, 3].

In general, drug interactions can be classified into two categories – those that involve *pharmacodynamics* (receptor interactions such as using opiates with benzodiazepines, "what the drug does to the body") and those that involve *pharmacokinetics* (pertaining to drug absorption and metabolism, "what the body does to the drug") [4–6]. Pharmacokinetic interactions are sometimes less intuitive or obvious and may be overlooked more frequently than pharmacodynamic interactions [2, 3]. Pharmacokinetic interactions are those that affect the absorption, distribution,

metabolism, and/or elimination of other drugs [3–7]. Absorption and metabolism interactions are the most common interactions between ART and psychotropics. Absorption is mostly affected by co-timed chelating or binding interactions with antacids [3, 8] since the ART integrase strand inhibitors (INSTIs) can chelate, or bind, with divalent cations contained in antacids and in iron- or calcium-containing products, leading to a reduction in antiretroviral absorption and effectiveness [3, 8, 9].

Metabolic interactions are the most common and relevant to patient care. Metabolic interactions often involve the CYP450 system, an enzyme system designed to eliminate or metabolize drugs [3–7]. Many CYP450 enzymes can be either inhibited (blocked) or induced ("revved-up" metabolism) by medications, by foods, and even by polyaromatic hydrocarbons in cigarette smoke. For example, when a medication *inhibits* a CYP450 enzyme, serum levels of concurrent, yet-to-be metabolized medications will generally *increase*. The potent CYP 3A4 (and other isoenzyme) inhibitor, ritonavir, significantly increases levels of triazolobenzodiazepines, e.g., midazolam, triazolam, and alprazolam, leading to significant and prolonged sedation [3, 10]. It is important to note that metabolic inhibition occurs nearly immediately, and prevents the metabolism of a parent drug, resulting in a buildup of that unmetabolized medication. Interestingly, if the parent drug happens to be an inactive prodrug that must be metabolized into a pharmacologically active drug (e.g., tramadol, which is dependent upon CYP2D6 in order to become an effective pain medication), inhibiting tramadol's metabolism may lead to inadequate treatment of pain. This may lead to the prescriber's concern that the patient may be "drug-seeking" for an opiate, when in fact, a co-administered drug such as ritonavir or paroxetine may be preventing the metabolism of tramadol into its effective, active metabolite [11].

Metabolic induction occurs when a medication "revs up" or "induces" the production of "metabolic factories" in cells, resulting in more rapid metabolism of drugs that are dependent upon that enzyme for metabolism. CYP450 enzymes that are prone to metabolic induction include CYP 3A4, the "workhorse" of metabolism, and 1A2, an important metabolic enzyme for antipsychotics. Perhaps the best example of a drug that is a "pan-inducer" of CYP450 enzymes is carbamazepine, an anticonvulsant and mood stabilizer. Carbamazepine is a potent CYP3A4 inducer that "revs up" RNA synthesis and the production of metabolic enzymes in our bodies. This process can take 7–10 days, so patients may have a therapeutic carbamazepine level in the hospital on day 4, but by day 10, have such an increase in their metabolic efficiency that their previously therapeutic daily dose of carbamazepine (which itself is dependent upon CYP3A4) and any other medication dependent upon CYP3A4 (such as ALL ART protease inhibitors) drop below therapeutic levels. As we will highlight later in the chapter, carbamazepine can reduce the serum levels of ART meds such as bictegravir and protease inhibitors, placing patients at risk for ART failure and viral resistance [3, 12, 13].

In HIV care, pharmacokinetic enhancers or "boosters" (drugs that inhibit metabolism of other drugs, usually at CYP3A4, thereby increasing serum levels and perhaps even CNS penetration) such as ritonavir and cobicistat are used deliberately in

patient care to increase drug levels of other medications also metabolized via 3A4 [3, 14, 15]. Some ART medications such as efavirenz and nevirapine are known to induce CYP3A4, and are also likely to interact by reducing serum levels of meds metabolized via 3A4 [3, 16, 17]. Regimens that do not involve boosters or inducers have a lower risk of drug interactions, but these "boosters" are still in use. Please see Chap. 16, for a detailed discussion of ART medications, as well as regularly updated and reputable HIV drug interaction online resources found in Table 17.1.

HIV and Psychotropics

Antidepressants

This segment will focus on the pharmacologic aspects of treatment of depressive disorders in PWHA, with the understanding that treatment should also involve comprehensive therapeutic interventions, such as psychosocial and psychotherapeutic care, and adherence to ART and general medical and HIV care [18]. General information concerning a drug's mechanism of action, common and serious side effects, adverse reactions, toxicities, and potential drug interactions are presented in Tables 17.2, 17.3, 17.4, and 17.5. HIV-specific considerations that cannot be adequately explained in table format are presented below. Please be sure to review the cases at the end of this section for practical review of treating depression and HIV.

PLWHA have significantly higher rates of depressive disorders than that of the general population. Comorbid depressive disorders are also associated with poorer antiretroviral adherence and HIV treatment outcomes [3]. Antidepressants are effective in treating depressive (and anxiety) disorders in PWHA, and may thereby improve adherence to ART, though they remain under-prescribed in PWHA [19, 20]. Meta-analyses have found that antidepressants are superior to placebo for treating depressive disorders in PWHA, but there is no one class of antidepressant drug that performs better than any other [21, 22]. When selecting antidepressants, balancing patient preference, drug effectiveness, drug-drug interactions, common side effects and adverse drug reactions, while alleviating HIV-related and ART-related symptom, is essential when making shared clinical decisions. After considering the factors for each antidepressant as presented in Table 17.2, the treatment of PWHA

Table 17.1 Select websites for reputable drug interaction information

Sponsor	Website links
University of Liverpool	www.hiv-druginteractions.org
HIV InSite, University of California, San Francisco	http://hivinsite.ucsf.edu/
clinicalinfo.hiv.gov/en/guidelines	www.aidsinfo.nih.gov/guidelines/html/1/adult-and-adolescent-arv/0

[a]All accessed on 29 September 2021

Table 17.2 Antidepressants in HIV care

Psychotropic	Mechanism of action	Side effects/adverse reactions	DDI with ART and potential clinical effect	Notable clinical considerations in HIV care
SSRIs				
SSRI common features	Selective reuptake inhibition of serotonin in presynaptic neurons	Drowsiness Sexual dysfunction Weight gain Insomnia Dizziness Anxiety Headache Potential for: SIADH Withdrawal syndrome Serotonin syndrome Platelet dysfunction Boxed warning: increased risk of suicidality in young people with mental illness	Potent CYP 2D6 inhibitors may increase serum levels of SSRIs	Start at low dose, monitor response, and titrate slowly Co-administration with NSAIDS may result in GI bleeding
Citalopram (Celexa)	Selective reuptake inhibition of serotonin in presynaptic neurons with minimal effect on dopamine and norepinephrine	See "common features" QTc prolongation	Lower potential for clinically meaningful interactions with ART Inhibited or "boosted" by "pan-inhibitor" PIs like ritonavir Potential for arrhythmia in doses over 60 mg if inhibited or "boosted" by "pan-inhibitor" PIs like ritonavir	Keep dosage at or below maximum recommended dose of 40 mg/day; consider lower doses if on CYP 2D6 inhibitor: Ritonavir RIT/lopinavir Efavirenz Max recommended daily dose for individuals > 60 years old is 20 mg/day

(continued)

Table 17.2 (continued)

Psychotropic	Mechanism of action	Side effects/adverse reactions	DDI with ART and potential clinical effect	Notable clinical considerations in HIV care
Escitalopram (Lexapro)	Selective reuptake inhibition of serotonin in presynaptic neurons with minimal effect on dopamine and norepinephrine	See "common features" QTc prolongation	Lower potential for clinically meaningful interactions with ART Inhibited or "boosted" by "pan-inhibitor" PIs like ritonavir Potential for arrhythmia in doses over 30 mg if inhibited or "boosted" by "pan-inhibitor" PIs like ritonavir	Keep dosage at or below maximum recommended dose of 20 mg/day; consider lower doses if on CYP 2D6 Inhibitor: Ritonavir RIT/lopinavir Efavirenz
Fluoxetine (Prozac)	Selective reuptake inhibition of serotonin in presynaptic neurons with minimal effect on dopamine and norepinephrine	See "common features" Insomnia Anxiety	Very-long-acting active metabolite Potent CYP 2D6 and 2C19 inhibition by fluoxetine may increase serum levels of: Antiarrhythmics Cobicistat (in Stribild) Metoprolol Oxycodone Phenobarbital Phenytoin SSRIs Tramadol Tricyclic antidepressants First-generation antipsychotics	
Fluvoxamine (Luvox)	Selective reuptake inhibition of serotonin in presynaptic neurons with minimal effect on dopamine and norepinephrine	See "common features" Sedation Nausea	Potent CYP 1A2 and 2C19 inhibition by fluvoxamine may increase serum levels of: Caffeine Olanzapine Phenytoin	

Paroxetine (Paxil)	Selective reuptake inhibition of serotonin in presynaptic neurons with minimal effect on dopamine and norepinephrine	See "common features" Sedation Weight gain Most severe withdrawal syndrome, especially in neonates	Potent CYP 2D6 and 2B6 inhibition by paroxetine may increase serum levels of: Antiarrhythmics Bupropion Metoprolol Oxycodone Tramadol Tricyclic antidepressants FGAs Potent CYP pan-inhibitors like ritonavir may increase serum levels of paroxetine	
Sertraline (Zoloft)	Selective reuptake inhibition of serotonin in presynaptic neurons with minimal effect on dopamine and norepinephrine	See "common features" Nausea Diarrhea	Least potential for clinically meaningful interactions with ART Becomes a more potent CYP 2D6 inhibitor at doses >200 mg/day	First line in most cases
SNRIs				
Desvenlafaxine (Pristiq)	Selective reuptake inhibition of serotonin and norepinephrine with weak effect on dopamine	HTN Weight gain Sexual dysfunction SIADH Boxed warning: increased risk of suicidality in young patients	CYP2D6 inhibition may increase serum levels of metoprolol and other CYP2D6-dependent meds	
Duloxetine (Cymbalta)	Selective reuptake inhibition of serotonin and norepinephrine with weak effect on dopamine	HTN Sexual dysfunction Weight gain SIADH Boxed warning: increased risk of suicidality in young people	CYP2D6 inhibition may increase serum levels of metoprolol and other CYP2D6-dependent meds	

(continued)

Table 17.2 (continued)

Psychotropic	Mechanism of action	Side effects/adverse reactions	DDI with ART and potential clinical effect	Notable clinical considerations in HIV care
Levomilnacipran (Fetzima)	Selective reuptake inhibition of serotonin and norepinephrine	Weight neutral HTN Sexual dysfunction SIADH Boxed warning: increased risk of suicidality in young people	Potent CYP 3A4 inhibitors like PIs may increase serum levels of levomilnacipran	
Milnacipran (Savella)	Selective reuptake inhibition of serotonin and norepinephrine	Weight neutral HTN Sexual dysfunction SIADH Boxed warning: increased risk of suicidality in young people with mental illness	Lower potential for pharmacokinetic interactions with ART	
Venlafaxine (Effexor)	Selective reuptake inhibition of serotonin and norepinephrine with weak effect on dopamine	Potential for: HTN Sexual dysfunction Weight gain SIADH Boxed warning: increased risk of suicidality in young people	Potent CYP pan-inhibitors like ritonavir may increase serum levels of venlafaxine	
Novel antidepressants				
Mirtazapine (Remeron)	Alpha2-adrenergic antagonist; 5-HT2, 5-HT3 receptor antagonist, H1 receptor antagonist	Weight gain Anti-nausea Sedating Boxed warning: increased risk of suicidality in young people		Least potential for clinical interactions with ART

Nefazodone (Serzone)	Reuptake inhibition of serotonin and norepinephrine; inhibition of 5-HT2 and alpha1 receptors	Headache Drowsiness Hepatotoxicity Boxed warning: increased risk of suicidality in young people	Potent CYP 3A4 inhibitors like nefazodone may increase serum levels of: Protease inhibitors Rilpivirine Maraviroc	Brand Serzone not available in the USA
Reboxetine	Primarily selective norepinephrine reuptake inhibitor with some serotonin reuptake inhibition	Boxed warning: increased risk of suicidality in young people	Potent CYP 3A4 inhibitors like PIs may increase and potent CYP 3A4 inducers may decrease serum levels of reboxetine	Not available in the USA
Trazodone (Desyrel)	Inhibits reuptake of serotonin and blocks H1 and alpha1 adrenergic receptors	Sedating, often used as sleep aid Rare priapism Boxed warning: increased risk of suicidality in young people	Potent CYP 3A4 inhibitors like PIs may increase serum levels and potent CYP3A4 inducers may reduce serum levels of trazodone	
Vilazodone (Viibryd)	Selective reuptake inhibition of serotonin and partial agonism of 5-HT1A	Diarrhea Nausea Headache Boxed warning: increased risk of suicidality in young people with mental illness	Potent CYP 3A4 inhibitors like PIs may increase serum levels and potent CYP 3A4 inducers may reduce serum levels of vilazodone	Must take with food for full absorption No data in PWHA
Vortioxetine (Brintellix)	Reuptake inhibition of serotonin, antagonism of 5-HT3, and agonism of 5-HT1A	Nausea Boxed warning: increased risk of suicidality in young people with mental illness	Potent CYP pan-inhibitors like ritonavir may increase serum levels of vortioxetine CYP pan-inducers[a] may affect vortioxetine serum levels	No data in PWHA

(continued)

Table 17.2 (continued)

Psychotropic	Mechanism of action	Side effects/adverse reactions	DDI with ART and potential clinical effect	Notable clinical considerations in HIV care
Tricyclic antidepressants (TCAs)				
TCA Common features	Reuptake inhibition of norepinephrine and serotonin; inhibition of histamine and acetylcholine	Constipation Dry mouth Weight gain Dizziness Drowsiness Toxicities: Arrhythmias Anticholinergic side effects, including delirium SIADH Boxed warning: increased risk of suicidality in young people with mental illness	All protease inhibitors may increase TCA serum levels to toxicity, especially pan-inhibitors CYP pan-inducers[a] may reduce TCA serum levels	Use therapeutic drug monitoring (TDM)
Amitriptyline (Elavil)	Reuptake inhibition of norepinephrine and serotonin; inhibition of histamine and acetylcholine	See "common features"	All protease inhibitors may increase serum levels to toxicity, especially pan-inhibitors CYP pan-inducers[a] may reduce TCA serum levels Active metabolite = nortriptyline	Use therapeutic drug monitoring (TDM)
Clomipramine (Anafranil)	Reuptake inhibition of norepinephrine and serotonin; inhibition of histamine and acetylcholine	See "common features"		Has US FDA indication for OCD

Desipramine (Norpramin)	Greater reuptake inhibition of norepinephrine than serotonin compared to tertiary amines	See “common features”	Least affected by PIs except the pan-inhibitors ritonavir and lopinavir, which may increase serum levels of desipramine	
Doxepin (Adapin, Sinequan)	Reuptake inhibition of norepinephrine and serotonin; inhibition of histamine and acetylcholine	See “common features”		
Imipramine (Tofranil)	Reuptake inhibition of norepinephrine and serotonin; inhibition of histamine and acetylcholine	See “common features”	Active metabolite = desipramine	
Nortriptyline (Pamelor)	Reuptake inhibition of norepinephrine and serotonin; inhibition of histamine and acetylcholine	See “common features”	Least affected by PIs except the pan-inhibitors ritonavir and lopinavir which may increase serum levels of nortriptyline	Therapeutic window = 50–140 ng/dl
Protriptyline (Vivactil)	Reuptake inhibition of norepinephrine and serotonin; inhibition of histamine and acetylcholine	See “common features”	Least affected by PIs except the pan-inhibitors ritonavir and lopinavir which may increase serum levels of protriptyline	
Trimipramine (Surmontil)	Moderate reuptake inhibition of norepinephrine and weak reuptake inhibition of serotonin; inhibition of histamine and acetylcholine	See “common features”		

(continued)

Table 17.2 (continued)

Psychotropic	Mechanism of action	Side effects/adverse reactions	DDI with ART and potential clinical effect	Notable clinical considerations in HIV care
NMDA antagonist				
Esketamine (Spravato)	NMDA receptor antagonist	Derealization Depersonalization Nausea Hypertension Boxed warning: must be monitored for at least 2 hours after administration due to sedation and dissociation risk; abuse potential; increased suicidal risks in adolescents with depression		

Based on data from [83]

Abbreviations: *CYP* cytochrome, *DDIs* drug-drug interactions, *UGT* uridine 52-diphosphate glucuronosyltransferase

[a]Pan-inducers: drugs that induce many if not all CYP P450 enzymes and include barbiturates, carbamazepine, ethanol, phenytoin, and rifamycins

Table 17.3 Antipsychotics in HIV care

Psychotropic	Mechanism of action	Side effects/adverse reactions	DDI with ART and potential clinical effect	Notable clinical considerations in HIV care
First-generation antipsychotics				
Common features of all *Fluphenazine (Prolixin)* *Haloperidol (Haldol)* *Mesoridazine (Serentil)* *Molindone (Moban)* *Perphenazine (Trilafon)* *Thioridazine (Mellaril)*	Postsynaptic D2 receptor antagonism	Increased risk of: Cognitive/motor impairment EPS, NMS, TD Hyperprolactinemia Leukopenia/neutropenia Orthostatic hypotension Greater risk for EPS, dystonia, and TD in PWHA Boxed warning: increased risk of death in elderly patients with dementia-related psychosis	Since these are older drugs, there are fewer data about specific metabolic sites and drug interactions Potent CYP pan-inhibitors like ritonavir and lopinavir may increase serum levels Potent CYP pan-inducers[a] may reduce serum levels Most are potent inhibitors of CYP2D6, and may increase serum levels of drugs dependent on CYP2D6	Consider second-generation antipsychotic as first line
Chlorpromazine (Thorazine)	D2 receptor antagonism	See "common features" Sedation Weight gain Orthostatic hypotension Anticholinergic		
Pimozide (Orap)	D2 receptor antagonism	See "common features" Prolongs QTc	Protease inhibitors may cause arrhythmias when co-administered with CYP3A4-dependent pimozide and are contraindicated	

Table 17.3 (continued)

Psychotropic	Mechanism of action	Side effects/adverse reactions	DDI with ART and potential clinical effect	Notable clinical considerations in HIV care
Second-generation antipsychotics				
Common features	D2 receptor antagonism with additional serotonin receptor (usually 5-HT2A) antagonism	Increased risk of metabolic syndrome (additive with PIs) Risk of: Cognitive impairment EPS, NMS, TD Hyperprolactinemia Leukopenia Neutropenia Orthostatic hypotension Priapism Seizures Many are associated with QTc prolongation risk (exceptions: aripiprazole, lurasidone, olanzapine, cariprazine, brexpiprazole) Boxed warning: increased risk of death in elderly patients with dementia-related psychosis	Most do not interfere with metabolism of other drugs (neither inhibit/induce) Combined treatment with ART increases risk of metabolic syndrome due to additive effects QTc prolongation is additive with drugs like saquinavir and lopinavir/ritonavir	None of the second-generation antipsychotics are approved for treatment of dementia- related psychosis
Amisulpride	D2 and D3 selective antagonism with possible 5-HT7 antagonism	See “common features”		Not available in the USA

Aripiprazole (Abilify)	Partial D2 and 5-HT1A agonism, as well as 5-HT2A antagonism	See "common features" Increased risk of akathisia/EPS	Potent CYP3A4 inhibitors, e.g., *PIs elvitegravir/cobicistat* Potent CYP2D6 inhibitors, e.g., *bupropion*, *diphenhydramine*, *paroxetine*, and *ritonavir*, may increase levels of aripiprazole Potent CYP3A4 inducers, e.g., "*pan-inducers*," *ritonavir*, and *some NNRTIs*, may increase levels of aripiprazole	Aripiprazole dose reduction 50% with: Potent CYP3A4 inhibitors, e.g., *PIs elvitegravir/cobicistat* Potent CYP2D6 inhibitors, e.g., *bupropion*, *diphenhydramine*, *paroxetine*, and *ritonavir* Aripiprazole dose reduction 75% with: *Combined* CYP3A4 and 2D6 inhibitors (and combinations of inhibitors of each), e.g., *ritonavir*, *efavirenz*, and *delavirdine* Aripiprazole dose increase of up to 100% (2×) with: CYP3A4 inducers, e.g., "*pan-inducers*," *ritonavir*, and *some NNRTIs*
Asenapine (Saphris)	D2 receptor and 5-HT2A antagonism	See "common features" QTc prolongation		Not recommended in patients with severe hepatic impairment Reduce paroxetine (CYP2D6 substrate and inhibitor) dose by 50% when co-administered
Blonanserin	D2, D3, and 5-HT2A antagonism	See "common features" High risk of EPS	CYP3A4 inhibitors, such as PIs, may increase levels of blonanserin	Not available in the USA Contraindicated with potent CYP3A4 inhibitors like PIs

(continued)

Table 17.3 (continued)

Psychotropic	Mechanism of action	Side effects/adverse reactions	DDI with ART and potential clinical effect	Notable clinical considerations in HIV care
Brexpiprazole (Rexulti)	Partial D2 and 5-HT1A agonism, as well as 5-HT2A antagonism	See "common features" Increased risk of akathisia	CYP3A4 inhibitors, such as PIs, and CYP2D6 inhibitors may increase levels of brexpiprazole CYP3A4 inducers may decrease levels of brexpiprazole	Brexpiprazole dose reduction 50% with: Potent CYP3A4 inhibitors, e.g., PIs and elvitegravir/cobicistat Potent CYP2D6 inhibitors, e.g., ritonavir, diphenhydramine, bupropion, and paroxetine Brexpiprazole dose reduction 75% with: *Combined* CYP3A4 and 2D6 inhibitors, e.g., ritonavir, efavirenz, and delavirdine Brexpiprazole dose increase of up to 100% (2×) with: CYP3A4 inducers, e.g., "pan-inducers," ritonavir, and some NNRTIs
Cariprazine (Vraylar)	Partial D2 and 5-HT1A agonism, as well as 5-HT2A antagonism	See "common features" Increased risk of akathisia Late-occurring adverse reactions (ADRs) due to long half-life	Co-administration with potent CYP3A4 inducers and "pan-inducers" may significantly lower serum clozapine levels	Monitor patients for several weeks after starting and each dose change Potent CYP3A4 inhibitors: reduce cariprazine dosage 50% Co-administration with potent CYP3A4 inducers and "pan-inducers" *not* recommended, may significantly lower serum clozapine levels

Clozapine (Clozaril)	D2/D4 and 5-HT2A antagonism, with alpha-adrenergic, histaminergic, and cholinergic antagonism	See "common features" Risk of agranulocytosis Cardiac risks: Bradycardia and syncope QTc prolongation Myocarditis/ cardiomyopathy Orthostatic hypotension Seizures Risk of: Anticholinergic toxicity: Caution with narrow angle glaucoma or other anticholinergic drugs Eosinophilia Pulmonary embolism Delirium	Potent CYP1A2 inhibitors increase clozapine serum level Potent CYP3A4 inducers and "pan-inducers" may significantly lower serum clozapine levels cigarette smoke (from tar, not nicotine) induces CYP1A2 and may decrease clozapine levels Synergistic bone marrow suppression if co-administered with treatments for Cytomegalovirus or Herpes Simplex Virus infections Risk of agranulocytosis heightened with carbamazepine	US mandatory registry, biweekly monitoring CBC, ANC x 6 months, monthly thereafter Must reduce clozapine to one-third standard dose with potent CYP1A2 inhibitors Co-administration with potent CYP3A4 inducers and "pan-inducers" *not* recommended Avoid co-administration with carbamazepine Reduce dose 30–50% if patient suddenly stops smoking
Iloperidone (Fanapt)	D2 and 5-HT2 antagonism	See "common features" Significant QTc prolongation	Potent CYP3A4 inducers and "pan-inducers" may reduce serum levels of iloperidone	Consider alternative medication if the patient has additional risk factors for QTc prolongation. Monitor K^+ and Mg^{2+} Not recommended in patients with severe hepatic impairment Potent CYP2D6 or CYP3A4 inhibitors: reduce iloperidone dose by 50%

(continued)

Table 17.3 (continued)

Psychotropic	Mechanism of action	Side effects/adverse reactions	DDI with ART and potential clinical effect	Notable clinical considerations in HIV care
Lurasidone (Latuda)	D2 and 5-HT2A antagonism, partial 5HT1A agonism	See "common features" More weight neutral	Potent CYP3A4 inhibitors may increase serum levels of lurasidone	Contraindicated: co-administration of lurasidone with potent CYP3A4 inhibitors such as protease inhibitors or potent CYP3A4 inducers such as rifampin Moderate inhibitors may be used, but lurasidone dosage should be reduced 50%
Olanzapine (Zyprexa)	D2 and 5-HT2A antagonism, as well as 5HT2C antagonism	See "common features" Sedation Weight gain Anticholinergic	Polyaromatic hydrocarbons in tobacco smoke are inducers of CYP1A2, and may reduce serum levels of olanzapine Potent "pan-inducers" may reduce serum levels of olanzapine Co-administration of fosamprenavir/ritonavir may reduce olanzapine levels	Olanzapine can be reduced by 10% each day until 40% dose reduction in patient who quits smoking
Paliperidone (Invega)	D2 and 5-HT2A antagonism	See "common features" QTc prolongation Gastrointestinal narrowing Dysphagia	Major active metabolite of risperidone Potent CYP3A4/P-gp inducers (e.g., carbamazepine) may reduce serum paliperidone levels Potent "pan-inducers" may reduce serum levels of paliperidone	Potent CYP3A4/P-gp inducers may require increased paliperidone dose Co-administration of divalproex sodium may require increased paliperidone dose

Pimavanserin	5HT2A antagonism/ inverse agonism and 5HT2C antagonist/ inverse agonist	See "common features" Nausea Confusion Edema	CYP3A4 inducers may increase levels of pimavanserin CYP3A4 inhibitors may reduce levels of pimavanserin	Indicated for Parkinson's disease psychosis Consider dose reduction by 50% with CYP3A4 inhibitors
Quetiapine (Seroquel)	D2 and 5-HT2A antagonism, as well as 5HT2C and 5HT7 antagonist, and 5HT1A partial agonism	See "common features" Anticholinergic Sedation Weight gain Hyperglycemia Orthostatic hypotension	Significant risk of priapism when co-administered with potent CYP3A4 inhibitors Substrate of p-glycoproteins, potential risk of worsening sedation with P-go inhibitors like protease inhibitors [49]	Routine screening recommended before starting treatment and every 6 months Potent CYP3A4 inhibitors: administer one-sixth standard quetiapine dose Potent CYP3A4 inducers: increase quetiapine dose up to 5–6× standard dose with chronic combination treatment [49] Discontinuing potent CYP3A inducer therapy: reduce quetiapine from 5× elevated dose to standard dose over 7–14 days after discontinuation of CYP3A4 inducer
Risperidone (Risperdal)	D2, 5-HT2A, and 5HT7 antagonism	See "common features" Associated with QTc prolongation EPS	Potent CYP3A4 and/or CYP2D6 inhibitors may increase serum levels of risperidone Potent CYP3A4 inducers and "pan-inducers" may reduce serum levels of risperidone	Co-administration with CYP3A4 and/or CYP2D6 inhibitors requires lower initial risperidone dose and maximum dose of 8 mg per day When co-administered with potent CYP3A4 inducers and "pan-inducers," increase risperidone dose up to 2× standard dose

(continued)

Table 17.3 (continued)

Psychotropic	Mechanism of action	Side effects/adverse reactions	DDI with ART and potential clinical effect	Notable clinical considerations in HIV care
Sertindole	D2 and 5-HT2A antagonism	See "common features" Significant, dose-related QTc prolongation	Potent CYP 3A4 and/or 2D6 inhibitors may increase serum levels of sertindole, increasing risk of QTc prolongation	Not available in the USA Potent CYP 3A4 and/or 2D6 inhibitors are contraindicated
Ziprasidone (Geodon)	D2 and 5-HT2A antagonism, as well as 5HT2C and 5HT1A antagonism	See "common features" Associated with significant QTc prolongation Severe cutaneous adverse reactions have been reported (DRESS, SJS, SCAR)	Taken with food increases absorption 2× May be least affected by CYP inhibitors or inducers	Contraindicated with drugs that also affect QTc Contraindicated in patient with recent acute myocardial infarction or with decompensated heart failure Should be avoided in patient with bradycardia, hypokalemia, hypomagnesemia, and congenital QT prolongation Intramuscular formulation not recommended in patients with significant renal impairment

Based on data from [83]

Bold CYP indicates **potent** inhibitor or inducer of that cytochrome P450 enzyme

Abbreviations: *CYP* cytochrome, *D2* doamine-2 receptor, *DDIs* drug-drug interactions, *EPS* extrapyramidal symptoms, *NMS* neuroleptic malignant syndrome, *TD* tardive dyskinesia, *UGT* uridine 52-diphosphate glucuronosyltransferase, *5-HT* 5-hydroxytryptamine receptor

[a]Pan-inducers: drugs that induce many if not all CYP P450 enzymes and include barbiturates, carbamazepine, ethanol, phenytoin, and rifamycins

Table 17.4 Mood stabilizers and antiepileptics and in HIV care[a]

Psychotropic	Mechanism of action	Side effects/adverse reactions	DDI with ART and potential clinical effect	Notable clinical considerations in HIV care
Lithium	Unknown May alter sodium transport across cell membrane in neurons, inhibit inositol monophosphate, reduce protein kinase C, increase neurotropic expression	Effect of cognitive slowing may be difficult in PWHA-related cognitive dysfunction Boxed warning: toxicity is directly related to levels and therefore monitoring should be available when prescribing Hypothyroidism Hyperthyroidism Hyperparathyroidism Diabetes insipidus Cardiac conduction delay Delirium Tremor Seizure	Lithium does not require hepatic metabolism, making it a reasonable choice for patients taking HIV medications that are cleared through the liver. Caution should be used in patients who develop HIV-related nephropathy, as lithium demands renal clearance to maintain safe serum levels	
Antiepileptic mood stabilizers				
Carbamazepine (CBZ, Tegretol)	Blockade of voltage-sensitive sodium channels	Potential for diminished white blood cell count, anemia, thrombocytopenia, aplastic anemia SIADH Hepatotoxicity Narrow therapeutic index Boxed warning: risk of aplastic anemia, Stevens-Johnson syndrome, and toxic epidermal necrolysis HLA-B (genotyping for pts. of Asian descent necessary)	CBZ is considered a "pan-inducer" and it auto-induces Potent CYP 3A4 inhibitors like PIs and elvitegravir/cobicistat may increase serum levels of CBZ Other "pan-inducers" may reduce serum levels of CBZ	High risk of ART failure and viral resistance unless ART dosing monitored and increased Monitoring and dose reduction of CBZ may be required with potent CYP 3A4 inhibitors
Lamotrigine (Lamictal)	Inhibition of voltage-sensitive sodium channels	Boxed warning: may result in life-threatening skin rash/Stevens-Johnson syndrome	UGT inducers like efavirenz, ritonavir, lopinavir, and nelfinavir may reduce lamotrigine serum levels	Do not co-administer with VPA

Table 17.4 (continued)

Psychotropic	Mechanism of action	Side effects/adverse reactions	DDI with ART and potential clinical effect	Notable clinical considerations in HIV care
Valproic acid (VPA, Depakote, Depakene, Depacon)	Inhibition of voltage-gated sodium channels	Boxed warning: hepatotoxicity, especially in those with mitochondrial disease; fetal risk of neural tube defects, pancreatitis Hyperammonemia SIADH Platelet dysfunction PCOS Hepatotoxic metabolite is not measured in standard lab tests	Very complicated and controversial interaction profile, to include P450s, and UGTs "Pan-inducers" ritonavir and NNRTIs like efavirenz may reduce VPA serum levels May inhibit glucuronidation of AZT and increase serum levels Hepatotoxicity, especially with CYP inducers like nevirapine, efavirenz, and ritonavir	Do not co-administer with lamotrigine

Based on data from [83]

Bold CYP indicates **potent** inhibitor or inducer of that cytochrome P450 enzyme

Abbreviations: *ABCB* ATP binding cassette B transporter (p-glycoprotein transporter), *CYP* cytochrome, *DDIs* drug-drug interactions, *PIs* protease inhibitors, *UGT* uridine 5^2-diphosphate glucuronosyltransferase

[a]This table includes antiepileptics (AEDs) considered effective for mania and bipolar disorder. For full table of AEDs in the care of PWHA, see Ref. [36]

[b]Pan-inducers: drugs that induce many if not all CYP P450 enzymes and include barbiturates, carbamazepine, ethanol, phenytoin, and rifamycins [81]

[c]Clobazam is a 1,5-benzodiazepine1–5 (BZD) that is used as an antiepileptic drug [81]

Table 17.5 Anxiolytics and hypnotics in HIV care

Psychotropic	Mechanism of action	Side effects/ adverse reactions	DDI with ART and potential clinical effect	Notable clinical considerations in HIV care
Antihistamines				
Diphenhydramine (Benadryl)	Antagonism of H1 histamine receptor	Sedation Constipation Dry mouth May cause delirium, confusion, urinary retention High risk medication in elderly patients, increasing risk of anticholinergic toxicity and delirium	Diphenhydramine as potent CYP 2D6 inhibitor may increase serum levels of: *Antiarrhythmics* *Metoprolol* *Oxycodone* *SSRIs* *Tramadol* *Tricyclic antidepressants* *First-generation antipsychotics*	
Hydroxyzine	Antagonism of H1 histamine receptor	Sedation Drowsiness Dry mouth May cause delirium, confusion, urinary retention High-risk medication in elderly patients, increasing risk of anticholinergic toxicity and delirium	Co-administration with CYP3A4 inhibitor may lead to increased hydroxyzine levels and potentially increase side effects	May also be anxiolytic Contraindicated in those with prolonged QTc interval

(continued)

Table 17.5 (continued)

Psychotropic	Mechanism of action	Side effects/ adverse reactions	DDI with ART and potential clinical effect	Notable clinical considerations in HIV care
Benzodiazepines				
Benzodiazepine common features	Binding to benzodiazepine receptors at GABA-A ligand-gated chloride channels and increase GABA inhibitory effects	Sedation Depression Dizziness Delirium Confusion Sleep eating/ walking Hyperexcitability Potential for: Respiratory depression Hepatic and renal dysfunction Boxed warning: concomitant use with opioids may result in respiratory depression and death		If tapering, consider 25% reduction every 14 days; this interval may need to be longer with chronic use
Benzodiazepines: *triazolobenzodiazepines (TriazoloBZDs)*				
Alprazolam (Xanax)	Binding to benzodiazepine receptors at GABA-A ligand-gated chloride channels and increase GABA inhibitory effects	See "common features"	Dependent upon CYP3A4 for metabolism Potent CYP3A4 inhibitors may increase and potent CYP3A4 inducers may reduce alprazolam serum levels	
Midazolam (Versed)	Binding to benzodiazepine receptors at GABA-A ligand-gated chloride channels and increase GABA inhibitory effects	See "common features"	Dependent upon CYP3A4 for metabolism Potent CYP3A4 inhibitors may increase and potent CYP3A4 inducers may reduce midazolam serum levels	IV preparation only

Table 17.5 (continued)

Psychotropic	Mechanism of action	Side effects/ adverse reactions	DDI with ART and potential clinical effect	Notable clinical considerations in HIV care
Triazolam (Halcion)	Binding to benzodiazepine receptors at GABA-A ligand-gated chloride channels and increase GABA inhibitory effects	See "common features"	Dependent upon CYP3A4 for metabolism Potent CYP3A4 inhibitors may increase and potent CYP3A4 inducers may reduce triazolam serum levels	
Benzodiazepines *(BZDs)*				
Clonazepam (Klonopin)	Binding to benzodiazepine receptors at GABA-A ligand-gated chloride channels and increase GABA inhibitory effects	See "common features"		
Diazepam (Valium)	Binding to benzodiazepine receptors at GABA-A ligand-gated chloride channels and increase GABA inhibitory effects	See "common features"		
Flunitrazepam (Rohypnol) "Roofies"	Binding to benzodiazepine receptors at GABA-A ligand-gated chloride channels and increase GABA inhibitory effects	See "common features"		

(continued)

Table 17.5 (continued)

Psychotropic	Mechanism of action	Side effects/ adverse reactions	DDI with ART and potential clinical effect	Notable clinical considerations in HIV care
Lorazepam (Ativan)	Binding to benzodiazepine receptors at GABA-A ligand-gated chloride channels and increase GABA inhibitory effects	See "common features"	Dependent upon glucuronidation (Phase 2) for metabolism Serum levels may be reduced by UGT inducers (e.g., tipranavir, nelfinavir, lopinavir, ritonavir) Serum levels may be increased by UGT inhibitors such as atazanavir	
Oxazepam (Serax)	Binding to benzodiazepine receptors at GABA-A ligand-gated chloride channels and increase GABA inhibitory effects	See "common features"	Dependent upon glucuronidation (Phase 2) for metabolism Serum levels may be reduced by UGT inducers (e.g., tipranavir, nelfinavir, lopinavir, ritonavir) Serum levels may be increased by UGT inhibitors such as atazanavir	
Temazepam (Restoril)	Binding to benzodiazepine receptors at GABA-A ligand-gated chloride channels and increase GABA inhibitory effects	See "common features"	Inhibitor of Phase 2 UGT metabolism May inhibit glucuronidation of: *Buprenorphine* (UGT2B7) *Norbuprenorphine* (UGT1A3)	

Table 17.5 (continued)

Psychotropic	Mechanism of action	Side effects/ adverse reactions	DDI with ART and potential clinical effect	Notable clinical considerations in HIV care
Non-benzodiazepine anxiolytic				
Buspirone (Buspar)	Agonism of 5HT1A, moderate affinity for dopamine D2, no effect on GABA directly	Dizziness Drowsiness	Potent CYP3A4 inhibitors may increase, and potent CYP 3A4 inducers may reduce buspirone serum levels	Risk of serotonin syndrome or akathisia if co-administered with metabolic inhibitors Risk of serotonin syndrome if metabolism inhibited or if co-administered with other serotonergic agents
Non-benzodiazepine hypnotics				
Non-BZD hypnotics common features	Z-drugs act through positive allosteric modulation of benzodiazepine receptor	Sedation Dizziness Amnesia Headache	Potent CYP pan-inhibitors like ritonavir and lopinavir may increase serum levels Potent CYP pan-inducers[a] may reduce serum levels	
Eszopiclone (Lunesta)	Positive allosteric modulator of benzodiazepine receptors	See "common features" Unpleasant taste Boxed warning: may result in complex sleep behaviors		
Zaleplon (Sonata)	Positive allosteric modulator of benzodiazepine receptors	See "common features" Hallucinations Boxed warning: may result in complex sleep behaviors		

(continued)

Table 17.5 (continued)

Psychotropic	Mechanism of action	Side effects/ adverse reactions	DDI with ART and potential clinical effect	Notable clinical considerations in HIV care
Zolpidem (Ambien)	Positive allosteric modulator of benzodiazepine receptors	See "common features" Hallucinations Boxed warning: may result in complex sleep behaviors	CYP3A4 inhibitors may increase levels of zolpidem and increase sedation	
Zopiclone (Zimovane/ Imovane)	Positive allosteric modulator of benzodiazepine receptors	See "common features" Unpleasant taste Impaired vision		
Dual orexin receptor antagonist (DORA)				
Suvorexant (Belsomra)	Inhibition of orexin 1 and orexin 2	See "common features"	Potent CYP 3A4 inhibitors like protease inhibitors may increase serum levels of suvorexant Potent CYP3A4 inducers may decrease suvorexant serum levels	Potent CYP 3A4 inhibitors like protease inhibitors are contraindicated Moderate CYP3A4 inhibitors require dose adjustment of suvorexant[b]

Based on data from [83]

CYP cytochrome, *DDIs* drug-drug interactions, *UGT* uridine 5[2]-diphosphate glucuronosyltransferase

[a]Pan-inducers: drugs that induce many if not all CYP P450 enzymes and include barbiturates, carbamazepine, ethanol, phenytoin, and rifamycins

[b]Individuals on moderate 3A4 inhibitors should be started on 5 mg of suvorexant, with an increase to 10 mg if clinically indicated

and comorbid depressive disorders should follow the principles of treating depressive disorders in the general population. That is, medications should be started at a low dose and titrated slowly to tolerability and response. The simplest regimen comprised of an agent (or agents) with the fewest interactions and adverse effects should be used, tailoring the side effect profile to each patient's potential comorbidities and sensitivities. Treatment may take up to 8 weeks of full adherence, at the full medication dose for full therapeutic effect, and should continue for at least 6–9 months after full remission of depressive symptoms to minimize risk of

recurrence. Longer treatment (e.g., 2 years or more) in those with a history of multiple major depressive episodes may be needed. As in the general population, augmenting antidepressant treatment with psychotherapy is likely superior to pharmacotherapy alone [23, 24].

If there is inadequate antidepressant response, the clinician may switch to a different agent or choose or augment existing medication with another antidepressant of a different mechanism of action, mood stabilizer, second- or third-generation antipsychotic, stimulant, or thyroid hormone [25, 26]. Esketamine has emerged as a treatment of acute suicidality and treatment of depressive disorders, but there is no literature on its use in PWHA. Similarly, repeated transcranial magnetic stimulation (rTMS) should be considered in cases of treatment-resistant depressive disorders, although there is minimal evidence currently supporting its use in PLWHA [27]. In cases of severe major depressive disorders with psychotic, melancholic, or catatonic features, the adjunctive use of antipsychotics and/or electroconvulsive therapy (ECT) should be actively considered [28].

Treating HIV-Related Symptoms

Specific properties of the antidepressants may be utilized to treat corresponding HIV-related symptoms [29]. Antidepressants with activating properties, such as bupropion and selective serotinin reuptake inhibitors (SSRIs), may also be used for fatigue [30]. However, the focus of treating fatigue should always remain on the underlying cause if not solely due to a depressive disorder. Sedating antidepressants, such as mirtazapine, tricyclic antidepressants (TCAs), and trazodone, can be used to treat insomnia [31]. Mirtazapine has also resulted in weight gain in HIV wasting syndrome [32]. TCAs have been shown to improve diarrhea in other medical conditions [33]. Although there are few studies assessing antidepressants in the treatment of HIV-associated neuropathic pain, duloxetine has been suggested as a treatment option due to its efficacy in diabetes mellitus-related neuropathy [34]. Similarly, TCAs would be expected to be beneficial for neuropathic pain.

Case Vignette 17.1a: Depressive Disorder (New HIV/New Depression Dx)
Mr. R was a 24-year-old man diagnosed with HIV 6 weeks prior to evaluation. At the time of his HIV diagnosis, he was started on ART with abacavir and lamivudine (both non-nucleoside reverse transcriptase inhibitors "NNRTI"s) plus dolutegravir (an integrase strand inhibitor "INSTI"). He presented to your office complaining of 2–3 weeks of depressed mood, fatigue, feelings of guilt, and lack of interest in leisure activities and ability to concentrate at work. You determine present that he meets criteria for major depressive disorder, depressive disorder due to HIV, or depressive disorder due to ART.

What Do You Do?
*See the box on page 444

Initial Steps in Every Case

1. Determine ART adherence, and address difficulties if poor adherence.
2. Review onset of symptoms and review if selected ART affects mood, address mood side effects with ART adjustment, and/or proceed with treatment of mood.
3. Assess patient's emotional response to new diagnosis.
4. Treat depressive symptoms: psychotherapy + psychopharmacotherapy.
5. Select psychopharmacologic agent (Fig. 17.1).

Case 17.1a – "Mr. R" is illustrative of a patient with a recent diagnosis of major depressive disorder superimposed on a recent diagnosis of HIV. Elements to consider in this case include the impact of the new HIV diagnosis, new long-term chronic illness diagnoses, and ART. In this treatment-naive patient, starting an SSRI, such as sertraline, citalopram, or escitalopram, or an antidepressant from another class, such as bupropion would be a good initial consideration. SSRIs are generally favored as first-line treatment because of their safety and side effect profiles. Treating the patient's depressive disorder can help determine if fatigue is ART- or HIV-related as opposed to being solely due to depressive disorder itself. Fluvoxamine, on the other hand, is historically poorly tolerated by PWHA and, critically, inhibits several enzymes that metabolize ART [35]. Paroxetine is a very potent CYP2D6 inhibitor that can interfere with NNRTI and protease inhibitor metabolism. Sertraline has fewer potent CYP2D6 inhibitor interactions at doses below 200 mg/day, and has a well-tolerated side effect profile [7, 36]. Citalopram and escitalopram are effective but have warnings about QTc prolongation in higher doses, effects that have not been studied in PWHA [37, 38].

TCAs are shown to be effective in treating depressive disorders in PWHA but have a higher rate of discontinuation due to side effects, especially anticholinergic side effects including dry mouth, blurred vision, constipation, and delirium. TCAs are also dependent upon CYP2D6 and CYP3A4 for metabolism and have a higher risk of toxicity if the patient is on a protease inhibitor, due to protease inhibitor interactions that raise serum levels of TCAs. This risk can be reduced by therapeutic drug monitoring (TDM) [39–41]. Since this patient is treatment-naive, he is a good

Fig. 17.1 Initial steps box

INITIAL STEPS IN EVERY CASE:

1. *Determine ART adherence, and address difficulties*
2. *Review onset of symptoms and if selected ART affects mood/anxiety/thoughts. Address these side effects with ART adjustment and/or proceed with treatment of psychiatric symptoms while maintaining ART*
3. *Assess patient's emotional response to new diagnosis*
4. *Treat symptoms: Psychotherapy + Psychopharmacotherapy*
5. *Select Psychopharmacologic agent*

candidate for an SSRI such as sertraline, which has few drug-drug interactions and documented use in PWHA. If fatigue continues despite improvement in mood, fluoxetine, another SSRI, or bupropion (which are more activating antidepressants) may be considered. However, fluoxetine is an inhibitor of the CYP 3A4 metabolism of protease inhibitors. Bupropion may add benefit if a patient is also tobacco/nicotine dependent (see section below), has no concurrent anxiety disorder, and has no serious CNS pathology or other concern for seizure susceptibility. If insomnia were a concern, citalopram and mirtazapine could be considered (mirtazapine is more predictably sedating), as both are generally well tolerated in PWHA. For patients with comorbid pain or anxiety, SNRIs might be considered, though their use in PWHA has not been well studied.

Case Vignette 17.1b: Depression (on ART)
Ms. O was a 61-year-old woman living with HIV for the past 15 years. She had a history of recurrent major depressive disorder and chronic lower back pain, historically well managed with nortriptyline, with a therapeutic serum level obtained 6 months ago. She was referred to the mental health clinic for evaluation of new depressive symptoms including poor sleep, irritability, worsening back pain, and sad mood. She had an undetectable viral load on a regimen of elvitegravir-cobicistat-tenofovir alafenamide-emtricitabine which she was switched to 3 months ago due to viral resistance on her previous regimen.

What Do You Do?
**See the box on page 445*

Case 17.1b demonstrates the likelihood that there was a CYP 2D6 drug-drug interaction between nortriptyline and cobicistat, perhaps with depressive and sleep symptoms augmented by the INSTI elvitegravir's potential to disrupt sleep and mood [42]. Nortriptyline is dependent upon CYP2D6 for metabolism, and the cobicistat-"boosted" ART regimen she was started on may be inhibiting the metabolism of nortriptyline, pushing it to an elevated level and out of therapeutic range. Nortriptyline, in particular, has a narrow therapeutic window, below and above which it is not effective. This case is a great reminder to utilize TDM with patients on complicated medication regimens, especially if they are older. It is an easy task to collect a nortriptyline serum level, and to review medication adherence as well as timing of the medication switch with the onset of symptoms. With patients over 60 years of age, assessing for comorbid conditions that affect sleep (e.g., obstructive sleep apnea, poor sleep hygiene, ingestion of sleep-altering substances) is also necessary. If her nortriptyline level is too high, lowering her dose may prove beneficial for her mood, sleep, and pain. It may also be helpful to review her ART medication options with her ART clinician, in case the patient might also benefit from a non-cobicistat- or ritonavir-boosted INSTI regimen, or if the patient might be switched

to a different INSTI with fewer neuropsychiatric side effects. Alternatively, we could switch her tricyclic antidepressant (TCA) to an SNRI to address her mood and pain, or an SSRI, but since these are also metabolized at 2D6, careful monitoring would be warranted, but perhaps with fewer concerns about toxicity if boosted too high by cobicistat.

Antipsychotics

This segment will focus on the pharmacologic aspects of treatment of psychotic disorders and delirium, with the understanding that treatment should also involve other therapeutic interventions, most importantly adherence to ART [18] and treatment of any underlying cause for delirium. General information about medications including mechanism of action, common and serious side effects, adverse reactions, toxicities, and potential drug interactions can be found in Table 17.3. HIV-specific considerations that cannot be adequately explained in table format are presented below. Please be sure to review the cases at the end of this section for practical review of treating depression and HIV.

Psychosis is an uncommon but validated complication of AIDS. PWHA and schizophrenia are at increased risk of morbidity and mortality when compared to the general population, and this risk rises in people who do not receive treatment with antipsychotics [43]. Post-marketing data have also revealed cases of acute reversible psychosis related to the use of efavirenz, zidovudine, and abacavir [44]. Both first-generation antipsychotics (FGA) such as chlorpromazine and second-generation antipsychotics (SGA) such as quetiapine have been used with success in PWHA, though there are no randomized trials evaluating antipsychotic use in PWHA who have a comorbid psychotic disorder [45]. In a review of the literature on antipsychotic use in PWHA, Hill and Lee identified only a single randomized trial evaluating antipsychotics (chlorpromazine versus haloperidol or lorazepam in AIDS dementia) in this population [29]. There were several open-label studies and case reports supporting the use of SGA, e.g., risperidone, ziprasidone, and clozapine, for AIDS-related psychosis [29]. As in patients without HIV, FGA use is associated with a greater risk of extrapyramidal syndromes. It should be noted that PWHA are more sensitive to both extrapyramidal and anticholinergic side effects of antipsychotic and other medications. Consequently, SGAs are generally preferred, although clinical decisions necessarily also require consideration of cost, availability, and risk of metabolic syndrome. Because there is no evidence available that demonstrates one particular antipsychotic to be superior to others in PWHA and schizophrenia, the process behind selecting a medication, like in those with a psychotic disorder without HIV, must include individual preference, prior treatment response, effectiveness, drug-drug interactions, and potential adverse effects [29, 46, 47].

Mechanism of Action Review

PWHA are at increased risk of developing EPS, including akathisia, dystonia, pseudoparkinsonism, and tardive dyskinesia especially in the advanced stages of HIV [48, 49]. Because of the concern for the increased risk of EPS, clinicians should consider avoiding most FGAs [46]. Antipsychotics with a lower risk of EPS may include quetiapine, olanzapine, aripiprazole, and ziprasidone, with the likelihood of EPS increasing in that order among these four agents [50]. A recent meta-analysis of 136 studies indicated that the following drugs were less likely to be associated with the use of antiparkinsonian drugs than haloperidol, starting with the least likely: clozapine, perazine, sertindole, placebo, olanzapine, quetiapine, asenapine, aripiprazole, thioridazine, amisulpride, iloperidone, brexpiprazole, paliperidone, ziprasidone, risperidone, lurasidone, zotepine, and chlorpromazine [51]. While the lowest rate of EPS occurs with clozapine, there are limited studies demonstrating effective and safe use of clozapine in PWHA, and the possibility of decreased absolute neutrophil count makes this choice problematic [52].

PWHA taking NRTIs or PIs are at greater risk for metabolic syndrome and lipodystrophy [53], especially when receiving lopinavir/ritonavir, saquinavir/ritonavir, tipranavir/ritonavir, or fosamprenavir/ritonavir [54]. Individuals taking both SGA and ARTs have higher mean BMI, blood pressure, and triglycerides, as well as increased rates of developing diabetes mellitus [55]. Clinicians should take this into consideration when prescribing clozapine, olanzapine, or quetiapine, and, to a lesser extent, risperidone. If metabolic syndrome is a concern, it may be better to consider the use of aripiprazole, lurasidone, or ziprasidone, with or without the addition of metformin [56].

QTc prolongation is also a significant concern for patients who are on SGAs and have comorbid risk factors for dysrhythmias or who are on other medications that prolong QTc, e.g., lopinavir, ritonavir, saquinavir, atazanavir, and efavirenz [29]. In patients who are on other medicines that can prolong the QTc interval, SGAs that are associated with significant QTc prolongation, such as ziprasidone and haloperidol, should be avoided. Aripiprazole, brexpiprazole, cariprazine, and lurasidone have been associated with the least QTc prolongation of the antipsychotics [56]. Additionally, if there are concerns about bone marrow suppression, be sure to avoid the combination of zidovudine and clozapine [57].

Treating HIV-Related Symptoms

As in the case with other classes of drugs, unique properties of antipsychotics may be used to treat HIV-related symptoms. In cases of insomnia due to efavirenz or persistent insomnia due to HIV-associated brain disease, low doses of sedating SGAs such as quetiapine or olanzapine may be helpful especially if insomnia is associated with delirium or psychosis. If not, then hypnotics with fewer side

effects than most antipsychotics should be tried first [58]. The SGAs clozapine, risperidone, and ziprasidone have been used in open-label studies and case reports of AIDS-related psychotic disorder, while the FGAs haloperidol and chlorpromazine have been shown in a single double-blind randomized trial to reduce Delirium Rating Scale scores in hospitalized AIDS patients with delirium [29]. Chronic wasting may benefit from antipsychotics that increase appetite such as olanzapine. However, given the risk metabolic syndrome and other risks mentioned above, antipsychotics should be used with caution and for the shortest duration possible.

DDIs

After considering patient preference and personal experience with medications, clinicians should review potential DDIs, as antipsychotics are usually metabolized by CYP3A4, CYP1A2, and CYP2D6, and ART may *inhibit* (i.e., result in increased drug toxicity) or *induce* (i.e., result in reduced drug effectiveness) these metabolic enzymes [59, 60]. NRTIs, integrase inhibitors, and CCR5 inhibitors are much less likely to lead to clinically significant interactions. Clinicians should also recall that the polyaromatic hydrocarbons ("tar") in cigarettes induce clozapine and olanzapine metabolism at CYP1A2, thereby lowering levels of both drugs [61]. When using the sedating antipsychotic quetiapine, it is important to recognize that the integrase strand transfer inhibitor (INSTI) elvitegravir (EVG), with its need for CYP inhibiting "boosters," can elevate quetiapine blood levels, while other INSTIs do *not* have such interactions. If initiating quetiapine in a patient receiving EVG, it is recommended to start with the lowest possible dose and titrate up as needed. If EVG is added to a patient receiving a stable dose of quetiapine, it is recommended to reduce quetiapine to 1/6 of usual dose [47].

Treatment Course

With the exception of the unique principles mentioned above, the treatment of schizophrenia in PWHA is otherwise similar to that in people without HIV. Some general principles, supported by APA practice guidelines, include using lower starting doses and slower titration, providing minimally complicated regimens, and maintaining awareness of interactions and adverse reactions as noted above [47]. After treatment is initiated, antipsychotics should be titrated according to therapeutic response and tolerability. Treatment response should be assessed over 2–3 weeks, during which time most of the response is likely to occur [62]. If this proves to be effective, the medication should be continued at the least effective dose. Transitioning to a long-acting injectable (LAI) may be reasonable, given evidence that LAIs reduce readmission and relapse in patients with schizophrenia, though there are no published studies evaluating their use in PWHA [63] and it has been recommended that they should be avoided in patients with advanced HIV [47].

If an antipsychotic is not tolerated due to side effects, drug interactions should be considered, before tapering to a tolerable dose or changing to a medication with a more favorable side effect profile. If medications prove to be ineffective due to non-adherence, a LAI may be considered. If not effective despite an adequate dose, antipsychotic serum levels can be obtained (if financially feasible and there is concern for adherence), adherence can be more closely monitored/supervised, or the medication can be substituted. Although definitions vary, if two to three drugs have been tried at a dosage equivalent to 1000 mg/day of chlorpromazine for a total duration of 4–10 weeks, the patient is deemed to have treatment-resistant illness [64]. Some experts argue that one of these trials should include olanzapine given its possible superiority to other SGAs [65]. If olanzapine also fails, clozapine should be tried given robust evidence supporting its effectiveness [66], though there are few studies reporting use of clozapine in PWHA [52].

Case Vignette 17.2a: Antipsychotics (New HIV dx)
Ms. G was a 30-year-old obese (BMI 31), homeless female smoker who was diagnosed with HIV 6 months prior to her psychiatric evaluation. She was started on dolutegravir (DTG) plus tenofovir/emtricitabine (integrase inhibitor/NRTI/NRTI). The preceding year, she had become more isolated with paranoid delusions and was noted to be responding frequently to internal stimuli. These have persisted despite a negative medical workup for causes of psychosis, and she was diagnosed with schizophrenia.

What Do You Do?
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Case 17.2a – "Ms. G." has HIV and newly diagnosed schizophrenia. Although she is on a combination of dolutegravir and tenofovir/emtricitabine for HIV, she requires an antipsychotic for her untreated schizophrenia. Ms. G. does not express a preference for any one particular medication, so we must next consider her ART regimen to avoid untenable DDIs. Fortunately, the dual NRTI combination of tenofovir/emtricitabine is neither metabolized by P450 enzymes nor does it induce or inhibit any specific isoenzymes. Dolutegravir, a second-generation integrase inhibitor, is metabolized by the Phase II metabolic system by uridine diphosphate glucuronosyltransferase 1A1 (major pathway) and cytochrome CYP3A4 (minor pathway), but neither induces nor inhibits CYP isoenzymes. Therefore, given that SGAs (our first-line antipsychotic in this case) do *not* induce CYP isoenzymes and only *minimally inhibit* a small segment of CYP enzymes, there are unlikely to be any clinically significant DDIs between SGAs and this patient's ART regimen.

Next, considering that she is obese (BMI of 31 kg/m^2), and that she is at risk for lipodystrophy due to NRTI and integrase inhibitor combination, we should avoid an obesogenic SGA and instead consider aripiprazole, lurasidone, or ziprasidone. However, seeing that she is experiencing homelessness, risperidone may be a better

option due to lower medication costs, despite the slightly higher risk of metabolic syndrome when compared to aripiprazole.

Patients such as Ms. G. should have their BMI, waist circumference, HbA1C, and lipids evaluated, to be obtained at baseline and periodically (at 3 months, and at least annually thereafter) while on an SGA [67, 68]. Although we could consider the addition of metformin due to its efficacy in reducing weight gain associated with SGAs, the benefits would need to be balanced with DDIs with dolutegravir, as this medication may increase the serum concentration of metformin [69]. If she were to need to transition to olanzapine or clozapine later in her course, it is important to keep in mind that she also has tobacco use disorder, and that she may need higher doses of these medications due to CYP1A2 induction by cigarette smoke impurities [70].

Case Vignette 17.2b: Antipsychotics (on ART)
Mr. H was a 60-year-old man with previously well-controlled schizophrenia (he was non-adherent to risperidone due to muscle rigidity) with history of well-controlled HIV (efavirenz/tenofovir disoproxil fumarate/emtricitabine) (NNRTI plus two NRTIs) for the previous few years who presented with worsening delusions and auditory visual hallucinations. His medical workup was unrevealing, and he has had no other changes to his medications.

What Do You Do?
**See the box on page 450*

Case 17.2b – "Mr. H" is unlike our first case, as this patient has been on treatment for both HIV and schizophrenia for some time. He has had a negative medical workup for systemic medical causes of his worsening psychosis and has been on an unchanged dose of efavirenz for years, so we do not suspect this is the etiology. This is supported by the fact that we have a better explanation for his clinical decompensation – nonadherence to risperidone due to bothersome rigidity, an adverse reaction which is more common in PWHA. However, since efavirenz is a dual CYP3A4 inhibitor and inducer and has been associated with numerous neuropsychiatric symptoms (including psychosis), it may be best to discuss transitioning to a different HIV drug regimen with his HIV provider. As discussed in the previous case, there are fewer concerns about interactions with NRTIs.

To avoid extrapyramidal symptom (EPS) in the future, we could consider switching from risperidone to quetiapine, olanzapine, aripiprazole, or ziprasidone. However, it is important to also consider whether he has any level of cognitive impairment, as the more anticholinergic SGAs (e.g., olanzapine, quetiapine, clozapine) may worsen cognition in this population.

A baseline EKG is recommended if he remains on both an SGA and efavirenz. Olanzapine would again be preferred (and ziprasidone should be avoided) if there are concerns about prolongation of the QTc interval [51].

Mood Stabilizers

PWHA have significantly higher rates of bipolar disorder with manic episodes than the general population. Comorbid mania/mood dysregulation is associated with poorer antiretroviral adherence and HIV treatment outcomes [3, 71]. For the first few weeks of treatment, mood stabilizers such as lithium and some antiepileptics may be combined with second-generation antipsychotics (SGAs) for additional antimanic activity and sedation (see section "Antipsychotics"). Benzodiazepines may also be used for sedation, and are discussed in "anxiolytics" later in this chapter. Mood stabilizers may take a week or more to reach effective levels, so effective control of agitation and sufficient sedation are important factors in early treatment [71].

Lithium is the least likely of the mood stabilizers to have metabolic interactions with antiretroviral agents. However, lithium has a narrow therapeutic index and an increased risk of cognitive side effects. Early studies with lithium and comorbid HIV – performed before the development of ART – showed a high incidence of side effects and increased viral titers (30). Lithium has also been considered neuroprotective [72, 73]. However, a recent randomized, controlled clinical trial found that adding lithium to ART for patients with established mild to moderate HIV-associated neurocognitive disorder (HAND) did *not* improve cognitive function, despite good tolerability of lithium [74]. Lithium was thought to be problematic in patients receiving concurrent tenofovir since both are dependent upon renal elimination and each is associated with renal toxicity. However, a recent randomized placebo-controlled study found no evidence of increased renal toxicity with lithium-tenofovir combinations [75].

Antiepileptics are also first- and second-line selections for the treatment of manic episodes and for mood regulation. Recent treatment guidelines and clinical reports indicate that first-line antiepileptic medications for the treatment of bipolar disorder with manic episodes are valproate, and lamotrigine, with carbamazepine as second-line treatment in the general population [76]. Careful monitoring is recommended for PWHA who are prescribed valproic acid and carbamazepine since each presents complicated metabolic interaction and toxicity profiles [77–79]. Valproate at one time was considered as a treatment for HIV per se due to its potential for reducing HIV reservoirs, but recent reviews do not support this claim [80].

Valproate is metabolized by CYP4502A and CYP2C, and by several uridine 5′-diphosphate glucuronosyltransferase (UGTs), and is a known inhibitor of these enzymes. The inhibition of UGTs by valproate may raise serum levels of medications that rely on UGTs for metabolism (e.g., AZT, zidovudine, lamotrigine) [81]. Additionally, valproate carries a risk of hepatotoxicity when taken with CYP-inducing medications, to include CYP-inducing ARTs (e.g., efavirenz, nevirapine) [82].

Many antiepileptics (e.g., carbamazepine, oxcarbazepine, phenobarbital, phenytoin) are significant inducers of CYP3A4 and P-glycoproteins. As a result, when combined with HIV medications, serum levels of ART may be reduced significantly. For example, all protease inhibitors that include ritonavir- or cobicistat-boosted

protease inhibitors, NNRTIs, and even INSTI-based regimens should be avoided with strong CYP3A4 inducers due to risk of treatment failure [47, 83].

Case Vignette 17.3a: Mood Stabilizers (New HIV dx)
Mr. A was a 40-year-old man with a diagnosis of bipolar I disorder since the age of 19. He tested positive for HIV during the current psychiatric hospitalization for a manic episode. He had often missed outpatient appointments and was poorly adherent to his regimen of lithium, due to breakthrough symptoms and finding it burdensome to have to get blood drawn. His lithium level was 0.8 mg/dL, CD4 count = 235 (21%), and HIV viral load 54,670 copies/ml as an inpatient. All other metabolic parameters, including liver function tests and renal function, were normal. The infectious disease consultant wanted to initiate HIV treatment with a standard initial regimen of dolutegravir/tenofovir/lamivudine. What pharmacological changes should be considered?

What Do You Do?
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Case 17.3a – "Mr. A" demonstrates a patient with newly diagnosed HIV who is nonadherent with his lithium for bipolar disorder. There are multiple things to consider when selecting psychotropics, and there may be a need to consider re-selecting his ART regimen, as well as consideration to augmenting his lithium with an SGA, or consider switching to valproate combined with an SGA.

In an ART-naive patient, the preferred regimen includes tenofovir alafenamide-emtricitabine (both are nucleoside reverse transcriptase inhibitors – "NRTIs") and an integrase strand transfer inhibitor (INSTI) like dolutegravir, which has a high barrier to viral resistance. Tenofovir is also active against hepatitis B and its use precludes the need for HLA-B*5701 testing (which is needed prior to initiation of therapy with other regimens for ART treatment-naive that include abacavir, to predict hypersensitivity to this agent). There is a recent evidence to support the safety and tolerability of a potentially nephrotoxic tenofovir-containing regimen even with lithium, but close monitoring of lithium levels and renal function is prudent [75]. If the patient opts to remain on lithium with close monitoring, it would also be reasonable to discuss switching initial ART to abacavir-emtricitabine with an INSTI to reduce the potential for renal interactions, as long as the patient is first HLA-B*5701 tested for a hypersensitivity predisposition to abacavir. Well-documented case reports suggest that INSTIs have potential drug-drug interactions with valproate, but there are no carefully constructed trials to provide treatment guidance. If a switch from lithium to valproate is considered, valproate levels, liver-associated enzymes, and virologic response must be monitored closely [77, 78]. Lithium and valproate will require close monitoring, and this patient would require careful community case management.

An important consideration for treating this patient's bipolar disorder would be the addition of an antipsychotic agent, potentially one available in a depot injection to increase adherence. Please refer to the section "Antipsychotics" for more information.

Case Vignette 17.3b: Mood Stabilizer (on ART)
Mrs. B was a 40-year-old woman, diagnosed with bipolar I disorder when she was 25 years of age when she had a single manic episode. She had continued reliably on carbamazepine monotherapy since that time. She was diagnosed with HIV at the age of 35. Finding the ideal ART regimen for Mrs. B had been challenging due to the multiple drug interactions that carbamazepine has with many of her original antiretroviral agents. Mrs. B had also experienced two medical hospitalizations in the previous 5 years due to carbamazepine toxicity and had also developed resistance to several antiretroviral agents. What considerations would you keep in mind for Mrs. B in managing her bipolar I disorder in the context of her multidrug-resistant HIV?

What Do You Do?
**See the box on page 453*

Case 17.3b – "Mrs. B" highlights the complications that can occur when co-administering carbamazepine and ART. Use of cobicistat- or ritonavir-boosted protease inhibitors concurrently with carbamazepine may increase the levels of carbamazepine and lead to toxicity due to inhibition of carbamazepine metabolism, while carbamazepine may also induce or "rev up" the metabolism of the protease inhibitors resulting in ART viral resistance. This combination is best avoided, but if it is clinically necessary, therapeutic drug monitoring (TDM) for the protease inhibitor and the anticonvulsant, plus close monitoring of viral suppression, would be helpful in avoiding toxicities and as viral resistance. Carbamazepine may interact with most classes of ART, and it may be worth considering a trial of lithium or valproate for this patient, as these have the fewest interactions with ART and are considered first-line treatment. The selection of her next ART regimen would then be guided by her viral resistance testing.

Anxiolytics

Medications used for patients with anxiety disorders include selective serotonin reuptake inhibitors (SSRIs), serotonin-norepinephrine reuptake inhibitors (SNRIs), buspirone, benzodiazepines, clonidine, and hydroxyzine. This section will discuss benzodiazepines, buspirone, and clonidine. Please see other sections of this chapter, as well as the embedded table details for information about anxiolytic antidepressants and hypnotics.

Anxiety is often comorbid with HIV. Patients may develop anxiety surrounding their healthcare following infection with HIV or anxiety may be a presenting symptom of HIV-associated conditions such as HIV-associated neurocognitive disorders (HAND). Some antiretroviral medications, e.g., efavirenz, raltegravir, and dolutegravir, may cause anxiety as a side effect, highlighting the importance of evaluating any new anxiety symptom thoroughly and systematically. After determining the onset and duration of anxiety in relation to HIV diagnosis, ART initiation or changes, and/or new comorbidities, as well as the removal or adjustment of potentially offending agents, the treatment of anxiety may proceed. It is preferable to treat anxiety symptoms or disorders in HIV with non-pharmacological measures such as cognitive behavioral therapy (CBT) [84]. If psychotropics are indicated, the SSRIs and SNRIs are generally first-line medications, and are generally well tolerated in PWHA. Please see the antidepressant section above and the associated table for details.

Buspirone may also be an appropriate option but has not been specifically studied in PLWHA. Benzodiazepines assist with acute anxiety, but are not ideal given the risks of drug-drug interactions and of dependence in a patient population that has increased prevalence of substance use disorders. In a cohort-matched retrospective insurance-based population study in Taiwan, PWHA had a greater risk of long-term use of benzodiazepines (as well as the non-benzodiazepine benzodiazepine-receptor agonists or "Z-drugs") than persons without HIV over a 13-year period [85].

Importantly, some benzodiazepines like the triazolobenzodiazepines (triazolam, alprazolam, and midazolam) are dependent upon CYP 3A4 for metabolism. They may have seriously prolonged effects, and the risk of oversedation if co-prescribed with CYP 3A4 inhibitors, e.g., protease inhibitors, or "boosted" ARTs containing ritonavir and cobicistat. Midazolam's bioavailability may be increased dramatically when administered to patients on stable lopinavir/ritonavir, with reports of prolonged sedation and dysrhythmias [86, 87]. Benzodiazepines that are not eliminated via CYP3A4 (such as those metabolized via glucuronidation, e.g., lorazepam, oxazepam, and temazepam) are generally safer alternatives for use in combination with antiretrovirals. The benzodiazepines that undergo only oxidative P450 metabolism (e.g., alprazolam, triazolam, midazolam) which places them at risk for inhibition and elevation of serum levels may also require dosage adjustment upward with metabolic inducers such as carbamazepine [88].

Case Vignette 17.4a: Antianxiety (New HIV dx)

Mr. J was a single, 35-year-old man with newly diagnosed HIV and a long-standing history of generalized anxiety disorder with panic attacks. He tried several antidepressants for his anxiety, but experienced negative side effects of nausea, diarrhea, and sexual dysfunction, and never continued any for greater than 6 weeks. He preferred taking medication as needed for his anxiety and took 1 mg of alprazolam for panic symptoms five to seven times/week.

How do you navigate management of Mr. J's anxiety in consultation with his HIV provider?

What Do You Do?

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Mr. J's case highlights the need to address suboptimal anxiety management with awareness of his new ART selection. It is common for patients who suffer from anxiety to prefer self-medication with rapid-action medications like benzodiazepines, and to have difficulty tolerating first-line treatments such as antidepressants which can take 8 weeks for full effect. Additionally, many first-line HIV ART treatments include INSTIs, which have been associated with new-onset neuropsychiatric effects such as headache, insomnia, depressive disorders, and suicidal ideation, any of which may worsen Mr. J's anxiety symptoms.

Mr. J's alprazolam is a CYP 3A4-dependent triazolobenzodiazepine, which would potentially have interactions with medications that inhibit this enzyme, such as the cobicistat-boosted elvitegravir, ritonavir-"boosted" ART, many NNRTIs, and all protease inhibitors, all of which may increase serum levels of alprazolam leading to worsened side effects to include oversedation and falls. If used in combination with bictegravir, dolutegravir, and raltegravir, no change in serum concentrations of benzodiazepines would be expected [89]. Switching his PRN benzodiazepine to one that bypasses the CYP450 system, such as lorazepam, oxazepam, or temazepam is another option, with the important consideration of a trial of cognitive behavioral therapy (CBT) along with a SSRI trial. Considering ART without potent CYP 3A4 inhibitors would also be helpful if the patient requires a CYP3A4-dependent antidepressant such as mirtazapine or remains on his alprazolam.

Case Vignette 17.4b: Anxiety (on ART)

Ms. P was a 40-year-old woman with a history of generalized anxiety disorder, alcohol use disorder (AUD) in remission, and a history of HIV for the previous 10 years. The patient's HIV regimen had been unchanged for the previous 10 years with an undetectable viral load, and included a boosted protease inhibitor. Her anxiety had been difficult to manage, with trials of multiple antidepressants and benzodiazepines. She had been on sertraline, 200 mg daily for 3 months without side effects. She was on scheduled lorazepam for several months and was recently cross-tapered to buspirone 7.5 mg BID by her primary care physician, with resultant breakthrough panic attacks up to 3x/week.

What considerations would you keep in mind for Ms. P in managing her anxiety disorder in the context of her ART regimen?

Buspirone is dependent upon CYP 3A4 for metabolism, so, as with the triazolobenzodiazepines in Case 17.4a, potent CYP 3A4 inhibitors, including protease inhibitors, some NNRTIs, and "boosted" ART, may increase serum levels of buspirone. Lower doses of buspirone than usual may be effective, and close monitoring is needed to assess for side effects and overdosage to prevent adverse drug interactions. There has been one case report of pseudoparkinsonism due to elevated

buspirone serum levels after administration of new ritonavir-containing ART [90]. Buspirone should be initiated at the lowest dose and titrated upward cautiously. Since Ms. P was having breakthrough panic, increasing the dose of buspirone cautiously may be beneficial, and she may not need to approach the recommended maximum dosage of 60 mg/day. Additionally, intensive non-pharmacological interventions such as CBT would be important to add to this patient's treatment plan. Additionally, a new or another trial of intensive cognitive behavioral therapy for anxiety should considered.

Hypnotics

Insomnia may impact more than 70% of PWHA [91]. The treatment of insomnia should begin with identification and management of the underlying cause of insomnia by starting with evaluation of sleep schedule and hygiene, following guidelines such as those established by the American Academy of Sleep Medicine. Medications for acute and chronic insomnia should only be initiated after issues of sleep hygiene and sleep-disordered breathing are addressed, and while offering a sufficient trial of CBT for insomnia [92–94].

There are multiple medication classes that can be used for the management of insomnia, including sedative-hypnotics (e.g., benzodiazepines and non-benzodiazepine "Z"-drugs that directly affect GABAergic transmission), sedating antidepressants (e.g., trazodone, citalopram, doxepin, amitriptyline, mirtazapine that block wake-promoting neurotransmitters and are antihistaminic), antihistaminic antipsychotics (e.g., quetiapine), antihistamines (e.g., diphenhydramine, hydroxyzine), orexin antagonists (e.g., suvorexant), and melatonin/melatonin agonists (e.g., Rozerem) [95]. This section will focus on the "Z"-drugs, orexin antagonists, antihistamines, and trazodone (see Table 17.5). For all other categories of drugs (e.g., anxiolytics, antidepressants, antipsychotics, mood stabilizers), please see previous sections of this chapter.

All sedating or hypnotic medications share the potential for oversedation which may lead to ataxia and falls. Additionally, confusion, delirium, and memory impairment are also a risk, particularly with anticholinergic, benzodiazepine, and "Z"-drugs in the elderly and medically ill, with the more subtle symptoms being missed clinically. Importantly, many of the commonly used hypnotics are metabolized by CYP 3A4, to include the non-benzodiazepine "Z"-drugs, triazolobenzodiazepines, sedating antidepressants, and the dual orexin receptor antagonist (DORA) suvorexant. Therefore, co-administration of any of these medications with potent CYP 3A4 inhibitors such as protease inhibitors and the cobicistat-"boosted" integrase strand transfer inhibitor (INSTI) elvitegravir may lead to elevated serum levels of the hypnotics resulting in oversedation, ataxia, confusion, and delirium [96]. Nucleoside reverse transcriptase inhibitors (NRTIs) and the CCR5 antagonist maraviroc do not pose significant interaction concerns and do not require adjustment of the dosage of medications for insomnia.

Trazodone, initially developed as a novel antidepressant, is often used as a sedating medication, as well as for its antianxiety effects. Potent ART pan-inhibitors such as ritonavir may significantly increase trazodone serum levels, and since ritonavir also inhibits CYP 2D6, may also raise serum levels of trazodone's neurotoxic metabolite mCPP [97]. The cobicistat-"boosted" integrase strand transfer inhibitors (INSTI) elvitegravir (EVG) may also increase trazodone levels, whereas the other INSTIs (bictegravir, dolutegravir, and raltegravir) which do not require potent CYP inhibiting "boosters" have fewer potential interactions with trazodone. Metabolic inducers such the NNRTIs efavirenz and etravirine may "rev up" the metabolism of trazodone, resulting in the need to titrate the dose upward for effect [96].

Antihistamines have been available as over-the-counter sleep aids for decades. They cause initial drowsiness and prolonged "grogginess" for many patients thanks to being histamine H1 receptor antagonists. All sedating antihistamines inhibit CYP2D6, and therefore may increase serum concentrations of many psychotropics (e.g., SSRIs, TCAs) [98]. Fortunately, ARTs are not dependent upon this enzyme for metabolism, so pharmacokinetic interactions should not occur via this route. Care should be taken with use of anticholinergic/antihistaminic drugs in PLWHA who have developed HIV-associated neurocognitive disorder (HAND) or who are elderly, as they may be more prone to anticholinergic delirium [99, 100].

Case Vignette 17.5: Insomnia (New HIV dx)
Mr. T was a 29-year-old man who exclusively had unprotected sex with men and learned 1 week previously that he was HIV positive. He was placed on a regimen of dolutegravir (DTG) plus tenofovir/emtricitabine. Since his HIV diagnosis, he had been experiencing considerable initial insomnia associated with a fear that he would not respond to the antiretroviral regimen. The patient contacted his internist asking for assistance with his sleeplessness. What would be the best next step for managing his insomnia?

What Do You Do?
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Case 17.5 – "Mr. T" involves a patient who is anxious about his new HIV diagnosis, which is likely the primary cause of his insomnia. Additionally, dolutegravir (DTG) may also disturb sleep. An initial step is to rule out causes of his insomnia other than health-related anxiety and assess for poor sleep hygiene. Additionally, reassurance and supportive therapy would be of benefit. It is also strongly recommended to offer or refer Mr. T for CBT for insomnia if initial interventions are not helpful. If non-pharmacological interventions are not effective, the brief use (up to 2 weeks) of a "Z" medication such as eszopiclone may be helpful. Tenofovir and emtricitabine are not inhibitors nor inducers of metabolism, and since DTG is an INSTI that is not boosted by the potent CYP inhibitors ritonavir or cobicistat, it is not expected to affect the metabolism of eszopiclone [101].

Medications for Substance-Related and Addictive Disorders

Nearly one in four PLWHA meet criteria for a severe substance-related disorder [102]. HIV-infected people who use drugs (PWUD) have an increased prevalence of psychiatric, medical, and substance use disorders as well as resultant morbidity and mortality compared with PLWHA who do not use drugs. Appropriate medication-assisted therapy (MAT) can improve adherence to antiretroviral therapy and improve health outcomes in PLWH. However, there is a greater risk for drug-drug interactions and adverse drug events in this population, so it is key that HIV-infected PWUD receive evidence-based treatments that consider these possible interactions [103]. Please refer to Chap. 11 for more information about SUDs in PWHA, as well as Table 17.6 here.

Opioid Use Disorder

There are three Food and Drug Administration (FDA)-approved medications for treating opioid use disorder: buprenorphine, a partial opioid μ-receptor agonist and κ-receptor antagonist; methadone, an opioid μ-receptor agonist; and naltrexone, an opioid μ-receptor antagonist. Methadone has been in use for nearly 50 years, but remains the most highly regulated form of MAT, with its use restricted to licensed opioid treatment programs. Buprenorphine may be prescribed in an office setting, but requires a waiver. Both have been shown to be cost-effective measures and to decrease illicit opioid use, mortality, HIV transmission, injection drug use, and criminality. They have also been shown to increase employment and ART adherence. The combination of buprenorphine/naloxone has resulted in lower retention rates as compared to high-dose methadone [104].

Methadone

Methadone is metabolized primarily by CYP2C19 and CYP2B6, as well as CYP2A4, CYP2D6, CYP2C9, and CYP2C8, and is an inhibitor of CYP3A4 and CYP2D6. The complexity of drug interactions makes predicting clinical drug interactions difficult, but as a general rule, CYP inhibitors may not lead to clinically significant interactions, while CYP inducers may decrease methadone effects, resulting in the need for increased dosages of methadone to prevent withdrawal. Metabolic inducers such as efavirenz, nevirapine, ritonavir, or combinations of darunavir/ritonavir or lopinavir/ritonavir may reduce serum levels of methadone. Alternatively, methadone may inhibit glucuronidation of zidovudine and result in increased zidovudine levels. Monitoring and possible dose adjustments beyond that done in opioid treatment programs may be necessary for PLWHA co-prescribed methadone and ART [105, 106]. Additionally, methadone must be titrated slowly

Table 17.6 Medication-assisted treatment for substance use in HIV care

Psychotropic	Mechanism of action	Side effects/adverse reactions	DDI with ART and potential clinical effect	Notable clinical considerations in HIV care
Opioid use disorder				
Buprenorphine	Partial opioid μ-receptor agonist and κ-receptor antagonist	Headache Constipation Nausea Orthostatic hypotension Boxed warning: concomitant use with benzodiazepines may result in respiratory depression and death	CYP3A4 inhibitors may lead to increased levels of buprenorphine	Monitor clinical effects and adjust dose as necessary
Methadone	Opioid μ-receptor agonist	Constipation Sedation QT_c prolongation Boxed warning: addiction potential, QTc prolongation, respiratory depression with concomitant use of benzodiazepines	CYP inhibitors may not lead to clinically significant interactions, while CYP inducers decrease methadone effects Methadone may inhibit glucuronidation of zidovudine and result in increased zidovudine levels	Monitoring and dose adjustments may be necessary
Naltrexone	Opioid μ-receptor antagonist	Nausea Dizziness Rarely causes eosinophilic pneumonia and hepatotoxicity	Unlikely to have any clinically meaningful interaction with ART	
Alcohol use disorder				
Acamprosate	NMDA modulation, reducing glutamate transmission, and increasing GABA transmission	Diarrhea Nausea Anxiety	No significant drug interactions in the literature	

(continued)

Table 17.6 (continued)

Psychotropic	Mechanism of action	Side effects/adverse reactions	DDI with ART and potential clinical effect	Notable clinical considerations in HIV care
Disulfiram	Acetaldehyde dehydrogenase inhibition	Metallic taste flushing, nausea, vomiting (if consumed with alcohol) Rare potential for: Hepatotoxicity Cardiorespiratory Depression (if alcohol consumed) Delirium	When co-administered with disulfiram, efavirenz has been associated with increased aldehyde dehydrogenase activity, while atazanavir co-administered with disulfiram has been associated with reduced aldehyde dehydrogenase activity	
Naltrexone	Opioid receptor antagonism, leading to decreased dopamine signaling	See above	See above	See above
Tobacco cessation				
Bupropion	See above	See above	See above	See above
Nicotine	Nicotinic-cholinergic receptor agonism	Headache Oral irritation	No known interactions with ART	
Varenicline	α4β2 partial agonism	Nausea Abnormal dreams Affect lability Insomnia Although initial post-marketing data indicated increased neuropsychiatric events, this has not been borne out in further literature and boxed warning has been removed	No known interactions between varenicline and ART	Behavioral and mood should be monitored and may prompt drug discontinuation

with careful monitoring, due to prolongation of QTc, and potential for overdose at high doses. Other side effects include constipation, diaphoresis, and temporary amenorrhea [103].

Buprenorphine

Buprenorphine has been shown to be effective for the treatment of opioid use disorder and can be prescribed in the outpatient setting with a prescribing waiver. Buprenorphine is primarily metabolized by CYP3A4, and its metabolite, norbuprenorphine, has minimal ability to cross the blood-brain barrier [107]. Although there is significantly less interaction potential with ART, limited research has been done in this area. Among NRTIs, NNRTIs, entry inhibitors, and integrase inhibitors, there have been no clinically significant interactions noted. The protease inhibitor, atazanavir, however, inhibits CYP3A4, leading to increased levels of buprenorphine. Buprenorphine has not been shown to alter levels of ART [103]. Buprenorphine has a somewhat better safety profile when compared to methadone and is unlikely to cause overdose or respiratory depression in the absence of other sedatives. However, due to higher affinity for the opioid μ-receptor, it may precipitate withdrawal when prescribed to someone on other opioids [103].

Naltrexone

The evidence for oral naltrexone is less robust. While a 2011 Cochrane review of 13 studies demonstrated that the oral formulation of naltrexone for maintenance treatment of opioid dependence did not outperform placebo or other pharmacological treatments, retention in these studies was quite low [108]. Extended-release naltrexone is more effective, however, and has been shown to be comparable to buprenorphine for opioid relapse prevention [109, 110], and improved viral suppression in incarcerated PLWHA transitioning to the community [111]. Unlike methadone or buprenorphine, naltrexone has no effect on CYP450 metabolism and is unlikely to have any clinically meaningful interaction with ART [104]. Naltrexone may cause gastrointestinal upset, fatigue, insomnia, and dose-related hepatotoxicity and is contraindicated in acute hepatitis and acute liver failure. Like buprenorphine, it may precipitate opioid withdrawal for someone actively using opioids. It is safe to use in PLWHA, HCV, and alcohol use [112].

Alcohol Use Disorder

There are three FDA-approved medications for alcohol use disorder (AUD): naltrexone, an opioid receptor antagonist that decreases dopamine signaling; acamprosate, an NMDA modulator; and disulfiram, an acetaldehyde dehydrogenase inhibitor.

Naltrexone

Naltrexone is effective in treating AUD [113] and safe in PLWHA [114]. Extended-release naltrexone has more evidence in PWHA and has been shown to decrease heavy drinking days in PLWHA [115]. As mentioned in the opioid use disorder section, there are no interactions between naltrexone and ART. The reader is also reminded that naltrexone may cause gastrointestinal upset, fatigue, insomnia, and dose-related hepatotoxicity and is contraindicated in acute hepatitis and acute liver failure. Like buprenorphine, it may precipitate opioid withdrawal for someone actively using opioids. It is safe to use in PLWHA, HCV, and alcohol use [112].

Acamprosate

Acamprosate is less effective than naltrexone in AUD, and studies reveal conflicting results in efficacy. It has not been studied in PWHA, and has a large pill burden, which may impact adherence [103]. Acamprosate does not undergo metabolism and is excreted unaltered in the urine. There are no significant drug interactions in the literature. Acamprosate also has a limited side effect profile. A Cochrane review found that only diarrhea was more common in acamprosate than placebo [116].

Disulfiram

Disulfiram has been shown to decrease the number of days of heavy drinking and increase the time to relapse in HIV-negative individuals but has not been studied extensively in PLWHA. Therefore, its use should generally be restricted to those who are familiar with the drug and its complications [117]. Disulfiram is metabolized by CYP3A4/5, CYP1A2-2A6, and CYP2D6, and is an inhibitor of CYP2E1 and CYP1A2. Although the literature is sparse on disulfiram use with ART, when co-administered with disulfiram, efavirenz has been associated with increased aldehyde dehydrogenase activity, while atazanavir co-administered with disulfiram has been associated with reduced aldehyde dehydrogenase activity. However, disulfiram had no effect on ART in the study [117]. In the absence of alcohol, disulfiram is associated with few and mild side effects, such as drowsiness, headache, and garlic taste sensation. Hepatotoxicity is a rare, but generally reversible, complication. When co-ingested with ethanol, significant headaches, nausea, and vomiting result [118].

Tobacco Use Disorder

In addition to nicotine replacement therapy, there are two FDA-approved medications for tobacco use disorder: bupropion, a norepinephrine/dopamine reuptake inhibitor and α3β4 nicotinic receptor antagonist, and varenicline, a α4β2 partial agonist.

Nicotine

Although numerous trials have demonstrated the efficacy of nicotine replacement treatments (NRT) in healthy populations, this has not been systematically studied in PLWHA. In general, the greatest abstinence rates in tobacco use come from combining NRT with bupropion or include multiple forms of NRT [119]. Nicotine is primarily metabolized by CYP2A6 and CYP2A13 and has been shown to interact with minimal medications, none of which are ART. It is important to consider that hydrocarbons in tobacco smoke are inducers of CYP1A1/A2 and 2E2 and changes in the level of smoking may necessitate dose alterations in medications dependent upon these CYP enzymes such as second-generation antipsychotics [120, 121]. Nicotine most commonly can lead to headache, dizziness, insomnia, and withdrawal, but can also rarely lead to tachyarrhythmia or hypertension [103].

Bupropion

Bupropion has been shown to be an effective treatment for tobacco use disorder in various groups, especially when combined with NRT, but has not been systematically studied for this indication in PLWHA. However, it has demonstrated efficacy and safety in treating depression among PLWHA [119]. Bupropion is discussed in the section "Antidepressants" and in Table 17.3.

Varenicline

In two recent placebo-controlled trials, varenicline has been shown to be safe and efficacious for short-term smoking cessation among PLWHA, but less effective than when used in the general population [122, 123]. Varenicline is a substrate of OCT2 and undergoes only minimal metabolism. There are no known interactions between varenicline and ART and it is thought to be generally safe in this population [119]. Adverse effects of varenicline tend to be mild, including nausea, abnormal dreams, affect lability, and insomnia. Although initial post- marketing data indicating increased neuropsychiatric events has not been borne out in further literature, behavioral and mood should be monitored and may prompt drug discontinuation [119].

Case Vignette 17.6: Opioid Use Disorder (Chronic HIV dx)
Mr. Y was a 45-year-old man with HIV and opioid use disorder who presented to the clinic to establish care after his move 1 week previously from out of state. He reported that he had been started on a regimen of efavirenz, emtricitabine, and tenofovir disoproxil fumarate prior to his move, though he was not sure why. He also took methadone for his opioid use disorder. He had noticed that since his ART change and his relocation, he had been having increased irritability, sweating, diarrhea, and "goose flesh" with significant cravings for heroin, which he quit years ago. His CD4 count was 800 cells/mm^3 and viral load was undetectable.

What Do You Do?

**See the box on page 463*

Case 17.6 highlights the gradual metabolic induction of methadone by efavirenz. Methadone is metabolized by CYP3A4 and levels may be reduced by inducers such as efavirenz. If his ART regimen remains the same, he will likely need an increase of methadone until his withdrawal symptoms subside [47, 82, 86, 124, 125].

Summary and General "Pearls"

Over the past three decades, significant advancements in antiretroviral therapy (ART) have led to the development of sophisticated and potent regimens. However, currently available antiretrovirals (ARV) still pose significant challenges to both clinicians and patients.

Commonly used antiretrovirals are associated with improved tolerability when compared to older drugs, but they may still cause debilitating neuropsychiatric side effects that can affect adherence and quality of life. Efavirenz, a non-nucleoside reverse transcriptase inhibitor (NNRTI) that is rarely used currently, is, classically, the ARV most often associated with neuropsychiatric side effects. However, integrase strand transfer inhibitors (INSTIs), which are commonly used and are often prescribed as part of the initial regimen for newly diagnosed patients, are also known to cause neuropsychiatric effects that may range from mild (e.g., anxiety, insomnia) to severe, including depressive disorders with suicidal ideation. Although all members within this class have the potential to cause similar side effects, dolutegravir is associated with the highest risk. For this reason, it is prudent to carefully assess patients for a history of psychiatric disorders prior to the initiation of INSTIs and to monitor new symptoms during treatment. Chapter 16 provides more details about current ARVs.

Drug-drug interactions are an additional challenge, including when ARVs are co-prescribed with psychotropic medications. The use of ARV regimens that include pharmacokinetic enhancers (also commonly referred as "boosters"), such as ritonavir and cobicistat, increase the risk of drug-drug interactions because these "boosters" are potent modulators of several metabolic enzymes of the CYP450 system. On the other hand, psychotropic medications may inhibit or induce the metabolism of ARVs, potentially causing toxicity or treatment failure, with the consequent development of drug resistance. Because drug interactions with ARVs are often complex, we encourage a firm understanding of drug interaction principles as well as the use of online databases/software such as the links provided at the opening of this chapter, which take into consideration the dynamic interplay of polypharmacy, and are frequently updated.

MCQs

1. A PWHA and an ART regimen without significant CYP430 interactions presents with comorbid depressive disorder exhibits a significant wasting syndrome, with profound fatigue, poor concentration, insomnia, and 25 # weight loss. Which of the following antidepressants should be tried first, in light of these systemic symptoms?

   (a) Correct – mirtazapine (page 8)
   (b) Distractor – paroxetine
   (c) Distractor – bupropion
   (d) Distractor – venlafaxine

2. Treatment of a comorbid psychotic disorder in HIV poses specific clinical challenges in balancing HIV and antipsychotic medication. Especially with a chronic illness such as HIV, the clinician needs to attend to risks of cardiac complications such as prolonged QTc interval, and choose antipsychotic medication accordingly. Which of the following agents has the least risk of QTc prolongation?

   (a) Correct – cariprazine (page 14)
   (b) Distractor – risperidone
   (c) Distractor – ziprasidone
   (d) Distractor – clozapine

3. Bipolar disorder is commonly comorbid with HIV and poses many clinical management challenges in maintenance mood stabilization. Which of the following medications used for bipolar disorder has the least risk of drug interactions with HIV medications?

   (a) Correct – lithium (page 21)
   (b) Distractor – valproate
   (c) Distractor – carbamazepine
   (d) Distractor – lamotrigine

4. PWHA commonly present with comorbid symptoms of anxiety, either as a separate symptom referable to side effects of HIV meds, as an element of an anxiety disorder, or with mixed anxious/depressed mood in a depressive disorder. Due to its metabolism involving the CYP 3A4 enzyme, which of these anxiolytics should generally be avoided in HIV, to minimize the risk of DDIs with HIV meds?

   (a) Correct – alprazolam (page 24)
   (b) Distractor – lorazepam
   (c) Distractor – oxazepam
   (d) Distractor – temazepam

5. Sleep disorders are common in chronic illness, especially HIV. Such sleep symptoms often require the use of hypnotic medication for relief and better patient function. Trazodone, initially developed and approved as an antidepressant, is a useful hypnotic at sub-antidepressant doses. In HIV, some HIV medications can reduce the metabolism of trazodone, increasing blood levels and leading to excess sedation. Among the following HIV medications, which is the most problematic in this regard?

   (a) Correct – ritonavir (page 27)
   (b) Distractor – bictegravir
   (c) Distractor –dolutegravir
   (d) Distractor – raltegravir

6. Methadone has a complex metabolic profile, impacting several CYP enzymes, making its use in HIV challenging. Methadone is known to be an inhibitor of which of the following?

   (a) Correct – CYP3A4 (page 44)
   (b) Distractor – CYP2D6
   (c) Distractor – CYP2C9
   (d) Distractor – CYP2C8

7. Which of the following HIV meds is classically considered to be the ARV most often associated with neuropsychiatric side effects?

   (a) Correct – efavirenz (page 40)
   (b) Distractor – dolutegravir
   (c) Distractor – ritonavir
   (d) Distractor – raltegravir

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Chapter 18
Treatment of Comorbid HIV/HCV

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Introduction

Chronic hepatitis C infection is an important global health problem, affecting approximately 71 million people worldwide. Prevalence rates vary among countries, with the highest rates reported in Eastern Mediterranean regions [1]. In the USA alone, it is estimated that nearly 2.4 million people were living with HCV from 2013 through 2016, corresponding to approximately 1% of the adult population [2]. HCV was formally identified in 1989, but it was first described over a decade earlier, in 1975, in patients with transfusion-associated hepatitis who tested negative for hepatitis A and B [3]. However, it was not until 1992 that blood products started being screened for HCV, a crucial step at that time, because the receipt of contaminated blood products was then the primary cause of infection [4].

Presently, the most common mode of transmission is percutaneous through injection drug use, but less common modes of transmission, such as sexual and vertical transmissions, are also possible. In 20% of cases, hepatitis C resolves spontaneously through innate and adaptive immunity [5], but in the remaining cases, HCV infection causes chronic hepatitis, which can lead to cirrhosis, end-stage liver disease, and hepatocellular carcinoma. Treatment early in the course of HCV

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infection is of utmost importance because it can prevent viral transmission and disease progression and decrease hepatic morbidity and mortality [6].

Historically, the standard of care for patients with chronic HCV infection was interferon- and ribavirin-based regimens [4]. Interferon was first demonstrated to have benefit against HCV infection in 1986, when 5–15% of patients achieved sustained virologic response (SVR) after a 6–12-month course of interferon-alpha. The later addition of the oral nucleoside analog ribavirin substantially further increased response rates [7]. The development of long-acting pegylated interferon (peginterferon) provided the next advance in HCV therapy, as the new drug preparation had improved distribution and increased half-life, and the combination of peginterferon and ribavirin demonstrated even higher response rates. However, efficacy depended heavily on HCV serotypes, and the combination peginterferon-ribavirin was poorly tolerated with a high incidence of side effects. The introduction of pangenotypic direct-acting antiviral (DAA) drugs revolutionized the treatment of HCV infection. Interferon-free combination regimens are now the standard of care, given their improved efficacy (over 95% of sustained viral response) and decreased treatment duration [8].

HIV and HCV co-infection can also occur, leading to complex clinical challenges. According to the World Health Organization, 2.3 million people living with HIV have serologic evidence of past or present HCV infection, corresponding to approximately 6.3% of the estimated PLWH worldwide [1]. In this chapter, we discuss the clinical implications of HIV/HCV co-infection, including its neuropsychiatric complications, principles of HCV treatment, and potential interactions with other drugs, including psychotropic medications.

HIV/HCV Co-infection and Psychiatry

The clinical courses of both HCV and HIV are changed by dual infection. Although HCV infection likely has little effect on HIV progression per se, HCV infection worsens and progresses more quickly, leading to accelerated fibrosis, cirrhosis, liver failure, hepatocellular cancer, and increased HCV-related death in patients who are co-infected [9, 10]. With these issues in mind, patients with co-infection require close monitoring and interventions to protect liver function. If patients are diagnosed simultaneously with HIV and HCV, they should initiate treatment with ART, without delay, both for control of HIV and the secondary benefit of slowing the progression of HCV-induced liver damage [11].

Currently, there are no clear data on the epidemiology of alcohol use disorders and the co-infection; however, between 8% and 43% of patients with alcohol use disorder and comorbid liver disease have evidence of HCV infection [12]. Alcohol use increases the rate of liver disease progression [13], and, therefore, patients with co-infection should be counseled about avoiding or limiting alcohol use and avoiding hepatotoxic drugs, be screened for liver cancer every 6–12 months, and be evaluated for potential treatment options.

The neurocognitive and other psychiatric comorbidities of HIV/HCV co-infection are far-reaching and significantly influence the clinical presentation, care, and outcomes of persons with co-infection. In addition, the etiology and pathophysiology of neuropsychiatric disorders associated with HIV/HCV co-infection remain poorly understood, as do the specific nuances of clinical assessment and treatment. This represents a clinical dilemma, particularly considering the high and growing rate of HIV/HCV co-infection. Furthermore, the resulting neuropsychiatric complications may correlate with a decline in functionality, medication nonadherence, and poorer systemic medical outcomes. This illustrates the importance of a thorough understanding of the etiology, pathophysiology, assessment, and treatment of the potentially comorbid neuropsychiatric disorders. It is crucial for clinicians to fully understand the recognition and treatment of HIV/HCV neuropsychiatric complications in order to help to improve the quality of life of persons living with co-infection.

The prevalence of HIV among individuals with psychiatric disorders ranges between 1% and 23%, and the prevalence of HCV ranges between 9% and 30% [14]. It is clear that the rates of psychiatric disorders within the group of patients with HIV who are co-infected with HCV are the highest [15]. In a cohort of 6782 HIV/HCV co-infected US veterans, 76.1% met criteria for a comorbid psychiatric illness; the most common psychiatric diagnoses were major depressive disorder (56.6%) and substance use disorders (68%) [16]. Another smaller cross-sectional review of psychiatric illness in 67 co-infected persons showed that the most common diagnoses included past opioid use disorder (81%), past cocaine use disorder (73%), past depressive disorder (71%), current depressive disorder (42%), and past alcohol use disorder (47%) [17]. Other common diagnoses in this study include past "dysthymia" (19%), PTSD (19%), past childhood conduct disorder (16%), and past and current generalized anxiety disorder (11% and 10%, respectively) [17].

While data on prevalence of anxiety and psychotic disorders in persons with co-infection remain sparse, depressive and substance use disorders represent significantly prevalent comorbidities in the population with co-infection. A cohort study ($N = 131$) by von Giesen et al. [18] demonstrated increased prevalence and severity of depression in persons with co-infection relative to persons with HCV monoinfection. Noteworthy studies of persons with HIV suggest an association between comorbid hepatitis C and more severe and highly prevalent depressive symptoms [19, 20]. In a study of 264 persons with HIV, Clifford et al. [19] found that persons with co-infection tended to present with more depressive symptoms than those with HIV infection alone. A questionnaire study of 484 persons with HIV conducted by Braitstein et al. [20] found that persons with HCV presented with significantly higher depression severity scores, increased fatigue, and poorer quality of life. A multivariate analysis of the Braitstein et al. study concluded that these findings are probably attributable to social and demographic factors, rather than to hepatitis C alone. Moreover, Yoon et al. [21] analyzed the connection between HCV and depression in patients with HIV. They reviewed the data from 764 patients with HIV, among whom 21% were co-infected with HCV, and found a higher prevalence of depression among the co-infected group (46% compared to 32% in the group

without HCV). This association between HCV and the prevalence of depression remained after considering the association between past or current substance use and presence of somatic manifestations [21].

Although more studies are needed, research has consistently shown a staggeringly high prevalence of depressive disorders in persons with comorbid HIV and hepatitis C infection. These prevalence rates well exceed those of the population at large, and are generally higher than those seen in studies of other chronic systemic medical illnesses, including coronary artery disease, diabetes mellitus, chronic respiratory disorders, stroke, and cancer [22]. These findings underscore the importance of incorporating screening tools for depressive disorders—in addition to identification of any predisposing psychosocial factors in the persons with HIV/HCV co-infection—into the many levels of health care for co-infected persons, particularly because rates of medical and psychotherapeutic treatment of depressive disorders remain low among the medically ill [23].

In efforts to individualize approaches to screening and assessment and to clarify goals for the treatment of depressive disorders in persons with co-infection, the quality of depressive symptoms in relation to infection status also has been a topic of investigation. In a study investigating this issue in people who inject drugs, persons with HCV infection were found to have higher indicators of psychological stress, phobias, and psychoticism; persons with HIV reported more hopelessness and preoccupation with being ill; and co-infected persons more frequently reported somatic complaints [23]. A study by Hilsabeck et al. [24] partially replicated these findings and suggested that persons with co-infection tend to focus clinical complaints on somatic symptoms, but there were no significant group differences for symptoms of depression, anxiety, fatigue, or quality of life. This finding was further supported by Clifford et al. [19], whose group found that persons with co-infection tended to present more frequently with somatic depressive symptoms and depressive affect than the persons with HIV monoinfection.

While research remains limited in this domain, findings clearly suggest a strong focus on the somatic elements of psychiatric disease in persons with co-infection. As such, it would strongly benefit health-care providers to focus screening questions for depression on associated physical symptoms that include fatigue, changes in energy and appetite, and pain associated with depression. We postulate that the same probably holds true in screening for other psychiatric disorders among persons with co-infection and strongly encourage the use of screening tools for depression. The PHQ version of the Primary Care Evaluation of Mental Disorders diagnostic instrument may be the most clinically useful depression screen. The PHQ-9 [25] includes the nine items used to screen, diagnose, monitor, and measure the severity of a major depressive episode. The PHQ-9 is a valid, quick screening instrument for depression that also can be used as a follow-up to a positive PHQ-2 result and to monitor treatment response [26]. Such simple screening measures should be incorporated into the standard assessment of patients in the HIV primary care setting to better identify patients who are in need of treatment [27].

Substance use disorders present significant comorbidity among people with co-infection. In their cross-sectional review of 67 persons with co-infection, Ryan et al.

found that rates for dependence on psychostimulants, cannabis, alcohol, cocaine, and opiates were, respectively, 11%, 19%, 47%, 73%, and 81% for past dependence and 2%, 3%, 10%, 16%, and 13% for current dependence. A comparison between this sample and a matched 49-person sample of persons with HIV revealed significantly higher probability of persons with co-infection having a history of opioid, cocaine, and/or other psychostimulant use disorders. In addition, this study suggests that the likelihood of depressive disorders secondary to substance use is significantly greater in persons with co-infection than in persons with HIV monoinfection [17]. Considering that 10% of patients living with HIV are co-infected with HCV, the co-infection rates among people who inject drugs go up from 50% to 90% [28]. Therefore, HIV and HCV have become overlapping crises with the opioid addiction [29]. Contrary to these findings, another study showed a high rate of both current and lifetime alcohol abuse and drug abuse but not significantly higher lifetime rates of other psychiatric illness [30]. Backus et al. [16] further demonstrated significantly higher rates of alcohol and other substance use among 6782 US veterans with co-infection relative to 11,567 who have just HIV alone.

The negative influence of depressive symptoms and substance use on the quality of life for persons with co-infection has been clearly established. A cross-sectional survey of 115 persons conducted by Marcellin et al. [31] revealed the negative influence of depressive and fatigue symptoms on quality of life for more than half of the persons with the co-infection. While there are no clear indicators of significantly worsened quality of life that is primarily due to co-infection [20], studies consistently demonstrate that the comorbid psychiatric conditions and psychosocial stressors often associated with co-infection are independent predictors of diminished quality of life [20, 31]. Furthermore, a more recent study showed that the higher the depressive level and distress symptoms in patients with co-infection, the lower the health-related quality of life (HRQoL) profile score [32].

The neuropsychiatric manifestations of HIV/HCV co-infection are summarized in Table 18.1.

Evidence for a synergistic effect of HIV/HCV co-infection on neurocognitive dysfunction is increasing. Reaction time and processing speed are slower in persons with co-infection than in persons who have either HIV or hepatitis C monoinfection [19, 33–35]. In studies examining the effect of hepatitis C on neurocognitive functioning in persons with HIV with comorbid substance use, hepatitis C has been found to negatively affect neurocognitive functioning, even after considering HIV-related variables and substance use [36–38]. Richardson et al. [35] found that 52.9% (37/70) of women using drugs and who had co-infection exhibited clinically significant neurocognitive dysfunction compared with 37.3% (28/75) who had HIV infection alone and 37.0% (10/27) who had HCV infection alone. Moreover, Ryan et al. [17] demonstrated that there was a trend for patients who are co-infected compared to individuals with HIV alone to demonstrate worse neurocognitive function. On tests of executive functioning, individuals with co-infection compared with individuals with HIV monoinfection exhibited a greater rate of overall cognitive impairment, and decrements in sustained attention, psychomotor speed, and set shifting. Differences in cognitive functioning were associated with HCV serology but did not

Table 18.1 Manifestations of HIV/HCV Co-infection

Neurocognitive features	Other psychiatric features
More prominent and impairing in co-infection vs. HIV or HCV monoinfection	More prominent and impairing in co-infection vs. HIV or HCV monoinfection
Commonly impaired: 1. Reaction time 2. Processing speed 3. Attention 4. Verbal retrieval 5. Set shifting 6. Long-term memory tasks	Increased prevalence of: 1. Depressive disorders 2. Substance use disorders 3. Posttraumatic stress disorder 4. Generalized anxiety disorder
May be due to synergistic effects of both viruses	May significantly affect: 1. Quality of life 2. Medication adherence 3. Perception of treatment success and prognosis 4. Morbidity and mortality rates for both infections
Screened using: 1. Hopkins Verbal Learning Test-Revised 2. Grooved Pegboard Test 3. Wechsler Adult Intelligence Scale-Third Edition Digit Symbol Test	Screening and monitoring of depression using PHQ-2 and PHQ-9

correlate with indices of liver disease severity. The patients with HCV were also more likely to be diagnosed with HIV-associated dementia [17].

More recently, a study analyzed the expression of cognitive disorders in three categories of patients: those with HIV, those with HCV, and those with co-infection. The results showed that close to 40% of all participants showed minor cognitive impairment, and the prevalence was significantly higher in patients with co-infection (54%) compared to the patients in each monoinfection group [39]. Another important finding from this study is the worst performance in long-term memory tasks and speed of mental information in the group with co-infection, and depressive disorder appears to be an independent risk factor for cognitive impairment [39].

Given the increased probability and severity of neurocognitive deficits in populations with co-infection, the assessment of neurocognitive functioning is vital in identifying persons at risk for functional impairment, HIV-associated dementia (HAD), and/or delirium. Fortunately, the neurocognitive functions affected by HIV infection and hepatitis C are similar, and the brief screening batteries suggested by Carey et al. [40] for HIV-associated neurocognitive impairment are likely to be sensitive to neurocognitive deficits in persons with co-infection. The presence of neurocognitive dysfunction in patients with hepatitis C may have treatment implications that are important in managing co-infection. Please see Chap. 5 of this text for a more detailed discussion of screening for psychiatric disorders in persons with HIV.

The specific etiology of increased neurocognitive dysfunction in persons with co-infection is unknown. As noted above, substance use alone cannot explain the additive effect, nor can depression or fatigue [38]. It is likely that a synergistic effect of the two viruses is responsible [41]. For example, both HIV and HCV replicate in monocytes/macrophages and B and T cells [42], and HIV infection has been shown to facilitate HCV replication in macrophages [43]. Also, greater liver fibrosis may exacerbate neurocognitive dysfunction in co-infected persons, especially given that HIV has been shown to accelerate the progression of liver fibrosis in persons with hepatitis C [44].

Management Challenges of HIV/HCV Co-infection

Specific to the setting of co-infection is the lack of treatment of one infection that appears to hasten the progress of the other. Untreated HIV infection is a risk factor for more rapid progression of liver impairment in persons with hepatitis C, and worsened liver impairment due to hepatitis C is a major cause of morbidity and mortality in the HIV-infected population. Being co-infected with HCV and HIV is likely to be a marker for multiple coexisting problems, such as psychiatric (including substance use) disorders, as well as social issues, including lack of housing, support, and transportation, that contribute to poor access to care and to treatment barriers including medication adherence challenges [45]. Poverty, homelessness, social marginalization, and mistrust of the health-care system may all serve as barriers to treatment. Counseling strategies addressing self-management of illness, coping skills, and social support network should be incorporated in the treatment plan [45].

Patients with co-infection present specific challenges in the evaluation and treatment process. The neuropsychiatric (including neurocognitive) manifestations could be either occurring in the context of the co-infection or preexisting to the current illness, or even induced by the side effect profile of the patient's medication regimen. Because services for persons with complex comorbidities, especially neuropsychiatric disorders, are usually provided by clinicians of different professional disciplines in varying settings, fragmentation of care can lead to catastrophic consequences, such as lack of access to treatment and medication adherence issues, and eventually poorer outcomes. In a patient-centered care model, strategies to enhance communication and ongoing collaboration may facilitate an integrated interdisciplinary approach. Different models for integration of care for patients with co-infection have been tested, including HIV/HCV co-located clinics, integrating care for hepatitis C into primary care for HIV infection, and substance use treatment such as integrated care for opioid addiction [46]. Although evidence for effectiveness consists primarily of observational studies of demonstration programs, targeted integrated strategies have the highest potential to improve outcomes [47, 48]. Table 18.2 delineates the elements of an integrated approach to managing patients with co-infection.

Table 18.2 Elements of an integrated treatment approach for patients with co-infection

Focusing on patient-centered approach
Establishing a nonconfrontational empathic and culturally sensitive therapeutic relationship
Providing primary care services for treatment of HIV and HCV
Providing education about the co-infection, interactions between the two infections, treatment options, and treatment response and factors associated with poor response
Discussing patient's attitudes and beliefs about treatment options
Incorporating motivational interviewing strategies and techniques to address readiness for treatment/engagement and adherence to medical care and medications
Reviewing and assessing risks and benefits of treatments
Addressing barriers to general medical, psychiatric, and substance use treatments
Incorporating medication and treatment adherence interventions and risk reduction strategies
Screening, diagnosing, and treating comorbid systemic medical and psychiatric (including substance use) comorbidities
Integrating medication and psychotherapeutic approaches in addressing psychiatric (including substance use) disorders
Involving concerned significant others and family members in treatment planning with patient consent
Providing on-site psychiatric, social services, case management, and peer navigation
Referring to specialty care if necessary

Hepatitis C Viral Life Cycle

HCV is a positive-sense, single-stranded 9600 kb RNA virus of the *Flaviviridae* family, which is transmitted through blood-to-blood contact and primarily targets liver cells. After attaching to the cell surface, virus particles enter the cell via endocytosis and are then transported to acidified endosomes, the virus capsid is destroyed, and the viral RNA is released into the cytoplasm. RNA replication and polyprotein translation then occur: the HCV polyprotein is translated and cleaved by host and viral proteases into three structural proteins (core, E1, and E2) and seven nonstructural proteins (p7, NS2, NS3, NS4A, NS4B, NS5A, NS5B) [49]. The positive-sense viral RNA is then encapsulated and transported to the Golgi apparatus to finalize maturation. When the maturation is complete, the virions are transported to the plasma membrane using the VLDL pathway (see Fig. 18.1). Direct-acting antivirals (DAAs) disrupt viral replication by targeting four specific nonstructural proteins and comprise three pharmacological groups: NS3/4A protease inhibitors, NS5A polymerase inhibitors, and NS5B polymerase inhibitors.

Treatment of HCV Infection

The goal of HCV treatment is attainment of a sustained virologic response 12 weeks posttreatment (SVR12), which is considered an HCV cure by consensus guidelines [50]. Currently available DAAs used to manage HCV infection produce SVR12 for

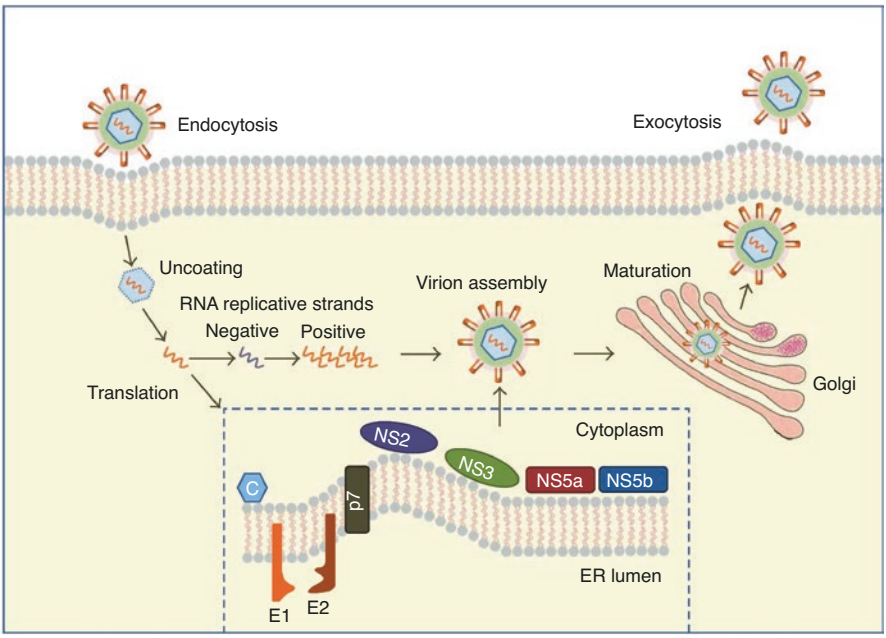

Fig. 18.1 HCV life cycle in host cell. (Reprinted from Lauletta et al. [83]. With permission from Creative Commons License 3.0: https://creativecommons.org/licenses/by/3.0/)

HCV in over 95% of patients [51–56], and similar results have been demonstrated in patients with HIV/HCV co-infection, a population who historically had lower response rates when treated with older HCV regimens [57–63]. Due to toxicity and inferior virologic response rates, regimens that utilized pegylated interferon with ribavirin are no longer recommended [50, 62–64]. Use of DAAs for HCV treatment has also been used with excellent SVR12 in patients who inject drugs (PWID) and in those using medication-assisted treatment for opioid use disorders [65–67].

DAA regimens are generally well tolerated, with the most common adverse events including headache, nausea, and fatigue [50–61]. Previous regimens that involved interferon-alpha were associated with significant and common adverse psychiatric symptoms, including severe depression in up to 30% of patients [62–64], but also agitation, anxiety, mania/hypomania, and psychosis, which have not been associated with newer DAA regimens [50–61]. In fact, in one small study evaluating DAA treatment, patients experienced no increase in depressive symptoms or sleep disturbances during DAA therapy [68]. Therefore, the need for active psychiatric care, especially centered around depression prior to and during HCV treatment with older regimens, is less common with DAA-based therapy [69]. However, psychiatry involvement is essential for patients undergoing HCV treatment, especially to promote treatment adherence, advocate for HCV treatment, and assess and monitor substance use disorders throughout HCV treatment. Since medications are efficacious, tolerable, and available across many populations, patients

should be encouraged to seek treatment for HCV, regardless of their comorbidities, including those with significant psychiatric disease.

The currently available DAAs recommended for use by the American Association for the Study of Liver Diseases (AASLD) guidelines belong to three classes of medications that target and inhibit HCV proteins: NS3/4A proteases and NS5A and NS5B polymerases [50]. Nomenclature for HCV medications has been standardized across different compounds, and the HCV enzyme target can be identified by the suffix of the generic name of the medication, e.g., all NS3/4A protease inhibitors end in "-previr," all NS5A inhibitors end in "-asvir," and all NS5B inhibitors end in "-buvir."

The AASLD has developed comprehensive guidelines for managing HCV infection; these should be consulted prior to initiating therapy for HCV, especially for patients who were treated previously and failed to respond, patients with end-stage hepatic disease, and/or patients with impaired renal function [50]. For untreated patients with minimal comorbidities, AASLD recommends the use of simplified treatment regimens, which involve the use of pangenotypic regimens glecaprevir/pibrentasvir or sofosbuvir/velpatasvir [50]. Both regimens provide excellent efficacy across all HCV genotypes (genotypes 1–6)—the reason why they are called pangenotypic—and have demonstrated SVR12 rates in over 95% of previously untreated patients [50–56]. In order to delineate which patients qualify for simplified treatment, AASLD also provides patient characteristics that are summarized in Table 18.3.

Prior to initiating HCV therapy with DAAs, a careful clinical assessment is recommended, including collecting key clinical information, which is summarized in Table 18.4 [50].

The availability of the pangenotypic regimens, which include glecaprevir/pibrentasvir and sofosbuvir/velpatasvir, has made the process of selecting medication for HCV easier, even though genotype-specific regimens may still be used. Differences in cost, duration of treatment (i.e., 8 weeks vs. 12 weeks), number of daily tablets, presence of end-organ damage, potential drug interactions, and other comorbidities are significant factors in DAA regimen selection [50, 55, 70–72]. For more detailed guidance on regimen selection, providers are encouraged to review the AASLD guidelines for further direction [50].

Table 18.3 Patients who do not qualify for simplified treatment

Patients who have any of the following characteristics:
Prior hepatitis C treatment
Cirrhosis (except for treatment-naive adults with compensated cirrhosis)
End-stage renal disease (eGFR < 30 mL/min/m^2)
HIV or HBsAg positive
Current pregnancy
Known or suspected hepatocellular carcinoma
Prior liver transplantation

Based on data from Ref. [50]

Table 18.4 Selected pre-treatment assessments for HCV treatment

Cirrhosis assessment: FIB-4[a] score > 3.25 **or** any of the following findings from a previously performed test:
Transient elastography indicating cirrhosis
Noninvasive serologic tests indicating cirrhosis
Clinical evidence of cirrhosis
Prior liver biopsy showing cirrhosis
Medication reconciliation: Record current medications, including over-the-counter drugs and herbal/dietary supplements and assess potential drug-drug interactions
Pretreatment laboratory testing:
Complete blood count
Hepatic panel (e.g., albumin, total and direct bilirubin, alanine aminotransferase [ALT], aspartate aminotransferase [AST])
Calculated glomerular filtration rate (eGFR)
Quantitative HCV RNA (HCV viral load)
HIV antigen/antibody test
Hepatitis B surface antigen
Serum pregnancy testing

[a]Fibrosis-4 index for liver fibrosis, which is a noninvasive estimate of liver fibrosis based on age, AST, ALT, and platelet count

Drug Interactions with DAAs

Despite excellent tolerability and efficacy with DAA-based regimens, drug-drug interactions continue to be a challenge. This is especially important when using HCV regimens that include an NS3/4A protease inhibitor and in patients with complex comorbidities such as HIV/HCV co-infection and in those who have undergone transplantation [50, 73, 74].

DAAs generally interact with other drugs through one of two broad mechanisms: those that effect either metabolism or absorption [50]. Because many of the DAAs are either substrates, inhibitors, or inducers of the CYP450 system and other transporters, the potential for drug interactions is significant [73–77]. The outcome of these interactions generally results in one of three results: (1) an increase in HCV medication levels that may lead to toxicity; (2) a significant reduction in HCV medication levels that may lead to HCV treatment failure or resistance; or (3) the HCV medications may lead to an increase in drug levels of concurrent medication, with potential toxicity. Table 18.5 lists the metabolism and genotype coverage for DAA-containing regimens.

As discussed in Chap. 16, the current US Department of Health and Human Services Guidelines for the Treatment of Adults and Adolescents have established consensus recommendations which guide initial therapy for patients with HIV [79]. Most patients infected in recent years are started on an integrase strand transfer inhibitor (INSTI)-based regimen with two nucleoside reverse transcriptase inhibitors. With the exception of elvitegravir (which requires cobicistat for pharmacokinetic boosting), INSTI-based regimens are less likely to interact with DDA regimens.

Table 18.5 HCV DAA regimens, genotypic coverage, and metabolism [50, 73–78]

HCV medication, mechanism, and genotype (GT) coverage	HCV medication drug metabolism
Pangenotypic regimens, simplified treatment regimens	
Glecaprevir/pibrentasvir NS3/4A protease inhibitor and an NS5A inhibitor	Glecaprevir and pibrentasvir are inhibitors of Pgp, BCRP, and OATP1B1/3; weak inhibitors of CYP3A4, CYP1A2, and UGT 1A1
Sofosbuvir/velpatasvir NS5B inhibitor and an N5a inhibitor	Sofosbuvir is a substrate for P-gp and BCRP; metabolism mediated by hydrolase and nucleotide phosphorylation pathways Velpatasvir is an inhibitor of Pgp, BCRP, OATP1B1, OATP1B3, and OATP2B1
GT 1 and 4 regimens, only	
Elbasvir/grazoprevir NS5A inhibitor and an NS3/4A protease inhibitor	Elbasvir and grazoprevir are substrates of CYP3A4 and P-gp Grazoprevir is a substrate of OATP1B1/3
Sofosbuvir/Ledipasvir NS5B inhibitor and an N5A inhibitor	Sofosbuvir is a substrate for P-gp and BCRP; metabolism mediated by hydrolase and nucleotide phosphorylation pathways Ledipasvir is an inhibitor of P-gp and BCRP
Pangenotypic regimen, reserved for prior treatment failures	
Sofosbuvir/velpatasvir/voxilaprevir NS5B inhibitor, N5A inhibitor, and NS3/4A protease inhibitor	Sofosbuvir is a substrate for P-gp and BCRP; metabolism mediated by hydrolase and nucleotide phosphorylation pathways Velpatasvir is an inhibitor of P-gp, BCRP, OATP1B1, OATP1B3, and OATP2B1 Voxilaprevir is a substrate for P-gp, BCRP, OATP1B1, and OATP1B3

P-gp P-glycoprotein, *BCRP* breast cancer resistance protein, *OATP* organic anion transporting polypeptide, *UGT* uridine glucuronosyltransferase

Patients receiving older non-nucleoside reverse transcriptase inhibitors (e.g., efavirenz, nevirapine) and protease inhibitor-based regimens are more likely to experience significant drug interactions when initiating DAA treatment. Management of DAA and HIV treatment interactions may lead to the selection of an alternative DAA regimen or require a change in HIV regimen to accommodate HCV treatment. Table 18.6 contains a list of DAA regimens and HIV medications that should be avoided [50, 73–77, 79].

Primary Care Medication Use with DAAs

As patients with HCV infection are often seen in complex medical settings, it is noteworthy to consider drug interactions with primary care medications. Numerous classes of medications may potentially lead to interactions with the DDAs used in HCV management. These include antacids, antiarrhythmics, anticoagulants, anticonvulsants, herbal products, and statins [50, 73–77, 79]. Because some DAAs

Table 18.6 HIV medications to avoid or monitor with HCV DAA therapy [50, 73–77, 79]

HCV DAA	HIV medication to avoid or monitor during DAA treatment
Glecaprevir/ pibrentasvir	Avoid with atazanavir-, efavirenz-, etravirine-, nevirapine-, or ritonavir-containing regimens Glecaprevir exposures are increased with elvitegravir/cobicistat; monitoring for hepatic toxicity is recommended
Sofosbuvir/ velpatasvir	Avoid with efavirenz, etravirine, or nevirapine Renal monitoring is recommended in patients taking tenofovir disoproxil fumarate and cobicistat- or ritonavir-containing regimens Tenofovir alafenamide may be an alternative
Elbasvir/grazoprevir	Avoid with cobicistat, efavirenz, etravirine, nevirapine, or any HIV protease inhibitor
Sofosbuvir/ledipasvir	Tenofovir levels increased when tenofovir disoproxil fumarate is administered with cobicistat- or ritonavir- containing regimens Renal monitoring is recommended during the dosing period Tenofovir alafenamide may be an alternative
Sofosbuvir/ velpatasvir/ voxilaprevir	Avoid with efavirenz, etravirine, nevirapine, ritonavir-boosted atazanavir, or ritonavir-boosted lopinavir Voxilaprevir exposures are increased with darunavir/ritonavir or elvitegravir/cobicistat monitoring for hepatic toxicity is recommended Potential increase in tenofovir levels when given with tenofovir disoproxil fumarate Avoided in those with an eGFR <60 mL/min Renal monitoring is recommended during the dosing period if tenofovir disoproxil fumarate is combined with cobicistat- or ritonavir-containing regimens

require an acidic environment for adequate absorption, the use of over-the-counter antacids, H2 receptor antagonists, and proton pump inhibitors may require dosage adjustments or dosage separation; this is particularly true for patients receiving sofosbuvir/velpatasvir, sofosbuvir/ledipasvir, and sofosbuvir/velpatasvir/voxilaprevir [75–77]. Post-marketing reports of severe bradycardia have been reported with concurrent sofosbuvir and amiodarone, especially in patients with underlying cardiac abnormalities and those receiving concurrent beta-blockers or experiencing advanced liver disease [80]. Due to its inhibition of P-gp transport pump, glecaprevir/pibrentasvir can increase digoxin levels by approximately 50% [74]. INR monitoring is also recommended for patients receiving sofosbuvir and warfarin [75–77]. Finally, the use of HMGCoA reductase inhibitors is also likely to interact with DAA-based therapy [50, 73–77, 79].

Psychotropic Medication Use with DAAs

Despite the risk of drug interactions with common primary care medications, the use of most psychotropic medications with DAAs is unlikely to result in significant interactions. Older anticonvulsants used for bipolar disorder can induce the CYP450

system and transporters involved with DAA metabolism leading to significant reductions in DAA drug levels. Carbamazepine, a known inducer of P-gp and CYP3A4, has been shown to reduce the drug levels of glecaprevir by 66% and of pibrentasvir by 51%; carbamazepine also reduced the levels of sofosbuvir by 48% [50, 74–77, 79]. Carbamazepine should be avoided with all DAAs due to the risk of HCV treatment failure and HCV drug resistance. Other anticonvulsants also known to induce hepatic drug metabolism, e.g., oxcarbazepine, phenobarbital, and phenytoin, should also be avoided with DDAs [50, 73–77, 79]. Primidone, which may be used in treatment-refractory bipolar disorder, is metabolized to phenobarbital and, therefore, a similar interaction would be expected [81]. St. John's wort, a supplement that can be used for depressive disorders, would also be expected to significantly reduce drug levels of all DAAs by inducing the CYP system as well as the P-gp [50, 73–77, 79].

CYP3A4 inhibitors (e.g., ritonavir, ketoconazole, cobicistat) may lead to increased drug levels and potential toxicity of concurrently administered medications. While this is more of a concern with strong inhibitors of CYP3A4 and P-gp, less potent CYP3A4 inhibitors still have the potential for increasing drug levels of other medications metabolized by the same isoenzyme. Glecaprevir/pibrentasvir is a weak inhibitor of CYP3A4, and therefore blood levels of psychotropic medications metabolized by CYP3A4 (including quetiapine, lurasidone, or aripiprazole) could be increased when combined with these DAAs [74, 82]. While these interactions have not been documented, providers should be cautious when combining these medications and monitor patients closely for antipsychotic toxicity, including prolonged QTc interval and excess sedation.

Online resources and tables are available for assistance in checking regimens for potential drug interactions [79, 82]. Providers are encouraged to utilize the *University of Liverpool Hep Drug Interaction Checker* or the DHHS Guidelines drug interaction tables to assist in reviewing drug interactions prior to starting DAA or psychotropic treatment [79, 82]. Please refer to Chap. 17 of this text for more detailed discussions of antiretroviral therapy and psychotropic medications.

In summary, use of DAA therapy for HCV results in SVR12 in over 95% for patients new to treatment. Guidance is available through the AASLD to assist with HCV regimen selection [50–56]. Treatment of HIV/HCV co-infection with DAAs may lead to interactions with HIV treatment, though the use of INSTI-based regimens has minimized their impact [50, 73–77, 79]. Use of DAAs with certain primary care medications may occur and interactions with psychiatric medications are manageable [50, 73–77, 79]. Medications known to induce CYP3A4 and P-p should be avoided with DAA regimens, including carbamazepine, oxcarbazepine, phenobarbital, phenytoin, primidone, and St. John's wort [50, 73–77, 79]. Patients receiving glecaprevir/pibrentasvir should be monitored closely for adverse events when combined with those psychiatric medications metabolized via CYP3A4 [82].

Conclusions

Infection with hepatitis C is prevalent throughout the world and is responsible for significant morbidity. In part because they share similar modes of transmission, co-infection with HIV and HCV is estimated to affect up to 6.3% of persons living with HIV infection. This finding has important clinical consequences because co-infection changes the natural history of each monoinfection. In particular, HIV is known to accelerate the progression of HCV-associated liver complications, underlying the importance of early diagnosis and treatment. Antiviral treatment for HCV has evolved in recent years from inadequately effective medications with significant side effects to well-tolerated highly effective drugs. The new direct-acting antivirals (DAAs) can achieve sustained viral response at 12 weeks in over 95% of the cases, but important drug-drug interactions must be considered, in particular with medications that affect the CYP3A4 system. Finally, HIV/HCV co-infection is associated with an increased prevalence of psychiatric disorders. Depressive disorders in patients with co-infection are more likely to present with somatic symptoms when compared to patients with HIV monoinfection. Substance use disorders often coexist with co-infection and may be the mode of transmission for both viruses. The diagnosis and treatment of alcohol use disorders are of utmost importance in this population because alcohol use can precipitate or exacerbate existing liver disease and therefore impact both the quality of life and mortality. Prevention, recognition, and treatment of both HIV and HCV have multiple and complex psychiatric and psychosocial implications and require a comprehensive and integrated approach to improve quality of life and decrease morbidity and mortality.

Questions

1. Which of the following statements is true regarding the neuropsychiatric aspects of HIV/HCV co-infection?

   A. Neurocognitive disorders are very well studied and are clearly distinct from HIV-associated neurocognitive disorder.
   B. It is important to screen patients for alcohol use disorders because of its implications in the progression of liver disease.
   C. Anxiety disorders are the most commonly described psychiatric complications in patients with HIV/HCV co-infection.
   D. Psychotic disorders are commonly associated with HIV/HCV co-infection.

Answer: Unfortunately, many neuropsychiatric aspects of HCV/HIV co-infection are still not well understood, including the pathophysiology and clinical presentation of neurocognitive disorders specific to co-infection. Depressive and substance

use disorders are the most common psychiatric disorders described in patients with co-infection, and studies have suggested that depressive syndromes tend to manifest with somatic complaints. Screening for alcohol abuse is of utmost importance in patients with co-infection, as alcohol use may increase the progression of hepatic complications in this population. Option B is correct.

2. Which of the following psychiatric medications can lead to a significant reduction in the blood levels of sofosbuvir?

   A. Escitalopram
   B. Haloperidol
   C. Lorazepam
   D. Carbamazepine

Answer: Sofosbuvir is metabolized by CYP3A4, and strong inducers of this isoenzyme, such as carbamazepine, can lead to a significant reduction in the blood levels of this antiviral and consequently to HCV treatment failure or HCV drug resistance. Escitalopram, haloperidol, and lorazepam are not strong inducers of the CYP3A4. Option D is correct.

3. Which of the following HCV treatment combinations are considered pangenotypic—i.e., they are effective in treating all HCV genotypes?

   A. Ledipasvir/sofosbuvir
   B. Sofosbuvir/velpatasvir
   C. Elbasvir/grazoprevir
   D. None of the above

Answer: Pangenotypic regimens include sofosbuvir/velpatasvir and glecaprevir/pibrentasvir—in addition sofosbuvir/velpatasvir/voxilaprevir would also cover all genotypes. Option B is correct.

4. Which medications listed below is classified as an HCV NS5a inhibitor?

   A. Glecaprevir
   B. Sofosbuvir
   C. Ledipasvir
   D. Voxilaprevir

Answer: Remember that all NS5a inhibitors end in "asvir," NS5b inhibitors end in "buvir," and all HCV protease inhibitors end in "previr." The correct answer is ledipasvir. Option C is correct.

5. Which of the following HCV treatment regimens are likely to interact with amiodarone?

   A. Ledipasvir/sofosbuvir
   B. Sofosbuvir/velpatasvir

C. Sofosbuvir/velpatasvir/voxilaprevir
D. All of the above

Answer: Post-marketing reports of severe bradycardia have been reported with the use of sofosbuvir-containing regimens, especially for those receiving concurrent beta-blocker therapy. The use of amiodarone with sofosbuvir should be avoided. Option D is correct.

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Chapter 19
Integrated and Collaborative Care

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Introduction

HIV affects the mind and body extensively. Biological stressors of HIV include viral persistence and inflammation in the central nervous system (CNS), secondary opportunistic CNS infections and neoplasms, and neurotoxicity of antiretroviral therapy. Alterations of the neuroendocrine axis [1] and autonomic nervous system [2], chronic immune activation, and impaired gut mucosal immunity [3] are some of the systemic effects of HIV. Several psychological reactions to having HIV have been described, which may cause distress and impede successful management of HIV [4]. In addition to biological and psychological factors, social, cultural, and political factors in the environment, such as HIV and mental illness stigma and discrimination, housing instability, incarceration, intimate partner violence, and discrimination due to minority status, are some of the social problems plaguing patients with HIV. These stressors contribute to an increased prevalence of comorbid neuropsychiatric disorders concomitant with HIV infection. Since neuropsychiatric disorders cause suffering, impact the course of HIV, and interfere with efforts to end the HIV epidemic, psychiatric care is vital to HIV care.

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Many patients with HIV receive care for neuropsychiatric disorders in HIV primary care clinics. This is at least partially due to a shortage of mental health specialists, which leads to long wait times and inadequate continuity of care. Stigma of mental illness can also be a major barrier to people seeking psychiatric care in mental health settings. In people with HIV, the stigma of mental illness is compounded by that of having HIV. Patients frequently fear discrimination and rejection and may avoid leaving HIV primary care settings to seek treatment in other settings. As a consequence, there is a need to provide psychiatric care in a setting that is accessible to, acceptable to, and supportive of the patient. Such a need also offers a tremendous opportunity to provide integrated biopsychosocial approaches to treat the whole patient with HIV.

There are several integrated care models by which psychiatric care can be provided to patients with HIV. Integrated models of care for HIV psychiatry refer to a psychiatrist specializing in HIV psychiatry working closely with patients and other physicians to provide coordinated care for complex patients with HIV. Rarely is any model implemented in "complete" form. Rather, implementing integrated care involves local adaptations, based on availability of clinical resources, acceptability in existing clinic culture, and additions of clinical resources to address gaps in treatment. Integration occurs on a continuum, often starting with small changes and building on gains. Successful integration efforts capitalize on the strengths of team members and structure, occur in stages, and allow for revision based on feedback from clinicians and patients. Maintaining a dialogue among those who are developing and are impacted by integrated care programs is essential. Input from all stakeholders impacted by healthcare integration is important to make the organizational changes necessary to properly implement an integrated care system.

Telepsychiatry is a useful technology to improve patients' access to psychiatric care and can be leveraged in any of the integrated care models [5]. It can enhance communication among clinical team members working at different sites. It can also be used to provide education and "curbside consultation" to HIV clinicians.

In this chapter, we describe four models of integrated care that can be applied to HIV psychiatry: the consultation and referral model, the co-located model, the patient-centered medical home (PCMH), and the collaborative care model. Within our discussion of collaborative care, we describe key components, summarize the evidence base for collaborative care, list roles of key members of the collaborative care team, and identify essential areas of workforce training. We detail a systematic approach to screening, diagnosis, treatment, and monitoring. Some of the complexities of providing collaborative care for HIV, including stigma, isolation, and high rates of neuropsychiatric comorbidities, will be illustrated via patient cases.

Consultation and Referral Model

Consultation-liaison psychiatrists with expertise in HIV psychiatry have long functioned in the consultation and referral model [6]. In this model, the HIV clinician recommends that the patient obtain assessment and treatment from a psychiatrist. The choice of psychiatrist may be one with whom the HIV clinician is familiar. The

psychiatrist need not be physically co-located with the primary medical team, nor must there necessarily be any formal communication between the psychiatrist and the referring clinician. While this model can provide valuable evaluation and treatment, the system-based elements necessary for optimum care integration are lacking. The psychiatrist and the referring clinician may use different health records, making reciprocal access to diagnostic formulations and treatment recommendations challenging. Patients may not be willing to go to a different clinic or office to see a psychiatrist and, consequently, recommended referrals are sometimes left uncompleted. There may be a shortage of available psychiatrists to accept referrals, making completion of the referral and provision of ongoing care challenging. Participation of the psychiatrist in integrated team meetings, shared electronic health records, and informal "curbside consultations" is often absent in this model. Contemporary standards of healthcare integration are often unmet in the referral and consultation model.

Co-located Model

In the co-located model, the psychiatrist works physically within the HIV clinic. The psychiatrist sees some of the patients in the HIV clinic. In some settings, health psychologists are also co-located in HIV clinics to provide psychotherapy services. This model is convenient for the patient, because mental healthcare is being given within the same physical location where other medical care is given. The patient may have an attachment to the institution, which may carry over to the relationship with the psychiatrist or the psychologist. Communication among the mental health clinicians and the HIV team members is improved, due to physical proximity and shared electronic health records. One of the limitations of the model is that the mental health clinician's panel of patients fills up quickly, leading to increased wait times and limited ability to provide continuity of care at the desired frequency. Psychiatrists often spend their time providing billable services for an individual patient's evaluation and management, and time may not be allocated for other services, such as curbside consultations or participation in team meetings of patients with complex needs.

As is apparent, there are many facets to integration of psychiatric care into HIV care: ready availability of psychiatric evaluation and treatment, working in the same physical space as the HIV physicians and staff, access to curbside consultations with a psychiatrist, involvement of a psychiatrist at team discussions of complex patients, and common record keeping in the form of shared electronic health records.

Patient-Centered Medical Home

The patient-centered medical home (PCMH) is a comprehensive integrated care model for organizing and delivering primary care that achieves many of the above-mentioned features of integrated care. In a PCMH, the primary care physician leads the treatment for the patient in the physical location of the medical home, making

use of specialists as needed. HIV-specific PCMH settings are useful due to the unique nature of HIV treatment (clinical complexity, social context of HIV, and gaps in HIV care) in PCMH [7]. Care in a PCMH spans preventive, routine, and acute care, and encompasses physical and mental healthcare.

As the name of the model would suggest, patient-centered care is a central tenet of a PCMH. A patient is the primary agent in his/her healthcare, and therefore is at the center of all care delivered. Responding to the individual needs of the patient, being respectful of the patient's values, prioritizing patient preferences, involving patients and their personal supports in decision-making, and providing culturally competent care are some of the elements of patient-centered care. Several minorities such as Latino/a, African-American, lesbian, gay, or transgender groups are disproportionally represented in HIV populations. Further, there are geographic areas where HIV is concentrated, causing micro-epidemics. Familiarity with the subcultures of patients and geographic regions in addition to understanding the history and values of each patient is relevant to providing patient-centered care to people with HIV.

Care in the PCMH is coordinated across the continuum of care – primary, specialty, hospital-based, home-healthcares, and community supports. Care coordinators are a vital component of a PCMH, organizing the various clinical team members' efforts and ensuring continuity of care as patients move between healthcare settings.

Mental health integration (sometimes called behavioral health integration) has become a priority in PCMHs. Such integration occurs on a spectrum, and the degree to which the primary care physician and the mental health clinician partner in caring for patients and families is variable. A psychiatrist who works in a PCMH may directly evaluate and treat complex patients as needed but could also provide a single in-person consultation or "curbside consultation" on a large volume of clinic patients. A psychiatrist's services can be provided in person or through telepsychiatry. Health information technology such as texting, emailing, and web-based platforms can be used to deliver education to HIV clinicians and care to patients. A PCMH provides the prospect of a high level of mental health integration [8].

The literature on PCMHs in HIV is sparse, and on mental health integration in HIV-specific PCMHs, even more so. A PCMH designed for homeless people with HIV and a comorbid psychiatric (including substance use) disorder found that care coordination and support delivered via patient navigators had a positive impact on housing stability and improved access to medical care [9]. Qualitative data from PCMH demonstration projects in HIV care settings acknowledge the need for integrated mental health given the disproportionate burden of psychiatric disorders including substance use disorders in HIV relative to non-HIV settings [10]. There is no consensus on what such mental health integration might look like in a PCMH specific to HIV. While the PCMH has many strengths and has the necessary scaffolding to provide full integration of mental healthcare with HIV care, applying the principles of a PCMH to proactively identify and systematically treat psychiatric disorders remained necessary.

Collaborative Care Model

The strides made in the PCMH provided the framework for the *collaborative care model*. The collaborative care model is an evidence-based, fully integrated care model that is well suited to providing mental healthcare for commonly co-occurring psychiatric disorders in a variety of chronic systemic medical diseases. The collaborative care model utilizes many of the principles of a PCMH, such as patient-centered care, population-based care, coordinated care, and evidence-based care, and applies them to the treatment of psychiatric disorders. The collaborative care model is derived from the field of consultation-liaison psychiatry. It is best implemented on the premises of the consultation-liaison psychiatry model and a biopsychosocial approach to care.

Evidence for the Effectiveness of Collaborative Care

The earliest trials of collaborative care for depressive disorders in the systemic medically ill patient derived from innovations in the 1980s and 1990s, such as the chronic care model and the patient-centered medical home, which identified the need to redesign healthcare delivery in order to more effectively treat chronic systemic medical conditions [11]. Because previous work identified a high prevalence of depressive disorders in primary care settings with significant associated systemic medical comorbidity and impact of comorbid psychiatric illness on general medical outcomes, these studies focused on deploying collaborative care in primary care settings in order to improve depression-related outcomes [12]. An early important study was the IMPACT (Improving Mood-Promoting Access to Collaborative Treatment) trial in which collaborative care was compared to treatment as usual among 1801 patients across 18 clinics spanning 8 healthcare systems and 5 states [13]. This large study found that collaborative care produced superior outcomes including symptoms of depression, patient satisfaction, and functional impairment. These superior outcomes were found 18 and 24 months out from the 12-month intervention [14].

Another important development in collaborative care research has been focusing on "natural clusters" of illnesses in order to develop collaborative care interventions that simultaneously target several linked comorbid conditions [12]. The rationale is that single interventions that target linked chronic conditions are more cost-effective than multiple interventions for discrete diseases. Addressing the prevalence and negative impact of depressive disorders in patients with diabetes mellitus and coronary artery disease, the TEAMcare trial examined the effect of a collaborative care intervention on a combined measure of health that included depression score, hemoglobin A1C levels, LDL levels, and systolic blood pressure, and found a significantly greater overall improvement in clinical outcomes with the collaborative care intervention than in the control group [15]. This focus on natural illness clusters

may have useful implications for HIV, where depression is linked to a number of HIV-related illness outcomes.

Further research has expanded beyond depressive disorders to include the effectiveness of collaborative care in management of bipolar disorder [16], PTSD [17], anxiety disorders [18], and chronic pain disorder [19]. Studies have also focused on specific populations such as the elderly [14, 20], adolescents [21], women [22], and patients with cancer [23]. There have also now been a number of large-scale collaborative care implementation efforts, including the Translating Initiatives for Depression into Effective Solutions (TIDES) model in the Department of Veterans Affairs [24], the Depression Improvement Across Minnesota, Offering a New Direction (DIAMOND) effort in Minnesota [25], a roll-out of collaborative care in the Kaiser Permanente healthcare system [26], and the Care Of Mental, Physical And Substance-use Syndromes (COMPASS) project [27].

Collaborative Care in HIV

The fact that depressive disorders are highly prevalent in patients with HIV [28, 29], are associated with poorer antiretroviral medication adherence, and are linked to poor HIV-related clinical outcomes [30] has generated interest in developing the collaborative care model to improve the management of depressive disorders and chronic illness management in persons with HIV. The Department of Veterans Affairs provides the most HIV care in the United States and had developed the TIDES model for collaborative care in general primary care settings and has now implemented and studied the impact of a model of collaborative care for HIV, known as HITIDES (HIV Translating Initiatives for Depression into Effective Solutions) [31]. In this intervention, an off-site site nurse depression care manager, pharmacist, and psychiatrist made up the depression care team and provided remote support to clinic HIV and mental health staff. They provided regular telephone follow-up with patients using a measurement-based, stepped-care algorithm supported by a web-based decision support system. A randomized controlled trial of this intervention among 249 patients in three VA clinics found that, compared with usual care, patients in the collaborative care intervention showed greater rates of depression treatment response and remission at 6 months [32]. Among its secondary outcomes, the study did not find a significant difference in antiretroviral adherence between the two groups, which may be explained by a ceiling effect produced by relatively high baseline adherence between groups [33].

In contrast to the HITIDES study which examined depression symptom response as its primary outcome, in the Strategies to Link Antiretroviral and Antidepressant Management (SLAM-DUNC) trial of collaborative care for depressive disorders in patients with HIV, the primary outcome was antiretroviral medication adherence [33]. In this study, 304 patients were randomized to either usual care or to the intervention arm, in which patients met at regular intervals with depression care managers for depression symptom measurement, antidepressant dosing recommendations,

and motivational interviewing for antiretroviral adherence. The results of the SLAM-DUNC study found no differences in antiretroviral adherence between groups; however, depression scores were significantly lower in the intervention group at 6 months [34]. Together, the HITIDES and SLAM-DUNC studies suggest that collaborative care is an effective model for treating depressive disorders in patients with HIV. However, the authors of both studies were not able to show a positive impact on antiretroviral adherence, even though limited research in other studies of depression treatment suggest the potential for treating depression to improve adherence [35, 36]. Further research is needed to develop specific collaborative care interventions to improve antiretroviral adherence and optimize HIV-related medical outcomes in addition to effectively treating depressive disorders.

In this chapter, we focus on collaborative care for depressive disorders in persons with HIV given the evidence base supporting it. However, collaborative care has been applied to other psychiatric disorders and can be adapted to the setting, the population, and the psychiatric disorder being treated.

Key Components of Collaborative Care

The key components of collaborative care are described below.

- Patient-centered, team-based case
  - The aforementioned principles of patient centered care – prioritizing the needs, values, and preferences of the patent – are integral to collaborative care. The care manager and the HIV primary care physician primarily interact with the patient. The care manager also acts as an intermediary between the psychiatrist and patient; the psychiatrist does not directly interact with the patient, except in rare cases. The care manager is therefore pivotal to all care delivered within the collaborative care model.
- Population-based care
  - A caseload of patients defined to be in collaborative care are proactively screened according to standard protocols, evaluated, and treated to enable early detection of psychiatric disorders, to minimize chronicity of disorders, and to ensure that patients are not lost to follow-up. A population registry facilitates this approach. Registries can be developed and updated either in the electronic health record or in a spreadsheet that is maintained outside the health record. A typical registry in collaborative care includes patient identifying information, initial screen, diagnosis, treatment interventions, and clinical outcomes.
- Measurement-based care
  - Often, when treating depressive and other psychiatric disorders, multiple changes in treatment may be necessary to achieve response or remission.

Monitoring progress toward treatment goals with a validated measurement tool, such as the PHQ-9 for depressive disorder, can guide treatment adjustments and improve outcomes (see Chap. 5 for detailed information on screening tools).

- Evidence-based care
  - Standardized evidence-based medication algorithms and brief evidence-based psychotherapies such as behavioral activation, motivational interviewing, and problem-solving therapy are implemented, with the care manager functioning in the role of the therapist. If patients do not improve with evidence-based medication algorithms and brief psychotherapies, they are referred to a psychologist for more intensive psychotherapy.
- Accountable care
  - Clinicians are responsible for outcomes and quality of care delivered. Clinical outcomes are often measured as remission or response of psychiatric disorders. Medicare and some commercial third-party payers apply incentives to physician practices for quality and value of care delivered. A biannual financial incentive for employing evidence-based practices at or above market rate, or maintaining cost below market rate, is an example of financial incentive. Conversely, practices can be financially penalized for falling short of quality and financial benchmarks.

Roles and Workforce Training

The collaborative care team is typically comprised of a care manager, the primary care physician (in HIV clinics the HIV physician), and psychiatric consultant. Figure 19.1 illustrates how communication flows between members of the care team. The patient is at the center of all care delivered [37].

Nurses or social workers are well suited to care manager roles. The recommended caseload for a care manager is approximately 100 patients. Table 19.1 illustrates the roles of various team members of the collaborative care team.

Care manager and HIV physician training begins with an overview of collaborative care and its key components. In addition, didactics on the following topics are an integral part of training team members in collaborative care for depressive disorders:

- Differential diagnosis of psychiatric symptoms specific to people with HIV
- The role of trauma in HIV, its impact on depressive disorders, and methods to treat the effects of trauma
- Brief psychotherapies such as behavioral activation, motivational interviewing, cognitive behavioral therapy (CBT), and problem-solving psychotherapy
- Commonly used psychiatric medications, titration schedule, and expected side effects

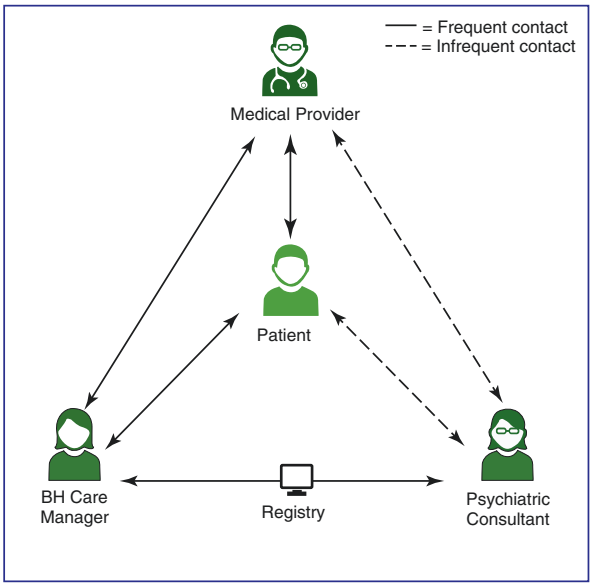

Fig. 19.1 Team structure of collaborative care Solutions AIMH [37]. (Copyright © 2017 University of Washington. All rights reserved)

Table 19.1 Roles of collaborative care team members

Care manager	Psychiatrist	HIV physician
Screening and assessing for psychiatric disorders (including substance use disorders)	Support the care manager and HIV physician	Introduces collaborative care to patient
Educating patients	Make treatment recommendations and develop care algorithms	Introduces care manager to patient
Tracking effectiveness	Provide training to care manager and HIV physician about collaborative care and essentials of psychiatric treatment	Works with collaborative care team to diagnose psychiatric conditions
Maintaining a registry for population outcomes	Be available on an as needed basis to HIV clinician and care managers for complex patients and nonresponders to routine care	Adjusts diagnosis over time based on new information and treatment response
Providing brief psychotherapies	Provide weekly consultation to care managers	Works with care team to implement treatment recommendations
Reviewing cases weekly with a consulting psychiatrist	Work with care manager to oversee care of a population of patients	Prescribes medications
Coordinating care for the patient	Provide educational seminars to HIV clinicians, care managers, and other staff	
Communicating recommendations to the HIV clinician and the patient		

Table 19.2 Benefits of collaborative care

Benefits of collaborative care
Live support from care managers in the HIV clinic
Evidence-based decision support from psychiatrist
Proactive management of a clinic population
Improved access to psychiatric care for patients
Improved clinic workflow and efficiency
Intensity of treatment tailored to complexity of psychiatric illness
Patient satisfaction
Clinician satisfaction
Shared decision-making

In general, collaborative care is well received by HIV physicians, other HIV clinicians, and HIV clinic support personnel. Skepticism about measurement-based care may be encountered, and having an HIV physician who is a champion of collaborative care may help to mitigate skepticism. As HIV physicians experience the benefits of collaborative care, which are listed in Table 19.2, skeptics often embrace this care delivery model.

Diagnostic and Treatment Considerations

Detection of depressive disorders in collaborative care begins with universal screening in the HIV clinic for depression symptoms, followed by evaluation of positive depression screens for other commonly occurring psychiatric disorders (anxiety disorders, posttraumatic stress disorder, psychotic disorders, and substance use disorders). A two-part process with the Patient Health Questionnaire (PHQ)-2, an ultra-brief screening tool for depressive disorders in HIV [38], followed by the PHQ-9 [38–40] is sensitive at identifying most cases of clinically significant depressive disorders. A score of ≥10 on the PHQ-9 is considered a cutoff for identifying clinically significant depressive disorders. The care manager meets with patients who score ≥10 on the PHQ-9 and completes a psychiatric diagnostic assessment spanning commonly occurring psychiatric disorders. Using a biopsychosocial approach to evaluation is essential in order to identify etiological factors in presenting depression symptoms. Medical causes of symptoms of depression need to be considered on the differential diagnosis. Common causes of depression symptoms in the medically ill and screening and evaluation for these causes are listed in Table 19.3. Some conditions such as delirium or dementia may at first glance appear to be "depression," but these neurocognitive disorder diagnoses can be clarified by careful evaluation. Some physical symptoms such as pain and fatigue are strongly associated with depressive disorders and may impact their course. Demoralization and a wish for hastened death may occur in patients with serious medical illnesses when distress becomes overwhelming or unbearable. Conditions that may confound

Table 19.3 Medical causes of symptoms of depression in the medically ill

	Conditions	Screening and work-up
Hematological disorders	Anemia	CBC
Organ failure	Renal or hepatic failure	BMP Hepatic function panel
Nutritional deficiencies	B12, folate, B6, vitamin D deficiencies	B12, folate, methylmalonic acid levels, 25-hydroxy vitamin D
Neoplastic	Many cancers, particularly brain, head and neck, pancreas, lung	Specific to particular cancer
Endocrine disorders	Hypothyroidism Diabetes Addison's disease Cushing syndrome Hypo- and hyperparathyroidism	TSH, T3, FT4 FPG, HbA1C Sodium, potassium, ACTH, cortisol, cosyntropin stimulation test, adrenal gland CT Plasma corticotropin level, 24-hour free urinary cortisol Calcium, PTH
Rheumatological disorders	Rheumatoid arthritis Systemic lupus erythematosus Systemic sclerosis Behcet's syndrome Polymyositis	ESR, CRP, and specific rheumatological tests, ± brain MRI
CNS infections	Neurosyphilis Tuberculosis Viral encephalitis, meningoencephalitis	Syphilis serologies, CSF studies, ± brain MRI CSF studies
Neurological disorders	Epilepsy Traumatic brain injury Primary and metastatic brain tumors Stroke Parkinson's disease	Electroencephalogram Brain MRI Brain CT

(continued)

Table 19.3 (continued)

Medications	Antiepileptics: levetiracetam, phenobarbital Antihypertensives: clonidine, methyldopa, thiazides, calcium channel blockers, beta-blockers, angiotensin-converting enzyme inhibitors L-dopa Antimicrobials Antibacterials: ethionamide, metronidazole, dapsone, cycloserine Antivirals/antiretrovirals: efavirenz, rilpivirine, nevirapine, emtricitabine, abacavir, raltegravir Antiparasitics: mefloquine Antifungals: amphotericin Endocrine modifiers: gonadotropin-releasing hormone agonists, progestin-releasing contraceptives, tamoxifen Antineoplastic gents: Interferon-alpha, interleukin-2, L-asparaginase, taxanes, vincristine, vinblastine, vinorelbine, procarbazine Anti-inflammatory and immunosuppressive agents: corticosteroids, hydroxychloroquine, mycophenolate mofetil, nonsteroidal anti-inflammatory agents, sulfasalazine Isotretinoin Opioids Sedatives, hypnotics, or anxiolytics Statins	Review of timing of onset of depressive disorder and correlation with medication use
Recreational drugs	Stimulant (cocaine and amphetamine) withdrawal Alcohol Benzodiazepines Phencyclidine and other hallucinogens Inhalants Opioids Sedatives, hypnotics, or anxiolytics	Urine toxicology screen

ACTH adrenocorticotropic hormone, *BMP* basic metabolic panel, *CBC* complete blood count, *CRP* C-reactive protein, *CSF* cerebrospinal fluid, *ESR* erythrocyte sedimentation rate, *FPG* fasting plasma glucose, *FT4* free thyroxine, *HbA1C* hemoglobin A1C, *PTH* parathyroid hormone, *TSH* thyroid-stimulating hormone, *T3* triiodothyronine

Table 19.4 Relatives and confounders of depressive disorders in the medically ill

Syndrome	Description
Delirium	Characterized by listlessness, withdrawal from the environment, and psychomotor slowing, which may also be present in a depressive disorder. Distinguishing features of a delirium are an acute onset, fluctuating consciousness, inattention, and accompanying cognitive symptoms
Apathy	Often present in neurocognitive and neurological disorders such as dementia and Parkinson's disease, and may be difficult to distinguish from depression
Pain	Common in patients with medical illness. Many patients with a depressive disorder may experience somatic amplification where physical symptoms including pain appear magnified. The relationship between depressive disorders and pain is bidirectional – they mediate each other and aggressively treating both conditions is essential
Fatigue	Strongly associated with depressive disorders and a frequent symptom in HIV and other chronic medical illnesses. Chronic fatigue syndrome is characterized by persistent fatigue worsened by exertion often accompanied by pain and sleep disruptions
Adjustment disorder	Characterized by psychiatric symptoms including symptoms of depression that impair functioning in the face of a stressor. The presence of physical symptoms such as pain, nausea, and fatigue and higher disease burden are correlated with an adjustment disorder. Stigma can contribute to the development of an adjustment disorder. A diagnosis of HIV is a major stressor for some and adjustment disorders are common in HIV. Adjustment disorders with depressed mood may resolve, remain chronic, or progress to a major or persistent depressive disorder
Wish to hasten death	Can occur in the face of an incurable and serious illness. The suffering, physical distress, and loss of control over one's life may activate a wish in some patients to end one's suffering by hastening death. Some patients may hold on to the possibility of hastening death in the future as a way of exerting some control over one's life
Demoralization	Syndrome that is distinct from a depressive disorder, often observed in the face of a chronic terminal illness. It is characterized by helplessness, hopelessness, and loss of meaning in one's life. Demoralization may hasten a wish for death

the diagnosis of depressive disorders or are related to depressive disorders in the medically ill are listed in Table 19.4.

Patients diagnosed with major depressive disorder are educated about the disorder and its clinical management. The goal of treatment of depressive disorders in HIV is remission – resolution of symptoms of depression, optimization of function, and mitigation of recurrence.

Care managers meet with patients every 2 weeks by phone or in person to assess patient engagement and tolerability of interventions. Psychiatrists evaluate patients directly only if patients do not improve with initial routine interventions. Once weekly, the care managers meet with the consulting psychiatrist to review each case. Following the depression care registry, a stepped-care algorithm-based approach is used, wherein treatment is intensified if patients do not respond or remit. Stepped-care is an evidence-based approach which algorithmically varies the

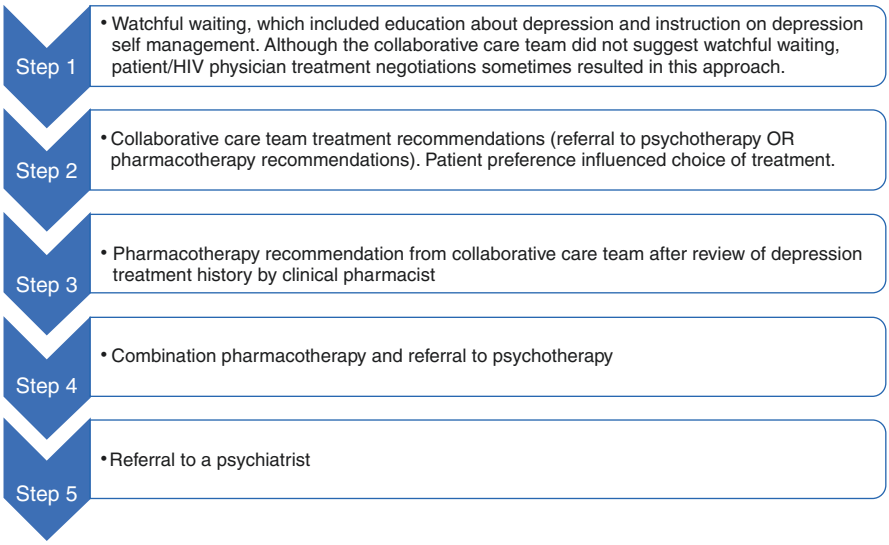

Fig. 19.2 Stepped-care algorithm of the HIV Translating Initiatives for Depression Into Effective Solutions Study (HITIDES). (Based on data from Ref. [32])

intensity of treatment strategies according to the patient's needs. An example of a stepped-care algorithm for collaborative care for depression is listed in Fig. 19.2. While this example of stepped-care was developed for a collaborative care program for depression in HIV [32], the principle remains the same and specifics of the algorithm vary depending on the psychiatric disorder being treated, the parameters of the measurement tool, and the treatments specific to the disorder, though the literature is most mature for management of depressive disorders by collaborative care.

Acceptability of interventions to patients impacts progression through the predetermined steps in stepped-care. Measurement tools are used to assess effectiveness of each of these interventions. Treatment is stepped up every 3 months if there is neither response nor remission or sooner if clinical assessment warrants.

When medications are used:

- A patient should receive an adequate trial of a medication defined as at least 12 weeks on a particular medication. Eight weeks of the 12 weeks need to be on a maximally tolerated dose (ideally the maximum dose) before determining a treatment failure, switching antidepressants, augmenting with another medication, or referring to a psychiatrist.
- Within the 12-week period of a medication trial, the care manager makes contact every 2 weeks to either assess tolerability of the medication, encourage adherence, and identify discontinuation of medications or facilitate dose titration.
- If a patient has tried a medication from one class and it has not worked in the past, a medication from another class may be tried (e.g., if patient has been on a selective serotonin reuptake inhibitor such as sertraline and it was ineffective, then try a serotonin norepinephrine reuptake inhibitor such as venlafaxine).

Some antidepressants are relatively unlikely to interact with antiretrovirals [41, 42]. Table 19.5 lists these antidepressants along with dose range, common side effects, and other treatment considerations. See Chap. 17 for more detailed information on drug side effects and drug-drug and drug-illness interactions.

Darius was a 25-year-old bisexual man who was referred to the HIV clinic for newly diagnosed HIV. He presented as dysphoric, tearful, and overwhelmed. He was referred to support groups, provided education about HIV management and outcomes, and acquainted with resources for individuals newly diagnosed with HIV. Depression screening was deferred for 6 months after diagnosis of HIV since there is often an initial period of emotional adjustment. When initially assessed, he scored 15 on the PHQ-9. He was dismissive of depression symptoms, but upon the encouragement of his HIV physician was open to meeting with the care manager. When he was evaluated by the care manager, he denied a previous history of a psychiatric disorder and recalled enjoying exercising daily when he was a college student at age 21. He also enjoyed spending time with his family and friends but had stopped doing so because he was unsure of how to navigate HIV/sexual orientation disclosure with them. The care manager reviewed the case with the consulting psychiatrist. The patient was diagnosed with a major depressive disorder, single episode. With the help of his care manager, he made a decision to disclose his HIV status to his sister and resumed visiting his parents weekly. He also incorporated going to the gym four times a week into his weekly routine after work. PHQ-9 score after 9 months of diagnosis was 10 and at 1 year following diagnosis was 4. A relapse prevention plan was developed to prevent recurrence of depression.

Complexities of Providing Collaborative Care for HIV

Bipolar disorder, PTSD, anxiety disorders, and substance use disorders all occur at a much greater frequency in persons with HIV than in the general population [29, 43–45] and add to the complexity of systemic medical management, thus are well-addressed by the collaborative care model. While not always feasible in a primary care setting, it is ideal to complete a full psychiatric assessment before starting medication. Patients may be unwilling to complete a full psychiatric assessment and/or the care manager may not be available to do so. Therefore, patients living with HIV who report depressive symptoms, especially those who do not respond as expected to first-line treatment, should be evaluated for comorbid conditions such as generalized anxiety disorder, bipolar disorder, and posttraumatic stress disorder. In these situations, the use of a brief standardized screening tool such as the Mood Disorder Questionnaire (MDQ), Posttraumatic Stress Disorder Checklist (PCL), and/or the Generalized Anxiety Disorder-7 (GAD-7) may be useful [46].

Aleisha was a 52-year-old HIV-positive woman presenting with chronic, moderate depressive symptoms which did not respond to standard trials of antidepressants (bupropion sustained release formulation, 200 mg twice a day for 12 weeks; venlafaxine extended release formulation, 375 mg once daily for 14 weeks; and sertraline

Table 19.5 Antidepressant dosing, side effects, and treatment considerations

Medication	Starting dose	Effective dose range	Side effects	Considerations
Citalopram (SSRI)	10–20 mg QAM	20 mg QAM → 40 mg QAM	Nausea, headaches, increased anxiety, and sexual dysfunction (decreased libido, erectile dysfunction, and anorgasmia) SIADH Serotonin syndrome Bleeding Citalopram can increase QTc interval	Nausea, headaches, and anxiety are reversible and usually resolve within 2 weeks Take with food to minimize gastrointestinal discomfort Sexual dysfunction may not resolve spontaneously; usually reversible if medication is discontinued; phosphodiesterase inhibitors are effective for erectile dysfunction in men Effective for anxiety disorders
Escitalopram (SSRI)	5–10 mg QAM	10 mg QAM → 20 mg QAM		
Sertraline (SSRI)	25–50 mg QAM	50 mg QAM → 100 mg QAM → 150 mg QAM → 200 mg QAM		
Mirtazapine	7.5 mg QHS	7.5 mg QHS → 30 mg QHS → 45 mg QHS → 60 mg QHS	Sedation and weight gain	Can help with poor appetite and weight loss No sexual side effects
Bupropion 12 h extended release form	150 mg QAM-150 mg BID	150 mg BID → 200 mg BID	Insomnia and restlessness Contraindicated in patients with seizures or traumatic brain injury	Second dose no later than 2 pm to avoid insomnia Can help with focus, concentration, and energy Can help attention deficit hyperactivity disorder symptoms
Bupropion 24 h extended release form	150 mg QAM	150 mg QAM → 300 mg QAM → 450 mg QAM		
Venlafaxine XR (SNRI)	37.5 mg QAM–75 QAM	75 mg QAM → 150 mg QAM → 225 mg QAM → 300 mg QAM → 375 mg QAM	Similar to SSRIs at low doses Can cause hypertension at moderate-high doses Duloxetine is hepatotoxic; avoid in liver disease	Effective for chronic musculoskeletal pain Venlafaxine is effective for anxiety and PTSD and duloxetine for anxiety disorders
Duloxetine (SNRI)	20 mg QAM–30 mg QAM	30 mg QAM → 60 mg QAM → 90 mg QAM → 120 mg QAM		

SIADH syndrome of inappropriate antidiuretic hormone, *SSRI* selective serotonin reuptake inhibitor, *SNRI* serotonin norepinephrine reuptake inhibitor, *QAM* every morning, *QHS* every night, *PTSD* posttraumatic stress disorder

200 mg daily for 16 weeks). Aleisha reported no change or worsening of symptoms and was unwilling to engage in individual psychotherapy or behavioral activation strategies. After numerous visits in the clinic, she agreed to a full mental health assessment and was ultimately diagnosed with bipolar disorder. Aleisha was started on lithium 600 mg every night. She stabilized with a lithium level of 0.8 mEq/L. Three weeks after initiation of lithium, her depressive symptoms began improving and continued to reduce over time. She had been more active and incorporated behavioral activation into her daily activities including reading and writing inspirational material, increasing social activities with family and friends, and attending HIV support groups [47].

Substance use disorders complicate the treatment of any other psychiatric illness and cannot be ignored. Khantzian has posited the self-medication theory of addictive disorders suggesting the multimorbid nature of addictive and other psychiatric disorders [48, 49]. The care manager is well-positioned to assess a patient's readiness, use motivational interviewing and interventions to encourage readiness for change, and facilitate entry into recovery programs when appropriate.

Finally, neurocognitive disorders and psychotic illnesses can complicate the lives of PLWH, more often than HIV-uninfected individuals, and are often associated with depressive symptoms [50, 51]. These disorders may go unrecognized or be misdiagnosed by the primary HIV physicians. The care manager may be the first to identify that additional testing or diagnostic evaluation is needed. The Montreal Cognitive Assessment and the International HIV Dementia Scale are brief cognitive screening tests that can be employed to screen for neurocognitive disorders. When patients screen positive, they can be referred to a neuropsychologist for neuropsychological testing. Often, the cognitive screen along with history from the patient and key informants and an assessment of functioning such as activities of daily living and instrumental activities of daily living are utilized to make a probable diagnosis of a neurocognitive disorder. This is especially true in resource-limited areas. Reversible causes of dementia should be evaluated for and treated. Please see Chap. 10 for a more detailed evaluation of neurocognitive disorders.

As outlined above, depressive symptoms are highly prevalent among PLWH, and while PLWH have high rates of major depressive disorder, the prevalence of bipolar disorder, anxiety disorder, posttraumatic stress disorder, severe mental illness, and neurocognitive disorders are also greater than in the general population.

Challenges and Barriers to Collaborative Care

Providing collaborative care in an HIV care setting can present specific challenges. There may be organizational barriers to implementing and sustaining collaborative care [52]. Administrators may not be aware of the impact untreated depressive disorders have on mental health and HIV outcomes. While, in the United States, Medicare now offers reimbursement for collaborative care services [53] as does Medicaid in some states, in many areas of the world, persons with HIV may have

no access to mental health care of any kind. HIV physicians may sometimes be uncomfortable with a model in which an additional person (the care manager) involved in care or having recommendations from a clinician (the psychiatrist) who has not directly interacted with the patient. Patients sometimes defer engagement in collaborative care, and there are many biopsychosocial reasons for doing so. When patients may not be ready to engage, clinicians may sometimes feel disillusioned about the model. Implementation of collaborative care requires buy-in at many levels as modifications to the electronic health record may be needed, staff will have adjustments in their workflow, and additional staff such as care managers may need to be hired and trained. Identifying a psychiatrist who is familiar with collaborative care, psychiatric care of people with HIV, and who is willing to consult may also be challenging.

Another challenge observed with collaborative care is that a subset of patients does not experience clinical improvement. High rates of multimorbidity and the interaction among these disorders may add to complexity of care. In a depression HIV collaborative care demonstration project, a latent growth class analysis to describe patient trajectories receiving collaborative care for depressive symptoms, self-reported trauma, and PTSD were associated with worsening or persistently severe depressive symptoms [54]. Treatment-resistant disorders, the course/natural history of the psychiatric disorder in the individual patient, and limitations of existing treatments are other biological factors that potentially play a role when patients are not improving clinically. Early life experiences and current relationships may affect a patient's self-worth, sense of value, and trust in others, which could complicate his/her relationship with healthcare team members. Social factors affecting engagement are myriad. Demands at home, lack of transportation, and being unable to take time off from work are a few of them.

Complex patients who do not improve when treated in the collaborative care model necessitate strategies to prevent burnout among care managers. Recognition that there several factors that impact how patients interact with the healthcare system and react to treatments is essential. Being cognizant of the demands on the care managers is likewise important to prevent burnout. Providing opportunities for care managers to debrief, limiting workloads of care managers, and encouraging self-care are some useful strategies. Despite these challenges, we believe that the collaborative care model offers more benefits than challenges.

Conclusions

HIV is associated with a myriad of biopsychosocial concomitants. Addressing the biopsychosocial aspects of HIV is essential to providing comprehensive care to patients. Several models for integrated care have been implemented since the onset of the HIV epidemic to address the mental health needs of patients with HIV. Among them are the consultation and referral model, the co-located model, the patient-centered medical home, and most recently the collaborative care model. With the

development of each successive model, greater integration is achieved. We focused on collaborative care in this chapter because it represents several principles of contemporary and effective healthcare integration: patient-centered care, measurement-based case, population-based care, evidence-based case, and accountable care. Integrated care models need to be adapted to accommodate the specific needs of patients cared for. In HIV primary care settings, high rates of stigma, isolation, and neuropsychiatric comorbidities such as substance use disorders, PTSD, bipolar disorder, and neurocognitive impairment add to the complexity of implementing collaborative care. Establishing processes to address complexities has the potential to improve outcomes. Working in an integrated care setting is a rewarding experience for all members of the healthcare team.

Helpful Resources

https://www.psychiatry.org/psychiatrists/practice/professional-interests/integrated-care
https://aims.uw.edu
https://www.integration.samhsa.gov/integrated-care-models
https://midusforhiv.org

Questions

QUESTION 1: STEM
Which of the following are core members of the collaborative care team?
Question 1 Key (correct answer)
Care manager, psychiatric consultant, and HIV physician
Question 1: First distractor
Social worker, peer specialist, and HIV physician
Question 1: Second distractor
Nurse, peer specialist, and psychiatric consultant
Question 1: Third distractor
Care manager, medical assistant, and psychiatric consultant

QUESTION 2: STEM
Some of the challenges encountered in implementing depression collaborative care in HIV populations include:
Question 2 Key (correct answer)
High rates of psychiatric comorbidities
Question 2: First distractor
HIV care management duplicates the work of depression collaborative care
Question 2: Second Distractor
Lack of validated measurement-based tools
Question 2: Third distractor
A shortage of trained mental health professionals

QUESTION 3: STEM
Collaborative care services are reimbursable under
Question 3 Key (correct answer)
Medicare and some states' Medicaid programs
Question 3: First distractor
None of the states' Medicaid programs
Question 3: Second distractor
All states' Medicaid programs
Question 3: Third distractor
All commercial payers

QUESTION 4: STEM
In collaborative care, progress can be monitored closely using which of the following clinical rating scales?
Question 4 Key (correct answer)
Patient Health Questionnaire-9 (PHQ-9)
Question 4: First distractor
Minnesota Multiphasic Inventory
Question 4: Second distractor
The Mini International Neuropsychiatric Interview®
Question 4: Third distractor
The Structured Clinical Interview for the DSM-5®

QUESTION 5: STEM
The core principles of collaborative care include
Question 5 Key (correct answer)
Patient-centered team-based care
Question 5: First distractor
Universally applying cognitive behavioral therapy
Question 5: Second distractor
Using clinical intuition to quantify severity of symptoms
Question 5: Third distractor
Maximizing billing for services delivered

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Chapter 20
Palliative and End-of-Life Care in HIV

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What Happens
What happens
do we become dust
do we dance with friends gone
awaiting friends to come
do we walk the tunnel of light
are our sins shown to us
in horrific detail
do we play and contemplate
is there music
do we plan our next adventure
do we wail and lament
do we scream
is there love
do we become part
of a whole
is there laughter

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do we become swirls of light
of energy
is there thought is the stench of decayed flesh
ever present
in our nostrils
is there memory
do we become etheric bodies
suffused with joy
do we become travelers
enlightened messengers
sent to sooth the sufferers
of other dimensions
do we see our former life
through noble eyes
do we become dust

—Glen Philip Kramer
persistent voices: Poetry by Writers Lost to AIDS [1]

Introduction

The advent of antiretroviral therapy (ART) has led to an overall improvement in outcomes of persons living with HIV. There has been a rapid reduction in progression of HIV infection and mortality in persons living with HIV. As a result, HIV has become a manageable chronic illness characterized by aging-related multiple morbidities and associated symptoms [2, 3]. Despite these advances, complications of end-stage HIV persist, and poor adherence to ART contribute to overall higher mortality among HIV-positive persons, compared to HIV-negative persons [4, 5]. Traditionally, palliative care was separate from curative care and only happened after there were no more treatment options. This view does not work very well for people with HIV and others with chronic illness who experience periodic crises alternating with periods when they return close to baseline functioning. Palliative care has been redefined as applicable at all stages of disease starting early in the course of illness in conjunction with other therapies that are intended to prolong life, particularly in light of prognostic uncertainty [3, 4].

Palliative care is a specialized medical care for people living with a serious illness. This type of care is focused on the goal of improving quality of life for persons living with HIV and their families through the relief and prevention of symptom suffering and stress of illness. This is accomplished by using a team approach to address the physical, psychosocial, and spiritual needs of persons living with HIV and their families [6]. Palliative care affirms life and regards dying as a normal process. The World Health Organization (WHO) recognizes palliative care as an essential component of HIV care, from the time of diagnosis through end of life [6, 7]. Early integrated palliative care is also recommended as standard of care for children and adolescents with life-threatening illness, including HIV [8, 9]. Comprehensive palliative care for persons living with HIV should include pain control, symptom

management, advance care planning (ACP), and spiritual, psychosocial, and psychiatric support [10]. When palliative care is provided alongside curative treatment and throughout the course of illness, it can help control physical symptoms (most commonly chronic pain, fatigue, and anorexia) in addition to psychological symptoms (most commonly depression and anxiety) [10], as well as symptoms of spiritual struggle, which are associated with poorer outcomes for persons living with HIV [11–14]. Benefits include improved adherence to ART, management of comorbidities, and enhanced quality end-of-life care [10].

Multimorbid conditions complicate symptom management and treatment of persons living with HIV. Pain among persons living with HIV is attributable not only to opportunistic infections, HIV infection, and medication toxicities but also to multimorbid systemic medical illnesses such as cancer, diabetes mellitus, and rheumatologic conditions. Pain management involves identifying the source of pain and treating the pain and symptoms associated with HIV. The WHO three-step pain analgesic ladder can be utilized in the management of pain [15] shown in Fig. 20.1. Assessment of symptoms should include a psychiatric review of symptoms, since depression and anxiety commonly intensify pain. Palliative treatment should take into consideration the symptom burden, risks, and benefits, such as the trade-off between pain management and alertness, in keeping with patient preferences [16, 17]. The Infectious Disease Society of America (IDSA) also provides guidelines intended to specifically assist the HIV clinician in the management of chronic pain among persons living with HIV who have coexisting substance use and other psychiatric disorders [18]. These guidelines also review information on potential pharmacokinetic interactions. IDSA guidelines recommend that persons living with HIV with chronic pain at end of life be referred to a palliative care specialist to assist with pain and non-pain symptoms, to address goals of care, and to provide support

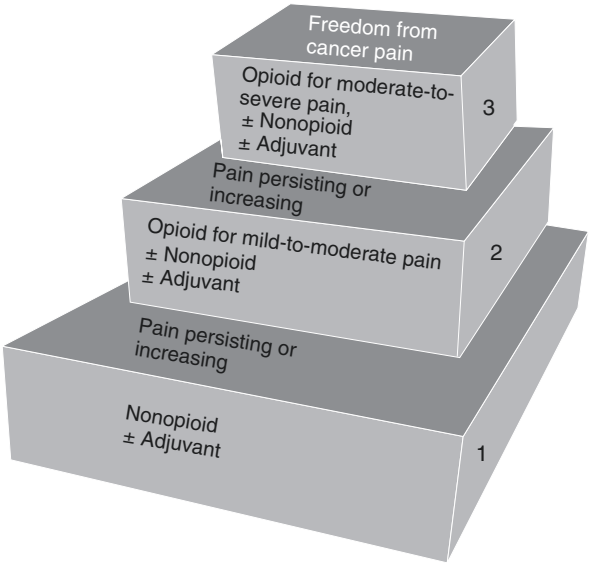

Fig. 20.1 World Health Organization's three-step pain relief ladder. (Reprinted from World Health Organization (WHO). WHO's cancer pain ladder for adults. Retrieved from: https://www.who.int/cancer/palliative/painladder/en/. Accessed January 11, 2020. With permission from World Health Organization (WHO))

beyond the capability of the primary care provider [18]. The Center to Advance Palliative Care (CAPC) offers free clinician-focused courses in pain management and communication, with CME and CEU credits [19]. See details for this and other resources in Tables 20.1, 20.2, 20.3, and 20.4. For further details on drug-drug and drug-illness interactions, please refer to Chap. 17.

Clinicians should explore patients' care preferences and goals, taking into account patient values, culture, and beliefs to help people plan for the future using ACP and by building a trusting relationship with the patient, family, and friends. ACP is a process of communication among individuals, their healthcare agents, and clinicians, to plan for a time when persons living with HIV may not be able to make their own healthcare decisions, in order to maximize patient self-determination [20–22]. In addition to systemic medical care, spiritual, psychosocial, and psychiatric concerns should be addressed through appropriate referrals to chaplains, social workers, psychologists, psychiatrists, and palliative care specialists, respectively. Bereavement counseling should be provided for families. Currently, the US Department of Health and Human Services (DHHS) recommends advance care planning for all individuals with chronic, life-limiting illness and those aged 55 years and older, regardless of health status [23].

Table 20.1 Palliative care resources for children, adolescents, and young adults

Resource tool	Description	Website
FOOTPRINTS SM	Model that assures continuity between hospital- and community-based medical services	http://www.mywhatever.com/cifwriter/content/41/pe1242.html
Hear My Voice	Family activity to explore thoughts, feelings, and values pertaining to a child's health condition and choices for care along the way	https://myhealth.alberta.ca/alberta/Pages/advance-care-planning-topic-overview.aspx
Hear Our Voice	A workbook for parents and guardians to support advance care planning for children and youth	https://docplayer.net/104547736-Hear-our-voice-a-workbook-for-parents-and-guardians-to-support-advance-care-planning-for-children-and-youth-people-feelings-meaning.html
Hello (formerly, The Gift of Grace)	Conversation game for families to address issues that matter the most (not intended for young children)	https://commonpractice.com/pages/comingsoon
Voicing My CHOiCES™	Research-informed document that provides adolescents and young adults living with a serious illness to communicate to family, friends, and caregivers how they want to be comforted, supported, treated, and remembered	https://fivewishes.org/shop/order/product/voicing-my-choices
My Wishes	Booklet that provides a place for children to express how they want to be cared for in case they become seriously ill	https://fivewishes.org/shop/order/product/pediatric-my-wishes

Table 20.2 Palliative care resources – planning tools for patients and their families

AARP End of Life Planning Resource Center	Provides materials (written and video) pertaining to end-of-life healthcare planning	https://states.aarp.org/tag/end-of-life-planning
Cake	An online advance care planning tool	https://www.joincake.com/
Caring Conversations from the Center for Practical Bioethics	A workbook that guides the process of advance care planning with a highly individualized focus. Available in English or Spanish and includes a Durable Power of Attorney for Healthcare Decisions form and Healthcare Directives	https://practicalbioethics.org/resources/caring-conversations.html
Five Wishes	Legal advance directive document that provides a place for adults to document references for medical care and also addresses emotional and spiritual needs	https://agingwithdignity.org
Lasting Matters	Planning tool to document and organize personal wishes and intentions related to end-of-life planning and planning for death	http://www.lastingmatters.com/
Physician's Orders for Life-Sustaining Treatment (POLST)	A POLST form gives medical orders to emergency personnel based on your current medical situation. These portable medical orders travel with the patient. POLST forms are completed by the healthcare provider after discussing with the patient what is likely to happen in the future, what treatment options are available, and what is most important (goals of care). A doctor (sometimes physician assistant or nurse practitioner – it depends on the state) must sign the POLST form for it to be valid	https://polst.org
Medical Orders for Life- Sustaining Treatments (MOLST)	Each state may call this form something other than POLST. For example, in Maryland the form is called MOLST. It consists of a statement of a person's wishes regarding future medical treatment options. They may also designate who will they wish to make decisions for them should they lose the ability to make choices for themselves	https://marylandmolst.org/pages/molst_form.htm
PREPARE	A step-by-step program with video stories to help persons with advance care planning. It includes an advance directive form where wishes can be put in writing and lists advance directives in each US state	https://prepareforyourcare.org/index.php/welcome https://prepareforyourcare.org/advance-directive-library

(continued)

Table 20.2 (continued)

The American Bar Association	A variety of self-help worksheets, suggestions, and resources that prompt continuing conversations about values, priorities, the meaning of one's life, quality of life, and whatever else is important to the individual	https://www.americanbar.org/groups/law_aging/resources/health_care_decision_making/consumer_s_toolkit_for_health_care_advance_planning/
The American Hospital Association	Put It in Writing: Key Links: Provides resources for advance care planning, by state and other consumer resources	https://www.aha.org/case-studies/2016-09-16-advance-care-planning-improving-conversation
Voicing My CHOiCES™	*Voicing My Choices* empowers young people living with a serious illness to communicate to family, friends, and caregivers how you want to be comforted, supported, treated, and remembered	https://fivewishes.org/shop/order/product/voicing-my-choices

Table 20.3 Palliative care resources – education and support tools for patients and their families

Go Wish	Card game by Coda Alliance that is a simple way to think and talk about what's important to individuals and their family members if someone becomes seriously ill	http://www.gowish.org/
National Hospice and Palliative Care Organization	Offers free, state-specific advance directives and advice for communicating wishes to family and close friends	https://www.nhpco.org/patients-and-caregivers/
Safe Beyond	A place to create digital messages for loved ones	https://www.safebeyond.com/
The Conversation Project	Provides tools to help people talk about preferences for end of life	http://theconversationproject.org/
Palliative Care: Conversations Matter®	Palliative care is a comprehensive treatment of the discomfort, symptoms, and stress of serious illness. The National Institute of Nursing Research (NINR) at NIH developed the Palliative Care: Conversations Matter® campaign to increase the use of palliative care for children and teens living with serious illnesses. Information is provided for patients, families, and providers, as well as the media	

Palliative Care in Racial, Ethnic, and Sexual Minorities

Racial, ethnic, and sexual minorities have higher risks for certain life-limiting illnesses, particularly HIV and other multimorbid systemic medical and psychiatric disorders. Even as persons with HIV live longer when they are able to adhere to antiretroviral treatment and participate in care, studies show premature biological aging and higher risk for cognitive deficits [24, 25]. Health inequality is well documented in minority populations [26]. HIV is overrepresented in minority communities, and disparities are compounded by the lack of services for historically disenfranchised persons living with HIV who would benefit from access to and provision of high-quality comprehensive psychosocial, medical, and palliative care.

Palliative care providers must appreciate the medical racism that has been institutionalized, as evidenced by data suggesting that ethnic and racial minorities do not receive the same degree of analgesia as whites in non-HIV-related illness [27]. Since persons living with HIV often have more than one site of pain, there is a risk for undertreatment for pain. For minority persons living with HIV with a history of substance use, particularly opioids, pain management at the end of life may be particularly challenging due to a lack of trust between patient and providers [28].

Inequities in the healthcare of racial, ethnic, and sexual minorities persist into end-of-life care [29]. Particularly in African Americans, there must be a "recognition, acknowledgement and respect of the exploitation, maltreatment and racism that African American persons living with HIV may have suffered and continue to suffer" [29]. In historically marginalized groups, the importance of religiousness and spirituality may be important in discussing end-of-life issues, while for those

Table 20.4 Palliative care resources for healthcare providers and researchers

Center to Advance Palliative Care (CAPC)	Toolkit on Designing an Office or Clinic Palliative Care Program in a community clinic or office setting. Each model has operational and financial trade-offs. Learn more in the "Designing the Service" section of this toolkit Other palliative toolkits and trainings are available	https://www.capc.org/toolkits/starting-the-program/designing-an-office-or-clinic-palliative-care-program/
FAmily CEntered (FACE®) pediatric Advance Care Planning (pACP)	FACE® pACP was developed for use with adolescents with HIV and with cancer and their families An adult version is also available. This model is an adaptation of the Next Steps: Respecting Choices Model® This program is recognized by the National Cancer Society's Research Tested Intervention Programs (RTIPS)	https://rtips.cancer.gov/rtips/programDetails.do?programId=17054015
Palliative Care Research Cooperative Group (PCRC)	The PCRC develops scientifically based methods that lead to meaningful evidence for improving quality of life of patients with advanced and/or potentially life-limiting illnesses, and their caregivers including family members and providers of care. *PCRC Investigator Development Webinar Series* https://palliativecareresearch.org/research/investigator-support-information/idc-webinar-series. Information for researchers interested in palliative care science and designed to support your research career *PCRC Pilot Funding Opportunities* https://palliativecareresearch.org/funding-opportunities/pilot-funding-opportunities. Small pilot research grants focused on generating pilot data and supporting investigator development for building the science of palliative care *Collaborating with the PCRC* https://palliativecareresearch.org/research/conduct-your-research-through-pcrc. The PCRC aims to help investigators overcome the challenges of multi-site research in palliative care. Investigators can collaborate with the PCRC in many ways from data sharing to site management	http://palliativecareresearch.org/
Respecting Choices®	Evidence-based model of advance care planning (ACP) for adults in any stage of illness, to prepare for future healthcare decisions, and a shared decision-making model that integrates individual's goals and values into current healthcare decisions This model also elevates the importance of building the infrastructure and tools necessary for effective utilization of advance care plans over the life of an individual, resulting in person-centered care that honors individuals' preferences and decisions Provides a variety of online learning, in-person courses, written materials, and consultation services	https://respectingchoices.org/

who are atheists or agnostic, existential and philosophical concerns may be primary for finding meaning at the end of life.

The process of ACP varies greatly with the degree of spirituality, family engagement around the illness, and acculturation. Assumptions based on specific racial or ethnic affiliation may not adequately assess the specific wishes and dynamics at play in a particular situation and individual [30]. Because HIV remains a highly stigmatized illness, relative to even cancer or cardiac illness, clinicians must evaluate each person's HIV illness with a contextual, psychosocial, and developmental approach. Families may harbor intense feelings and fears that the medical establishment may not provide equal or fair care to minorities and/or (conversely) may be offering palliative care *prematurely* to avoid having to extend the lives of racial minority patients. The legacy of the Tuskegee research on syphilis and overt racism in the structural access to healthcare for African Americans and Latino Americans, as well as undocumented persons, may pose formidable challenges to engaging families when palliative and/or hospice care may be the medically appropriate approach. ACP varies with racial and ethnic affiliations and culturally sensitive ACP should be provided to interested persons [31–34].

Some persons living with advanced HIV disease who see others living longer lives may harbor a belief that the healthcare system is to blame and/or a belief that a "cure" is being withheld. Any sense of declining health may be attributed to unequal treatment, rather than the consequence of comorbid medical conditions (often due to years of avoidance of treatment for other medical conditions, such as hypertension, diabetes mellitus, or cancer). Nonjudgmental support of and acknowledgment of persons living with HIV, who may have received discriminatory treatment in the past as a result of stigma vulnerability, or who observed friends or families receive unequal treatment, should be treated with compassionate care. Clinicians can offer assurance that they will provide equitable care and honor their patients' goals and treatment preferences in the spirit of patient self-determination and patient-centered care. Palliative care is well suited to addressing these concerns within the continuum of "Cure versus Care" [35].

Efforts are ongoing to reduce stigma and provide equitable access to palliative care services, ACP, and racially and ethnically appropriate care at the end of life. One trial, FAmily CEntered (FACE®) ACP, reported increases in ACP and documentation of advance directives using a two-session intervention (adapted Next Steps: Respecting Choices® and Five Wishes®) with African American and non-African American persons living with HIV in Washington, DC [36]. Surrogate decision-makers chosen by persons living with HIV via transparent processes and incorporation of specific religious or cultural practices may help to reduce fears of unequal treatment due to race or ethnicity.

Persons living with HIV who identify as a sexual minority on the basis of sexual orientation and/or gender identity face specific stigma and wide-ranging reactions from clinicians. Many self-identified sexual minorities may not disclose either sexual orientation or gender identity due to earlier traumatic experiences with society at large and/or the healthcare system [37]. Such nondisclosure can lead to presumptions about care and lead to a lack of engagement or nonadherence to care. LGBTQ

Table 20.5 Definitions of healthcare terms

Healthcare Proxy: a document that names someone trusted as the *proxy*, or *agent*, to express one's wishes and make *healthcare* decisions if the person becomes unable to speak for themselves. One does not have to be terminally ill to designate a *healthcare proxy*
Healthcare Agent: a person named to make medical treatment decisions if one becomes too sick or injured to make or communicate those decisions for themselves, or if a court ever declares the person to be incompetent. A *healthcare agent* can be named in a medical emergency or critical care plan and in an advance care plan
Healthcare Power of Attorney (HCPOA) or surrogate decision-maker: a legal document that allows an individual to designate another person to make *medical* decisions when the person cannot make decisions for themselves
Healthcare Surrogate: an adult who is appointed to make healthcare decisions for someone if they become unable to make them for themselves
The main *difference* between a *medical power of attorney* or *surrogate decision-maker* and a *healthcare surrogate* is that one appoints a *medical power of attorney* representative to make healthcare decisions for themselves for when they become unable to make them for themselves. One has no say in who becomes their *healthcare surrogate*

have varying legal arrangements for healthcare proxies, living wills, and powers of attorney that can impact decision-making at the end of life. See Table 20.5 for definitions of terms.

Working with LGBTQ people in the course of their illness requires a sensitive and nonjudgmental discussion about the patient's wishes should they become more ill and they were unable to make decisions for themselves. The rights of non-married partners vary by jurisdiction, and practical discussions can reduce anxiety and fear if providers begin these discussions in a supportive, compassionate way before the patient's illness becomes more advanced. For couples who are not legally married, there have been conflicts and ethical dilemmas when the parents of a person dying of AIDS have refused the partner of many years the rights to visit or make decisions about the disposition of the person's remains.

The transgender population fares even less well in terms of preparation for end-of-life care than other sexual minorities [38]. Transgender persons were less likely (50–70%) than other sexual minorities to have a living will, a will, or healthcare proxy. Transgender youth, particularly youth of color, often do not access healthcare even when they are diagnosed with HIV, are often homeless, and often use sex work for survival. They are often extruded and estranged from their families of origin and have few psychosocial supports to help them engage in healthcare, leading to premature aging and illness. Further complicating the care of transgendered persons at end of life is the isolation and high prevalence of physical and sexual trauma and stigmatization, and lack of access to supportive and affirming healthcare. Nevertheless, progress is being made as specialized hospital-based gender-affirming care clinics have been successful in engaging transgender youth in the United States, from the Youth Pride Clinic at Children's National Hospital in Washington, DC, to Kaiser Permanente's Gender Pathways Clinic in San Francisco (https://www.zanderkeig.net/youth-gender-clinics/). In a study of advance care planning with HIV-positive adults, all transgendered persons who were approached

Table 20.6 Ten recommendations to improve care for LGBTQ people facing advanced illness

Individual level	1. Avoid using heterosexually framed or assumption-laden language 2. Demonstrate sensitivity in exploration of sexual orientation or gender history 3. Respect individual's preferences regarding disclosure of sexual orientation or gender identity 4. Carefully explore intimate relationships and significant others, including biological and chosen family (friends) 5. Explicitly include partners and/or significant others in discussions
Service/institutional level	6. Make clear statement of policies and procedures related to discrimination 7. Include content regarding LGBTQ communities in training on diversity and discrimination 8. Increase LGBTQ visibility in materials (in written content and images) 9. Provide explicit markers of inclusion (e.g., rainbow lanyards or pin badges) 10. Initiate partnerships and/or engagement with LGBTQ community groups

Adapted from Bristowe et al. [40]. With permission from SAGE Ltd. Publications
LGBTQ lesbian, gay, bisexual, transgender, queer or questioning

agreed to participate, suggesting that the problem may be lack of access and provision of this service in hospital-based HIV clinic settings [36]. Early engagement by palliative care providers to document the end-of-life care wishes of the person can be extremely helpful in enhancing trust and comfort at the end of life. Engagement of a bioethics team or obtaining a legal opinion might be useful when a person's preferences are not being honored.

A major issue is the lack of training in healthcare professionals about specific issues for the LGBTQ population. This includes both knowledge and confidence in communication skills and comfort in talking to the LGBTQ patient who is in a vulnerable and dependent medical situation [39]. Clinicians must learn about the different needs of each member of the LBGTQ population. This starts with a comprehensive assessment that pays attention not only to the individual meaning of sexuality and gender (developmentally) but also how specific medical problems affect self-esteem, isolation, and connections with others. Although not specific to HIV, Bristowe et al. [40] make ten recommendations, listed in Table 20.6, to help reduce the health inequality faced by LGBTQ people. Many of these recommendations are also ideally suited to working with HIV at the end of life. These recommendations include using questions that do not start with heterosexually framed assumptions, nonjudgmentally exploring relationships without premature assumptions, explicitly engaging the appropriate members of the patient's family/network in discussions, and displaying LGBTQ culture visibly in healthcare settings.

For racial and ethnic minorities who also identify as a sexual or gender minority, the compounding of social/cultural issues, and beliefs about the medical healthcare system, must be understood in going forward with a palliative care plan, particularly in persons living with HIV who may feel distrustful of the system that has historically pathologized their identity. Not uncommonly, the discovery of HIV infection

leads to the discovery of a minority gender identity and/or sexual orientation. Persons living with HIV, when forced "out of the closet" due to illness, may be subject to violence, abandonment, and rejection by family, friends, and even religious groups. When dual identity persons living with HIV are abandoned by their family and/or community, physicians and other clinicians can mitigate some of the emotional fallout.

Clinicians must assume the responsibility to learn about the special vulnerabilities and needs of racial, ethnic, and sexual minorities who are dealing with HIV, multimorbid conditions, and the emotional aspects of health inequities and stigma. Palliative care teams must examine unintentional micro-aggressions, that is, racism or homophobia that is so subtle that neither victim nor perpetrator may entirely understand what is going on. Micro-aggressions are often perceived but go unmentioned by persons living with HIV in vulnerable and dependent situations. Direct, honest, and transparent discussions about patient wishes and beliefs from the beginning of patient-provider relationships can enhance mutual trust. Please see Chap. 7 for further discussion of AIDSism and the multiple stigma affecting persons with HIV and AIDS.

Case Vignette 20.1

Mr. D was a 43-year-old African American male living with HIV. He completed an ACP discussion with a facilitator as part of the FAmily CEntered (FACE®) ACP) clinical trial. Throughout the two sessions, he discussed past experiences with death and dying. He was invited to share his story. The research facilitator (interventionalist) listened without rushing him. A few years earlier, Mr. D developed an infection requiring hospitalization. He had difficulty fighting the infection due to his compromised immune system. His health deteriorated and the doctors thought the end of his life was near. Mr. D was a self-identified gay man, estranged from his parents because of his sexual orientation and HIV status. He was not married but did have a partner whom he had designated to as his surrogate medical decision-maker. However, this was a verbal designation and was not documented. The treatment team gave priority to the family at the bedside, overriding the partner's advocacy for Mr. D's wishes. There was no legal healthcare proxy or surrogate decision-maker at the time. Mr. D did not want to be put on any machines to prolonged life. Unfortunately, when the time came that Mr. D was unable to make medical decisions, Mr. D's parents – who were next of kin – agreed to a feeding tube and ventilator. Mr. D. survived the illness episode, but he was distressed that his wishes for his partner to make medical decisions were not honored, saying "I didn't want that," Mr. D affirmed. "I was hooked up to all these tubes. Even worse, my parents were involved in the decision-making when I was clear I didn't want that." Mr. D was wary of repeating this situation in the future. He was interested in completing an advance directive, but nervous that the medical community would not respect his preferences. With the facilitator

and his partner, Mr. D made a dissemination plan after completing the ACP process. Numerous copies of his Five Wishes® document were made, for himself, his partner, his friends, and his healthcare professionals. A copy was also entered into the electronic health record of the hospital where he received his HIV care, and another copy was sent by encrypted email to his treating physician. By working to complete and disseminate a legal advance directive to the people he chose, Mr. D felt empowered. He felt like he could use the Five Wishes® as a tool to advocate for himself. If Mr. D had only completed Five Wishes®, without first engaging in a facilitated ACP conversation with his partner, his partner may not have known what Mr. D wanted. Listening to Mr. D's story was vital to overcoming his medical mistrust and to ensuring his partner knew his treatment preferences in different situations. Listening to his story in full helped him feel heard and allowed the facilitator and his partner to address his fear of receiving unwanted care, by explicitly promising Mr. D that his treatment preferences would be honored and by his partner's willingness to commit to act as his surrogate decision-maker, if Mr. D could not make decisions for himself.

Case Vignette 20.2

Ms. E was a 72-year-old female with past medical history of HIV diagnosed 19 years previously. Her last CD4 count 250/mm^3. Medical history included HIV cardiomyopathy-induced heart failure with reduced ejection fraction, hypertension, hyperlipidemia, atrial fibrillation, morbid obesity, and poor medication adherence. Ms. E. presented to the emergency department with complaints of fatigue, shortness of breath, palpitations, decreased appetite, and abdominal fullness and pain. Her exam was significant for severe dyspnea, cough and bilateral lower extremity pitting edema to the thighs, cool extremities, and bilateral crackles on lung auscultation. She was started on inotropy support with diuresis and admitted to the ICU for cardiogenic shock. After several days in the ICU, the patient was close to her dry weight, but could not be weaned off dobutamine due to worsening biventricular failure. Ms. E was not a candidate for heart transplant due to her multiple systemic medical illnesses. The palliative care team was consulted. Without existing literature to guide weaning of cardiac inotropes, the palliative care and advanced heart failure physicians and pharmacists collaborated to create palliative inotrope weaning parameters for milrinone and dobutamine to address cardiogenic shock symptom management [41]. Ms. E had not completed an advance directive, nor Physician Orders for Life-Sustaining Treatment (POLST). However, Ms. E had intact decisional capacity and changed her code status from full code to do not resuscitate/do not intubate. She wanted to

stop taking her HIV medication due to high pill burden. Ms. E was on destination-dobutamine therapy, which carried risks of fatal arrhythmias and she was unlikely to survive the hospitalization. Her family was contacted and informed of Ms. E's poor prognosis. The family did not know Ms. E's HIV status. Ms. E had not appointed a healthcare proxy, which complicated the situation. When Ms. E's cardiac status suddenly deteriorated and she became delirious, her children were adamant about doing "everything possible" to keep their mother alive. This was in contrast with Ms. E's expressed preference that she did not want her life to be prolonged. As a result, her family's wishes were inconsistent with the desires expressed, but not documented by Ms. E.

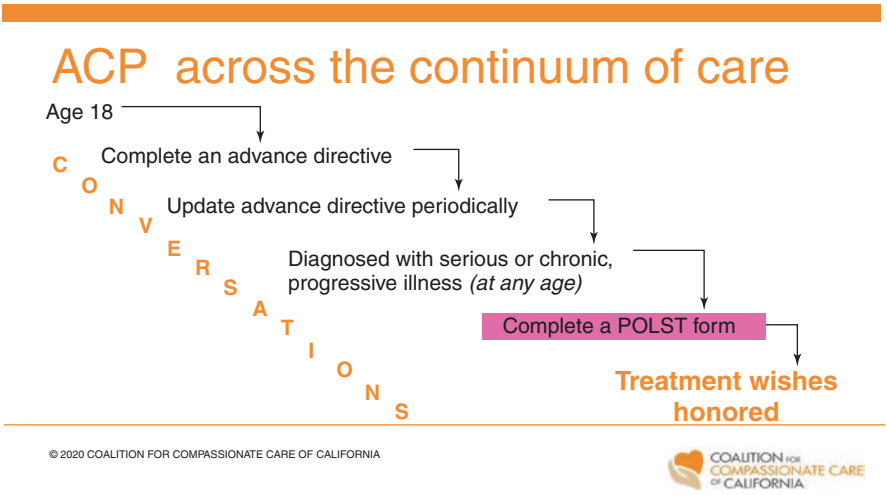

Fig. 20.2 How a POLST and advance directive work together. (Materials used with permission from the Coalition for Compassionate Care of California, CoalitionCCC.org)

Why ACP in the Days of Antiretroviral Medicine?

ACP conversations often result in documents that communicate patients' preferences and decisions for future healthcare. The quality and usefulness of these documents are dependent on the quality of the process that informs their completion. A quality ACP conversation will result in a clear and unambiguous document, useful in guiding medical treatment decisions when the individual is unable to speak for him/herself. Figure 20.2 illustrates how an advance directive and POLST form work together.

Advance Directive

Different jurisdictions utilize different terms for advance directives such as healthcare proxy, living will, and power of attorney for medical decision-making. Regardless of the term used, an advance directive describes a document that provides guidance about what types of medical procedures or care an individual may or may not want to receive in a future, medical crisis during which time the individual does not have the capacity to make their own medical decisions. The creation of an advance directive included preparing a document but may also include the designation of a specific substitute decision-maker. For a living will, it is not necessary to appoint a surrogate decision-maker. For a healthcare proxy, a healthcare agent must be designated, and an option is available for an alternate agent to be designated in the event that the healthcare agent is unavailable. When a healthcare agent or surrogate is designated, it is important not only to inform the healthcare agent/surrogate of this role but also to discuss advance directives and wishes for the patient's medical care. While all of the documents are valid in most jurisdictions, only certain documents, such as power of attorney for medical decision-making, require an attorney to prepare. Healthcare proxy/surrogate appointment documents do not require an attorney, nor do they require the use of specific forms. Healthcare proxies do require witnesses, but the witnesses can be any two individuals who know the identity of the patient. They are meant only to ensure that the designation of the healthcare agent/surrogate was *not coerced*. In most ACP models, completing an advance directive, which designates a surrogate decision-maker, is part of ACP, and is recommended for anyone living with a serious illness regardless of age and for all adults over the age of 55.

Physician Order for Life Sustaining Treatment (POLST) Form

There may be different terms for this in different jurisdictions as well such as Medical Order for Life-Sustaining Treatment (MOLST), but, regardless of the term, a POLST form is a medical order for the specific medical treatments a person wants during a medical emergency. POLST forms are appropriate for individuals with advanced illness or frailty. Advance directives and POLST work together. All adults should have an advance directive, but consider if POLST is also appropriate by asking the question, "Would you be surprised if the patient were to die within the year?" If the answer is no, POLST may be appropriate in addition to the advance directive.

Historically, adolescents and young adults (AYAs), even those living with advanced illness, have not been involved in their own end-of-life care planning. Discussions may be withheld, because of healthcare professionals' concern that "raising the subject" could cause patient anxiety. End-of-life discussion may also not be held due to healthcare professionals feeling uncomfortable, unprepared, and

unskilled in initiating these conversations with young, seriously ill patients [42–50]. Data supporting the engagement of adolescents living with HIV and their family members in conversations about goals of care and ACP are associated with beneficial outcomes, including greater understanding of end-of-life wishes, fewer physical symptoms, and reduced parental anxiety [51–54]. AYAs have expressed both desire and ability to share their values, beliefs, and preferences for treatment at end of life [55–59]. The American Academy of Pediatrics, the Institute of Medicine, and the World Health Organization recommend involving minors in care decisions as much as possible, to the degree that are developmentally and emotionally ready [60, 61]. However, few resources exist to aid AYAs in addressing their changing physical, emotional, and social needs and wishes around end of life.

Case Vignette 20.3
Ms. F was a 20-year-old African American adolescent diagnosed with HIV at age 7, who was hospitalized in critical condition. The cause of her HIV infection was unknown. Her grandmother, who had been her legal guardian and raised her, had passed away shortly before her hospitalization. Comorbidity included tuberculosis. Primary symptom was pain. Ms. F's prognosis ranged from a few weeks to a year, and her physician had contacted palliative care services to provide a consult during her prolonged in-patient stay. Ms. F's decisional capacity, defined as the ability to comprehend information, to make an informed choice, and to communicate that choice, specific to the decision at hand, was not formally assessed. Nevertheless, disease progression and treatments for pain had impaired her alertness and attention for complex health decisions, although probably not for designating a surrogate decision-maker. However, she was never asked. The treatment team nurse who had a close relationship with Ms. F visited her routinely while on her evening shift. One night, Ms. F came out of a semi-comatose state and told her nurse, "Who the hell ever gave my uncle permission to make decisions for me?" Ms. F's uncle had become her surrogate decision-maker and consistently requested intensive treatment for her because he believed that treatment would extend Ms. F's life, which would continue his receipt of her social security disability check. The psychologist working with the treatment team recommended an ethics consultation by the hospital's Ethics Committee, who confirmed Ms. F's decision-making capacity. This resulted in Ms. F receiving hospice care in the hospital in a homelike "hospice" room (lighting sensitive to day and night, no machines, curtains on the windows). The treatment team social worker facilitated the appointment of a guardian ad litem to represent Ms. F's best interests.

In 2006, Lyon and Wiener planned to collaborate in a trial of a structured pediatric ACP (pACP) intervention for adolescents living with HIV and their families. However, by the time funding was awarded to test a pilot, the HIV clinic at the

National Institutes of Health (NIH) had closed. Although this opportunity was lost, Lyon and Wiener branched off in complimentary directions to develop pACP protocols that are sensitive to adolescent developmental needs, include adolescent input, and ensure that seriously ill adolescents have a voice in future treatment decisions.

In 2008, Wiener et al. [55] published a study evaluating *Five Wishes*®, an advance directive document with AYAs living with advanced cancer or HIV infection. While designed for persons aged 65 and older, *Five Wishes*® was the only ACP guide found at the time that included issues of comfort, future planning, and spirituality along with choosing a durable power of attorney and specific life support options. Most participants reported that an advance directive like *Five Wishes*® would be "helpful" or "very helpful" to themselves (95%) and to others (90%).

Using the feedback and recommendations obtained, the study team designed an AYA-specific ACP guide, *My Thoughts, My Wishes, My Voice*. *My Thoughts, My Wishes, My Voice* was then compared to *Five Wishes*® for further refinement of AYA preferences. The study also evaluated the feasibility and clinical benefits of providing a developmentally appropriate advance care document for seriously ill AYAs. Results suggested that AYAs living with a life-threatening illness want to be able to choose and record the kind of medical treatment they want and do not want. They also want to document how they would like to be cared for, what they want their family and friends to know, and how they would like to be remembered. These results were incorporated into a new document named *Voicing My CHOiCES*™ which provides youth, families, and clinicians an opportunity to reduce the silence around the dying process by allowing an opportunity to share one's voice. A paper describing how to introduce *Voicing My CHOiCES*™ to AYAs is available [62].

Since becoming available in 2012, nearly 54,000 copies of *Voicing My CHOiCES*™ have been requested and distributed worldwide by the nonprofit organization, Aging with Dignity. A multi-institutional study is underway investigating the perceived helpfulness of *Voicing My CHOiCES*™ to determine whether revisions are needed, and whether engaging in ACP using *Voicing My CHOiCES*™ is associated with reduced anxiety and/or improved communication about ACP with family and healthcare providers. AYA ages 18–39 (NCI definition of AYA) complete a baseline assessment of anxiety and communication. Preliminary results indicate that adolescents talk less about their preferences for care with their clinicians than their family members, preferring that clinicians raise these issues with them, rather than the other way around [63]. Anxiety around end-of-life planning decreased significantly between baseline and follow-up. Over 90% reported the VMC questions to be helpful. Several changes were suggested and an updated version of *Voicing My CHOiCES* ™ is being designed. These data suggest that age-appropriate tools such as *Voicing My CHOiCES*™ can facilitate discussions about ACP preferences. In summary, *Voicing My CHOiCES*™ is a conversation guide for professionals to use with adolescents and young adults which encourages them to communicate with their family and physician.

The FAmily CEntered (FACE®) (pACP) intervention was developed and adapted for adolescents living with HIV using the Respecting Choices™ interview as the core intervention for communication between adolescents and their families,

balancing interdependence on families with respect to autonomy so as to ensure that families knew what their child wanted for end-of-life care if the worse were to happen. The FACE® pACP model is sensitive to the developmental needs of adolescents and culturally sensitive to the needs of our primarily African American adolescents living with HIV who wanted their families involved in ACP and who requested more than one session to begin this process. Evidence supported a weekly three-session approach (independent completion of ACP survey, dyadic goals of care conversation, dyadic completion of advance directive) which maximized feasibility and acceptability [64].

In the FACE® model, a trained/certified facilitator completes the Respecting Choices™ ACP facilitator curriculum. Trained/certified facilitators ranged in background from graduate students in psychology, counseling, and public health to case managers, social workers, and nurses. Trial results demonstrated training and monthly supervision to ensure fidelity to the protocol is sufficient to facilitate these conversations between the adolescent and family. In the FACE® pACP model, the facilitator meets with the adolescent and family together to facilitate the Respecting Choices™ pACP structured conversation followed 1 week later by completion of the *Five Wishes*®, a legal advance directive. Documentation is then placed in the medical record. A copy is given to the treating physician and the family and adolescent with instructions to the adolescent about how to update the advance directive, as people are known to change their mind if their illness progresses. This process is labeled the "beginning of a conversation."

Subsequent testing in a 5-year five-site NIH-funded single-blinded randomized controlled clinical trial demonstrated efficacy with respect to acceptability [51]; families' understanding of their adolescents' EoL treatment preferences overtime [52]; a willingness to limit treatments, compared to controls [51]; decreased physical symptoms in persons living with HIV [53]; and decreased family anxiety [54]. Social quality of life outcomes were determined by religious and spiritual beliefs, not the FACE® intervention [14]. Religious beliefs also strongly influenced treatment preferences among intervention adolescent/family dyads [65]. This protocol was later tested with adolescents with cancer [66] and is recognized as an evidence-based intervention on the National Cancer Society's Research Tested Intervention Programs (RTIPS).

FACE® results were replicated in a randomized clinical trial with adults living with HIV in Washington, DC, using the FACE® model and discussed earlier [13, 36, 67]. Cross-sectional studies of adult ACP have been published from the AFFIRM Care study. Study investigators enrolled adults living with HIV/AIDS in Baltimore, Maryland, who had histories of illicit drug use to examine ACP. Findings included (1) the importance of including caregivers in decision-making; (2) the need for patient education to document healthcare preferences; (3) clear preferences for treatment decisions; and (4) higher odds of patient reports of discussing ACP with their physician if they had chronic pain, had past experience of family conflict about end-of-life medical decisions, and felt comfortable talking to their family about problems [68–70].

Payment Issues in Palliative Care in the United States

In the United States, there is acceptance of the Centers for Medicare & Medicaid Services decision to reimburse physicians for discussing patient preference regarding end-of-life care. CPT code 99497 pays for "ACP, including the explanation and discussion of AD such as standard forms (with completion of such forms, when performed), by the physician or other qualified healthcare professional, first 30 minutes, face-to-face with the patient, family member(s), and/or surrogate," and code 99498 reimburses for each additional 30 minutes. Code 99498 is an add-on code and so can only be used along with code 99497 [71]. See referenced article for ten tips for using ACP codes in palliative care [72].

Funding Models in Palliative Care: The International Experience

A recent review of the literature on funding models in palliative care internationally had three main findings: (1) provider payment is rarely linked to population need and often perpetuates existing inequitable patterns in service provision; (2) funding is frequently characterized as a mixed system of charitable, public, and private payers; and (3) the basis on which providers are paid for services rarely reflects individual care input or patient needs [73]. The authors concluded that cross-national comparisons of costs and the impact of palliative care cannot be calculated at this time, as the funding mechanisms are not well understood and sometimes have perverse incentives caused by activity-based payments [73]. The reviewers could not draw any conclusions by the nature of the data and how they are collected. However, desirable features of a funding model in palliative care are identified.

Hospice

Hospice care is also changing. Persons living with HIV and physicians are no longer forced to make the choice between hospice and curative care, which in the past often delayed hospice enrollment. Under the Patient Protection and Affordable Care Act (ACA), Medicare and Medicaid now allow "concurrent care." The concurrent care model – also referred to as open access or simultaneous care – was developed to remove financial and psychological barriers to persons opting into hospice care. Persons living with an advanced illness do not need to choose hospice, palliative care, and curative treatments in isolation, and may thus have a more gradual transition into hospice. Access to hospice care, however, may be limited depending on the state's ACA implementation. Some cites like Washington, DC, and San Francisco, have hospices devoted to providing services to persons living with HIV with AIDS,

such as Joseph's House in DC (https://josephshouse.org) which offers compassionate end-of-life care for homeless men and women with HIV and cancer in Washington, DC, and the recently closed Zen Hospice Project affiliated with the San Francisco Zen Center. As the stigma of AIDS has decreased, persons living with HIV appear to be more open to accessing hospice services. In a survey of 223 adults receiving services for HIV in Washington, DC, of whom 85% were African American, 89% reported that they had heard of hospice with 67% knowing someone who had used hospice services. Of those who had heard of hospice, 64% reported they would want hospice support, if dying, while 30% were unsure (Lyon, unpublished). Among primarily African American adolescents living with HIV ($N = 48$) in the geographical south of the United States, 73% had heard of hospice but only 7% would want hospice support, if dying [58].

Medical-Assisted Dying

There are two forms of medical-assisted dying. In the first form, *physician-assisted dying* entails making lethal means available to the patient to be used at a time of the patient's own choosing. In the second form, *voluntary active euthanasia* entails the physician taking an active role in carrying out the patient's request, and usually involves intravenous delivery of a lethal substance. The latter is the most controversial, given the nature of the patient-physician relationship which affects trust in the relationship and in the profession, and fundamentally alters the medical profession's role in society. At the time of writing this chapter, voluntary euthanasia and/or physician-assisted dying is legally available in many countries and states in the United States.

The Netherlands and Belgium are the only two countries in the world that permit euthanasia of minors. The Netherlands, however, restricts euthanasia to minors above the age of 12. However, adolescents rarely ask for this option, because of a desire to protect their parents, in the clinical observation of one Belgian palliative care specialist (Personal communication with Lyon). A 2016 review found typical persons requesting physician-assisted dying are older, white, and well-educated; and pain is mostly *not* reported as the primary motivation [74]. A large portion of persons receiving physician-assisted death in Oregon and Washington reported being enrolled in hospice or palliative care, as did persons in Belgium [74]. In no jurisdiction was there evidence that vulnerable persons have been receiving euthanasia or physician-assisted death at rates higher than those in the general population [74]. Reasons that individuals choose physician-assisted dying are concerns about being less able to engage in enjoyable activities, loss of dignity, need for perceived control, and fear of dependency. In 2000, Emanuel et al. found the following factors to be associated with being *less likely* to consider physician-assisted dying were feeling appreciated, being 65 years or older, and being African American [75].

Society's focus at the end of life should be on efforts to address suffering and the needs of dying persons and families, including improving access to effective hospice and palliative care.

To protect vulnerable dying persons, guidelines and safeguards exist and standards have been developed for psychiatric assessment which include assessment of decisional capacity, psychiatric status over the previous 30 days, formal rating scales, narrative regarding seeking of physician-assisted dying, diagnostic formulation, and documentation of the elements of decision capacity rubric (Understanding/Appreciation /Rationality/Communication of Choice) [76]. To summarize, physician-assisted dying is increasingly being legalized, remains relatively rare, and primarily involves persons dying of cancer. Existing data do not indicate widespread abuse of these practices.

Conclusions

Despite progress in reducing HIV-related mortality over the past decade, slow decreases in incidence, combined with stagnated funding for related interventions, means that many countries in the world and rural areas in the United States in the geographical south will experience slow decreases or increases in incidence of persons living with HIV [77]. While we search for a cure and implement proven HIV prevention initiatives, the need remains to provide evidence-based and compassionate palliative care from the time of diagnosis until the end of life for persons living with HIV. This care includes psychosocial and spiritual supports that recognize a person's search for meaning [78], the importance of social support [79], and a sense of purpose [80] to minimizing suffering and maximizing quality of life for all human beings.

Multiple Choice Questions

QUESTION 1: STEM [52, 53]
Advance care planning for adolescents living with HIV:
Question 1 Key (correct answer)
Is beneficial for adolescents living with HIV and their families
Question 1: First distractor
Is appropriate only for those whose disease has progressed and who are experiencing distressing symptoms
Question 1: Second distractor
Is too distressing for adolescents living with HIV and their families and should be deferred by their healthcare team until the physician would not be surprised if the patient died within a year
Question 1: Third distractor
Is misplaced and limited resources should be allotted to antiretroviral adherence

QUESTION 2: STEM [6, 7]
Palliative care is BEST defined as:
Question 2 Key (correct answer)
Treatment of physical symptoms and the provision of advance care planning and mental, emotional, and spiritual support from the time of diagnosis until the end of life
Question 2: First distractor
Treatment of physical symptoms, particularly pain, at the end of life
Question 2: Second distractor
Treatment of physical symptoms that are beyond the experience of the primary clinician at the end of life
Question 2: Third distractor
Care provided in a hospice setting at the end of life

QUESTION 3: STEM [29]
Palliative care with racial, ethnic, and sexual minorities must:
Question 3 Key (correct answer)
Address fears that the medical establishment is offering palliative care to avoid having to extend the lives of those in historically marginalized communities
Question 3: First distractor
Provide persons living with HIV a link to a website about advanced care planning so they can complete a document online
Question 3: Second distractor
Provide healthcare professionals training in communication skills
Question 3: Third distractor
Assure persons living with HIV that clinicians are not biased and encourage persons living with HIV to choose a biological relative to be their surrogate decision-maker

QUESTION 4: STEM [15, 16]
Pain management with persons living with HIV should:
Question 4 Key (correct answer)
Follow the World Health Organization three-step pain analgesic ladder
Question 4: First distractor
Minimize the use of opioids among injection drug users
Question 4: Second distractor
Encourage persons living with HIV to wait until pain is severe before starting pain medications
Question 4: Third distractor
Trigger a referral to the Center for Palliative Care

QUESTION 5: STEM [81]
Under hospice care:
Question 5 Key (correct answer)
Concurrent care is allowable in some states in the United States
Question 5: First distractor

Persons living with HIV and physicians must make the choice between hospice and curative care
Question 5: Second distractor
Reimbursement is not available under the Affordable Care Act
Question 5: Third distractor
Physicians must estimate that persons living with HIV have less than 3 months to live

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Chapter 21
Legal and Ethical Aspects of HIV Psychiatry

Maria Tiamson-Kassab, William McColl, and Kenneth Ashley

Introduction

In this chapter, we review legal and ethical issues related to HIV. As the nature of the epidemic and the course of the illness have changed, the focus on individual rights and confidentiality has shifted to the expansion of testing, increased early identification, and earlier entry into treatment. To facilitate these goals, current issues were updated to include less rigorous pre- and post-test counseling, expansion of testing with opt-out instead of opt-in protocols, and the conflict between confidentiality and mandated reporting of HIV status, including partner notification. There is also a discussion of HIV criminalization and lifting the ban on blood donations from men who have sex with men.

HIV Testing

About 38,000 new HIV infections still occur in the United States annually [1]. Approximately 14% of people who have HIV do not know it and need to be tested, while around 37% of people who know they have HIV do not have it under control and need treatment. At the most recent assessment, four out of ten infections are

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transmitted by individuals who did not know they had HIV in 2016 [2]. To end HIV transmission, individuals should get HIV testing.

According to the WHO, the introduction of the "treat all" recommendation (ART for all people living with HIV regardless of CD4 cell count) supports the rapid initiation of ART, including the offer of same-day initiation where there is no clinical contraindication. The US Preventive Services Task Force (USPSTF) found convincing evidence that early initiation of ART for HIV infection, regardless of CD4 cell count, improves clinical outcomes and reduces the risk of sexual transmission. The clinical benefits of ART outweigh the potential risks of treatment in persons living with HIV [3].

Informed Consent

Written informed consent, in the early years of the HIV AIDS epidemic, was an important element of public policy. It was viewed as providing vulnerable population the necessary protection from stigma, privacy intrusions, and the deprivation of the fundamental right to choose whether or not to be tested. Thus, it became the standard of care throughout the United States, in addition to pre- and post-test counseling. With the advent of effective antiretroviral therapy in 1996, it became apparent that early identification and intervention were essential to prolong the lives of HIV-infected individuals. The awareness of HIV status would help facilitate access to timely and appropriate HIV prevention, treatment, and care [4]. In 2006, the US CDC revised its recommendations to include the routinization of HIV screening that involved an "opt-out" approach to consent and the elimination of specific written informed consent. This became a hotly debated issue for years, and, in the end, while state laws vary widely in the degree of protection provided, all 50 states followed the CDC recommendation to remove the requirement for written informed consent for HIV testing [5].

Pre- and Post-test Counseling

With the focus on early identification and intervention, the pre-test counseling has been simplified, particularly in high-risk populations. Other elements previously associated with pre-test counseling, such as individual risk assessment and risk reduction, are now covered during post-test counseling. Pre-test counseling may be provided in various ways, such as individual sessions, couples, or group health information discussions with the provision of appropriate printed materials. See Table 21.1 for information to be included during pre-test counseling.

One important aspect of pre-test counseling is the inclusion of drug use assessment, as part of an individual risk assessment, so that risk reduction can be encouraged and each person is also informed that the HIV test screens for HIV only, and

Table 21.1 Information to be included during pre-test counseling

Reason the test is being recommended
Clinical benefits of testing, including risks
Services available in case of negative or positive result
Information that the confidentiality of the result will be maintained
The individual has the right to decline testing without any impact on affect access to other services
If the result is positive, disclosure to the individual's partners who may be at risk is encouraged

Table 21.2 Information to be included in post-test counseling

Persons with negative test results	Persons with positive test results
An explanation of the test result	Deliver the result simply and clearly, making sure that each individual understands and is given time to consider the result and ask questions
Information about the window period for the appearance of HIV antibodies and a recommendation to retest if the exposure is recent	Give help in coping with the emotional response to the test result
Basic advice on HIV prevention and risk reduction, including a discussion of PrEP and PEP	Discuss concerns and offer immediate support and describe the follow-up services that are available
Access to substance use treatment	Provide information on HIV prevention (e.g., provision of sterile needles and condoms) and relevant preventive measures
Guidance on the use of condoms and other prevention methods, and safe injection advice	Discuss disclosure of the result and encourage partners and children to be tested
Appropriate time for a follow-up test	Provide advice on other tests that may be appropriate (e.g., hepatitis panel, sputum for AFB, pregnancy test)
	Assess risk for suicide, violence, drug overdose
	Arrange for a specific date and time for follow-up visits, linkage to HIV care, and referrals for other treatments, as necessary

nothing else. There are special considerations when pre-test counseling is provided to pregnant women, adolescents, sex workers, MSM, transgender persons, and seriously ill persons. If an individual declines HIV testing, the refusal should be noted in the chart, and a discussion about HIV testing and counseling should be attempted at the next visit.

A fundamental component of HIV counseling is the post-test counseling. Regardless of whether the result is positive or negative, persons tested for HIV should be counseled. Counseling should be given individually, face-to-face, and preferably by the same clinician. See Table 21.2 for information to be included in the post-test counseling.

For pregnant women whose test results are positive, in addition to what has been mentioned, there are other issues that need to be addressed, such as childbirth plans, the use of antiretroviral drugs, maternal nutrition, infant feeding options, HIV testing for the infant and the follow-up that is necessary, and partner testing [6].

If the HIV test result is indeterminate, this should be explained to the individual, and specific inquiry about recent symptoms which may suggest seroconversion should be done. The patient should be retested in 3 months and the importance of safer sexual practices needs to be emphasized.

Opt-In/Opt-Out Testing

In 2006, the Centers for Disease Control and Prevention revised its HIV testing guidelines to recommend non-targeted opt-out HIV testing. Routine HIV testing would help in early identification of patients with HIV and thus initiate intervention early. In opt-out testing, the individual is told that routine HIV testing will be done unless the patient declines. In opt-in testing, the individual is informed that tests are available but are not tested unless it is requested. Active choice is a third option recommended by a study by Montoy et al. [7]. In this option, the patient is asked to choose whether they would like to be tested or not. Their protocol begins with "We are offering routine HIV tests to all of our patients. It is a rapid test with results available in one or two hours." With opt-in, it is followed by "You can tell me, your nurse or your doctor know if you would like to be tested today." In active choice, which used to be considered a form of opt-in testing, it is followed by "Would you like a test today?" and with opt-out, it is followed by "You will be tested unless you decline." The authors reported that simply asking patients if they would like a test increased test acceptance.

Self-Testing

One approach to rapidly increase HIV testing, especially in vulnerable populations who have minimal access to healthcare, or in high-risk populations who may not get tested, is HIV self-testing. With this approach, the individual collects his or her own specimen (oral fluid or blood), performs an HIV test, and interprets the result, in private or with someone they trust. Self-testing is not definitive and should be followed by confirmatory testing by a healthcare clinician [8].

Clinician-Initiated Testing in Pregnancy

One of the most important preventive strategies for HIV is to test and counsel pregnant women and start treatment as early as possible to reduce the risk of mother to child transmission. HIV screening should be included in the routine panel of prenatal tests

for all pregnant women. Women who decline should be encouraged to be tested at a subsequent visit. Women who are HIV-infected and pregnant, or thinking of becoming pregnant, should receive education and counseling about perinatal transmission risks, strategies to reduce those risks, and potential effects of HIV infection or HIV treatment on the course or outcomes of pregnancy. Psychiatrists should refer pregnant or preconception HIV-positive women to a comprehensive program for HIV prenatal care.

At the time of labor, any woman with unknown or undocumented HIV status should be screened with a rapid HIV test unless she declines. If she declines, reasons for the decline need to be explored. At the time of delivery, if HIV status is still unknown, she should be screened immediately postpartum with a rapid HIV test unless she declines. At the time of postpartum, if the HIV status of the mother is still unknown, rapid testing of the newborn as soon as possible after birth is recommended so antiretroviral prophylaxis can be offered to HIV-exposed infants. Neonatal antiretroviral prophylaxis shows the best benefits when initiated within 12 hours after birth.

Reporting of Positive Results

Physicians and laboratories in all 50 US states are required to report positive HIV tests to their local or state Department of Health. The state Department of Health sends the information to the US Centers for Disease Control and Prevention who tracks national public health trends. However, HIV reporting requirements differ among the states. It is imperative that you find out what the laws are in your jurisdiction. Many states also have partner notification laws. State statutes also vary as to whether a patient's HIV status can be disclosed to contacts. See Table 21.3 for the different types of laws.

The tremendous variation of these provisions indicates that physicians should always seek advice from public health departments and their own attorneys to understand their legal responsibilities.

HIV Criminalization

Beginning early in the HIV epidemic, many US states passed laws that criminalized the exposure of others to HIV. Although there are multiple definitions of "HIV criminalization," we will rely on the Center for HIV Law and Policy's definition in

Table 21.3 Partner notification laws

Mandates that the physician provide the contact's name to the state health agency; the state health agency then notifies the contact
The physician has the choice of notifying either the state health agency or the third-party contacts directly
The disclosure to a state agency is optional

Based on data from Ref. [9]

Table 21.4 HIV criminalization

"The reliance on a person's positive HIV status, either under criminal laws that apply explicitly to people living with HIV (PLHIV), or under general criminal laws or sexually transmitted infection (STI) laws, as the foundation for criminalizing otherwise legal conduct or for increasing crimes and punishments related to solicitation or sex offenses" – Center for HIV Law and Policy [10]

Table 21.4. In addition to state laws, the US Uniform Code of Military Justice (UCMJ) criminalizes HIV as well [10]. This issue is not limited to the United States but rather is a worldwide phenomenon with at least 75 countries having laws exposing people living with HIV to criminal punishment [11].

Many of these laws established extraordinary punishments for exposure to HIV, often with extreme sentencing requirements ranging into decades. Additionally, many of the laws required sex offender registration post-release and created onerous conditions on people already living with the disease. The issue of criminalization was not limited to individual states, as the creation and implementation of these laws was actually accelerated by passage of the federal Ryan White Comprehensive AIDS Resources Emergency (CARE) Act of 1990. The Act required that to be eligible for funding, a state must show that it was capable of prosecuting an individual for exposure of others to HIV [12]. In 2018, a CDC overview of the issue noted that 26 states had specific HIV criminalization laws [13]. At the same time, many more states had prosecuted people living with HIV for exposure to others under general criminal statutes [10].

Unfortunately, such laws have been shown to be both ineffective and counterproductive to the goal of ending the HIV epidemic. Many of the original HIV criminalization laws were based on prejudicial and inaccurate understanding of the risk and basis of transmission of HIV in the beginning. Particularly as science has advanced including understanding of antiretroviral medications that control HIV, laws enacted in the 1980s and early 1990s have become increasingly outdated.

As understanding of HIV has increased, criticism of HIV criminalization laws has also increased, and efforts at reform have become of paramount concern of people living with and affected by HIV. Perhaps the basic issue that there is virtually no evidence that HIV criminalization laws have been shown to accomplish the primary goal of reducing HIV transmission, particularly at a population level that could affect the course of the epidemic [14].

At the same time, the laws fail to account for actual levels of risk and are not based on current scientific understanding of the disease. One result is criminalization of behavior in which there are no provable cases of transmission, including biting, spitting, or scratching [15]. Astonishingly, despite the presumed impossibility of viral transmission, a case in Texas resulted in a 35-year sentence for a man living with HIV who spit in the mouth and an eye of a police officer [16]. In contrast, New York moved away from this standard by dismissing a count of aggravated assault after an HIV-positive person bit a police officer [17].

Moreover, many HIV criminalization laws do not allow a defense for exposure (actual transmission of HIV is not required for prosecution). A person living with

HIV who uses a condom or engages in an extremely low-risk sexual activity such as oral sex continues to be subject to the law (and have often been given long sentences, such as 25 years in an Iowa case that eventually prompted reform and was overturned [18], 30 years in Idaho [19] and 7 years in Michigan [20]). It is not unusual for the only defense to be actual disclosure of HIV status, which can be extremely difficult to prove. The long sentences noted above are often highly disproportionate and have sometimes exceeded sentencing for homicide cases.

Laws based on exposure to HIV additionally create a disincentive for people to be tested. One issue is that merely knowing that one is HIV-positive and having sex without disclosure is the only element of the crime. Thus, one major defense to the crime is for a person to not actually know their HIV-positive status. This creates a disincentive to get tested. This is contrary to the public health goal for all people living with HIV to be aware of their status, and further undermines the goal ending the HIV epidemic [20].

Of particular concern to psychiatrists and others in the health professions is that health officials can be required to disclose HIV status from medical records, which has the potential to create distrust in patients [21]. Unfortunately, in some states, health officials create evidence against people living with HIV by forcing them to sign forms acknowledging criminal liability for exposure. This has sometimes occurred as a routine part of a positive HIV test at a vulnerable moment when people living with HIV are still dealing with the impact of learning that they are HIV-positive.

A further concern is that HIV criminalization laws are often grounded in direct animus and create additional stigma and prejudice toward people living with the disease. See Table 21.5. Since HIV status is an immutable characteristic after it has been acquired (sometimes from birth), such prejudice can deeply affect people living with HIV. It may add bigotry toward people and communities that have higher rates of the disease including gay and transgender, African American and Latinx, and other already stigmatized groups perceived to be at risk.

Punishments for people living with HIV have not only resulted in onerous sentences such as those described above, but in addition, people living with HIV who are convicted under HIV criminalization laws may be required to register as sex offenders [10]. This has very impactful consequences including on the potential for employment, places to live, direct stigma as a result of having a notation on a driver's license, and more.

Table 21.5 A Williams Institute study showed California HIV criminal statutes and enhancements prior to reform disproportionately affected

Women
People of color
Immigrants living with HIV
LGBTQ youth
Transgender women of color

Based on data from Ref. [22]

Finally, educating the broader general public and even populations that are likely to be most affected by HIV criminalization laws about the negative consequences of criminalization is difficult. In a 2008 study, 65% of gay men agreed that it should be illegal to have anal sex without disclosure of HIV status [23]. Many people view the issue in a "strong law and order" framework and have a sense, contrary to the evidence, that the laws are working to protect people from HIV. This creates an even larger problem in the sense that people who are HIV-negative may rely on the criminal laws to protect themselves while failing to take action to prevent HIV, such as obtaining pre-exposure prophylaxis (PrEP) or condoms. This puts the onus to keep people from infection solely on an HIV-positive partner, potentially undermining HIV prevention efforts and keeping sexual partners from taking mutual responsibility for health.

Efforts for Reform

Many advocacy groups have been calling for reform for decades. Advocates have long urged the introduction and co-sponsorship of bills in the House and Senate to reform HIV criminalization laws. Now, as greater awareness about the negative impact of HIV criminalization laws has grown, many efforts have taken place to begin reforming and changing the laws.

A particular issue for advocates of reform in the United States is that each jurisdiction controls its own criminal laws. Consequently, reform is needed on a 50-state basis (as well as in Washington, D.C., Puerto Rico, the Virgin Islands, and other territories). This represents a significant use of resources and effort. Although some HIV advocates advocate simple and full repeal of the laws, others have noted that this may not represent a comprehensive solution since, as noted above, prosecutions can still occur under general state criminal laws. Nevertheless, there have been efforts at state-by-state reform in addition to the efforts listed above.

Significant reforms at the state level have taken place, often in response to HIV criminalization cases which resulted in outlandish sentences. See Table 21.6 for states/year of reforms. In 2014, a major reform took place in Iowa as a result of a case in which a defendant, Nick Rhoades, received a 25-year sentence for exposing a sexual partner to HIV despite having used a condom and other factors that decreased risk factors for transmission to his partner [18]. As a result of this effort, the new law removed sex offender requirements and added potential defenses (such as condom use) to the law. At the same time, it added other diseases eligible for prosecution to the law and did not affect incarceration of individuals already convicted [24]. The case focused energy onto the issue and became a *cause célèbre* within the HIV community.

In another major reform, Colorado eliminated a provision that required mandatory testing for someone accused of sex work. Colorado also reduced the maximum sentence for people living with HIV charged for sex work, in part by eliminating a felony enhancement for a person living with HIV engaging in sex work. California

Table 21.6 States that have enacted HIV criminalization reforms

State	Year
Texas	1994
Illinois	2021
Iowa	2014
Colorado	2016
California	2017
North Carolina	2018
Michigan	2018
Washington	2020

Based on data from Ref. [24]

reformed its HIV criminalization law in 2017 resulting in a potential model law for other states. It reduces penalties for intentional exposure, sex work (one of the largest groups that were prosecuted under the old law), requires specific intent to transmit for prosecution, and creates new privacy protections.

Perhaps the earliest significant federal step in addressing HIV criminalization was the release of the first National HIV/AIDS Strategy in 2010 under President Obama. The Strategy called for updating criminalization laws consistent with current science. Under goals it called for state legislatures to "consider reviewing HIV-specific criminal statutes to ensure that they are consistent with current knowledge of HIV transmission and support public health approaches to preventing and treating HIV" [25]. Subsequently, the Department of Justice issued a best practices guide calling for the reform of state laws [26].

Notably, as the movement to end the HIV epidemic has taken root within the Trump administration, HIV advocates have continued to amplify the message that HIV criminalization laws must be reformed to meet the goals of ending the HIV epidemic. The calls have become even more unequivocal in tone. The HIV community created proposal, "Ending the HIV Epidemic in the United States: A Roadmap for Federal Action" states bluntly its recommendation for federal action should be to "support and pass legislation to end HIV criminalization" [27].

In Congress, Representative Barbara Lee (D-California) has repeatedly introduced the Repeal Existing Policies that Encourage and Allow Legal (REPEAL) HIV Discrimination Act of 2017 calling on the Attorney General and other cabinet members to review federal (including military) and state laws and policies on criminal and civil commitment cases involving people living with HIV, establish best practices, and establish an integrated monitoring and evaluation system to measure state progress [28]. Much of the agenda of the initial REPEAL Act has been accomplished via the National HIV/AIDS Strategy, and it is expected that a newer version will be introduced in the future.

Even as advocates have struggled to contain and reform current HIV criminalization laws, new challenges continue to arise. Among newer issues, molecular HIV surveillance, a technique of analyzing genetic sequences of HIV resistance testing, has the potential to help public health officials to rapidly find and respond to new

cases of HIV (and to then do early testing among friend groups or other people identified at risk). This is a new use of HIV resistance testing data that has been reported to public health officials. One unexplored consequence of this use of data is the potential that people whose identities are associated with the data could be targeted for prosecution under state HIV criminalization laws. As of now, the data cannot show the direction of transmission; however, there is ongoing potential for development of that possibility as well as for prosecution. While the Centers for Disease Control and Prevention and other health professionals see molecular HIV surveillance as a potential tool to create a rapid response to the spread of HIV within a community, advocacy groups continue to weigh concerns about privacy and prosecutions against the potential benefits of intervention [29].

Other challenges to people living with HIV and their advocates are deeply familiar including educating the general public and working with lawmakers who may continue to stigmatize groups associated with HIV as well as the disease itself. HIV criminalization laws remain a source of great anxiety for any person living with HIV. It is perhaps the most personal and impactful issue faced by many people living with HIV. Moreover, it signals state-licensed discrimination against people living with HIV.

Still, it is a hopeful sign that many of the state-level changes to HIV criminalization laws have occurred in conservative states, often due to strong activism by HIV advocates based directly on the states. Despite these challenges, the zeal for advocacy on HIV criminalization within the HIV community remains high. There is now a conference devoted specifically to this issue and advocacy resources in multiple states and at the federal level. At the same time, public health officials seem clear that HIV criminalization undermines efforts to end the HIV epidemic and in many cases law officials, attorney generals, and prosecutors are also on board. Ultimately, change to the laws is being driven by people living with HIV who are willing advocates for themselves and for others, and one should never underestimate the ability of HIV advocates to make change.

Bans on Blood Donation by HIV+ People

Beginning in 1983, the US Food and Drug Administration (FDA) implemented a policy banning people in high-risk categories from donating blood throughout their lifetime [30] (see Table 21.7). There are other bans on donating blood that are not population based, including travel to other countries in the midst of transmissible epidemics (e.g., mad cow disease in the United Kingdom), or contracting a bloodborne disease such as hepatitis.

At the time of implementation of the lifetime ban, little was understood about the newly emerging HIV illness, and it was clear that the emergency conditions warranted a strong response. Indeed, many thousands of other people were infected from contaminated blood transfusions, blood products, or organ/tissue transplants prior to the blood ban being implemented. Of an estimated 10,000 hemophiliacs in

Table 21.7 Categories of individuals banned from donating blood

Men who have sex with men (MSM) after 1977 (even if just once)
Transgender people
Haitians (stipulation removed in 1990)
Women who had sex with MSM
Sex workers
Injection drug users

Based on data from Ref. [30]

the United States, 5000 became infected with HIV and 4000 died [31]. In part due to the restrictions and protective measures in the blood supply (the FDA screens every unit of blood donated for infectious diseases prior to entering the donation pool), the risk of transmission is now almost nonexistent.

Calls for Change

As more was learned about HIV in the following decade, and particularly after the development of effective antiretroviral medications in the mid-1990s, people and organizations concerned with HIV began to refocus their attention on the ban. As early as 1997, AABB (formerly the American Association of Blood Banks) began to call for changing the lifetime donation prohibition for gay men to 12 months. In 2006, AABB, America's Blood Centers, and the American Red Cross jointly called for a 12-month prohibition for MSM (not for other groups) at the meeting of the FDA's Blood Products Advisory Committee, the primary body tasked with advising the FDA on the safety, effectiveness, and appropriate use of blood [32]. They noted that the lifetime prohibition for MSM was medically and scientifically unwarranted and that the deferral criteria should be made comparable to other groups at risk for increased infection. They noted that there was a perception that the differentiation between groups was unfair and that such perception was also leading to cancellation of some blood drives. The FDA did not accept the proposal stating its concerns about the studies cited.

Influential criticisms of the policy continued to mount during the following decade. In particular, development of a nucleic acid test (NAT) for HIV improved detection windows to approximately 9–11 days following infection (significantly shorter than the previous antibody test). Consequently, blood banks were much better able to detect HIV in the blood supply [32].

During this time period, other countries began to experiment with shorter prohibitions or with individualized reporting systems that specifically assess levels of risk (e.g., Italy, Spain). By 2015, Argentina, Australia, Brazil, Hungary, Japan, Sweden, and the United Kingdom had all instituted a 1-year prohibition [33]. As a result of these changes, many HIV policy groups began to strongly recommend that the United States move not to a shorter prohibition period but to individualized risk assessments [34].

Table 21.8 Statement by GMHC (formerly Gay Men's Health Crisis)

"The (blood donation) policy effectively excludes virtually all gay and bisexual men, regardless of whether they have engaged in high-risk or low-risk sexual behavior. Because the MSM policy is not narrowly tailored to exclude only those MSM engaging in sexual behavior posing the highest risk of HIV infection, such exclusion reinforces negative stereotypes and perpetuates harmful stigmas against gays and bisexuals as a whole" – GHMC [35]

Critics noted that the FDA policy imposed special burdens on gay and bisexual men. An early critic, GMHC (formerly Gay Men's Health Crisis) noted that in school or workplace settings, there was a potentially high social and stigmatizing impact of not participating in blood drives (leading in some cases to cancellation of blood drives) (see Table 21.8). Additionally, the FDAs criteria allowed people other than men who have sex with men to donate, potentially increasing risk while excluding MSM who engage in safer sex practices resulting not only in a discriminatory policy but a reduced blood supply [35].

Anecdotally, critics suggested at the time that gay or bisexual men who were being discriminated against did not necessarily comply with deferral guidelines. A 2017 survey study found "that 42.0% of all (study) participants had not complied with the deferral policy and have donated blood at least once, with a mean number of donations of 4.84. Additionally, 85.9% of participants would be willing to donate blood if the deferral were changed" [36]. This suggests that the policy may be weakening over time becoming less effective unless greater fairness is perceived.

Current Status of the Ban

As a result of concerns raised and specifically after conducting requested research from the Blood Products Advisory Committee in 2010, the FDA decreased the deferral period on the men who have sex with men community for blood donation to a 1-year ban in December 2015 [37] and then further changed the ban for all categories of deferred donors (including people who have engaged in sex for money or drugs or in nonprescription injection drug use) to 3 months in April of 2020 [37]. The report additionally notes that "In the context of the donor history questionnaire, FDA recommends that male or female gender be taken to be self-identified and self-reported" [37]. Essentially this means that transgender people may identify as they wish and that any deferrals should be subject to their self-reported status. Even at 3 months, reaction continues to be mixed, as many groups noted that even a 3-month ban on sexual activity would effectively exclude many gay men and others from donating and called for the FDA to move forward toward a system of donation based on individualized risk. In its recommendation, the FDA stated that there was not enough scientific evidence to move toward such a plan and instead called for studies to be completed.

In June of 2016, a gunman shot and killed 49 people and injured many more at a gay nightclub, "Pulse" in Orlando. The mass shooting, the largest at that time, prompted widespread horror. It provoked a particularly strong reaction in the

LGBTQ community, as most gay men could not donate blood due to the then 12-month ban, despite calls from local authorities in Orlando for blood donation. To many within the community, the ban continues to be seen as discriminatory against individuals who practice monogamy and safer sex as well as scientifically out of date given the short window required for testing. The shooting also produced a reaction in Congress with Members circulating a "Dear Colleague" letter to the Commissioner of the US Food and Drug Administration (FDA) calling for the Food and Drug Administration (FDA) to end the ban on gay and bisexual men from donating blood [38].

The Future of HIV and Blood Donation

As has happened in recent years, it is likely that the continued pressure to increase the blood supply and end stigma related to blood donation will continue to facilitate policy change. The most recent changes to 3 months would alleviate some of the issues but would still likely exclude a majority of men who have sex with men or people in other risk categories from donating. Similarly, a new dialogue related to the review of other categories of deferred individuals such as people who use drugs or who engage in sex work who are still subject to the lifetime ban may develop.

It is also inevitable that scientific and medical knowledge will continue to increase. New technologies such as "pathogen inactivation," a system that eliminates pathogens such as viruses and bacteria from donated blood, are currently effective on platelets and plasma (with research into other blood products ongoing) [39]. Technologies that would eliminate new viral agents would begin to obviate the need for specific screening and may create a technical answer leading toward equality.

Finally, the FDA stated, in its revised recommendations, that there was not enough evidence to move toward individual assessment of donor risk; however, the FDA noted that the topic could be explored in the future. Studies designed to assess donor questionnaires have the potential to provide further means to eliminate disparities and move toward an individualized risk assessment that would both be more accurate in screening. Ultimately, this may help reduce some of the stigma felt by the people most impacted by the deferral policy including gay and transgender men and women. Ensuring that policy is aligned with current technology will also help end stigma and educate all donors about their risks for HIV transmission while increasing blood donations and continuing to keep the blood supply safe from infection.

Conclusions

In this chapter, we reviewed several of the most significant ethical and legal issues surrounding HIV including issues related to confidentiality, privacy, and criminalization. As a result of the recognition of the crucial role of early identification and intervention in ending the HIV epidemic, HIV testing recommendations have been

updated to eliminate potential barriers. The elimination of the requirement for written informed consent and opt-out testing has simplified and routinized the HIV testing process.

Evaluation of current HIV criminalization laws revealed that they are prejudicial and out of date with current scientific knowledge. Moreover, such laws have been shown to be both ineffective and counterproductive in ending the HIV epidemic. As a result of tireless work by increasing numbers of advocates, scientists, and politicians, legal reforms or elimination of existing HIV criminalization laws is occurring in jurisdictions throughout the United States. Vigilance must be maintained as new scientific knowledge and technologies develop, bringing with them the possibility of new criminalization laws. While the FDA ban on the donation of blood by men who have sex with men remains in place, there was a change in the length of the ban. More recently, although the FDA did not change the restrictions on donation, it noted that it would continue to explore the topic.

These changes are the result of the use of current scientific knowledge and technologies to update the legal and ethical issues surrounding HIV. There still remains work to do and it will be important to continue to assess and revise policies based on updated scientific knowledge.

Multiple Choice Questions

1. With the focus on early identification and intervention, HIV pre-test counseling has been simplified, especially in high-risk populations. Which of the following elements is no longer part of pre-test counseling?

   A. Reason the test is being recommended.
   B. Services available in case of negative or positive result.
   C. Individual risk assessment and risk reduction.
   D. Clinical benefits of testing.
   E. Information that the confidentiality of the result will be maintained.

   Answer: C
2. Routine HIV testing would help in early identification of patients with HIV and thus initiate intervention early. When told, “We are offering routine HIV tests to all of our patients. It is a rapid test with results available in one or two hours,” which of the following refers to “opt-out” testing?

   A. “You can tell me, your nurse or your doctor if you would like to be tested today.”
   B. “Would you like a test today?”
   C. “You will be tested unless you decline.”
   D. “The HIV test is available, but you will not be tested unless you request it.”
   E. “Would you rather be tested in another facility?”

   Answer: C

3. Since 2010 at least seven US states have reformed HIV criminalization laws and many other states are considering further changes to such laws. Which of the following statements would not be considered a reason people advocate for the reform of such laws?

   A. Laws based on exposure to HIV additionally create a disincentive for people to be tested.
   B. Most state HIV criminalization laws do not require actual transmission of HIV for prosecution.
   C. Risky activities such as spitting and biting are never prosecuted.
   D. The laws are not based on current scientific understanding of the disease.
   E. Criminal statutes and enhancements prior to reform disproportionately affect groups such as women, people of color, immigrants living with HIV, LGBTQ youth, and transgender women of color.

   Answer: C – these are non-risk activities that have actually been prosecuted resulting in high and disproportionate sentences.

4. The US Food and Drug Administration (FDA) implemented a policy banning people in high-risk categories from donating blood throughout their lifetime which in 2015 was altered to a yearlong ban and then in 2020 was to a 3-month ban. Advocacy organizations have suggested that further changes could be made to this system on all but which of the following bases?

   A. New technologies such as "pathogen inactivation."
   B. Reducing stigma experienced by the people most impacted by the deferral policy.
   C. The current system works well and the exclusion of population-based categories is warranted.
   D. Creating a new system that moves toward individual assessment of donor risk.
   E. A majority of men who have sex with men or people in other risk categories continue to be unable to donate under current standards.

   Answer: C – the use of population-based categories has excluded people who could safely donate on the basis of immutable characteristics leading to a perception that the differentiation between groups was unfair and that such perception was also leading to cancellation of some blood drives.

5. All of the following are policies currently in place and part of the goal of ending the HIV epidemic, except:

   A. The routinization of HIV testing via opt-out testing.
   B. US laboratories mandating reporting positive HIV tests to local or state department of health.
   C. The California statue requiring specific intent to transmit HIV for prosecution.
   D. The elimination of the FDA ban on blood donation by MSM.
   E. The discontinuation of the requirement for written informed consent for HIV testing.

   Answer: D

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Chapter 22
The COVID-19 Outbreak and the HIV Pandemic

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Introduction

The outbreak of COVID-19 leading to the ongoing pandemic has had a considerable impact on society at a global level causing disruptions in many spheres of life, most notably in the functioning of healthcare systems. As the pandemic has diverted substantial resources from treating other illnesses and imposed an additional burden of illness across the board, HIV care has been notably affected. There are several issues in the COVID-19 pandemic that are specific to individuals with HIV, and each presents a formidable challenge for HIV patients to negotiate during the pandemic. With each challenge, however, come the unexpected, rare opportunities for strengthening individual coping skills and for providing strength and support to the broader community.

Perilous COVID-19 and HIV Comorbidity

As of April 2021, there were 135,646,617 confirmed cases of SARS-CoV-2, including 2,930,732 deaths and millions of recovered cases. In the United States, 31,025,033 Americans had confirmed COVID-19, and 559,172 people lost their lives while infected with SARS-CoV-2. Although there are questions about whether patients lose their lives due to COVID-19 or with COVID-19, the scientific

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community unanimously acknowledges the increased severity of SARS-CoV-2 infection in susceptible elderly patients and in persons who have multiple comorbidities, as well as how it has tremendously strained healthcare systems.

SARS-CoV-2 invades human cells by means of the ACE2 receptor. About 83% of ACE2-expressing cells are expressed in alveolar epithelial type II cells (AEC-II), which can serve as a reservoir for viral invasion, which may explain why the lung is the major source for infection [1]. ACE2 is also highly expressed on the luminal surface of intestinal epithelial cells [2], functioning as a co-receptor for nutrient uptake, in particular for amino acid resorption from food. This may partially explain why some patients have initial presentations of COVID-19 with GI symptoms and associated malnutrition through the course of their illness due to reduced intestinal absorption. Notably, patients who have obesity and significant atherosclerosis seem to have an increased mortality associated with myocardial injury when facing a systemic inflammatory condition due to plaque instability, and patients infected with SARS-CoV-2 do have an increased risk for thromboembolic events [3].

People living with HIV are notably at risk for atherosclerosis, and one of the ominous hallmarks of HIV is the weakening of the immunological system that makes HIV patients more susceptible to other infections. It is a grim scenario that leaves individuals with compromised immune systems exposed to the potentially deadly SARS-CoV-2 virus that causes COVID-19. Because it is a novel virus and humankind has heretofore been immunologically naïve to it, there is almost universal susceptibility that also encompasses HIV individuals, making COVID-19 infections among HIV individuals inevitable, probably at a higher rate than in the population at large.

Indeed, there have been clusters of patients with HIV who have been infected with SARS-CoV-2 [4]. Several studies, including studies that reviewed other HIV-coronavirus coinfections, indicate that both morbidity and mortality among HIV patients do not differ significantly from the general population [4–8].

At least one study found HIV patients on ART less likely to contract COVID-19 [9]. As the use of immunosuppressants (e.g., corticosteroids) emerges as one of the cornerstones in treatment of COVID-19, it is plausible to imply that the naturally immunosuppressed status of HIV patients may offer some advantages [10]. Some anecdotal reports and animal models suggest that the inability of an HIV patient to mount a robust immunological response may have a protective effect from developing a "cytokine storm," a massive immunological reaction that has been associated with difficult cases with poor prognosis [11, 12]. Another explanation would be that, with steady use, ART may have created a milieu that aided HIV individuals in fighting off COVID-19 [13].

Case Vignette 22.1

Mr. A was a 30-year-old man who was employed as a bus driver since 2017. In June 2019, he experienced symptoms of fatigue, sore throat, diarrhea, dry cough, and "itchy skin." He was diagnosed as having *Pneumocystis jirovecii*

pneumonia and AIDS by his primary care physician. Mr. A was referred to an HIV clinic where he was educated about his illness and started on antiretroviral medications. His viral load successfully decreased to over 50% after 3 months of treatment, and he was pleased to have his energy level back. However, his CD4 counts were consistently low, under 100 cells/microliter, and his nurse practitioner opted to continue the prophylactic combination of dapsone, pyrimethamine, and leucovorin to prevent toxoplasmosis and pneumocystis reactivation, as he was allergic to penicillin. In March 2020, Mr. A started reading about COVID-19 and how it impacted large cities in the Northeast USA, especially transportation workers. He became extremely fearful of coming to work, as his CD4 counts were still low and he did "not want to die because of his work." He became fearful of working at his job as a bus driver and tried to contact his nurse practitioner to help him address his fears and obtain advice.

Stigma

Infectious diseases frequently come with the shroud of stigma. While *biologically*, even *theologically*, stigma may carry a signal to keep "social distance" from an afflicted individual who may be contagious, *socially* the expectation of "keeping away from the diseased" has progressed into a group tendency to stigmatize and excessively ostracize persons who are infected and to banish them into isolation, away from the "healthy." This has been a universal characteristic of all human societies – from the preliterate ones and the way people treated leprosy and lepers to the "modern" ones and the way people treat individuals with HIV, Ebola, or COVID-19 [14].

HIV has a particularly loaded experience with stigma because its social stigmatization of the disease was intertwined with the discrimination against one's sexual orientation and, often, race, gender, and/or socioeconomic status. With COVID-19 outbreak, individuals with HIV simply add yet another potential layer of discrimination to a, already loaded, palette. Persons with HIV may expect to be additionally stigmatized and discriminated against should they, their loved ones, or members of their community become ill with COVID-19.

While clearly present, discrimination against individuals with only COVID-19 is not as pronounced, for a number of reasons, which include social attitudes toward the illness and its stigmatization and, more importantly, a lack of physical features that may help identify an individual as a COVID-19 patient. From that perspective, stigma of COVID-19 pales in comparison with the systemic, perennial stigma that HIV individuals struggle to overcome. It is, nevertheless, very socially challenging to be "doubly stigmatized," to develop COVID-19 while already living with HIV.

As an upside, many individuals with HIV have developed coping skills that they utilize to address and overcome stigma and discrimination. As such, they may even

be in a position to serve as a resource to COVID-19 patients in their community who previously never had to deal with stigma on the "outside" and guilt and shame on the "inside," but now they and their families may be singled out and ostracized. See Chap. 3 of this textbook for further discussion of HIV stigma.

Case Vignette 22.2
Mr. B was a 55-year-old supermarket manager who was living with HIV for over a decade. He presented with symptoms of COVID-19 and was admitted to the inpatient internal medicine service for hypoxia requiring supplemental oxygen via nasal cannula. He was found to have mildly elevated transaminases. The senior internal medicine resident consulted the infectious diseases service to see if there would be benefit in adding lopinavir-ritonavir to his regimen, given "anecdotal evidence he heard in his group text" about its efficacy against SARS-CoV-2. When the infectious disease team came to evaluate Mr. B, he had already been transferred to the step-down unit due to hypoxemia, requiring him to have a reservoir mask. The infectious disease consultation service recommended avoiding endotracheal intubation because Mr. B was hemodynamically stable and comfortable and had an oxygen saturation above 95%. The decision not to intubate was also, in part, based on the information that their department director had "read some Chinese studies" showing that premature endotracheal intubation was associated with adverse clinical outcomes in COVID-19. The senior resident from the step-down unit had to be reassigned to the intensive care unit due to staff shortage, and a new intern from ophthalmology was assigned to Mr. B. The new intern wondered if they should intubate Mr. B while he was still hemodynamically stable, since he was not sure of the impact of HIV on the patient's risk for acute respiratory distress syndrome.

Isolation, Loss, and Struggle for Meaning

Serious infectious diseases come with a certain proportion of fatalities, which make them a serious public health issue and a thus threat in the eyes of the public. Both COVID-19 and HIV can be fatal, but in a vastly different proportions and with different modes of causing death.

Grappling with HIV often implies a lifelong struggle with isolation, loss, and a quest for meaning. Isolation and loss are both *symbolic*, as is the case with stigma and rejection, and *physical*, as in prolonged isolation due to opportunistic infections or loss of partners and friends to HIV. Finding an ongoing sense meaning in the face of protracted, burdensome adversities presents itself as a herculean task for individuals with HIV, a task that greatly affects both quality of life and overall survival. Developing coping skills to address loss and to find meaning requires time and resources that, albeit insufficient, may be available through peer support and mental health services integrated into HIV clinics.

COVID-19, on the contrary, strikes suddenly and non-selectively. It rips apart families by separating individuals who are seriously ill from those who are relatively healthy. A relatively short period of isolation may end with a sudden loss of a loved person, leaving family members to reel in the wake of an unanticipated grief.

Having HIV and then having to deal with isolation and loss imposed by COVID-19 may have deleterious effects on individuals with HIV. For persons with HIV, coping resources may have already been challenged by a string of losses and by having to revise life goals and recapture the meaning in life in general [15].

At the same time, as with stigma, individuals with HIV may have developed resilience to unexpected, seemingly arbitrary, and meaningless losses, to the extent that they may arguably be *better* prepared to absorb the blows dealt by COVID-19. In such cases, individuals with HIV may become a resource to their families, their circle of friends, or even their community in helping survivors mourn the loss and find meaning in their lives.

Case Vignette 22.3
Ms. C was a 46-year-old trans woman with HIV. She and her partner, Mr. C, moved from New Mexico to New York City where Ms. C worked as an online dancer for a private company that was relocating its activities. In New Mexico, Ms. C's viral load had been negative for 10 years on stable doses of antiretroviral therapy in the care of a primary physician. She was adherent to care with consistent follow-up. She had "mild symptoms of anxiety." For 2 weeks after the move to New York, Ms. C called multiple primary care clinics to make sure she would not run out of her medications "while living in the big city." However, it was challenging for Ms. C to find a new primary care physician since the COVID-19 pandemic had started, as some of the clinics did not accept her insurance, "were not receiving new patients because of COVID," or "had limited experience seeing transgender patients." Tearful and anxious about continuing antiretroviral medication, but wanting to pursue this great career opportunity, Ms. C desperately called her primary care physician in New Mexico. This physician suggested a visit to a local urgent care center as a walk-in to receive a follow-up appointment.

Burden on Resources and Limited Access to Care

COVID-19, like HIV, is a communicable infectious disease, and its treatment is guided by the input provided by infectious diseases (ID) specialists. Those are, incidentally, the same physicians who have been treating HIV patients for decades. As the COVID-19 pandemic tears through communities like a brushfire, the demand for ID physician services rises sharply and often results in ID physicians being pulled away from treating HIV patients to treating or consulting on treatment of COVID-19 patients.

Access to care becomes even more limited by implementation of community-wide social distancing measures, so even the programs and resources that were not redeployed away from HIV management become temporarily effectively unavailable. Patients of HIV-centered programs can thus be forced to temporarily cease attending most, if not all, of them and are reduced to periodic and sporadic telephone and/or telemedicine contacts with various clinicians.

On top of all that, the very lifeline for HIV patients – access to antiretroviral medications (ART) – may be severely curtailed due to redeployment of public health resources and/or the COVID-19 pandemic disrupting manufacturing and distribution of ART. In July 2020, WHO reported that 36 countries, with 45% of global ARVs-receiving population, reported disruption in ART distribution in prior months [16].

Finally, with no definitive cure available yet for COVID-19, many medications have been tried in combating the disease, including ARTs. Preliminary studies have suggested a modest effect against SARS from antiretroviral drugs [17]. Some advocate for early triple antiviral therapy with interferon beta-1b, lopinavir-ritonavir, and ribavirin to ameliorate symptoms and shorten the duration of viral shedding and hospital stay related to COVID-19 [18], and clinical trials are underway. If proven to be an effective treatment strategy against COVID-19 in randomized clinical trials, this could pose a major challenge in treatment availability for people living with HIV, as governments would attempt to secure enough stock to treat their citizens in the midst of the pandemic. To date, the role of ARTs to improve clinical outcomes or prevent infection among patients at high risk of acquiring COVID-19 is still uncertain [19].

These are serious logistical challenges that are not easy to overcome, particularly during a pandemic during which fears for their own well-being affect patients, other clinicians, and physicians alike [20]. What individuals with HIV may see work to their advantage are the previously forged connections and communication channels with their physicians and other caregivers. Persons with HIV may be able to reach clinicians via personal phones, and clinicians, well familiarized with their patients' conditions, may be able to meet patients' needs even in the absence of the direct face-to-face contact. Familiarity with clinicians may also be the case when persons with HIV are infected with SARS-CoV-2; they would most likely be treated by the same team that regularly treats their HIV.

Conclusions

Managing and treating persons with HIV during the COVID-19 pandemic adds an additional layer of challenges to an already delicate process of caring for patients who, even under far better circumstances, struggle with isolation, stigma, discrimination, and access to care. It is, therefore, important for physicians and other clinicians to understand those challenges that range from novel comorbidities and additional health risks to repetitive stigma and isolation to diminished access to

care and to lifesaving medications. Once these challenges are understood, it is equally as important for clinicians to communicate to their patients that they have the understanding, knowledge, and competence needed to overcome those challenges while maintaining a strong therapeutic relationship with their patients. Done correctly, this process will not only ensure continuity of care for individuals with HIV but may even create opportunities for HIV activists and advocates to serve as resources for the entire COVID-19-affected communities and populations.

Multiple Choice Questions

1. SARS-CoV-2 invades human cells by means of a specific receptor highly expressed in lungs and the gastrointestinal system, namely:

   (a) CXCR4
   (b) ACE1
   (c) *ACE2*
   (d) Toll-like receptor

   Answer: (c)
2. COVID-19 and HIV disease are often associated with stigma, isolation, and psychological distress. Which of these is a unique consequence associated with COVID-19?

   (a) Reporting its diagnosis to the health authorities, as it is a communicable disease
   (b) Increasing stress and stigma in local communities
   (c) Risk of fatal outcome if untreated
   (d) *Separating individuals who are seriously ill from those who are relatively healthy*

   Answer: (d)
3. Which of the following are considered at-risk populations for death due to COVID-19?

   (a) Young adults with no comorbidities
   (b) *Elderly smokers with multiple comorbidities*
   (c) Children with allergic rhinitis
   (d) Nonsmoker middle-aged adults

   Answer: (b)
4. Which of the following is often present in HIV populations and may increase mortality during COVID-19 infection?

   (a) Coinfection with HSV
   (b) Positive anti-HBsAg antibodies
   (c) Use of antiretroviral medications
   (d) *Obesity and metabolic disturbances*

   Answer: (d)

5. Which of the following uniquely predisposes discrimination against people living with HIV, when compared with those affected with COVID-19?

   (a) Being infected with a virus that is potentially fatal
   (b) *Self-stigma, shame, and blame after being diagnosed with a lifelong medical condition*
   (c) Being isolated by the community after being diagnosed with an infectious disease
   (d) Having a lack of understanding on the true pathophysiology of the condition

   Answer: (b)

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