Chapter 12
Psychiatric Comorbidities in HIV Infection

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Keywords Psychiatric comorbidities • Neuropsychiatric features • HIV-associated neurocognitive disorder • Mood disorders • Severe mental illness • Substance abuse

Core Message

1. Psychiatric comorbidities place individuals at risk for HIV infection and transmission.
2. Clinicians need to distinguish between pre-existing psychiatric disorders and CNS manifestations of HIV infection.
3. Treatment of comorbid psychiatric disorders is important for HIV-related outcomes.
4. Non-pharmacological interventions have shown promise for treatment of psychiatric disorders in HIV-infected persons

12.1 Introduction: HIV Psychiatry

The shift in public knowledge, concern, and attention to the HIV epidemic has resulted in a number of efforts toward prevention that include early screening, public distributions of condoms, and community needle exchange programs [1] https://www.cdc.gov/hiv/pdf/policies_nhas.pdf. For those recently diagnosed, there are a growing number of "linkages to, retention in, and re-engagement in HIV care" (LRC) programs [2]. For LRCs, entering and staying in care are pivotal in the care continuum, which begins with the diagnosis of HIV infection, entry into, and

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retention in HIV medical care, access, and adherence to antiretroviral therapy (ART) and viral load suppression.

Psychiatric comorbidities pose considerable challenges to the success of these intervention efforts. For example, risk reduction interventions assume that the individual has the capacity to make informed decisions about his or her behavior (e.g., engaging in risky sex). Interventions that use contingency management principles (i.e., the use of proximal awards for positive behavior change) assume that the patient has intact cognitive/neural reward systems. Among individuals with psychiatric illness, cognitive resources may be grossly limited and even further compromised in the context of HIV infection (see [3–7]).

In primary care settings, psychiatric disorders are often under-detected, misdiagnosed, undertreated, or treated improperly. Psychiatric disorders are more common in the HIV-seropositive population (~63%) as compared with the HIV-seronegative population (~30.5%) [8, 9]; therefore, the need for psychiatric presence in HIV care settings has become increasingly recognized [10]. Psychiatric comorbidities, particularly depression and substance abuse, are one of the most consistent barriers cited for nonadherence to antiretroviral therapy [11–17]. Findings also support that depression and recreational drug use contribute to continuous engagement in high-risk sexual behavior [18–20].

Early in the epidemic, a substantial majority of HIV-infected persons presenting for intake to an HIV primary care clinic suffered from depression, substance dependence, or another current psychiatric disorder; however, clinicians failed to identify most cases [21]. Similarly, population-based studies have found that individuals meeting the criteria for major depression are commonly undiagnosed and untreated [22, 23]. A more recent study examined attrition across four stages of care: (1) clinical recognition of depression, (2) treatment of depression, (3) adequacy of treatment, and (4) treatment response [24]. They estimated that among individuals with HIV, only 45% of individuals meeting the criteria for depression were clinically recognized; only 40% of recognized cases received treatment, only 40% of patients treated are treated according to standard guidelines, and only 70% of patients receiving adequate treatment achieve remission. This data suggested that among HIV individuals with depression, only 18% receive treatment, and only 5% achieve remission, which indicates that identifying and treating depression remain a problem. This is particularly concerning due to the fact that a majority (72%) of depressed HIV patients should achieve remission if properly identified and treated [25]. Toward this end, screening tools for depression (e.g., PHQ-9) have been evaluated for feasibility and show considerable promise for use within busy outpatient clinics [26, 27]. Nevertheless, more work is needed to fully understand the manifestations of psychiatric symptomatology and fluctuations throughout the course of the disease.

As such, it is foreseeable that psychiatric screenings and assessments will be a major component of HIV clinical care, if not at the forefront. Screening for mood disorders, anxiety, and psychosis in HIV-infected people is crucial because of the downstream impact of mental health on HIV-related health outcomes. Clinicians will need to be able to recognize psychiatric conditions that place individuals at risk for HIV or for worsening of HIV (if already diagnosed) versus those that occur secondary to infection or treatment. This is no easy task given that psychiatric

symptoms may manifest for a number of reasons including psychosocial stressors, medication side effects, neuroinflammation, and immune system complications (e.g., reduction in CD4 count, rise in viral load, or onset of brain infection – for a review, see [28, 29]). Once a psychiatric diagnosis is made, it is necessary to determine appropriate treatment – whether that is in the form of pharmacotherapy, behavioral or psychotherapy, or combined treatment.

12.1.1 History of HIV Psychiatry

Loewenstein and Sharfstein [30] were among the first to describe the clinical *sequelae* of psychiatric disorders in seven AIDS patients referred for consultation. These cases were identified as having organic neurologic disease, which included central nervous system (CNS) cytomegalovirus (CMV) infection, cryptococcal meningitis, and disseminated lymphoma. Subsequently, Hoffman [31] reported two AIDS patients with organic mental disorder, one with progressive dementia and one with severe delirium. Although the exact etiology was unknown, both patients shared similar clinical presentations [32]. Behaviorally, patients presented with fluctuations in sensorium, behavioral responses, speech, and cognitive processes, which did not correlate well with any objective factors such as normal EEG findings. These findings suggested that organic brain dysfunction should be considered despite normal EEG findings [31]. Following these observations, several studies described cases of clinical syndromes that included affective symptoms [33], delusions [34], and features of dementia [35] that were attributed to infection of the CNS.

12.2 Psychiatric Disorders Before Highly Active Antiretroviral Therapy (i.e., Pre-HAART)

Pre-HAART studies vary in the reported prevalence of comorbid psychiatric disorders, though most studies agree that the rates of psychiatric disorders are higher among individuals diagnosed with HIV/AIDS than in the general population. Differences in the reported rates of psychiatric disturbance may be attributed to the use of convenience samples as well as differences in clinical severity. Notably, some earlier reports used patients who had met the criteria for AIDS, whereas others used patients who were identified as HIV seropositive but had not yet advanced to AIDS. Studies generally reported a higher rate of mood disturbance among patients diagnosed with HIV and/or AIDS [36–38], and rates increased even further when factoring in the history of intravenous drug use [38]. In the same study, a diagnosis of depression continued to independently predicted serostatus after factoring in the history of intravenous drug use. An investigation of 60 patients referred to the

liaison psychiatric service over the course of 1 year found that the most common reason for referral was affective disorder (58%), adjustment reaction (15%), paranoid states (10%), personality changes (6%), and schizophrenia (3%) [39]. In this same study, 23 patients underwent CT scan, and of those, 17 showed brain abnormalities. Walkup and colleagues [40] found that 5.7% of persons listed on the New Jersey HIV-AIDS registry had received a diagnosis of schizophrenia, which is much higher than the national prevalence rate of 1.1%. They also found that 6.8% of persons on the registry had received a diagnosis of a major affective disorder, for a total of 12.5% with a serious mental illness.

In contrast to the aforementioned studies, Bialer and colleagues [41] did not report a higher rate of mood disturbance among AIDS patients in their large-scale investigation of patients who were referred for inpatient psychiatric consultation at Beth Israel Medical Center. Rather, they reported an increased prevalence of dementia among persons with AIDS in comparison with non-HIV patients, whereas substance use disorder and personality disorders were more likely to be found among HIV-seropositive patients in comparison with persons with AIDS. For many of the earlier studies, concerns have been raised that HIV-induced organic mood disorders were misdiagnosed as functional depression [36, 42–45], as data suggest that the two entities generally have different clinical manifestations. Early studies failed to find that depression was related to markers of neurologic compromise such as cognitive impairment [46, 47]. In fact, a common clinical impression was that individuals who seemed the most depressed and anxious would perform well on neurocognitive testing, whereas others who were calm and showed normal affect (possibly reflecting a lack of awareness) would show impairments in cognitive functioning [46]. Thus, features such as apathy, withdrawal, mental slowing, and avoidance of complex tasks associated with early HIV-induced organic mental disorders may be differentiated clinically from low self-esteem, irrational guilt, and other psychological features of depression. Collectively, these studies highlight the relationship between clinical severity and the prevalence of mood disturbance and the importance of identifying an organic etiology.

12.3 Prevalence of Psychiatric Disorders in the HAART Era

The advent of HAART has transformed HIV from a fatal disease to a manageable chronic illness. This was achieved through restoration of the immune system that allowed patients protection against opportunistic infections [48–51]. However, neurological deficits and cognitive disorders were still found to persist or progress in some patients with treatable infections [52]; therefore, the benefits of HAART on HIV-associated neurocognitive disorders were not as clear at the time [53].

The HIV Cost and Services Utilization Study (HCSUS; [54]) examined mental health and substance use in a large, nationally representative sample of adults receiving care for HIV in the USA. Study participants were administered a brief instrument that screened for mental health disorders and drug use during the previous 12 months.

Approximately 50% of the sample screened positive for a mental health disorder, primarily major depression (approximately 1/3 of the sample) and dysthymia (approximately 1/4 of the sample). These rates were similar to those reported in pre-HAART. Nearly 40% reported using an illicit drug other than marijuana, and 12% screened positive for drug dependence. Physicians from the Moore Clinic at Johns Hopkins Hospital [55] reported that more than half of the patients seeking HIV medical care have a major psychiatric disorder other than substance abuse or personality disorders, with approximately 20% with cognitive impairment [56].

Since these reports, there has been a demographic shift in the HIV population. Changing from a disease that once targeted homosexual, white men from middle-class communities, new infections are highest among people of color, in women, and in low-resourced communities. Although the majority of people currently living with HIV in the USA are men who have sex with men (MSM), heterosexual transmission accounted for 27% of all newly diagnosed AIDS cases in 2009 – which is approximately ten times the rate reported in 1985 [57]. In the USA, the rates of HIV among injecting drug users (IDU) has decreased significantly over time. In 2009, the Centers for Disease Control and Prevention estimates that about 9% of the 50,000 of annual new infections in 2011 were among IDUs. Women of color are a subgroup that is particularly affected.

HIV tends to be concentrated in highly vulnerable, marginalized, and stigmatized populations such as ethnic/racial minority populations. Racial/ethnic minorities are particularly vulnerable to aquiring HIV-infection, as this group is more likely to live in poverty, report histories of abuse and incarceration, and have social networks that place them at risk for both HIV and mental health problems. In 2010, African-Americans accounted for 50% of all AIDS cases diagnosed during the year, even though they accounted for only 12% of the population. Among African-American women, the figures are even more alarming – representing up to 72% of all new HIV cases in American women [57]. African-American/Black women accounted for two-thirds (64%) of new AIDS diagnoses among women in 2010; Latinas represented 17% and white women 15%. As such, cultural considerations in the diagnosis and treatment of psychiatric disorders are also critical for HIV care among these demographic subgroups.

12.4 Psychiatric Disorders and Risk for HIV Infection and HIV Transmission

As mentioned throughout this chapter, pre-existing psychiatric disorders are common in HIV infection and must be distinguished from those that occur secondary to infection. A number of psychiatric disorders, including substance use disorders, are associated with increased risk of HIV/AIDS and interfere with treatment [12]. Data from 645 South Africans who participated in a community-based study demonstrated that 33% reported depression, 17% reported alcohol abuse, and 15%

reported post-traumatic stress disorder. After adjusting for demographic characteristics, the presence of any of these three conditions was strongly associated with HIV risks, which included forced sex and transactional sex [58]. When identifying patients who are at risk for contracting HIV, clinicians should consider that patients with substance use disorders, patients with severe mental illness, and victims of sexual abuse/crimes have specific risks for becoming infected with HIV. Psychiatric disorders increase risk behaviors such as sexual contact with multiple partners, injecting drug use, and unsafe sex practices [59]. For example, in the Multicenter AIDS Cohort Study [60], the proportion of gay and bisexual men reporting the use of an illegal drug in the prior 6 months ranged from 92% to 55%, between 1985 and 1989. Among HIV-negative psychiatric patients, nonadherence ranges between 28–52% for major depressive disorder and 20–50% for bipolar disorder. A recent investigation found that loss of a loved one has consistently been associated with various health risks. Little is however known about its relation to STIs. A large population-based study of women from the Swedish Multi-Generation Register found that women who had experienced bereavement were at significantly higher risk for all of the STIs studied [61].

12.5 Comorbid Conditions

Comorbid mental illness among HIV-infected individuals in the USA is substantially higher than in the general population, with rates ranging between 5% and 23%, compared with a range of 0.3%–0.4% among the general population [62]. Mood disorders can result in the most adverse outcomes, as patients with mood disorders are at greater risk for suicide and failure to adhere to medications. Some studies suggest that depressive and anxiety comorbidities accelerate HIV disease progression [63–66], which may be mediated by such factors as changes in medication adherence [67] and lack of health-promoting behaviors [68]. A meta-analytic review of studies conducted in South Africa and other sub-Saharan African countries reported similar findings with respect to higher prevalence rates among those with HIV/AIDS, although the range in prevalence is large across studies (from 5% to 83%), which may result from differences in tools and populations studied [69]. In a study of an HIV-infected sub-Saharan population, [70] there was a substantial prevalence of both major depression (35%) and post-traumatic stress disorder (15%). In another investigation of individuals in South Africa, the prevalence of depression, PTSD, and alcohol dependence/abuse was 14%, 5%, and 7%, respectively [71]. Similar to US findings, studies of HIV+ individuals with late-stage disease found that common mental disorders such as depression tended to increase, while the use of HAART was shown in one study to improve general mental health [72–74] (Table 12.1).

Table 12.1 Clinical diagnoses and symptoms

Clinical disorder (DSM-V code) [75]	Description
Major depressive disorder (296.2×/.3×)	Feeling sad, empty or hopeless most of the day, guilt, fatigue, loss of motivation, sleep disturbance, and cognitive impairment. Apathy, irritability, demoralization, and neurovegetative symptoms may overlap or present as separate/independent features in HIV
Bipolar disorder (296.4×/5×)	Symptoms of a manic episode include elevated or irritable mood, increased activity, increased self-esteem, irritability, decreased need for sleep, and racing thoughts. Certain symptoms may overlap with HIV-related CNS disruption
Post-traumatic stress disorder (309.81)	Exposure to threat or violence, intrusive symptoms, avoidance, and negative thoughts or mood of the event
Substance-related and addictive disorders (305.00–312.31)	General features may include impaired control over substance, social/functional impairment, risky use of substances, tolerance, and withdrawals
Cluster B personality disorders (301.7–301.81)	Antisocial personality disorder, disregard and violation of rights of others; borderline personality disorder, instability in relationships, emotional lability, and impulsivity; histrionic personality disorder, emotional lability and attention-seeking behaviors; narcissistic personality disorder, grandiosity, persistent need for admiration, lack of empathy

12.5.1 Major Depressive Disorder (MDD)

A diagnosis of major depressive disorder is made when five (or more) of the following symptoms have been present during the same 2-week period and represent a change from previous functioning: (1) depressed mood most of the day (nearly everyday), (2) markedly diminished interest or pleasure in activities, (3) significant weight loss when not dieting or weight gain or decrease or increase in appetite nearly everyday, (4) insomnia or hypersomnia, (5) psychomotor agitation or retardation, (6) fatigue or loss of energy nearly everyday, (7) feelings of worthlessness or excessive or inappropriate guilt, (8) diminished ability to think or concentrate or indecisiveness, and (9) recurrent thoughts of death, suicidal ideation, or suicide attempt or plan [75].

Studies have found significant relationships between depression and mortality in HIV-infected individuals [76–78], whereas others have not [79, 80]. For example, in the San Francisco Men's Health Study, a 9-year longitudinal study of HIV-seropositive men, higher levels of depression at the beginning of the study were associated with faster progression to AIDS [81]. In another study, involving 414 HIV-infected gay men studied over 5 years, baseline depression was associated with shorter time to death but not change in CD4+ count or progression to AIDS [78]. An analysis of 1809 gay men from the Multicenter AIDS Cohort Study found no relationship between depression measured with the Center for Epidemiological Studies Depression Scale (CESD) at study entry and progression of HIV infection during

8 years of follow-up [80]. Disease progression was defined as time to AIDS, death, or decline in CD4+ T lymphocytes. In later analyses of these data, the authors found that self-reported depressive symptoms appeared to rise during the 1.5 years before an AIDS diagnosis [82]. The authors interpret these findings as an indication that depression may increase toward the later stages of HIV infection and thus may be a manifestation of the disease process. While diagnosing depression uses standard criteria for all populations, certain symptoms may be more prevalent in individuals with HIV thereby obscuring clinical assessment of depression. Specifically, appetite and sleep disturbances are more frequently reported in HIV-seropositive patients as compared to HIV-seronegative patients [83]. Demoralization can be difficult to distinguish from major depression, but there are distinctive features between the two syndromes. Depression is characterized by persistent anhedonia, and demoralization is being often characterized by helplessness and linked to recent events or ongoing life circumstances [84–86]. Patients with major depression respond relatively well to antidepressant medications; those with demoralization tend to respond well to psychotherapy and not to medications [87, 88].

The diagnosis of comorbid MDD in HIV-infected persons may be difficult, because the neurovegetative symptoms of premorbid MDD (such as lack of energy, fatigue, anorexia, and sleep disturbances) may also be caused by the biological effects of HIV [89]. HIV infection stimulates increasing levels of proinflammatory cytokines such as interleukin-6, interleukin-1-beta, tumor necrosis factor-alpha, and interferon-gamma [90–92], which are associated with sickness behavior (fever, hypersomnia, anorexia, decreased motor activity, and loss of interest in the environment). In differentiating between pre-existing MDD and the neurovegetative symptoms of HIV, it may be useful to remove the somatic depression symptoms included in diagnostic instruments such as the Beck Depression Inventory-II (BDI-II) and the CESD. Indeed, studies have found that removing somatic subsets of depression symptoms improved the clinical utility of the BDI and CESD [83, 93].

Chronic stressors associated with HIV infection may exacerbate mood disorders. Studies have documented dysregulation of the HPA axis and blunted adrenocorticotropic hormone (ACTH) responses among HIV-infected individuals [78]; thus, it is plausible to expect that HIV status may increase vulnerability to depression HPA-axis dysregulation. Several studies have reported that HIV-seropositive individuals with a major depressive episode or self-reporting depressed mood on standard instruments may demonstrate reduced performance than non-depressed individuals in some cognitive domains (e.g., memory tasks) or report more cognitive complaints [94–96]. However, none of these studies reported an association with neurocognitive impairment. In contrast, others studies have suggested a possible link between increased depressive complaints and lower cognitive function [93, 97, 98]. A longitudinal study of 227 HIV-positive adult men who did not meet the criteria for a current major depressive episode at baseline reported no neurocognitive performance differences in association with lifetime or incident depression and suggested that neurocognitive impairment and major depression be considered two independent processes [99].

HIV-infected individuals who are at greatest risk for developing depression are those with a history of depression, homosexual men, women, or intravenous drug users (IVDUs [100]). Other risk factors associated with developing major depression in HIV-seropositive persons include social stigmatization, isolation, lack of social support, death of friends as a result of HIV/AIDS, and gender [101, 102]. In a longitudinal study of HIV-infected and HIV-uninfected men, lifetime prevalence of major depression or other psychiatric disorders did not differ between the groups. However, at 2-year follow-up, those with symptomatic HIV disease were significantly more likely to experience a major depressive episode than individuals who were either in the HIV asymptomatic or control group. However, HIV disease progression did not predict the presence of neurocognitive impairment [103].

Differential diagnosis in a patient with a complaint of depression includes (1) major depression and related mood; (2) demoralization and grief states related to the losses and stresses associated with HIV; (3) delirium, a waxing and waning mental state associated with global cerebral dysfunction and possibly disease acceleration; and (4) dementia, including AIDS dementia and other forms of subcortical damage.

12.5.2 Apathy and Irritability

Apathy (a loss of goal-directed behavior and motivation) and irritability are common neuropsychiatric features of HIV [104, 105]. Approximately 26% of HIV-seropositive individuals meet the criteria for clinically significant apathy, and multiple studies have shown both apathy and irritability to be more common/severe relative to HIV-seronegative controls [104–106]. The clinical importance of apathy has been debated [107, 108]. Nevertheless, within the HIV population, apathy is related to some meaningful outcomes, such as medication adherence [14], but only minimally related to other meaningful outcomes, such as quality of life [106]. We are unaware of any studies or clinical trials examining treatments of apathy in HIV. In general, treatment of apathy in other populations (such as Parkinson's disease or Alzheimer's disease) has not been promising, and findings have been inconsistent regarding the superiority of medications over placebo (for review, see Drijgers [109]). Future investigations of treatments for apathy may be particularly important as pathophysiology of apathy may dramatically differ from other common mood disorders, such as depression. In fact, Selective Serotonin Reuptake Inhibitors (SSRIs), a common treatment for depression, may be related to worsening of apathy [110]. Investigations into non-pharmacological treatments for apathy, such as behavioral activations, are also warranted.

Apathy and irritability are of particular interest in HIV because they are thought to reflect disruption of the central nervous system (CNS). In contrast other psychiatric symptoms (such as depression and anxiety) are less related to a neurologic insult and may reflect adjustment to social, medical, or financial stressors [104]. Although symptoms of apathy and depression may overlap, apathy has been

shown to be a unique construct, separate from depression [106, 111]. The high occurrence of apathy and irritability is thought to be related to disruption of frontal-subcortical networks important for initiation and monitoring of behavior [112]. Indeed, neuropsychological and neuroimaging studies have found support for apathy and irritability reflecting CNS disruption [113]. Frontal-subcortical networks are known to be an important mechanism for executive functioning. Among HIV-infected individuals, apathy and irritability, but not depression or anxiety, are associated with impairments in executive functioning [104, 105]. Studies using diffusion tensor imaging have shown that white matter tracts subserving the medial prefrontal cortex (an area important for motivation and goal-directed behavior) are less intact in HIV-infected individuals relative to HIV-uninfected controls [114–117]. White matter integrity in these regions was related to the severity of apathy in a study of HIV-infected individuals [114]. A similar study found the relationship between apathy and white matter integrity to be independent of depression and to be stronger among individuals with more severe HIV (lower CD4 counts). Such findings support that apathy may be a syndrome that arises from HIV-associated frontal-subcortical disruption.

12.5.3 Mania

HIV-infected patients with secondary mania, termed "HIV mania," may present as agitated, disruptive, sleepless, having high levels of energy, and being excessively talkative [89]. They have a high rate of psychotic symptoms such as auditory or visual hallucinations and paranoia. HIV mania is reported to be associated with irritability rather than euphoria. Unlike primary mania, cognitive deficits are usually present. Mania occurring in the early stages of HIV infection may represent bipolar disorder in its manic phase, whereas mania in persons with AIDS is secondary mania linked to the pathophysiology of HIV brain infection [118].

A first episode of HIV mania typically occurs in the context of a CNS disorder, such as CNS opportunistic infection (OI). The mechanisms are poorly understood; however, the HIV nef protein is reported to alter CNS dopamine metabolism leading to hyperactive, manic-like behaviors in animal models [119]. Reports of HIV mania have decreased coincidently with the widespread use of ART [120], but it remains a problem among untreated and undertreated persons [121]. The differential diagnosis of brain disorders underlying suspected HIV mania includes substance use (especially stimulants), alcohol withdrawal, metabolic abnormalities (e.g., hyperthyroidism), and CNS OI. Evaluations should include a neurologic and mental status examination, brain MRI scan with and without contrast, serology for syphilis, urine toxicology, and cerebrospinal fluid (CSF) examination (if medically safe), including tests for OI and a quantitative HIV CSF polymerase chain reaction (PCR) (viral load in CSF) [89]. HIV+ patients with comorbid bipolar disorder are less likely to be adherent to antiretroviral and psychiatric medications [122]. Therefore,

promoting adherence in this subgroup is critical in protecting against poor HIV outcomes.

12.5.4 Anxiety Disorders

Anxiety disorders include disorders that elicit fear, anxiety, and behavioral disturbances. Anxiety disorders include mild adjustment disorders, panic disorder, phobias, obsessive-compulsive disorder, post-traumatic stress disorder, acute stress disorder, and generalized anxiety disorder. The prevalence of anxiety disorders in the HIV populations ranges from about 25% to 40%. Manifestations of anxiety disorders, such as adjustment disorder, are more prevalent at diagnosis and during new treatment or acute illness [123]. It is important to recognize and treat anxiety disorders in the HIV-positive population. Increased rates of anxiety disorders are associated with treatment dropout, high-risk behaviors, and suicide. While the rates of anxiety disorders in the HIV population are generally similar to those of the general population, one of the more common anxiety disorders that disproportionately affect HIV patients is post-traumatic stress disorder. An assessment of an HIV-infected patient presenting with symptoms of anxiety disorder should first evaluate a patient's recent medication and substance use history (especially stimulants like cocaine and methamphetamine), previous psychiatric history, and sleep patterns. Because most anxiety disorders appear in adolescence or young adulthood, patients will often have a history of symptoms predating HIV [124].

12.5.5 Post-traumatic Stress Disorder

A diagnosis of post-traumatic stress disorder is made when the following criteria are met: (1) exposure to actual or threatened death, serious injury, or sexual violence; (2) presence of one (or more) intrusion symptoms associated with the event, (3) persistent avoidance of stimuli associated with the traumatic event(s), beginning after its occurrence; and (4) negative alterations in cognitions and mood associated with the traumatic event(s) [75]. Rates of PTSD have been found to range anywhere from 22% to 64% and tend to be higher among marginalized and stigmatized populations, such as ethnic/racial minorities, homosexuals, and low-income. Symptoms associated with PTSD include intrusive memories, avoidance of trauma reminders, numbness, hyper-arousal, and experiencing distorted or negative thoughts about oneself [75]. PTSD comorbidity among HIV+ individuals is prevalent among individuals with histories of early trauma and stress [125–127] and has been hypothesized to be linked to HIV-related neurobiological alterations which may render the system more vulnerable to stress (for review, see Neigh [128]). PTSD predicts worse HIV-related outcomes for both women [129, 130] and men [131]. While the research is correlational in nature, studies have suggested that individuals with

PTSD have a more negative course and progression of HIV/AIDS, continue to use drugs, and have altered immune levels. It has been found in some studies (although not all) that HIV-positive individuals who have been exposed to a traumatic event show a more rapid decrease in CD4+/CD8+ cell ratios as compared to HIV-positive individuals without a trauma history. A recent study of virologically suppressed HIV-infected patients found that those with PTSD had significantly higher total white blood cell counts, absolute neutrophil count, CD8%, and memory CD8%, lower naïve CD8%, and higher rate of high-sensitivity C-reactive protein than participants without PTSD [132]. In one study of HIV risk behaviors, PTSD was associated with increased HIV risk behavior, whereas depression was associated with increased condom use [58]. Elevated stress and emotional reactivity have been linked to increased sexual transmission risk behaviors [133, 134].

12.5.6 Substance Use Disorders

Substance use disorders are characterized by a cluster of cognitive, behavioral, and physiological symptoms indicating that the individual continues use despite significant consequences related to use. Drug use, especially the injection of drugs, has been associated with poor HIV-related outcomes. HIV-infected drug users have increased prevalence and frequency of medical, psychiatric, and substance use disorders that increase morbidity and mortality compared with age-matched HIV-infected non-users [135]. The number and range of these comorbid disorders complicate diagnosis and treatment, resulting in several challenges in the provision of comprehensive care. Injection drug use has been found to be highly prevalent among individuals with a psychiatric disorder, particularly mood disorders [136]. Studies of heroin users have documented elevated rates of major affective and anxiety disorders including PTSD [137, 138]. While injection drug use is a more direct route of HIV transmission, other substances such as alcohol can place individuals at risk for infection. For example, rates of injection drug use are high among alcoholics in treatment [139, 140].

Alcohol use disorders are common in people living with HIV/AIDS and in IDUs. Heavy alcohol use increases risk of HIV transmission to others [141], decreases retention in care [142], decreases treatment adherence [143, 144], increases HIV risk behaviors [145–147], and decreases likelihood of suppression of HIV [148, 149]. Earlier studies reported that individuals with a history of heavy alcohol use are more likely to report engaging in high-risk sexual behaviors, including multiple sex partners, unprotected intercourse, sex with high-risk partners (e.g., injection drug users, prostitutes), and the exchange of sex for money or drugs [139, 140]. According to McKirnan and Peterson [150], alcohol use may be used as an excuse for engaging in socially unacceptable behavior or to reduce conscious awareness of risk. This practice may be especially common among men who have sex with men. Treatment of alcohol abuse has the potential to positively affect HIV treatment outcomes and reduce HIV transmission.

Across studies conducted in South African and other sub-Saharan African countries, it was found that problem drinkers were more likely to be men, to engage in more risky sexual practices, and have a more frequent history of sexually transmitted infections (STIs) [151, 152]. Kalichman et al. [153] found that alcohol use in the context of a sexual encounter partially mediated the relationship between sensation seeking and HIV risk. In a study that compared a skills building and HIV risk reduction counseling session with didactic HIV-educational/control intervention, effects of increased condom use and decreased drinking prior to sex was found at 3-month but not 6-month follow-up, suggesting that the positive effects of behavioral risk reduction among problematic users may be time limited [154].

Contrary to popular belief, crack cocaine was not always considered a risk factor for HIV acquisition and transmission. In 1988, researchers in New York City suggested the adoption of crack smoking, in lieu of intravenous cocaine use, as a mechanism of AIDS risk reduction [155, 156]. However, a series of studies followed which indicated that when compared with intravenous drug users, crack smokers may be at equal or greater risk for HIV and other STD infections [157–160]. Methamphetamine (METH) use has been found to be associated with nonadherence [122, 161–163]. In a study of HIV+ individuals with and without a lifetime history of METH use and comorbid antisocial personality disorder (ASPD), major depressive disorder (MDD), and attention deficit disorder (ADD), results indicated that co-occurring ADD, ASPD, and MDD predicted ART nonadherence. Current METH use regardless of comorbidity was significantly associated with lower adherence [122].

Although the use of marijuana is more common among individuals with HIV relative to the general population, very few studies have examined the relationship between marijuana and HIV-related outcomes or risk. Specifically, 23–56% of individuals with HIV reported using marijuana in the last month of the survey period compared to 8.4% of the general population [164, 165] (Substance Abuse and Mental Health Services Administration, 2011). Individuals with HIV report they use marijuana to reduce anxiety/depression, to increase appetite and weight gain, and to treat pain [164]. In contrast, marijuana has been associated with negative outcomes such as cognitive impairment and lower adherence to ART, relative to non-marijuana-using HIV patients [166, 167]. Similarly, marijuana use has been found to be associated with unprotected sexual intercourse [168, 169] as well as STD infection [170]. However, these relationships tend to be moderated by such factors as HIV severity and amount of marijuana use. For example, Cristiani and colleagues [166] found that marijuana use was associated with cognitive impairment among symptomatic HIV participants but to a lesser extent among asymptomatic HIV participants. Regarding ART adherence, lower adherence, higher viral load, and more severe self-report symptoms of HIV/medication side effects were reported among individuals with HIV who met the criteria for cannabis dependence, but not casual/nondependent marijuana users. In addition, marijuana is also related to risk of contracting HIV, particularly for young adolescents [168].

12.5.7 Severe Mental Illness (SMI)

In a meta-analytic study of 52 studies, the majority of adults with SMI were sexually active, and many engaged in risk behaviors associated with HIV transmission (e.g., unprotected intercourse, multiple partners, injection drug use) [19]. HIV risk behaviors were correlated with factors from the following domains: psychiatric illness, substance use, childhood abuse, cognitive-behavioral factors, and social relationships. HIV prevention efforts targeting adults with SMI must occur on multiple levels (e.g., individual, group, community, structural/policy), address several domains of influence (e.g., psychiatric illness, trauma history, social relationships), and be integrated into existing services (e.g., psychotherapy, substance abuse treatment, housing programs) [19, 20]. While epidemiological evidence suggests that individuals with severe mental illness are more likely to live in risky environments that make them vulnerable to HIV [171, 172], the findings are mixed with regard to the link between HIV risk and psychotic-spectrum disorders, with many reporting small associations [173]. In a study by Carey et al. [173] that reviewed records of 889 patients with mental illness, it was found that only 11% reported HIV risk behavior. They found no direct association between psychiatric disorder and risky sex. In a follow-up study, 1558 records were reviewed and the numbers increased to approximately 23% [171]; however, risk behavior was less common among patients diagnosed with a schizophrenia-spectrum disorder. Similarly, in a study of 228 female and 202 male outpatients (66% mood disorder, 34% schizophrenia), it was found that risk behavior was more frequent among patients diagnosed with a mood disorder (compared to those diagnosed with schizophrenia) and/or with a substance use disorder (compared to those without a comorbid disorder).

12.5.8 Personality Disorders

Personality disorders (PD) are diagnosed if there is a pattern of inner experience and behavior that deviates markedly from the expectations of the individual's culture. The pattern is manifested in two (or more) of the following areas: (1) cognition, (2) affectivity, (3) interpersonal functioning, and (4) impulse control. The pattern must be inflexible and pervasive across many personal and social situations as well as lead to significant distress or impairment in social, occupational, or other areas of functioning [174]. Personality disorders that fall under the cluster B category of personality disorders (i.e., antisocial personality disorder (ASPD), borderline personality disorder (BPD), histrionic personality disorder, and narcissistic personality disorder) have been the most reliably associated with risk-related behaviors and outcomes in HIV. The literature supports a higher rate of PD in HIV-positive individuals, in particular BPD and ASPD. ASPD is characterized by a pattern of irresponsible, impulsive, and remorseless behaviors beginning in childhood or early adolescence and continuing into adulthood. ASPD is highly prevalent among drug

abusers [175–177]. ASPD participants reported higher rates of IVDU, frequency of needle sharing, and a number of equipment-sharing partners and lower rates of needle cleaning [178–181].

In a randomized HIV prevention study, Compton and colleagues [182] compared the effectiveness of standard HIV testing and counseling protocol to a four-session, peer-delivered, educational intervention for out-of-treatment cocaine users with and without ASPD and major depression. While all groups, regardless of assignment to standard vs. peer-delivered intervention or psychiatric status, improved significantly in outcomes of crack cocaine use, injection drug use, and number of IDU sex partners and overall number of sex partners, ASPD was associated with significantly less improvement in crack cocaine use and less improvement in having multiple sex partners and having IDU sex partners. Personality disorders are the most unreliably diagnosed out of all the psychiatric disorders, and it becomes more challenging when diagnosing BPD in the context of culture. Symptoms related to unstable self-image, impulsive substance abuse, and mood instability due to societal stigma and pressures may be the norm within certain cultures. For example, adolescents and young adults with identity problems may display transient behaviors that appear like BPD. Hence, clinicians should be cognizant to conduct thorough assessments when considering a PD diagnosis.

12.6 Psychiatric Assessment and Treatment

Central to conducting a psychiatric assessment of the HIV/AIDS patient is an adequate fund of knowledge about the pathophysiology and virology of HIV, epidemiology of HIV/AIDS, transmission of HIV, pathogenesis, staging of HIV disease, HIV treatment, and HIV effects on the central nervous system. The clinician should be prepared and well versed in a wide range of assessment tools and skills such as structured interviews, comprehensive diagnostic evaluations, and medical work-ups to rule out or consider new-onset symptoms [89]. Clinicians should also be aware of cultural and linguistic differences that may influence self-reporting of mental health problems, stigmas associated with both HIV and mental health problems, and social support networks. According to the guidelines set forth by the American Psychiatric Association Working Group on HIV/AIDS [183], (shown in Table 12.2), the clinician must be able to:

The development of a psychiatric treatment plan for patients with HIV infection requires a holistic approach accounting for the biopsychosocial context. Upon first diagnosis and throughout the course of the illness, there may be signs of bereavement and grief with various physical changes as well as the anticipatory loss of life [88]. The symptoms of bereavement (i.e., sadness, insomnia, poor appetite, and weight loss) overlap considerably with depression. Diagnostic decisions must follow a standard diagnostic practice, without minimizing or misattributing symptoms to the burden of having HIV. Depressed patients may also overstate their cognitive and functional limitations. A study by our group compared subjective complaints to

Table 12.2 American Psychiatric Association Working Group on HIV/AIDS

Practice guidelines for the treatment of patients with HIV/AIDS	
Establish and maintain a therapeutic alliance	Gather information of a patient's understanding of the illness and coping strategies. Discuss whether the treatment relationship should include family and/or significant others
Collaborate and coordinate care with other mental health and medical providers	Keep up-to-date with the evolving information about HIV by collaborating with infectious disease physicians, primary care, and other disciplines
Diagnose and treat all associated psychiatric disorders	Treatment should include active monitoring of substance abuse
Identify barriers in adhering to the overall treatment plan	Provide psychoeducation about adhering to treatment regimens. If necessary consider outreach efforts with public health services for adherence
Provide education about psychological, psychiatric, and neuropsychiatric disorders	To educate other clinicians and patients about the neuropsychiatric complications of HIV infection and to initiate and encourage treatment of current or emergent psychiatric disorders
Providing risk-reduction strategies to further minimize the spread of HIV	Assess the risk for HIV transmission from their HIV-infected patients to others and to provide risk-reduction counseling. Psychotherapy may help some individuals who are unaware of motivations that promote ongoing risk behavior. Risk assessment should be repeated when there are changes in the patient's clinical status or social situation, such as the onset of binge drug or alcohol use or new sexual relationships
Promote psychological and social/adaptive behavior	The clinician should consider the role of religion/spirituality, preparing the patient for issues related to HIV disability
Identify sources of social support	This could include significant others/family. The clinician should be able to educate family members about HIV disease

actual cognitive and functional performance and found that "over-reporters" – those who presented with complaints regarding cognitive function and performance on daily tasks (e.g., managing medications) but who performed normal on objective measures of function – exhibited higher levels of depressive symptoms compared to those whose self-reports matched their actual performance [184]. On the other hand, clinicians must caution not to quickly diagnosis a mood disorder without consideration of the context. It is common for patients to present with symptoms that mimic a major depressive episode or anxiety disorder shortly after learning about their HIV diagnosis. Usually these symptoms will subside over time as the patient begins to adjust to their illness.

The symptoms of major depression can be masked by symptoms that accompany other HIV-related illnesses. Overlapping symptoms include fatigue, sleep and appetite disturbance, general malaise, and feelings of illness. One study by Pugh and colleagues [185] found no difference in symptoms of fatigue, insomnia, or cognitive dysfunction between early-stage HIV-infected homosexual men and uninfected homosexual controls. When these symptoms do occur in early-stage HIV

infection, they are more likely to result from mood disturbance than HIV disease progression. Additionally, increased fatigue and insomnia at 6-month follow-up were highly correlated with worsening of depression but not CD4 count, change in CD4 count, or disease progression by CDC category.

12.6.1 Treatments

Extensive reviews of various types of pharmacological treatments for psychiatric disorders in HIV patients can be found elsewhere [186–188]. However, we would be remiss not to provide a brief overview of the various treatments for the more common comorbid psychiatric disorders. Treating psychiatric illness among individuals with HIV infection is frequently complicated by concurrent HAART regimens. The clinician must closely monitor drug-drug interaction and be alert to potential side effects and metabolizing profiles.

12.6.1.1 Antidepressants (Standard and Alternative)

As with treating depression among individuals without HIV, antidepressant medications are commonly used for treatment. In the early epidemic, tricyclic antidepressant (TCA) medications were often used [189, 190] with demonstrated efficacy. However, because of the high rates of negative side effects and concerns of lethality attributed to the use of TCAs, clinicians started to use SSRIs for treating depression [188]. SSRIs are now the most widely used antidepressant treatment for major depression among HIV-infected persons because of their more benign side effect profile and evidence of treatment efficacy [191]. In a study of a 6-week open-label trial with SSRIs, subjects who completed 6 weeks of SSRI treatment experienced significant reductions in both affective and somatic symptoms, which were initially attributed to HIV infection rather than depression [192]. A smaller trial showed no benefit of adding fluoxetine to structured group therapy versus group therapy alone; however, this study was limited by a small sample size of 20 individuals [193]. Another study compared fluoxetine and placebo in depressed patients receiving group psychotherapy [194]. Fluoxetine resulted in a significantly greater percentage of patients (64% vs. 23%) with a reduction in HAM-D score after 7 weeks. This study also showed that patients with mild to moderate depression may benefit from psychotherapy alone, but patients with severe depression did better with a combination of psychotherapy and fluoxetine. Overall, fluoxetine appears to have the most evidence for treating depression in HIV patients, with response rates between 50% and 75%. Limitations of many of the studies include exclusion of patients with active substance abuse and few studies with HIV-infected women.

Psychostimulants have also been used to treat depressive symptoms in patients with advanced HIV, especially when symptoms such as depressed mood, fatigue, and cognitive impairment are present. In a clinical trial's study of standard and

alternative antidepressants among HIV patients with depression, each treatment resulted in significant improvement after both 2 and 6 weeks of treatment according to the Hamilton Depression Rating Scale [195].

12.6.1.2 Anxiolytics

SSRIs are the first-line pharmacologic therapy for several anxiety disorders [196] including generalized anxiety disorders, panic disorders, social phobia, obsessive-compulsive disorder, and post-traumatic stress disorder in HIV. Specific agents have been approved by the Food and Drugs Administration for each of the major anxiety disorders: generalized anxiety disorder (paroxetine), social phobia (paroxetine), OCD (fluoxetine, sertraline, paroxetine, and fluvoxamine), and PTSD (sertraline). Buspirone has a low abuse potential. It is minimally sedating and has no known withdrawal effects [197]. Buspirone may, however, take up to 4 weeks before producing noticeable therapeutic effects. When a benzodiazepine is required, it is recommended that a low dose is prescribed and used only for short periods of time to minimize, respectively, the risk of abuse and adverse effects (confusion, sedation, cognitive impairment, disinhibition) and interactions with antiretroviral therapy [198].

12.6.1.3 Mood Stabilizers

Lithium, valproic acid, and carbamazepine are effective mood stabilizers in patients with bipolar affective illness. Lithium is the least likely to have specific drug interactions with antiretrovirals [187]. In HIV-infected patients, lithium has the potential to cause nausea, vomiting, diarrhea, tremor, thyroid dysfunction, and kidney problems at therapeutic doses [199]. el-Mallakh [200] described 14 cases and reported that AIDS-associated mania are responsive to lithium but that AIDS patients with associated neurologic and cognitive dysfunction may be more prone to neurocognitive side effects. Valproic acid can cause elevated transaminase levels and severe hepatitis, and it has been recommended that physicians observe liver enzymes periodically [187]. In a retrospective chart review of 11 HIV+ patients with an acute manic episode, Halman [201] found that neuroleptics and anticonvulsants were an effective alternative among those with poor tolerance of lithium. A number of factors must be taken into consideration when prescribing anticonvulsants to HIV+ individuals. Carbamazepine is metabolized via CYP3A4 and induces its own metabolism, increasing metabolism of protease inhibitors [202] and non-nucleoside reverse transcriptase inhibitors [203]. Such autoinduction and the potential for bone marrow suppression make its use complicated. There is clinical evidence of carbamazepine toxicity resulting from its use in combination with CYP3A4 inhibitors, such as ritonavir [204].

12.6.1.4 Antipsychotics

Antipsychotic drugs (also called neuroleptics) include both older "typical" drugs and the newer "atypical" (second-generation) medications that are FDA approved for the treatment of schizophrenia, bipolar disorder, and other psychotic disorders [204]. The typical neuroleptics (characterized by chlorpromazine and haloperidol) are specific dopamine receptor (D2) antagonists. Newer antipsychotics also interact with other receptor families, such as serotonin [187]. Newer antipsychotics are often preferred because of their efficacy in treating psychotic conditions and the decreased frequency of extrapyramidal adverse effects associated with their use. However, significant metabolic adverse effects (like hyperglycemia, weight gain, and hypercholesterolemia) often make newer neuroleptics less appealing. Clozapine, a very effective neuroleptic, has the potential to cause agranulocytosis, necessitating weekly blood count measurements for the first 6 months. In addition, this medicine can cause significant weight gain, orthostasis, sialorrhea, and seizures [199]. Molindone (20–180 mg/d), an atypical antipsychotic, was first reported to be beneficial for HIV-associated psychosis and agitation with minimal side effects [44]. Clozapine has been demonstrated to be effective and generally safe in treating HIV-associated psychosis (including negative symptoms) in patients with prior drug-induced Parkinsonism [205]. Risperidone (mean dose 3.3 mg/d) was reported to be effective in treating HIV-related psychotic and manic symptoms [206]. CYP inhibitors have the potential to increase the concentration of the antipsychotics, clozaril and pimozide. For this reason, these drugs have been contraindicated with antiretrovirals with CYP inhibition, such as ritonavir. In addition, the potential for toxic increases by CYP inhibitors exists in other antipsychotics, including chlorpromazine, haloperidol, olanzapine, and risperidone [207]. Antipsychotics do not generally significantly inhibit or induce P-450 enzymes and can safely be added to HAART regimens without causing toxicity or HAART failure [208]. Another concern with the administration of antipsychotics and antiretrovirals is the overlapping toxicities of metabolic disturbances, primarily with atypical antipsychotics. Metabolic disturbances are seen in 2–36% of patients treated with atypical antipsychotics [209]. In sum, patients with HIV infection are generally very sensitive to medication side effects as they often metabolize drugs more slowly and have compromised blood-brain barrier functioning [208]. Although most patients ultimately tolerate standard doses of most medications, it is advised to start at low doses and slowly increase over time.

12.6.1.5 Behavioral Interventions

For many HIV patients, psychotherapy and psychosocial interventions have been invaluable in the search for meaning during the course of living with HIV [210]. Psychotherapy can be an important intervention to address conditions that may interfere with a patient's acceptance of HIV illness or their ability to work

cooperatively with their healthcare team as well as addressing changes in role definitions and life trajectory as well as treatment adherence challenges.

Non-pharmacological interventions have been used to treat depression and increasing stress management for individuals with HIV. These interventions have consisted both cognitive (i.e., challenging and restructuring automatic negative thoughts) and behavioral approaches (i.e., progressive muscle relaxation), either in combination or separately. Reviews and meta-analyses found these approaches to be effective in terms of improving psychological symptoms (such as depression or anxiety). Additionally, these approaches were effective in improving psychosocial functioning, such as social support, medication adherence, quality of life, and decreasing engagement in risky sexual behaviors [211, 212]. However, there was only limited evidence that improvements in psychological functioning are generalized to improvements in markers' immunological functioning, such as stress hormones, CD4 counts, or T-cell counts.

Mindfulness-based interventions focus on increasing one's ability to purposely pay attention in the present moment, without judgment [213]. Mindfulness-based interventions have become a popular research topic within the last decade, but the research is still in its infancy, particularly as it relates to the HIV population. However, preliminary findings are optimistic, as the effect sizes have ranged from medium to small in terms of improvement in positive affect [214]. Perhaps even more impressive, mindfulness-based interventions were found to have a medium-to-large effect size in terms of healthier CD4+ cell counts, relative to HIV+ controls [214, 215]. Future studies are needed in examining the efficacy of mindfulness-based interventions in terms of other important outcomes, such as medical adherence, risk behaviors, and specific mood symptoms (rather than global affect).

In addition to therapies differing in terms of theoretical orientation, therapies can differ in the modality of administration. A past review found that 95% of intervention using behavioral techniques to improve stress management were delivered in a group format [216]. Although the use of group therapy is beneficial for delivering services to multiple individuals at once, one criticism was that group therapy may not be available/feasible for individuals living in rural or underserved populations. To address this concern, interventions delivered remotely, either over the phone or via the computer, may be of interest. Indeed two recent randomized controls trials found that a cognitive-behavioral therapy and a contingency management program delivered over the phone improved medication adherence among HIV+ individuals [217, 218]. More research focused on delivering psychological services to underserved populations is needed.

Limited research has been conducted in terms of examining other moderators that may be important for psychological therapies. In terms of dosage, one meta-analysis found that interventions consisting of ten or more sessions were more efficacious in improving depressive and anxiety symptoms, relative to interventions consisting of less than ten sessions [212]. A separate study is focused on the efficacy of stress-reduction interventions among different HIV subpopulations, including older adults, women, and individuals with a history of childhood sexual abuse [211].

Although very few intervention studies have focused on these subpopulations, the review has found preliminary evidence for decreased psychological distress and health risk behaviors following stress-reduction management.

12.7 Summary

Comorbid psychiatric features and disorders are important when working with and treating individuals diagnosed with HIV/AIDS. Thus, recognizing predictors of medication adherence among patients with dual psychiatric and substance use disorders is essential for identifying at risk individuals. The presence of pre-HIV psychiatric illness is the strongest predictor of psychiatric diagnosis after knowledge of seropositivity. As discussed throughout this chapter, psychiatric illness from the biological effects of HIV, CNS OI, prescribed medications, or substance abuse can arise. Optimum management of patients at high risk for HIV infection involves a wide range of psychiatric skills: comprehensive diagnostic evaluations, assessment of possible medical causes of new-onset symptoms, and initiation of specific treatment interventions. Early screening and assessment are essential for proper treatment for many persons infected and affected by HIV/AIDS which requires making important distinctions between overlapping symptoms in order to provide accurate diagnoses and treatments.

Conflict of interest The authors report no conflicts of interest.

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