CHAPTER 1

Epidemiology of Psychopathology in HIV

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THE CO-MORBIDITY AND IMPACT OF PSYCHIATRIC DISORDERS IN HIV INFECTION

The HIV epidemic has been called 'an unprecedented reversal of human health progress' [1]. Psychiatric or mental disorders are common co-morbidities amongst people at risk for or infected by HIV, and the epidemic will not be adequately controlled, even with treatment as prevention, unless these co-occurring disorders are addressed. Consistent with the diagnostic approaches of both the Diagnostic and Statistical Manual of Mental Disorders DSM-V and International Classification of Diseases ICD-10 of the World Health Organization, we use the terms 'mental disorders' and 'psychiatric disorders' to include substance use diagnoses, other mental illnesses, and neurocognitive impairment.

Mental and substance use disorders are the leading cause of years lived with disability (YLDs) worldwide [2]. Effects of mental disorders are magnified by their propensity to increase the risk for communicable and non-communicable diseases and by their contribution to unintentional and intentional injury [3]. Further, health conditions such as diabetes, coronary artery disease and infection with HIV increase the risk for mental disorders, and co-morbidity complicates help-seeking, diagnosis, treatment and prognosis [3–6]. Mental disorders are associated with the acquisition and transmission of HIV and other sexually transmitted infections, reduced coping capacity at the time of HIV diagnosis, poor HIV-related disease prognosis, failure to access HIV care and treatment, erratic adherence to antiretroviral regimens, diminished quality of life, greater social burden, increased health-care costs and higher mortality [7–13].

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The Treatment Gap of Mental Disorders in HIV Care

Addressing mental disorders as part of HIV care and treatment must be seen in the larger context of the mental health treatment gap – the proportion of persons who need but do not receive care. This gap is large for both severe and common mental disorders worldwide [3, 14], but is more pronounced in low- and middle-income countries (LMICs) and in low-resource areas of high-income countries [15, 16]. LMICs comprise more than 80% of the global population, yet hold less than 20% of the worldwide resources to treat mental disorders [17]. When treatment is provided, it frequently is below minimum acceptable standards and often lacks respect for human rights [18]. Even where psychiatric care has improved, people with mental disorders continue to be stigmatized [19–24] within multiple systems (e.g. education, housing, work-force, judicial, health and even mental health,) [25–32]. Affected people commonly internalize these negative stereotypes about what it means to have a mental illness, expecting discrimination and devaluing themselves [33], which can interfere with their the ability to choose their sexual partners and negotiate safer sexual behaviours [34]. Antiretroviral treatment scale-up to stem the HIV epidemic is unlikely to bring community viral load and new infections to zero if addressing mental disorders is left out of the plan.

The Epidemiology of Mental Disorders in HIV Infection

Understanding the epidemiology of mental disorders amongst people living with HIV and AIDS (PLWHA) can help better define priorities and needed resources to reduce the incidence, the prevalence and the burden of HIV disease on individuals with these disorders and on the communities in which they receive care. The majority of HIV-infected individuals will experience a diagnosable psychiatric disorder [35], with the proportion of psychiatric disorders amongst those living with HIV being nearly five times greater than in the general population [36]. Psychopathology can occur as a risk factor for HIV infection, coincidentally with HIV infection; as a psychological response to HIV infection and its complications, as a result of direct effect of HIV on the brain; as a consequence of HIV-related opportunistic diseases and as side effects of HIV-related treatments. Despite the impressive reduction of HIV-related morbidity and mortality where antiretroviral therapy (ART) is available, psychiatric and neuropsychiatric repercussions of HIV disease are expected to become more relevant in the coming years [8].

Most of the published epidemiology of mental disorders amongst PLWHA focuses on the distribution or point prevalence. Incidence, predictors, morbidity and course of disease data require longitudinal prospective studies which are rare. For all disorders discussed in this chapter, important caveats must be taken into consideration. First, accuracy of available prevalence estimates is unclear because most studies of psychiatric disorders amongst people with HIV used convenience

samples, often of the historic risk groups, had small sample sizes, or were confined to specific geographical areas. Population-based estimates of psychiatric disorders amongst HIV-positive individuals are scarce. Second, comparisons between studies are complicated by variability of screening and diagnostic measures used by different studies. Further, even if gold standard measures were used, the lack of validation of measures across studies has not always occurred, complicating confidence in prevalence data [37]. Finally, in places where the increased availability of ART treatment allows PLWHA to live longer, the cumulative prevalence of chronic disorders such as mental disorders also may increase.

We begin with prevalent neurocognitive disorders defined by the presence of neuropsychiatric manifestations of HIV's direct effects on the central nervous system (CNS). We then discuss the most commonly seen psychiatric disorders amongst people with HIV: substance abuse or dependence; depression; anxiety (including post-traumatic stress disorder (PTSD); and psychosis. We also discuss significant psychiatric co-morbidities. We conclude with basic principles to guide treatment and prevention.

HIV-ASSOCIATED NEUROCOGNITIVE DISORDERS

Neuropathological and Clinical Aspects

HIV is a neurotropic virus that enters the CNS at the time of initial infection and persists there causing neurocognitive syndromes that can vary from subtle neuropsychological impairments to profoundly disabling cognitive and motor dysfunction known as HIV-associated dementia (HAD) [38, 39]. HAD confers an increased risk for early mortality, independent of medical predictors, and is more frequently seen in advanced stages of HIV disease but can occur even in individuals having medically asymptomatic HIV infection [10, 40]. In untreated HIV infection, symptoms are predominantly subcortical and include decreased attention and concentration, psychomotor slowing, reduced speed of information processing, executive dysfunction and, in more advanced cases, verbal memory impairment. However, this pattern of brain injury and the nomenclature used to describe it have evolved with new advances in detection and treatment. The use of ART has seen the neuropsychiatric complications of HIV evolve from a predominantly subcortical disorder to one that now prominently includes the cortex, with volumetric loss and ventricular enlargement [41]. Finally, increased life expectancy in HIV patients may add cerebrovascular or degenerative encephalitis to the clinical presentation of HIV neurocognitive disorders [10]. Although for the moment neurocognitive complications are usually mild and survival is not compromised [42, 43], they may negatively affect quality of life [43], independence in daily activities [44], employment [44], driving [44], or treatment adherence [44]. In addition, neuropsychiatric complications of HIV may be associated with increased risk

behaviours and decreased adherence to medication [8, 45]. The clinical aspects of neurocognitive syndromes are discussed in more detail in chapter 3.

Research Classification of HAND

Since 2007, the term HIV-associated neurocognitive disorder (HAND) has been established to capture the wide spectrum of HIV-related neurocognitive deficits [46]. Depending on the severity of symptoms, HAND diagnostic research categories include asymptomatic neurocognitive impairment (ANI) without significant impact on day-to-day functioning, mild neurocognitive disorder (MND) with mild-to-moderate impairment, and debilitating HIV-associated dementia (HAD) [46]. The research diagnostic criteria of HAND require a comprehensive neuropsychological evaluation seldom available in most settings, including in high-income countries [47, 48]. Clinical assessment or brief screening tools are the norm although their validity is still being evaluated [49, 50].

HAND in the CART Era

The introduction of effective ART in the mid-1990s and the widespread use of primary prophylaxis against opportunistic infections have dramatically decreased the incidence of the most common HIV-related opportunistic diseases affecting the brain [51–54]. However, neurological complications of HIV infection still cause considerable morbidity and mortality, and greater than 50% of patients develop neurological disorders, even in the ART era [52, 54–56]. Conservative estimates from resource-rich countries estimate that the number of individuals of all ages living with HIV neurocognitive disorders will increase 5- to 10-fold by 2030 [57].

Prior to effective ART, HAD prevalence estimates were approximately 15–20% in AIDS cases [58, 59], whereas more recent estimates are less than 5–10% [60–62]. Amongst HIV-positive patients who received ART, the proportion of HAD as a percentage of all AIDS-defining illnesses rose from 4.4% to 6.5% between 1995 and 1997 [62]. This shift is thought to reflect the decrease in rates of other AIDS-defining conditions, thereby leading to the relative rise in HAD cases. Even though some initial studies reported a decrease in incidence of HAD from 21.1/1000 person years in 1990–1992 to 14.7/1000 person years in 1995–1997 [62, 63], others reported HAD incidence irrespective of the use of ART [64].

Despite the widespread use of ART, HAND continues to occur with a high prevalence of 28–50%, although mostly in mild forms [40, 65–71]. A recent review found that 11 out of 15 studies of neurocognitive changes in HIV-positive samples initiating ART demonstrated some improvement in neurocognitive test performance after an average of 6 months on combination ART; however, most studies had relatively small sample sizes and did not control for practice effects of repeated testing [45]. Unfortunately, longitudinal studies on the neurocognitive

responses to ART in treated patients have documented high persisting rates of mild-to-moderate neurocognitive impairment [40, 72]. The variability of responses to ART amongst individuals within these samples included responders who at follow-up performed within the 'normal' range (but with no apparent correction for practice effect), but also patients who experienced incident impairment at follow-up [40, 43, 69], even in spite of good virologic response (undetectable HIV RNA in plasma on ART) [49]. Several possibilities have been suggested to explain the lack of response of HAND to ART such as incomplete viral suppression in the CNS due to poor ART CNS penetration, presence of drug-resistant viral strains, neurotoxicity of ART drugs, metabolic abnormalities, neurovascular pathology or the neurocognitive effect of syphilis or chronic hepatitis in the brain [10, 40, 66]. In addition, Hepatitis C virus (HCV) is highly co-morbid with HIV, and HCV can create its own neuropsychiatric problems as well as exacerbate those caused by HIV. Screening for HCV is relatively straightforward, but therapy for HCV infection has been poorly tolerated and not effective in a substantial number of patients [73]. Approximately 100 million people worldwide are infected with HCV; yet, it has been estimated in resource-rich countries that less than 30% of people with HCV know they are infected [74]. HCV is an important diagnosis of exclusion in the evaluation and treatment of the neuropsychiatric complications of HIV. Moreover, rapidly developing HCV treatment advances will make detection and treatment of HCV increasingly more important to the health of those who are co-infected with HIV.

Regional Differences in HAND

The above findings summarize resource-rich geographic realities (e.g. North America, Europe and Australia) as well as reports from several countries in Asia, Africa and Latin America [45, 61, 71, 75–82]. Although the prevalence of HAND is well-established in regions where the most prevalent HIV subtype is clade B (e.g. Americas and Europe), which is considered to be the most neurotoxic subtype, some data exists on HAND prevalence in areas where HIV clade C predominates, such as Sub-Saharan Africa and South East Asia [71, 78, 79], or where clade D is prevalent, such as in Uganda [81]; these reports demonstrate clinical neurotoxicity of clades C and D.

Implications of Mild HAND

The prevalence of HAND is high even in long-standing aviremic HIV-positive patients [49]. Subtle neuropsychological impairment, or ANI, may be found in 22–30% of otherwise asymptomatic patients with HIV infection [83, 84]. Before effective ART, the prevalence of MND (which was classified as Minor Cognitive Motor Disorder prior to 2007) was estimated at 20–30% for HIV-asymptomatic

patients and at 60–90% for HIV late-stage patients [85]. Following effective ART, these rates have remained fairly constant for the latter group (late-stage disease), but have increased for the HIV asymptomatic patients by about 20% in most studies [86], but up to 52% after ART [49, 87]. ANI raises important ethical issues as well as diagnostic and therapeutic implications by categorizing patients who do not have any symptoms as neurocognitively impaired [86]. This research definition should not be used to establish a clinical diagnosis, especially in patients with ongoing effective antiretroviral treatment. With no evidence that patients with ANI are at increased risk to develop more severe impairment or have a need for any specific intervention, an ANI diagnosis may also lead to anxiety and impact on that person's life and employment [86].

HIV-associated Delirium

Delirium has long been the most common neuropsychiatric diagnosis in hospitalized or critically ill HIV patients, with an estimated prevalence of 40–65% [8, 88]. A recent retrospective study [54] of HIV-infected patients admitted to a medical intensive care unit (ICU) with neurological complications between 2001 and 2008 found that delirium was the most frequent of all neurological complications (45%), followed by coma (39%), seizures (32%) and/or intracranial hypertension (21%). Delirium may be observed as early as acute HIV infection or, more frequently, in later stages when it is associated with infections, malignancies, metabolic abnormalities, hypoxemia or anaemia [88].

THE MOST COMMON PSYCHIATRIC DISORDERS AMONGST PEOPLE WITH HIV: SUBSTANCE ABUSE OR DEPENDENCE, DEPRESSION, ANXIETY AND PSYCHOSIS

HIV more often than not co-occurs with other conditions such as tuberculosis, particularly in developing countries, and Hepatitis C worldwide. Whilst such conditions are readily identifiable through medical tests routinely offered to PLWHA, psychiatric co-morbidities are also common but often present considerable difficulty for HIV care providers to recognize and address. Below we summarize the data in the published literature on the epidemiology of mental disorders amongst PLWHA. A majority of studies has been conducted in the United States but we also include studies from other high-income countries as well as LMICs.

Epidemiology of psychiatric disorders in HIV

It is important to bear in mind that psychiatric disorders are often co-morbid with one another, and concern about the co-morbidity of addictive and non-addictive disorders has received particular attention. The US National Comorbidity Study [89]

showed that substance use disorders are highly co-morbid with other psychiatric disorders (e.g. bipolar disorder, depression, psychotic disorders, anxiety disorders and antisocial and borderline personality disorders). Possible explanations for this have been suggested, including that these disorders share common underlying aetiologies; that mental illness leads to self-medication with alcohol and other drugs; and that substance use leads to symptoms of mental illness. It is often impossible to know which disorder came first or is primary, although onset of non-addictive mental disorders appears to occur at a younger age relative to addictive disorders [89]. In clinical settings of any kind it is prudent to screen patients with one type of disorder for the other type of disorder.

In spite of the methodological issues in the published data, the body of available research points to rates of mental disorders of about 50% but up to 75% amongst HIV-infected men and women in low, middle and high-income countries [90–96]. Sub-Saharan African studies have found a wider range of prevalence of psychiatric disorders in PLWHA (5–83%) [97]. In these studies, PLWHA were more likely to screen positive for depression, PTSD and schizophrenia than HIV-negative controls; results were mixed regarding the prevalence of anxiety in PLWHA [97]. Two important studies provide a thorough picture of the prevalence of psychiatric disorders in HIV-infected individuals in the United States. The first one, the 1996 landmark HIV Cost and Services Utilization Study (HCSUS) [90] administered a brief structured psychiatric instrument that screened for psychiatric disorders (major depression, dysthymia, generalized anxiety disorders and drug use). Results showed that in this large, nationally representative probability sample of adults receiving medical care for HIV in early 1996 ($N = 2864$: 2017 men, 847 women) rates of mental disorders were almost twice that found in the general population [90, 96, 98–102]: 36% prevalence of depression, 16% prevalence of anxiety and 12% prevalence of drug dependence. There was also an 8% rate of heavy drinking and a 50% rate of drug use. The study did not assess for rates of psychosis, bipolar disorder, alcohol abuse or dependence and substance abuse. The more recent (2004–2005) National Epidemiologic Survey on Alcohol and Related Conditions (NESARC) Wave 2, a large nationally representative sample of US adults ($N = 34{,}653$; 149 HIV positive: 79 women, 70 men), also reported that HIV status was significantly associated with 12-month prevalence of psychiatric disorders [103], consistent with previous reports [90, 96, 104]. Amongst HIV-positive adults, 64% of the men and 38% of the women had a psychiatric disorder, respectively. HIV-positive men had significantly greater odds of having any mood disorder (7.17), any anxiety disorder (3.45), and any personality disorder (2.66) than HIV-positive women. Comparing the prevalence of psychiatric disorders amongst HIV-infected individuals with HIV-negative ones, HIV-positive men had significantly greater odds of having a mood disorder (6.10), major depressive disorder/dysthymia (3.77), any anxiety disorder (4.02) and any personality disorder (2.50). In contrast, HIV-positive women were not significantly more likely than HIV-negative women to have psychiatric disorders.

Impact of psychiatric disorders on health outcomes

In a systematic review ($n = 82$ studies) investigating the impact of mental disorders on ART adherence in PLWHA [105], untreated depression was associated with lower adherence in most of the studies examining depression [105]. Seven out of the nine studies evaluating the impact of antidepressant treatment on ART adherence found improvement [105]. The majority of studies examining one or more anxiety ($N = 17$), psychotic ($N = 3$), bipolar ($N = 5$) and personality disorders ($N = 2$) found no association with adherence to ART [105]. However, the diversity of measurement methods calls for further research in this area. A study of PLWHA in care in the United States ($N = 5119$) found that a concurrent mental health disorder and illicit drug use was associated with lower use of ART, and more than a doubling in the likelihood of using inpatient services [106]. And in a review of studies that included more than 10,000 PLWHA, concurrent illicit drug use and a mental disorder were associated with lower odds of attaining complete HIV viral suppression compared to patients with either illicit drug use or mental health disorders alone, or with neither condition [107].

ALCOHOL AND DRUG USE DISORDERS

Amongst HIV-infected individuals with or without hepatitis B or C, heavy drinking predicts HIV end-stage disease and mortality [108–110]. Prior to ART, the Multicenter AIDS Cohort Study found no association between alcohol use and HIV disease progression [111]. However, post-ART availability, alcohol use amongst PLWHA with current or past alcohol problems prospectively assessed for up to 7 years found that in PLWHA who were not on ART, heavy alcohol consumption was associated with a lower CD4 cell count but not with higher HIV viral load [112]. Amongst women who were on ART, heavy alcohol consumption was not associated with a lower CD4 cell count or higher HIV viral load [113]. Patient's visit time, high viral load and drug use were predictors of alcohol use in women with HIV, which in turn was associated with depression and then HIV disease progression [113].

Epidemiology of Alcohol and Drug Use

The WHO estimates that 2 billion people consume alcohol, 76.3 million of whom have diagnosable alcohol use disorders [114]. World regions with lower alcohol use have lower HIV rates; conversely, regions with higher alcohol burden also have massive HIV burden (e.g. Southern Africa and Eastern Europe) [110]. The lifetime prevalence for alcohol use disorders amongst HIV patients is in the range of 22–64% and for drug use disorders 23–56% [8, 115, 116] compared to the general

population lifetime prevalence of 5–24% and 1–12% for alcohol and other drugs, respectively [98, 117, 118]. Across studies both in resource-rich and resource-poor countries, the prevalence for any current alcohol and drug use disorder amongst people with HIV infection has been estimated to have a wide range of 8–73% [8, 103, 119–123], and co-morbidity with other psychiatric disorders is estimated at 69% [124]. In large studies, the prevalence of current alcohol use disorders amongst people with HIV infection has been estimated to range from 8% to 12% [96, 103, 115, 116, 125–128], compared to the general population where the prevalence of current alcohol use disorders was estimated to be 5–10% [98, 117, 118]. Similarly, the prevalence of current drug use disorders amongst HIV-infected individuals was estimated at about 12–19% [90, 103, 115, 116, 125, 126], compared to a prevalence rate of current drug use disorder in the general population of about 1–3% [98, 117, 118].

Impact of Alcohol and Drug Use on Health Outcomes

Whilst marijuana use is very common amongst PLWHA, and has been associated with decreased medication adherence [129], heavy non-marijuana drug use has been associated with increases in HIV-related morbidity and mortality, especially amongst PLWHA who are continuous active drug users, as opposed to those who use intermittently [130]. The use of heroin or prescription opioids has been linked to lower ART and other treatment adherence, and reduced viral suppression, and to higher rates of opportunistic infections, disease progression, and HIV-related mortality [130–132]. Crack-cocaine use facilitates HIV disease progression by reducing adherence in those on ART and by accelerating disease progression independently of ART [133]. However, amongst women, persistent and intermittent crack users in active and abstinent phases showed greater CD4 cell loss, higher HIV viral load levels, and greater development of new AIDS-defining illnesses compared to non-users [132]. Food insecurity and viral load are associated with HIV-related wasting, which continues to be common amongst PLWHA active drug users, even amongst ART recipients [134].

Some studies have found that these increases in morbidity and mortality may be independent of adherence to ART [127]; however, substance use disorders can interfere with the ability of patients to access care, and once in care, to be adherent to ART [135–137]. Providers also may delay starting ART because of substance use disorders even though a thorough assessment may reveal that adherence to ART may not be compromised by the substance use disorder [10]. Besides injection drug use as a source of HIV transmission amongst those who inject, alcohol and drug use has been associated with increased transmission through sexual risk behaviours in many studies, but not in all [97, 138–142].

Although substance use is a clear risk factor for worse clinical outcomes in PLWHA, substance abuse treatment has been shown to improve clinical outcomes.

A longitudinal study of drug and alcohol use amongst individuals with HIV infection found that switching from active substance use to non-use was followed by a significant improvement in ART adherence and HIV viral suppression [131]. In a study of 659 PLWHA on ART, patients with a history of substance use problems who were currently in treatment were as adherent to ART as individuals who had no history of substance use [143], and survival rates for intravenous drug users were the same as for non-users after adjusting for differences in ART adherence [144]. The high estimates of alcohol and drug disorders amongst PLWHA wherever these studies are conducted, together with the well-established impact on HIV transmission, adherence, morbidity and mortality, requires addressing substance use via prevention, screening, comprehensive assessment and treatment [142].

Tobacco Use in PLWHA

Tobacco use is reported by approximately 50–75% of PLWHA, which is approximately three times the rate amongst the non-infected population [145]. There are conflicting data on whether cigarette smoking is associated with HIV progression but some evidence suggests that CD4 cell counts of smokers may decline at a faster rate that that of non-smokers. However, most studies have not demonstrated progression to clinical AIDS to be higher amongst smokers. As ART has increasingly become available, chronic diseases, such as tobacco-related diseases, are increasingly becoming the causes of morbidity and mortality in PLWHA. Cigarette smoking is associated with increased respiratory infections, particularly pneumocystis pneumonia (PCP) and bacterial pneumonia, and non-infectious lung disease [146–148] and all-cause mortality. Smoking appears more likely to impact HIV-related morbidity and mortality as effective HIV treatment has become more widespread [146]. Along these lines, a recent study of a large cohort of HIV infected patients in Denmark found that among HIV infected smokers the rate of non-AIDS-related deaths was raised more than 5-fold with markedly increased risk of death caused by cardiovascular disease and cancer. Whereas HIV infection among those who never smoked shortened life span on average by 5.1 years relative to the general population, current smoking in the context of having HIV infection shortened life span on average by 12.3 years relative to the general population [149].

MOOD AND ANXIETY DISORDERS

The major mood and anxiety disorders are five to ten times more prevalent in HIV-positive individuals than in the general US population, [98] with a similar increased risk found in other low, middle and high-income countries [150]. Although mood disorders encompass the range of unipolar and bipolar conditions, none of the

studies that have described prevalence rates of depressive disorders in HIV-positive populations has included bipolar disorder [151]. However, mania secondary to HIV infection is rare, generally occurring in late stages of AIDS [10]. By contrast, depression and anxiety disorders are seen throughout the course of HIV infection, and the conditions commonly coexist [152]. There is an increased likelihood of the emergence of symptoms during pivotal disease points (such as HIV antibody testing, declines in immune status, and occurrence of opportunistic infections) [10].

Depression

Epidemiology of depression

Depression is the most common reason for psychiatric referral amongst people with HIV infection [153] and the most common mental health disorder amongst HIV patients, with estimates of its prevalence in most countries raging from 7% to 61% [90, 103, 154–158], and always greater than in the general population (4–40%) [98, 103, 118]. The few studies conducted in middle or low-income countries have reported rates of depression ranging from 0% to 63.3% amongst HIV-positive participants [154, 159]. One study in a population of HIV-positive patients in South Africa documented an 8.1% incidence of major depressive disorder (MDD) at 6 months of follow-up [91]. On the other hand, a US study found a 22% incidence of depression at 6–12 month follow-ups, with deleterious effects on adherence to ART [160]. A 2-year prospective study comparing PLWHA men and uninfected same risk-group controls found that the 2-year cumulative rate of a major depressive episode was about 40% in those with symptomatic advanced illness compared to about 20% for asymptomatic individuals and for same risk-group controls, which were also higher than the epidemiologic community surveys, which range from 4% to 10% [98, 117, 161]. After baseline disease stage and medical variables associated with HIV infection were controlled, a lifetime history of major depression, or of lifetime psychiatric co-morbidity (two or more psychiatric disorders), predicted subsequent major depressive episodes. By contrast, neither HIV disease progression during follow-up, nor the baseline presence of neurocognitive impairment, clinical brain imaging abnormality, or marked life adversity predicted a later major depressive episode [161].

Amongst HIV-infected patients referred for psychiatric evaluation, rates of major depression range from 8% to 67% [91, 152, 162, 163], and up to 85% of HIV-seropositive individuals report some depression symptoms [162, 164]. People with HIV are almost twice as likely as those who are HIV negative to be diagnosed with major depression, and depression is equally prevalent in people with both symptomatic and asymptomatic HIV [99–102], although the deleterious effect of untreated depression on adherence to ART deepens the burden amongst those with symptomatic illness. Depression rates tend to be lower amongst community-based

HIV-positive samples and are highest amongst injection drug users (IDU) and women. Risk factors for depression amongst PLWHA include female gender, prior history of depression, co-morbid psychiatric disorders/problems (e.g. substance abuse, PTSD, generalized anxiety disorder and lifetime attempted suicide), family history of psychiatric disorder, HIV-related physical symptoms, psychosocial impairment, unemployment and food insecurity, use of avoidance coping strategies and increasing negative life events [10, 163, 165]. Several studies have not found an association between biological markers of direct HIV involvement, such as neurocognitive impairment, CD4 counts and body mass index, and depression, perhaps suggesting a minimal role for the neurotoxic effects of the HIV virus in the aetiology of depression [163].

Most studies reporting on the prevalence of depression amongst PLWHA have not assessed subjects for bipolar disorder [150], an important rule-out diagnosis. Many studies screened or assessed people for depressive symptoms, and without further evaluation, no distinction can be made between subclinical depression and other depressive disorders besides major depression [181–183]. The few studies that have evaluated study participants with a diagnostic interview have neither reported on subclinical depression nor lifetime depressive disorders [91, 184, 185]. Knowledge of the prevalence of specific depressive disorders would allow for better resource allocation to provide the required treatments (e.g. pharmacotherapy and psychotherapies) [37, 186, 187] whilst management of lifetime depression would focus on relapse prevention using psychosocial interventions and maintenance medication.

Impact of depression on health outcomes

Studies have shown that untreated depressive disorders increase HIV transmission risk behaviours [165, 166], decrease immune status [156, 167] and decrease adherence to ART [160, 168–170], which may result in decreased clinical effectiveness and potential development of drug resistance [171, 172]. Thus, depression poses challenging barriers to effective medical care at multiple points along the continuum of HIV medical care engagement and treatment (i.e. ‘HIV treatment cascade’) [158]. Untreated depression has been associated with a lower likelihood of receiving antiretrovirals [173, 174], poor adherence [166, 175], and increased morbidity [176–179] and mortality [156]. Depression is a predictor of clinical progression independently of non-adherence behaviours [178]. Depression is frequently under-diagnosed and when recognized, it is often poorly treated, particularly in primary medical settings where HIV/AIDS patients receive care [10, 180]. Mounting evidence suggests that effectively treating depression in HIV patients may have benefits for their HIV-treatment retention, ART adherence, and virologic suppression, and, therefore, for community viral load [158].

Depression and associated co-morbidities

Suicidal behavior

Suicidal ideation is common amongst HIV-infected persons, including increased rates of suicide attempts (21.4%) and suicide deaths (3.3%) [188–190]. In the absence of ART, this elevated suicide rate amongst HIV-positive persons may be explained either by the functional limitations related to advanced HIV disease or by the threat of death [191]. The suicide rate declined in the ART era, but still remains more than three times higher amongst HIV-positive persons than in the general population [192, 193]. Risk factors associated with suicide attempts in HIV patients include HIV-related symptoms, psychiatric morbidity, substance abuse, personal or family history of suicide, multiple losses in relation to HIV infection, lack of a support network, external locus of control and unemployment [188, 194].

Mania

Differentiating bipolar depression from unipolar depression is important because treating a bipolar patient with antidepressants alone may trigger a manic episode. Unfortunately, bipolar disorder is rarely assessed in most studies reporting on the prevalence of depression amongst the HIV infected [151]. The US NERSAC Wave 2 study assessed for bipolar disorders I or II and found that HIV-positive men had a 12-month prevalence of 17% compared to 5% amongst HIV-positive women; HIV-negative men and women had 3% and 4% 12-month prevalence for bipolar I or II, respectively [103]. Mania or hypomania (characterized by the presence of increased energy, decreased sleep, restlessness, pressured speech, flight of ideas, elevated, expansive, or dysphoric mood, delusions or hallucinations) may be the result of bipolar disorder, substance or alcohol abuse, primary HIV encephalitis, progression to AIDS, or side effects of medications (i.e. zidovudine, ganciclovir, acyclovir, interferon, efavirenz, steroids and meperidine) [8, 183, 195, 196]. Rates of mania amongst HIV-infected individuals are similar to community samples during early HIV infection, but increase after the onset of AIDS to become the main cause for psychiatric hospitalization. Most cases of new-onset mania occur in advanced HIV disease and they are often associated with the presence of substantial cognitive impairment [197]. In addition, patients with secondary mania were significantly more likely to have paranoid delusions, visual and auditory hallucinations and pronounced irritable mood, with increased severity and persistent course besides cognitive slowing and dementia. Antiretroviral agents capable of penetrating the CNS have been shown to be effective for the prevention of manic reactions [198].

Anxiety Disorders

Estimates of the prevalence of anxiety disorders in HIV/AIDS patients range from almost negligible to as high as 40% [115, 126] [8, 115, 125, 150, 199–203]. The differences in prevalence across studies may be explained by numerous factors including a host of psychosocial correlates because anxiety frequently coexists with depression and substance use problems, as well as lack of rigorous diagnostic criteria used in most studies [8]. Despite the wide range of prevalence estimates, a pattern emerged in the late 1990s: several studies show a point prevalence of anxiety disorders in HIV-seropositive patients that are not significantly different from that of HIV-negative clinical comparison groups, although lifetime rates are higher in the HIV clinical population than in the general population [115, 126, 202]. However, the NERSAC Wave 2 study found that HIV-positive men had a 12-month prevalence of 33% compared to 24% amongst HIV-positive women; HIV-negative men and women had 11% and 21% 12-month prevalence for any anxiety disorder, respectively [103].

Higher rates of anxiety disorders are generally seen as HIV illness progresses. The rates of other major anxiety disorders in HIV patients, such as panic and obsessive–compulsive disorders, do not appear to be markedly elevated above community norms. Symptoms of anxiety may increase HIV fatigue and physical functional limitations [204].

Post-Traumatic Stress Disorder

PTSD has received substantial attention from HIV researchers. The rate of PTSD amongst individuals infected with HIV varies across studies for reasons similar to other mental disorders (e.g. varying assessments, diagnostic criteria, symptomatology, sample size and characteristics) [205–208]. Diverse definitions of qualifying traumatic events or trauma indexes [209], the traumatic histories of many of the most vulnerable groups affected by HIV and the variability of traumatic events that surround those infected with HIV make determining PTSD prevalence and comparison of the rates to the general populations a complex task.

PTSD may precede an HIV diagnosis because of previously experienced traumatic events, or may emerge post-HIV diagnosis as a result of the stress of being diagnosed with a life-threatening illness [209, 210] or subsequent challenges over the course of the HIV disease trajectory. Stresses include fears and worries about physical decline and disability, access to appropriate treatment, the welfare of dependents, loss of employment, stigma, discrimination, possible isolation and dying or traumatic events [207, 211–215]. As with HIV-negative populations, the level of PTSD amongst PLWHA also has been found to be positively correlated with the total number of traumatic life events experienced [216, 217]. Further, PTSD co-morbid with other mental disorders such as

schizophrenia, schizoaffective disorder and bipolar disorder can be an important predictor of HIV infection [218]. Greater psychological trauma and PTSD have been associated with several adverse health outcomes amongst PLWHA, including AIDS-defining illnesses or mortality, substance use, high-risk behaviours and decreased medication adherence [219–221].

Available studies mostly from North America and Africa suggest that the lifetime prevalence of PTSD amongst PLWHA ranges from 30% to 64% [207, 208, 217, 222–224], higher than that in the general population of 7.8% (5–6% in males and 10–11% in females) in the United States. [225, 226]. Amongst recently diagnosed HIV-positive South African individuals, an estimated PTSD rate of 15% and 26% was determined at baseline and follow-up, respectively [91] compared to the South African general population lifetime and 12-month prevalence of PTSD of 2.3% and 0.6%, respectively [118, 227]. Amongst the 15% who met the criteria at baseline for PTSD, patients reported as their index trauma in decreasing order, being informed of their HIV-positive diagnosis (36%), being raped (23%), being robbed or assaulted (14%), being the victim of intimate partner violence (9%), experiencing a serious accident (9%) and the death of someone close to the individual (9%) [91, 228]. Another South African study found a lifetime PTSD rate of 54% and an incidence of HIV-related PTSD of 40% [210].

Psychosis

Psychotic symptoms may be part of a major depressive disorder, schizophrenia, mania, obsessive–compulsive disorder, medication side effects, or secondary to drug or alcohol abuse, CNS complications or medications. Thus, the pathophysiology of psychosis in HIV infection is complex, and a multifactorial aetiology of psychotic symptoms is likely in many cases. However, there are many reports of psychotic symptoms in HIV-infected persons in the absence of concurrent substance abuse, iatrogenic causes, evidence of opportunistic infection or neoplasm or detectable cognitive impairment. A common clinical feature of new-onset psychosis in HIV-infected patients is the acute onset of HIV symptoms. In one study, HIV/AIDS was the leading cause of death amongst young patients experiencing their first hospitalization for a psychotic episode [229]. New-onset psychotic disorder is found most often in late stages of the disease, particularly in subjects with neurocognitive disorders [8, 120, 230, 231]. Estimates of the prevalence of new-onset psychosis in HIV-infected patients vary widely, from less than 0.5% to 15%, [39, 232–234] [8, 120, 230, 231], with post-ART studies indicating a prevalence closer to 3% [235, 236]. The NERSAC Wave 2 study found that HIV-positive men had a 12-month prevalence of 9.2% compared to 3.4% amongst HIV-positive women for any psychotic disorder in the last 12 months; HIV-negative men and women had a 0.6%12-month prevalence for any psychotic disorder [103].

Personality Disorders

Personality disorders can be detected in up to 30% of HIV-positive subjects [237]. Borderline, antisocial, dependent, histrionic and not otherwise specified are in this order the most frequent personality disorders amongst HIV-positive individuals [8, 203, 237, 238]. Evidence suggests that the presence of pathological personality traits or disorders may potentiate risk of HIV infection and transmission, adversely affect adherence to HIV treatments and contribute to disease progression [239, 240]. Recently, the NERSAC Wave 2 study found that HIV-positive men had a 43% 12-month prevalence of having a personality disorder compared to 19% amongst HIV-positive women; HIV-negative men and women had 23% and 20% 12-month prevalence for any personality disorder, respectively [103]. The NERSAC study [103] found amongst HIV-positive men and women the following 12-month prevalence rates: schizotypal (16% vs 8%), schizoid (14% vs 7%), paranoid (15% vs 6%), borderline (19% vs 9.8%), narcissistic (15% vs 7%) and avoidant (13% vs 11%).

CONCLUSIONS

Although estimates of mental disorders amongst PLWHA are subject to the usual limitations of research methodology, rates presented in this chapter nonetheless warrant our attention if we are to strengthen both the evidence base from which treatment and prevention planning can be sustainably implemented and the quality of care individuals receive for their co-morbid conditions.

Now that effective preventive and treatment interventions for mental disorders exist and can be used in high-income as well as in middle- and low-income countries, appropriate psychiatric interventions must also be brought to bear to prevent the spread of HIV and the impact of HIV infection on individual and public health and well-being. Further research is needed to understand the epidemiology of psychiatric disorders in settings where it has not been conducted and follow-up studies are needed to capture the incidence of mental disorders and the impact of treatment. However, the research must also focus on implementation and dissemination of strategies to decrease the current gap in mental health treatment.

Even in resource-rich settings where service delivery systems (medical care, substance abuse treatment and the care of other psychiatric illnesses) exist, they are often structured to work separately for different disorders (historically due to different funding streams), and efforts to navigate multiple systems often fail. Integrated HIV mental health care remains the exception [241], and comprehensive regional HIV mental health service agencies are rare. Patients may not themselves recognize the role that mental health problems are playing in their health [242]. As a result, HIV/AIDS medical service providers may be unable to integrate HIV/AIDS, mental health and substance abuse treatment services

adequately, even through existing referral networks, let alone to diagnose and treat mental health disorders [243]. Disentangling psychiatric, substance-related and other co-morbidities requires careful differential diagnosis and awareness that the presence of some disorders precludes making other diagnoses. In LMICs where resources to treat mental disorders are usually scarce, efforts are required to provide funding for training and supervision using stepped-care and task shifting within a model of mental health integration within primary (HIV) care.

There are important, basic principles that guide treating mental health problems in HIV illness based on the available epidemiology of mental disorders and HIV illness [10]. These principles include taking into account multiple co-morbidities and knowing how to prioritize their treatment; ruling out a new medical cause for any change in mental status (HIV-related or not); starting with lower doses of psychotropic medication and slowly titrating them upward; checking for drug interactions and overlapping toxicities between psychotropics, antiretrovirals, and any other medications being taken (*Psychiatric Medications and HIV Antiretrovirals: A Guide to Interactions for Clinician*s http://www.nynjaetc.org), including non-prescribed substances; and offering adherence support to patients whose cognitive or psychiatric symptoms interfere with taking regular medication.

We also can foster non-judgmental prevention (with a wide range of safer sex and drug use options according to the specific person's needs and lifestyle), educate HIV-infected patients about associated CNS problems, monitor psychiatric sequelae, adherence and quality of life issues (e.g. pain, sleep and sexual functioning), and assist in managing the psychosocial impact of the disease on infected people and their relatives.

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