Curr HIV/AIDS Rep (2013) 10:371–379
DOI 10.1007/s11904-013-0179-3

BEHAVIORAL ASPECTS OF HIV MANAGEMENT (RJ DICLEMENTE AND JL BROWN, SECTION EDITORS)

Treatment Considerations for HIV-Infected Individuals with Severe Mental Illness

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Published online: 26 October 2013

Abstract There has been a general recognition of a syndemic that includes HIV/AIDS and serve mental illnesses including schizophrenia, major depression, bipolar disorder, post-traumatic stress disorder, and others. The pathophysiology and direction of effects between severe mental illness and HIV infection is less clear however, and relatively little work has been done on prevention and treatment for people with these complex, co-occurring conditions. Here we present the most recent work that has been published on HIV and mental illness. Further, we describe the need for better treatments for "triply diagnosed persons"; those with HIV, mental illness, and substance abuse and dependence. Finally, we describe the potential drug-drug interactions between psychotropic medications and anti-retrovirals, and the need for better treatment guidelines in this area. We describe one example of an individually tailored intervention for persons with serious mental illness and HIV (PATH+) that shows that integrated community-based treatments using advanced practice nurses (APNs) as health navigators can be successful in improving health-related quality of life and reducing the burden of disease in these persons.

Keywords Syndemics · Severe mental illness · HIV · Substance abuse · Triply diagnosed · Drug-drug interactions · Treatment guidelines · Depression · Schizophrenia · Bipolar disorder · Anxiety disorder · PTSD · PATH+

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Introduction

A majority of HIV/AIDS patients in every clinical center suffer from co-occurring affective disorders (e.g., major depression and bipolar disorder), substance abuse disorders, cognitive disorders, psychotic disorders and/or anxiety disorders. Often these "syndemic patients" have often been excluded from randomized clinical trials investigating new drugs and other treatments. This practice emphasizes the internal validity of experiments over the external validity of having samples that equate to those living in the "real world" where people often have multiple co-morbid illnesses. Consequently, there has been a missed opportunity to provide informed guidance to clinicians faced with patients who have these comorbid problems. Syndemic illness refers to the co-occurrence of two or more diseases or conditions within a population where there is some biological interaction or synergy that exacerbates the negative effects of the diseases or illnesses and complicates treatment [1]. There has been a growing interest in syndemics and their treatment as the health and public health community has increasingly recognized that health disparities are largely linked to social conditions including social ecological factors such as poverty, stress,

violence, and other adverse conditions that contribute to environmental toxicity. Here we address syndemic illness and their treatment for persons with HIV and a serious mental illness (SMI). Importantly, SMI is not a diagnosis per se, rather it is used to refer to a broad category of persons who are disabled by any number of mental illnesses, and is often used to determine eligibility for a variety of entitlements.

A now established body of research documents that persons with mental illness are at increased risk for contracting and transmitting HIV [2, 3]. This increased risk is thought to be due to high rates of substance use including injection drug use (IDU), risky sexual behavior, sexual victimization, and prostitution among those with SMI [4]. 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 [5•]. Adherence to HIV treatment regimens is sometimes markedly compromised when a person has an SMI, which can pose a public health threat by increasing community viral load and potentially developing ART resistant virus strains. When this happens, the person with mental illness may serve as a vector of HIV transmission. Therefore, there is a need for methods of improving continuity between increasing their access to HIV treatment, then reinforcing their treatment adherence. Research also makes clear that these adverse outcomes are far from inevitable, as people with SMI receiving good quality care can achieve adherence rates comparable to non-SMI counterparts. In fact, the evidence reviewed here shows that they can adhere to treatments with appropriate supports, and some have found that they are less likely to discontinue ART than others [6].

Prevalence Estimates from Convenience Samples

Risk factors associated with HIV infection among persons with SMI mirror those in the general population and include unprotected sex and injection drug use (IDU) [3, 7–9, 10•, 11]. The evidence needed to establish accurate estimates of co-occurrence have come from several sources. First, in samples of patients with SMI during the 1990s and early 2000s using convenience samples, estimations of HIV prevalence ranged from 1-23% [12–16]. Prevalence estimates observed from these studies vary a great deal mainly due to methodological differences related to sampling frames, particularly the reliance on convenience samples, which tended to be restricted to institutional or geographically restricted areas, as well as different approaches to adjustment for confounding effects of factors associated with HIV. Given the low absolute rates of infection, estimates were also necessarily affected by small sample sizes. The extent to which these early prevalence estimates reflect current infection patterns is not known.

Prevalence Estimates from Administrative Data

A second source of data come from administrative health care claims from Medicaid, often linked to other administrative data sources, such as state HIV or AIDS registry files. These likewise report evidence of elevated associations. For example, in an analysis of claims linked to the New Jersey HIV/AIDS registry, Walkup and colleagues found 5.7% had a diagnosis of schizophrenia [2], which can be compared to general population prevalence rate for schizophrenia of around 1% [17]. After controlling for a range of socio-demographic variables available through welfare records, Blank and colleagues found schizophrenia spectrum disorder patients were 1.5 times as likely to have claims indicative of HIV infection, and those major affective disorder were 3.8 times as likely [3]. Administrative medical records from a national sample from the Veterans Administration also point to elevated rates of HIV in severely mentally ill patients [7].

Estimates based on true epidemiological samples are rare. Perhaps due to shortcomings in existing detection systems, these estimates are often limited in their ability to shed light on people with more severe psychotic illnesses; they offer psychiatric diagnoses based on structured interviews with carefully designed sampling frames. A recent study using the National Epidemiologic Survey on Alcohol and Related Conditions reported that, compared to their HIV-negative counterparts, men with HIV were significantly more likely to merit a range of diagnoses, including major depressive disorder/dysthymia, and any personality disorder [18].

Prevalence Estimates from Remnant Blood

More recently, some findings suggest administrative claims may produce underestimates when not all HIV diagnoses are captured and for those that are, they may not be reliably linked to confirmed HIV positive tests within administrative databases. In order to address this issue, Rothbard, Blank and colleagues conducted HIV testing on remnant blood specimens collected from patients on two inpatient psychiatric units in the City of Philadelphia [16]. When using this more direct case ascertainment strategy, HIV infection was observed in 10.1% of patients. In contrast, when the review was restricted to chart review only, a full one-third of the individuals identified by remnant blood testing as HIV positive did not include documentation of an HIV positive diagnosis. These results identify some serious shortcomings even in inpatient care, which suggests that persons with mental illness are likely underserved with regard to identification of infectious diseases including HIV.

A Lack of Treatment Guidelines

Relatively few guidelines have been developed for clinicians who provide treatment for persons with comorbid HIV/AIDS and mental illness, and the ones that have been provided by the American Psychiatric Association may now be considered outdated [19]. Previous studies have attempted to query clinicians regarding their preferred treatment options for PLWHA who have co-occurring psychiatric disorders. One web-based survey of the membership of the Organization of AIDS Psychiatry found among the 39% of responding clinicians that first-line medication for depression was escitalopram/citalopram; first line treatment for psychosis and secondary mania was quetiapine; and first line medication treatment for anxiety was clonazepam [20•]. Another national survey queried members of the American Academy of HIV Medicine regarding how they made decisions regarding initiating HAART for HIV+ people with schizophrenia [21] and found that clinicians recognized the importance of recommending antiretroviral treatment to HIV infected people with co-occurring schizophrenia and avoided using antiretroviral medication with known neuropsychiatric side effects. One result of these kinds of studies has been a fledgling effort toward developing biopsychosocial curricular components of residency training for psychiatrists [22].

There is a growing need to establish an evidentiary base of how to translate and implement interventions that have been shown to be effective in other populations among PLWHA with co-occurring psychiatric disorders. Toward that end we discuss research conducted within a prior two year period (2011–2013) to identify emerging themes as well as more enduring and challenging tasks associated with testing and treatment adherence for individuals at risk for HIV as well as people living with HIV.

Treatment Challenges

Major Depression and Bipolar Affective Disorder

Depression and other affective disorder are common co-morbidities of all chronic illnesses including HIV infection, where they provide particular challenges to clinical care. They diminish people's ability to adhere to treatment and engage in self-care, quality of life, and biomedical outcomes. It is probable that they also interfere with an ability to benefit from other health promotion interventions [23]. A meta-analytic review found that, across 95 independent samples, depression was significantly associated with medication non-adherence [24•].

Prevalence estimates of major depressive disorder among persons living with HIV/AIDS (PLWHA) range from 20% to as high as 37% [23]. This is more than three times the rate of major depression in the general population, which has been shown to range between 5% and 12% [25]. Because HIV is a chronic and life-threatening illness and like other such illnesses, can be stressful to manage, PLWHA are particularly vulnerable to depression and other affective disorders. The life-threatening nature of HIV infection itself may instigate fears of impending mortality. Moreover, the medical sequelae of HIV infection such as HIV associated neurocognitive disorders (HAND), associated opportunistic infections, and the side effects of antiretroviral treatment can mimic symptoms of depression (i.e., fatigue, concentration problems, somatic symptoms, decreased appetite/weight loss). From a cognitive-behavioral perspective, these physical symptoms can be part of a cycle of continued depression [23]. Other factors that might account for the high level of depression and other affective disorders among PLWHA are unique to HIV. Specifically, PLWHA disproportionately belong to socially disadvantaged and marginalized populations who are already at risk for depression because of their racial, ethnic, or sexual minority status, poverty, current or prior substance use, sex work, and trauma and the argument has been made that providing quality treatment to these individuals is effective prevention [26]. Because HIV is associated with all of these marginalized statuses, many PLWHA face high levels of stigma. Like stigma for mental illness, HIV stigma can lead to problems including nondisclosure of HIV serostatus, social isolation, and stress which further enhances the risk of depression and other affective disorders.

Depression rates do not appear to decline with age in HIV populations as they do in the general population [27]. This is important because as many as one quarter of all U.S. HIV+ adults are now 50 years or older [28]. As people live longer due to medical advances, depression in a gradually aging HIV cohort will remain an issue that needs to be addressed clinically and accounted for in HIV research. While there is evidence that the presence of severe psychiatric illness can negatively impact HIV care, particularly medication adherence, studies also underline the importance of individualized assessment and the potential positive impact of good psychiatric and substance abuse care. Carrico, Bangsberg, and colleagues used a mobile outreach van to recruit a probability sample of homeless and unstably housed men [29•]. Those who tested positive for HIV were given the Diagnostic Interview Schedule to screen for psychiatric disorder. Participants on HAART were compared to those eligible for HAART but not receiving it. Mental health treatment in the past 90 days significantly increased the odds of HAART receipt. No significant impact on odds of HAART receipt was found for current SMI, major depression, or PTSD, but among those on HAART, SMI was independently associated with six times higher viral load. Associations between progression of HIV disease and depression have been

linked to its impact on medication non-adherence in an analysis of outcome data from participants in a behavioral intervention [30•].

Psychotherapeutic interventions may be well suited to address the psychosocial difficulties as well as the distress associated with HIV. Of note, telephone-based cognitive behavioral therapy (T-CBT) has emerged as a feasible, acceptable and efficacious treatment for major depression. One recent randomized controlled trial found that among HIV positive people with major depression those randomized to receive T-CBT were as likely as those randomized to face-to-face psychotherapy treatment to have significant reductions in depression. However, those who received the T-CBT were significantly more likely to maintain their adherence to antiretroviral medication compared to the face-to-face treatment. This may suggest that T-CBT may not only reduce depressive symptoms but do so in a way that improves adherence to antiretroviral medication [31•].

Bipolar disorder, also known as manic-depressive illness, causes unusual shifts in mood, energy, activity levels, and the ability to carry out day-to-day tasks. Symptoms of bipolar disorder can be quite severe and can result is a manic state where thinking and judgment are significantly impaired. Diagnostic criteria for bipolar disorder includes but is not limited to behaving impulsively and engaging in pleasurable, high-risk behaviors including high-risk sexual behaviors. These impulsive, high-risk behaviors in the context of impaired judgment may put people in the manic phase of bipolar disorder at increased risk for becoming infected with HIV as well as for transmitting it to others.

Research with PLWHA shows that they are significantly more likely to have bipolar disorder than the general population. A recent study of HIV-infected patients in Brazil found high rates of bipolar disorder (BD) on the Mood Disorder Questionnaire (MDQ) [32]. The sample included 196 HIV-infected adults who were interviewed with the Mood Disorder Questionnaire (MDQ). Positive MDQ screening was found in 13.2% (N=26) and the BD diagnosis was confirmed in 8.1% (N=16) of the sample. This represents almost four times higher prevalence of BD among the PLWHA in the sample (8.1%) than in the general population from the USA (2.1%). The variables associated with the diagnoses of BD were sex with commercial partners, sex outside the primary relationship, alcohol use disorders, and illicit drug use. The most common psychiatric comorbidity in the BD group was substance abuse (61.5%).

Another recent study in the US examined HIV in individuals with bipolar disorder (BD). HIV transmission risk behavior was examined among 63 patients with BD, major depressive disorder, and no mood disorder; half also had substance use disorders (SUDs). Patients with BD were more likely than others to report unprotected intercourse with HIV-negative partners and less than 95% adherence to antiretroviral medications. In multivariate models, BD and SUD were independent predictors of both risk behaviors. Participants with poorer medication adherence were more likely to have detectable HIV viral loads and unprotected intercourse with HIV-negative partners. Patients with BD deserve careful evaluation and HIV prevention services to reduce HIV transmission risk behaviors [33].

Anxiety Disorders

Studies examining the prevalence of anxiety disorders among HIV-infected individuals suggest that as many as 16–36% of HIV-infected individuals have anxiety disorders [34] and the HIV Cost and Services Utilization Study (HCSUS) study found that 16% of HIV-infected individuals in their sample met criteria for generalized anxiety disorder, and that 10.5% met criteria for panic attacks [35]. Among PLWHA with anxiety symptoms, adjustment disorder with anxious mood was found to be most common, followed by generalized anxiety disorder (GAD) and panic disorder (PD). Adjustment disorder can be distinguished from other anxiety disorders, as the severity of symptoms for anxiety disorders are of greater severity than those typically found with adjustment disorders. Anxiety disorders are also a common co-morbidity among those with depression, underlining the importance of careful assessment for anxiety symptoms among those presenting with depression. SSRIs are a common treatment and effective for anxiety disorders, however, Vitiello and colleagues found that 63% of the medications prescribed for anxiety among HIV-infected individuals were benzodiazepines [36]. That finding was of some concern considering the high rates of substance abuse among HIV-infected persons and the potential for abuse of benzodiazepines. Hopefully, the use of benzodiazepines to treat anxiety among persons who are HIV infected has declined markedly in the decade since that review was conducted.

Posttraumatic stress disorder (PTSD) is a highly prevalent chronic and disabling psychiatric disorder that is frequently comorbid with major depression [37]. Among individuals who are HIV-infected, the rate of lifetime PTSD and incidence of HIV-related PTSD has been estimated at 54% and 40% respectively [38•]. Despite the high co-occurrence and harmful effects of PTSD in HIV-infected individuals, there is relatively little research on the efficacy of treating PTSD in this population and not all studies have found antidepressant medication to be efficacious in treating HIV-positive individuals with PTSD [39]. Prolonged exposure (PE) therapy is a well-supported psychotherapeutic treatment for PTSD and has demonstrated efficacy in a wide range of trauma populations. PE has been shown to be effective in reducing symptoms of PTSD and symptoms of comorbid depression in one study to date [40].

Schizophrenia

Schizophrenia spectrum disorders are a complex constellation of severe psychiatric illnesses that are characterized by positive symptoms (i.e., hallucinations and delusions), negative symptoms (i.e., alogia, anhedonia), disorganized thinking and cognitive impairment that leads to social and occupation dysfunction. Onset of schizophrenia is typically in late adolescence and early adulthood in both men and women, during the developmental period where sexuality and sexual behaviors typically increase in frequency and importance. This dynamic combined with the increased vulnerability to abuse and exploitation of persons with disordered thinking makes these persons particularly vulnerable to contracting and transmitting HIV and other infectious diseases. Antipsychotic agents are the treatments of choice regardless of the underlying diagnosis. Open studies and case reports support the use of standard antipsychotic agents for psychotic symptoms in PLWHA, and there have been recommendations made that the atypical antipsychotics are efficacious with fewer extrapyramidal side-effects than traditional antipsychotic medications like haldol and thioridazine [41]. However, there is consensus that the widespread use of many psychiatric medications, particularly the newer atypical antipsychotics, heighten the risk of obesity and metabolic syndrome. In general, studies suggest that individuals experience greater weight gain with the atypical neuroleptics than with older antipsychotics such as haloperidol [42]; however weight gain with older neuroleptics such as chlorpromazine and thioridazine is also well documented [43].

What is needed are evidence-based treatment guidelines based on biological and behavioral studies of the treatment of mental illness among individuals in treatment for HIV/AIDS to develop innovative, integrated treatments to optimize psychiatric, behavioral, and medical outcomes and to achieve a better understanding of the biological mechanisms underlying these combined illnesses and treatments [44].

Treatment for Co-occurring Substance Abuse and Mental Illness Among HIV Positive Individuals (Triply Diagnosed Persons)

The interaction between symptoms of mental illness and HIV risk behaviors is complex and recursive, and the symptom to infection pathway needs to be understood in the context of multiple environmental and behavioral factors. As with any serious chronic illness, HIV itself often produces depression and anxiety in persons, and the virus has been shown to have direct neurotoxic effects that can results in HIV-associated neurocognitive disorder (HAND), a complex syndrome characterized by a wide variety of neurological and performance deficits. The severity of mental illness symptoms has been found to be associated with higher risk for being HIV infected in a study that examined the association of HIV risk and psychiatric symptom severity using the Colorado Symptom Index (CSI) [45•]. That study found a 47% increased risk for HIV among persons with CSI scores greater than 30 (a criterion score for severe psychiatric symptoms) compared to those with scores lower than 30, indicating that psychiatric symptom severity was associated with HIV infection.

To further add to the complexity of the problem, there is a now an established empirical base that clearly demonstrates the co-morbidity between HIV, mental illness, and substance use [46]. There is compelling evidence that the addition of substance abuse profoundly raises the risk of HIV in people with mental illness. In a large sample of patients with schizophrenia spectrum disorders treated through the VA system, Himelhoch and his colleagues found an interaction where people with schizophrenia and co-morbid substance abuse were at markedly greater risk for HIV infections, but in the absence of a substance use diagnosis people with schizophrenia alone were actually at lower risk for HIV infections than the general VA population [7]. These findings have been echoed in a paper using Medicaid claims to examine new HIV diagnoses among SMI patients in eight states [47•].

Care must be taken in drawing conclusions from data patterns based on diagnosis, and in translating findings into clinical practice [48•]. As we noted earlier, HIV testing practices among SMI can produce undercounts. If people with SMI but no substance abuse are particularly unlikely to be tested, HIV diagnoses in this group will underestimate true rates. Given that underestimates are possible, the clear evidence that cases of HIV continue to go undetected in psychiatric settings, and the probability that many people who present with an SMI eventually develop substance use problems, integrated service delivery with prevention and treatment services provided for both disorders seems desirable. Including substance use in HIV risk assessment for those presenting with an SMI is needed, and availability and promotion of HIV testing should be increased across settings. The spread of routine testing may provide improved opportunities to estimate true rates of infection across groups and, more important, should reduce the probability of missed cases.

Clearly, comprehensive routine opt-out HIV testing and screening for HIV risk among persons with mental illnesses needs to include a substance abuse screen. As such, research geared toward community implementation of HIV prevention interventions that are relevant to persons with SMI and substance abuse has great public health significance, since these individuals seem disproportionately prone to contracting HIV themselves, and perhaps to spreading the disease to others.

Medication Monitoring and Drug-Drug Interactions

When prescribing psychotropic medication in the context of antiretroviral therapy, it is important to monitor for untoward side effects, as well as to consider possible drug-drug interactions. For example, people prescribed second generation antipsychotic medication are at increased risk for developing symptoms associated with the metabolic syndrome. These symptoms include weight gain, hyperglycemia and hyperlipidemia. Similar symptoms associated with the metabolic syndrome are also associated with treatment with antiretroviral medications (i.e., protease inhibitors). Clearly monitoring of weight, fasting blood glucose, and lipid profiles is integral to treatment for people taking any of these medications. Clinicians need to also be careful to review and identify any drug-drug interactions (i.e., cytochrome P-450 system) between antiretroviral mediation and psychotropic medications. For example, specific benzodiazepines may be contraindicated when taken with protease inhibitors and care must be taken when prescribing methadone in the presence of specific non-nucleoside reverse-transcriptase inhibitors (NNRTIs). A careful history about use of over the counter medications and herbal remedies is also recommended. In particular, St. Johns Wort may be contraindicated when used in conjunction with antiretroviral treatment.

Treatment Innovations: Preliminary Evidence for Tailored Treatment and Nurse Health Navigators

Preventing AIDS through Health for HIV Positive persons (PATH+) was a regimen management intervention study for persons who also had a SMI that was carried out by advanced practice nurses (APNs) who provided in-home services and coordinated participants' care [10•, 49, 50•]. In PATH+ an adaptive treatment design [51] implemented through an "intervention cascade" was used to titrate the intensity (and expense) of the intervention to actual adherence outcomes. As described by Blank & Eisenberg [10•], the PATH+ intervention cascade is an individually tailored intervention to promote adherence in HIV positive persons with co-occurring mental illnesses. The PATH+ intervention consisted of assignment of the services of an APN who provided in-home consultations and coordinated medical and mental health services for one year. The APNs collaborated with prescribing providers, pharmacists, and case managers to organize medication regimens and help participants cope with barriers to medication adherence and promote the participant's ability to self-care. The protocol included a meeting with the participant at a minimum of once a week. The basic intervention consisted of psycho-education along with pillboxes and beeping watches and was provided to all participants in the intervention group. In addition, the APN served a health navigator, and coordinated physician and other appointments for the client and would also attend them with the patients when there was a problem with a medication, communication, or other issues needing physician attention.

Adherence to HIV and psychiatric medications was calculated weekly. If adherence fell below 80%, the intervention cascade was implemented until adherence was maintained equal to or above 80% for three weeks. The intervention cascade represented a gradual increase in intensity and included activation of social networks, the use of reminder beepers with alphanumeric displays, and then prepaid cellular phones to encourage participants to follow their regimen. If all else failed, the final step in the intervention cascade was directly observed therapy.

A total of 238 community-dwelling, HIV-positive subjects with SMI who were in treatment at urban CMHC's between 2004 to 2008 were enrolled. The main outcome measures were viral load and CD4 count. Results of the intervention showed significant reductions in viral load at 12 months [10•], and latent growth curve models showed significant changes in viral load, CD4, and health-related quality of life over 24 months [52•].

Conclusion

The increased risk for HIV infections among persons with severe mental illness and the disproportionate burden of disease it represents for these people require more attention and more effective individualized treatments. Here, we briefly outline what is known regarding HIV risk and treatment for persons with schizophrenia, depression and other affective disorders, bipolar disorders, and anxiety disorders including PTSD. A brief discussion of what little information exists regarding drug-drug interactions between psychotropic medications and anti-retrovirals is included. Moving away from DSM-diagnostic groupings, we then go on to discuss prevalence and treatment issues for triply diagnosed PLWHA with substance abuse or dependence, and a co-occurring severe mental illness. We use an example from Preventing AIDS through Health for Positives (PATH+), an intervention that was individually tailored to promote adherence to complex treatment regimens among these persons, to show that these individuals can be treated successfully when given appropriate supports.

Acknowledgments This project was in part supported by P30-AI45008 (Hoxie, PI) Penn Center for AIDS Research (CFAR), and by P30 MH097488-01 (Evans, PI) Penn Mental Health AIDS Research Center.

Compliance with Ethics Guidelines

Conflict of Interest James Walkup received honoraria, payment for development of education presentations, and travel/acommodations expenses covered or reimbursed by the Columbia University HIV Mental Health Training Project.

Michael B. Blank, Seth Himelhoch, and Marlene M. Eiensberg declare that they have no conflict of interest.

Human and Animal Rights and Informed Consent This article does not contain any studies with human or animal subjects performed by any of the authors.

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