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Preface

The HIV/AIDS epidemic, now in its fourth decade, remains a major public health challenge. Major strides were made in the first two decades in terms of describing the neurologic effects of the virus, and the importance of combining antiretroviral agents in achieving adequate clinical outcomes. Substantial efforts in recent years have seen how the brain may be affected early in infection, how the blood brain barrier may restrict treatment effects, and how co-occurring substance abuse, depression and other mental disorders may impact on functional impairment.

This book represents an attempt to draw together current knowledge from a truly global set of experts on how HIV affects the brain and mind. These authors set about explaining mechanisms of neuro- and psychopathology, its manifestations and its treatment. The impact of HIV is not limited to neurocognitive effects: comorbid psychiatric disorders add complexity to the assessment and treatment of people living with HIV/AIDS. Our knowledge of these is only partial at this time.

In the absence of treatment, the characteristic brain effects of HIV follow the subcortical pattern of infection, with memory impairment, slowing and apathy. With the advent of antiretroviral therapy (ART), a different spectrum of neurocognitive deficits, including cortical problems, can be detected. Our knowledge of the effects of HIV on the brain has grown exponentially through neuroimaging, biomarker and cerebrospinal fluid (CSF) studies. Despite these advances, many individuals with HIV-associated brain disease remain impaired, with evidence of ongoing or persistent disease. We therefore have included commentaries providing up-to-date insights into these issues.

The psychiatric disorders associated with HIV arise from the varying combinations of the biologic effects of HIV on the brain, underlying host genetic vulnerability factors, treatment effects and the psycho-social environment. Indeed, people living with HIV (PLWH) may face several unique psycho-social stresses, including the stigma of living with HIV, bereavement and multiple medical comorbidity. We have invited the contributors to include information on how psychiatric disorders may co-occur with neurologic manifestations of HIV. Particularly, we wanted to illustrate how frequently these disorders exist in PLWH; how they may arise in the context of untreated and treated HIV infection; and how different groups, including men who have sex with men, women and children, may be uniquely impacted.

The neurocognitive and psychiatric manifestations of HIV infection share many common features throughout the world. But there are also differences. These
include the viral sub-types, which may impart unique neurovirulence; but also patterns of substance misuse, rates of coinfection and gender distribution. The impact of social factors, including resource limitations and access to ART remain key issues. We have sought to present a global view of HIV/AIDS and psychiatry, whilst including specific references to regional influences.

In attempting to lay out these problems, we have used the format of Wiley’s *Evidence and Experience* series, published in collaboration with the World Psychiatric Association. There are five sections, which link developmentally with each other. These section authors have provided comprehensive state-of-the art reviews on the epidemiology, aetiology, clinical features and treatment of psychiatric disorders in HIV. The final section provides a key exposition of special groups of individuals affected by HIV, such as women and children, and men who have sex with men. Each section is then followed by a series of shorter commentaries. The commentators provide perspectives and fresh insights from additional angles.

We are grateful to the authors of both the review chapters and commentaries for their work, and to Joan Marsh and Wiley for encouraging this volume.

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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].
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 than 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 ranging 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