Depressive Disorders in HIV/AIDS: A Clinically Focused Narrative Review

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Abstract: Depressive disorders and human immunodeficiency virus/acquired immunodeficiency syndrome (HIV/AIDS) are associated with major socioeconomic burdens. The negative impact of depressive disorders on HIV/AIDS is well known, including on treatment outcomes. Unfortunately, depressive disorders are underdiagnosed and undertreated in seropositive persons. This review summarizes clinically useful information on depressive disorders in HIV/AIDS. More specifically, we address assessment, differential diagnosis, contributing factors, management, and common challenges in the treatment of depressive disorders in seropositive individuals. Assessment and diagnosis of depression may be challenging in seropositive persons because of several biopsychosocial particularities associated with HIV/AIDS. One of the difficulties is the overlap between depression and HIV/AIDS symptoms, particularly in individuals with advanced AIDS, requiring consideration of a broad differential diagnosis. Several factors related to HIV/AIDS status contribute to the higher rates of depressive disorders, including infectious-immunological, psychosocial, and exogenous factors. The treatment of depressive disorders in HIV/AIDS involves three groups of interventions: (1) pharmacological interventions, (2) psychotherapeutic interventions, and (3) management of other contributing factors. Challenges in management include poor adherence to treatment and the risk of suicide. We provide evidence-based recommendations to improve assessment and management of depressive disorders in seropositive persons.

Keywords: AIDS, consultation-liaison psychiatry, depression, HIV, psychosomatic medicine

Depressive disorders and human immunodeficiency virus/acquired immunodeficiency syndrome (HIV/AIDS) are associated with major socioeconomic burden. Globally, depressive disorders are a leading cause of disability,[1(p 1817, Table 1)] while HIV/AIDS ranks eleventh.[2] Depressive disorders are a group of disorders characterized by the presence of sad, empty, or irritable mood, accompanied by somatic and cognitive changes that significantly affect the individual's capacity to function. Included in this context are conditions such as major depressive disorder (MDD), substance/medication-induced depressive disorder, and depressive disorder due to another medical condition.[3] The main depressive disorder in terms of prevalence and burden is MDD, with approximately 300 million individuals affected worldwide.[4] Previous evidence suggests that persons with HIV/AIDS have a significantly greater risk of developing depressive disorders than the general population, including a two- to four-fold higher risk of developing MDD.[5–9] MDD is also the most common psychiatric condition in individuals with HIV/AIDS,[10] with an estimated prevalence ranging from 20 to 42%.[5,8,11–13]

The negative impact of depressive disorders on HIV/AIDS is well known. For example, MDD is associated with poorer compliance to anti-retroviral therapy (ART),[14,15] higher rates of detectable viral load,[16] lower CD4 counts,[17] poorer functionality, and lower quality of life.[16,18,19] Depressive disorders have also been associated with greater mortality.[20,21] For example, Sudfeld and colleagues[20] found that 36% of the deaths in Tanzanian women with HIV over the course of two years were attributable to depression.

Depressive disorders are underdiagnosed and undertreated in individuals with HIV/AIDS.[22] Proper detection and management of depressive disorders improves HIV/AIDS outcomes, leading to better compliance to ART, higher CD4 counts, and increased rates of undetectable viral load.[14,23–27] Therefore, a practical review addressing clinically relevant aspects of depressive disorders in HIV/AIDS is timely.

Despite vast and good-quality research on depression in HIV/AIDS, clinician-friendly, updated reviews of the scientific literature are much needed. In spite of their strengths, the majority of literature reviews on this subject tend to focus on particular aspects of depression in HIV/AIDS such as adherence to ART[25,28,29] or HIV/AIDS progression,[17,30] or on specific

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types of treatment for depression.[7,31,32] The objective of this literature review is to provide an updated, practical, and global overview of depressive disorders in HIV/AIDS.

More specifically, we will address the following questions:

(1) How should clinicians assess and diagnose depressive disorders in HIV/AIDS?
(2) What are the factors contributing to the development of depressive disorders in HIV/AIDS?
(3) How should clinicians manage depressive disorders in HIV/AIDS?
(4) What are common challenges in the treatment of depressive disorders in HIV/AIDS, and how should clinicians approach these?

METHODOLOGICAL STRATEGY

We manually reviewed articles from May 1983 (when the virus that caused AIDS was discovered) to September 2019. We used the electronic databases Google Scholar, MEDLINE/PubMed, Embase, and Cochrane Database, and reviewed articles regardless of language. We also included manuscripts cited as references in the articles obtained in the initial search. The search terms used were as follows: human immunodeficiency virus, acquired immunodeficiency syndrome, HIV, or AIDS, *and* depression, depressive, major depressive disorder, or antidepressants.

This review included manuscripts that addressed depressive disorders in patients with HIV or AIDS. We prioritized articles that were useful for clinical practice (i.e., understanding of contributing factors, assessment, diagnosis, clinical management, challenges in treatment, and therapeutic decision making). In addition, this review preferably selected articles with high levels of evidence (systematic reviews, meta-analyses, and original reports with longitudinal data or large samples), and recent reports (particularly in the last 15 years).

HOW SHOULD CLINICIANS ASSESS AND DIAGNOSE DEPRESSIVE DISORDERS IN HIV/AIDS?

Depressive disorders are vastly underdiagnosed in HIV/AIDS,[22,26,33] primarily because of the lack of assessment by providers.[26] Although screening questionnaires have relatively modest evidence in this population,[33] they might optimize and facilitate the recognition of depression in HIV/AIDS in clinical settings. American and European guidelines recommend depression screening, ideally annually.[34,35] The nine-item Patient Health Questionnaire (PHQ-9) and Kessler-10 are short, easy to administer, widely used instruments that have been validated in HIV/AIDS.[9,36–38] There are also successful reports of depression screening in HIV/AIDS using the two-item Patient Health Questionnaire (PHQ-2), which assesses depressed mood and anhedonia, and can be followed by full PHQ-9 in positive cases.[39] Careful consideration of differential diagnosis assures that patients receive the most effective treatment for their neuropsychiatric conditions.

Assessment and Diagnosis

The assessment and diagnosis of mood disturbances may be challenging in seropositive persons because of several biopsychosocial particularities associated with HIV/AIDS.[9,11,33] One of the difficulties is the overlap between depression and HIV/AIDS symptoms,[9,11,33] including decreased energy, fatigue, insomnia, reduced appetite, and psychomotor slowing.[11,14,40,41] Appropriately excluding other diagnoses assures that the most appropriate treatment is delivered to patients with depressive symptoms.

Differential Diagnosis of Depression in Patients with HIV/AIDS

Major depressive disorder Rates of MDD are hard to estimate in patients with HIV/AIDS for the reasons outlined above, but the prevalence is thought to be greater than in the general population.[5–9] According to the *Diagnostic and Statistical Manual of Mental Disorders*, fifth edition (DSM-5), the same diagnostic criteria for MDD in someone without HIV infection should be used in a seropositive person.[3] Nonetheless, some clinicians utilize alternative diagnostic criteria for MDD, especially in patients with significant somatic complaints or advanced HIV/AIDS. For example, Endicott substitute criteria replace the DSM criteria for changes in weight or appetite, sleep abnormalities, fatigue/impaired energy, and psychomotor changes, with additional psychological/cognitive symptoms such as tearfulness, social withdrawal, pessimism, and lack of mood reactivity.[42] Other clinicians prefer to use the Hospital Anxiety and Depression Scale, which was developed for medically ill patients and does not assess somatic complaints. Some of the most specific symptoms for MDD are anhedonia and diurnal mood variation.[43]

Depressive disorder due to another medical condition This diagnosis can be made when there is a clear clinical and laboratorial association between the mood disturbance and the presence of another medical condition.[3] The diagnosis requires only the presence of depressed mood or anhedonia, without other neurovegetative symptoms. Pertinent depression-related medical conditions that may be more common in HIV/AIDS include hypothyroidism, seizures, central nervous system (CNS) lymphoma, opportunistic infections, other malignancies, and neurosyphilis.[11,44] Low testosterone, which is common in HIV+ men, may also cause depressive symptoms. In older individuals, post-stroke depression should be considered.[44] Though it remains a subject of debate whether HIV infection alone can be pathophysiologically responsible for the development of depression, in general, if a patient had no history of depression prior to being diagnosed with HIV/AIDS, a diagnosis of depressive disorder due to HIV/AIDS should be considered.

Substance/medication-induced depressive disorders These disorders occur in the setting of the use of a substance that is etiologically associated with depressive symptoms.[3] In contrast

to MDD, the individual needs only to have depressed mood or anhedonia as symptoms to be diagnosed with substance/medication-induced depressive disorder.[3] The depressive symptoms usually disappear about one month after the end of use or withdrawal.[3,45] Frequent causes of substance-induced depressive disorder in HIV/AIDS are withdrawal ("crashing") from cocaine and methamphetamine, as well as chronic use of alcohol and opioids.

ADJUSTMENT DISORDER Adjustment disorder is an abnormal response to a stressor, characterized by marked distress or functional impairment.[3,46] The available research suggests that approximately one-third of the individuals with HIV/AIDS experience adjustment disorder at some point in the illness course.[46] Commonly, adjustment disorders occur at the time of the initial diagnosis, with patients developing symptoms as a result of learning of their status. Adjustment disorders may also occur in the setting of worsening medical symptoms or the development of complications of the virus. Adjustment disorders may manifest with depressive symptoms, anxiety, or conduct disturbances.[3] A diagnosis of adjustment disorder can be based on less severe and shorter-lasting symptoms than are required for MDD, though the symptoms must begin within three months of a stressor and persist less than six months from relief of the stressor.[3,47,48] If a patient meets criteria for MDD or depressive disorder due to a general medical condition, adjustment disorder is not diagnosed. Treatment of adjustment disorder primarily relies on psychotherapeutic interventions with supportive, cognitive-behavioral, or psychodynamic foundations.[48] Sometimes antidepressants may be used; however, the evidence in adjustment disorder is modest.[48]

DEMORALIZATION Demoralization is described "as a psychological state characterized by helplessness, hopelessness, a sense of failure and the inability to cope" or a state of psychological impotence in which the individual feels that his problems have no solution.[49] A chronic medical illness such as HIV/AIDS is a common precipitant for the development of demoralization, and available research suggests that 20% of seropositive individuals experience demoralization.[50] Several studies suggest that demoralization is a clinically distinct entity from MDD and from adjustment disorder.[49,51] Unlike depressed persons, demoralized individuals usually have reactive affect and tend not to present depressive core symptoms such as anhedonia and poor concentration.[51] Specifically, patients with demoralization in the setting of chronic illness will often express a desire to engage in activities that previously gave them pleasure, but also a frustration with the fact that physical limitations prevent them from doing so. Demoralization presents in a way that is qualitatively similar to adjustment disorder but often less severe.[49,51] Further research in demoralization is needed to fully establish it as a distinct entity and to facilitate its inclusion as a codable diagnosis in diagnostic manuals. Demoralization responds primarily to psychotherapeutic interventions focused on encouragement, validation, understanding, and enhanced engagement.[51] In the case of demoralization secondary to a chronic illness, education about the illness is also a key component of treatment, to allow patients a sense of ownership of the illness and awareness of its likely course.

BIPOLAR DISORDER The rates of unipolar depression are much higher than those of bipolar disorder in HIV/AIDS, but the rate of bipolar disorder may be higher in HIV+ individuals than in the general population. Estimates of the rate of bipolar disorder in HIV+ persons range from 2.6% to 9.1%.[52] Bipolar disorder may also increase the likelihood of contracting HIV as a result of the impulsivity, increased libido, and increased goal-directed activity that can accompany episodes of hypomania or mania.[53,54] Clinicians should always assess patients for bipolar disorder; the treatment differs substantially from that for unipolar depression.[55,56] Antidepressants may switch bipolar patients to hypomania/mania and cause more mood lability, particularly in individuals with a family history of bipolar disorder or suicide, with early onset of depression, or with psychotic features.[55,56]

PERSONALITY DISORDERS The rates of personality disorders, particularly Cluster B personality disorders such as borderline personality disorder and histrionic personality disorder, are higher in patients with HIV and AIDS than in the general population.[14,57] Patients with some personality disorders may be at increased risk for contracting the virus because of characteristics such as impulsivity, recklessness, and a disregard for one's own well-being[14,57,58] Patients with borderline personality disorder, in particular, may be prone to episodes of low mood or characterologic dysphoria, which may mimic depressive symptoms.[59] Distinguishing such episodes from depression is important, as the former may be less likely to respond to antidepressants and may require interventions such as dialectical behavior therapy instead.[59,60] Borderline personality disorder, when compared to depression, tends to be associated with more pronounced emotional instability, to have preserved mood reactiveness, and to present with more impulsivity.[61]

HIV-ASSOCIATED NEUROCOGNITIVE DISORDERS (HAND) HAND are a spectrum of disorders, characterized by cognitive impairment, that arise as a result of the virus invading the CNS and producing neuronal injury.[62] They include asymptomatic neurocognitive impairment, mild neurocognitive disorder, and HIV-associated dementia. Patients with mild neurocognitive disorder may experience decreased concentration, fatigue, anhedonia, and depressed mood, and their symptoms overlap significantly with MDD. In the era of antiretroviral therapy, HIV-associated dementia is less common than previously,[63] though depressive symptoms often accompany the severe cognitive impairment. For this reason, conducting a thorough cognitive exam in HIV+ individuals with depressive symptoms is important in order to rule out HAND as a

contributor. Patients with HAND will most commonly demonstrate deficits in processing speed and executive functioning; bedside tests such as Trails A-B, Luria sequencing and clock draw are most likely to reveal deficits. Though patients with MDD can also exhibit executive dysfunction, any signs of movement disorders or visuospatial deficits, and any more severe and persistent cognitive deficits should raise suspicion for HAND.

Table 1 presents information on the differential diagnosis of depressive symptoms in HIV/AIDS, including in relation to MDD.

WHAT ARE THE FACTORS CONTRIBUTING TO THE DEVELOPMENT OF DEPRESSIVE DISORDERS IN HIV/AIDS?

Several factors related to HIV/AIDS status contribute to the higher rates of depressive disorders in seropositive individuals than in the general population. These factors may be divided into three groups: (1) infectious-immunological factors, (2) psychosocial factors, and (3) exogenous factors (see Figure 1). Infectious-immunological factors include biological abnormalities that result either from direct damage caused by the HIV virus or from increased inflammatory response to the HIV virus. Psychosocial factors encompass impaired human interactions and subjective experiences that are frequent in the setting of HIV/AIDS. Finally, exogenous factors include medications and addictive substances that may be used by seropositive persons.

Infectious-Immunological Factors

HIV/AIDS is associated with infectious-immunological changes that predispose seropositive individuals to depressive disorders. The infectious-immunological changes include direct brain damage by the virus as well as an abnormally prolonged immunological response to the virus. The virus has a strong tropism for the CNS and reaches it early in the disease course.[81] The viral proteins gp120 and Tat have neurotoxic properties, especially toward CNS dopaminergic pathways.[81,82] These dopaminergic abnormalities may predispose seropositive individuals to depressive symptoms.[81,82]

The intensity of inflammatory responses over the course of HIV/AIDS fluctuates, varying from intense activation in the infection's early phases to immune deficiency in later phases.[83,84] In the initial phases of the disease, there is a pathological activation of immune system that is reactive to the HIV virus both systemically and in the CNS.[11,81,83,84] As a result, proinflammatory cytokines such as IL-1, IL-6, interferon γ and tumor necrosis factor alpha (TNF-α) are released, and several neurobiological changes occur that predispose the individual to mood disturbance. These changes include increased oxidative stress, decreased availability of serotonin in the CNS, and impaired brain-derived neurotrophic factor (BDNF) action. BDNF is an important molecule for neurogenesis and cell survival, and decreased BDNF expression has been linked to depressive symptoms.[14,74,81]

This exacerbated inflammatory response is, in the vast majority of the cases, unable to control the virus.[83,84] Consequently, HIV is able to replicate and to destroy important components of the immune system, leading to significantly reduced inflammatory response.[83,84] AIDS, the most advanced phase of HIV infection, is characterized by a deficient immune response, and it develops, on average, 10–15 years after initial HIV infection.[85] Therefore, in later phases of HIV/AIDS, inflammation seems to have a secondary role in the development of depressive symptoms.

The prolonged inflammation is also closely related to hypogonadism in men. The exacerbated immune response is linked to reduced testicular steroidogenesis, gonadal autoimmune damage, and decreased luteinizing hormone production, resulting in lower levels of testosterone.[86] Low testosterone is common in HIV/AIDS and has been linked to depressive symptoms, including low energy, anhedonia, decreased libido, and depressed mood.[86,87]

Psychosocial Factors

Psychosocial factors contributing to the development of depressive disorders in HIV/AIDS include chronic life stressors, stigma, and social isolation. Both depressive disorders and HIV/AIDS are more frequent in persons with significant life stressors, including those from low socioeconomic backgrounds, underserved minority groups, and men who have sex with men (MSM).[9,88,89] Common chronic life stressors in individuals with depression or HIV/AIDS are homelessness, poverty, marginalization, unemployment, poor access to health care, exposure to crime and violence, and reduced self-efficacy.[9,89,90] Some evidence also suggests that even among vulnerable groups, depressive disorders and HIV/AIDS disproportionately affect those with increased rates of stressors.[89] For example, African Americans with low socioeconomic status have a higher prevalence of MDD than African Americans of higher socioeconomic status,[89,91] possibly due to greater exposure to violence and decreased access to health care.[92]

Stigma is a significant psychosocial factor that is associated with depressive disorders in HIV/AIDS.[93] Approximately 80% of HIV+ individuals report experiencing some type of stigma related to HIV/AIDS status.[94] Stigma may be experienced in three different ways: (1) *enacted stigma*, where seropositive persons experience overt stigmatizing behavior, (2) *anticipated stigma*, where these individuals are concerned about being victim of stigma in the future, and (3) *internalized stigma*, where these individuals have negative beliefs and self-image because of their HIV/AIDS status.[67] All three types of stigma seem to be distressing. Data obtained from seropositive MSM, however, suggest that anticipated stigma seems to be the most significant stigma-related risk factor for MDD[68] and possibly also for other depressive disorders.

Shame and guilt are commonly seen as two subconstructs of internalized stigma that may have an important impact on health outcomes in persons living with HIV/AIDS.[79] Shame is a distressing, self-conscious emotion wherein the individual

Table 1

Differential Diagnosis for Depressive Symptoms In HIV/AIDS, and How They Differ from MDD, the Most Studied Depressive Disorder

Condition	Main characteristics	Differences from MDD
Depressive disorder due to another medical condition	Etiologically related to another medical condition[3] Temporal relationship between comorbidity and depression[3] Hypothyroidism and malignancies are common causes[11,44] More common in patients with advanced AIDS	More neurocognitive symptoms than MDD Lower response rates to antidepressants than MDD Weaker family history of MDD Need to treat underlying medical disorder
Substance/ medication-induced depressive disorders	Etiologically related to a licit or illicit substance[3] Common in stimulant withdrawal (cocaine, methamphetamine) Common in chronic use of depressants (opioids, alcohol) Efavirenz and interferon may cause them[64,65]	Resolve about 1 month after end of withdrawal/ intoxication[3,45] Lower response rates to antidepressants than MDD[45] Higher proportion of males than MDD Need to address substance use
Bipolar disorder	Depressive and manic/hypomanic episodes[3,66] Strong genetic component[67,68] Impulsive behavior increases risk of acquiring HIV/AIDS [69,70] Pharmacotherapy is key to reduce morbidity and suicide	Presence of hypomanic/manic episodes[3,66] Antidepressants may worsen clinical presentation[67,68] Stronger family history of bipolar disorder than MDD[67,68]
Personality disorders	Persistently dysfunctional emotional and behavioral pattern[71] Pronounced deviation from cultural norms[3] Divided into 3 clusters; Cluster B frequently mimics MDD[3] Benefit more from psychotherapeutic interventions[71]	Depressive symptoms in PDs are usually reactive to stressors[72] PDs have pronounced affective fluctuations over time[64,71,72] In PDs, there is a pronounced instability in self-perception[3] Persistent sadness in PDs has limited response to medications
HIV-associated neurocognitive disorders	Include neurocognitive disorders of different severities[65] Direct result of the virus invading the CNS[65] Characterized by cognitive impairment and mood shifts[65] More common in persons with CD4 lower than 200/mm[65,73]	More pervasive neurocognitive deficits in HAND Overt confusion is more frequent in HAND Apathy, rather than depressive mood, is common in HAND HAND have poor response to antidepressants
Adjustment disorder	Exacerbated response to a life stressor[3,74] Starts within 3 months of a stressor[3] Resolves no longer than 6 months after the end of the stressor[3] May occur secondary to HIV/AIDS diagnosis	Less severe depressive symptoms than MDD[3,75,76] Always occurs as a response to a stressor[3,74] Primarily treated with psychotherapy[75]
Demoralization	Normal reaction to life stressors[77,78] Psychological state of disempowerment and impotence[79,80] Common after diagnosis of serious illness such as HIV/AIDS Frequent existential distress[79,80]	Always occurs as a response to a stressor[78] Primarily treated with psychotherapy Less anhedonia and less concentration impairment than MDD[78] Affect reactiveness is often present[78]

CNS, central nervous system; HAND, HIV-associated neurocognitive disorders; MDD, major depressive disorder; PD, personality disorder.

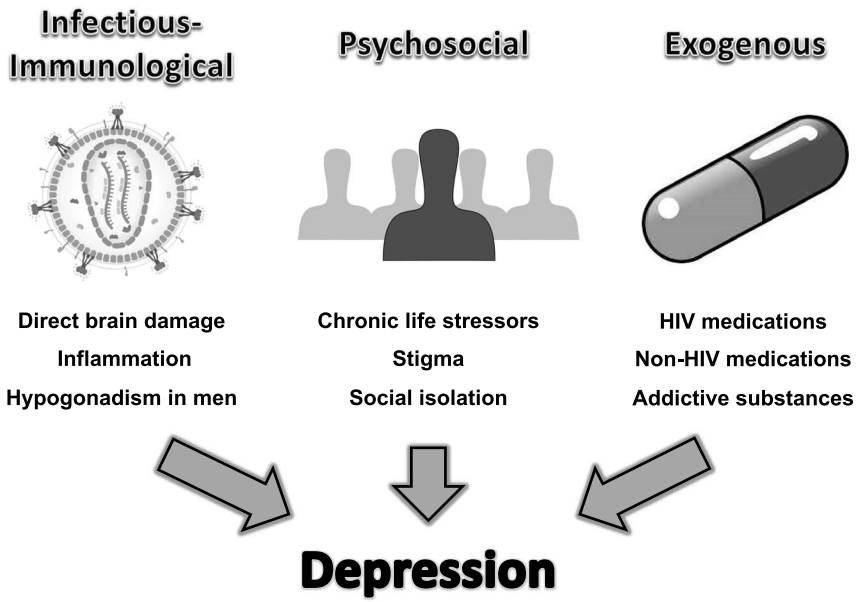

Figure 1. Main factors that contribute to the development of depressive disorders in individuals with HIV/AIDS.

sees himself as defective and a failure;[79] by contrast, guilt is a feeling of deserving blame for past actions or behaviors. Shame is strongly associated with avoidance of care for HIV/AIDS, poor health-related outcomes, HIV/AIDS progression, and depressive symptoms, and is a frequent cause of nondisclosure.[75,79]

Social isolation is another common psychological concern in individuals with HIV/AIDS.[93] A multinational survey of 2035 individuals with HIV found that 37% of participants reported loneliness and social isolation resulting from their HIV status.[94] Social isolation is even more pronounced in older adults with HIV/AIDS (45% of patients in the United States with HIV are over 50 years old),[66,93] and it represents a risk factor for mood disturbances in all seropositive persons.[10] Social support may act as a protective factor against depressive disorders in HIV/AIDS by buffering chronic and multiple life stressors.[69,93,94] There is also a negative correlation between social support and perceived stigma, where seropositive persons with increased concern about discrimination may avoid socialization because of their fear of rejection.[69]

Patients with HIV/AIDS also struggle with existential issues that may affect their mood. Seropositive patients often feel that they do not have control over their own lives and that they failed to make meaningful contributions during their lives, and they may have a heightened perception of their mortality.[70] Survivor's guilt is also common, particularly among individuals who acquired the illness in the beginning of the epidemic, many of whom witnessed the deaths of friends and loved ones.[95] All of these existential concerns have been shown to be correlated with increased rates of depression.[96]

Exogenous Factors

Exogenous factors that may potentially contribute to the development or worsening of depressive disorders include anti-retroviral therapy, other medications, and addictive substances.

Among ART agents, efavirenz has been most commonly implicated in contributing to depressive symptoms.[71] Though there are conflicting studies, some evidence suggests that the rates of severe depressive symptoms are approximately 2.5 higher in people taking efavirenz than in controls.[64] Moreover, the recently developed integrase inhibitors (such as dolutegravir, elvitegravir, and raltegravir) have also been linked to higher rates of depressive symptoms.[72] Interferon is a non-ART medication that is more commonly prescribed to individuals with HIV/AIDS, particularly in developing countries. This medication, used to treat hepatitis C, has been known to exacerbate fatigue, irritability, and low mood.[65] In the United States, interferon has largely been replaced by newer and more specific medications (direct-acting antiviral medications) that have not been associated with depressive symptoms.[73]

Addictive substances may also contribute to the development or worsening of depressive disorders. Estimates suggest that up to half of individuals with HIV/AIDS have a comorbid substance use disorder.[76] The current prevalence of clinically relevant depressive symptoms in persons with HIV/AIDS and substance use disorder is close to 70%.[77] A cohort of 10,652 HIV+ individuals in the United States found that the most common substance-specific use disorders were cannabis (31%), alcohol (19%), methamphetamine (13%), cocaine (11%), and opioids (4%). One-fifth of the subjects met criteria for multiple substance use disorders.[76]

HOW SHOULD CLINICIANS MANAGE DEPRESSIVE DISORDERS IN HIV/AIDS?

Depressive disorders are not only underrecognized in HIV/AIDS but, when diagnosed, are often not treated or properly managed.[22,33] For example, only 18% of seropositive individuals with MDD receive treatment, and just 7% have access

to adequate therapeutic interventions.[22] The treatment of depressive disorders in HIV/AIDS consists of three groups of interventions: (1) management of contributing factors (previously described in Figure 1), (2) pharmacological interventions, and (3) psychotherapeutic interventions. A summary of the treatment for depressive disorders is displayed in Figure 2.

Management of Contributing Factors

One of the most important interventions in addressing depression in seropositive patients is to ensure proper care of HIV/AIDS. Poor infectious-immunological status predisposes individuals to HIV-associated fatigue, neurological damage, opportunistic infections, hypogonadism, and other factors that may worsen depressive symptoms. In depressive disorders secondary to other causes such as substance/medications or medical conditions, co-treatment of the underlying cause of mood changes is the most important intervention. Psychoeducation is another low-cost intervention that may reduce stigma and improve adherence to treatment. Psychoeducational interventions may be delivered in group settings, by lay health workers, or online.

Pharmacological Interventions

Clinicians should be particularly aware of the potential for higher rates of side effects with neuropsychiatric medications in individuals with HIV/AIDS.[21] Gastrointestinal complaints (e.g., nausea and diarrhea), weight gain, metabolic issues, extrapyramidal symptoms, and falls are all more common in HIV/AIDS patients.[21,78] In order to minimize side effects, it is important to start with low doses and increase slowly, maintaining awareness of drug-drug interactions that may increase medication levels.

Antidepressants are helpful in managing depressive disorders in HIV/AIDS, particularly in treating MDD. They shorten the time to recovery and reduce the negative impact of MDD in seropositive individuals.[11] Substance/medication-induced depressive disorder and depressive disorder due to another medical condition may be less likely to fully respond to antidepressants alone, though many patients do report improvement in symptoms.[45]

No one group of antidepressants has been demonstrated as superior to others.[7] Selective serotonin reuptake inhibitors (SSRIs) are the most studied antidepressants in HIV/AIDS and have no known negative impact on the immune system.[80] Because of their better side-effect profiles and fewer drug-drug interactions, sertraline, citalopram, and escitalopram are preferred over other SSRIs.[97,98] Tricyclic antidepressants have also been widely studied and are effective, though attention must be paid to side effects. Some evidence suggests that nortriptyline and protriptyline may be good choices in this

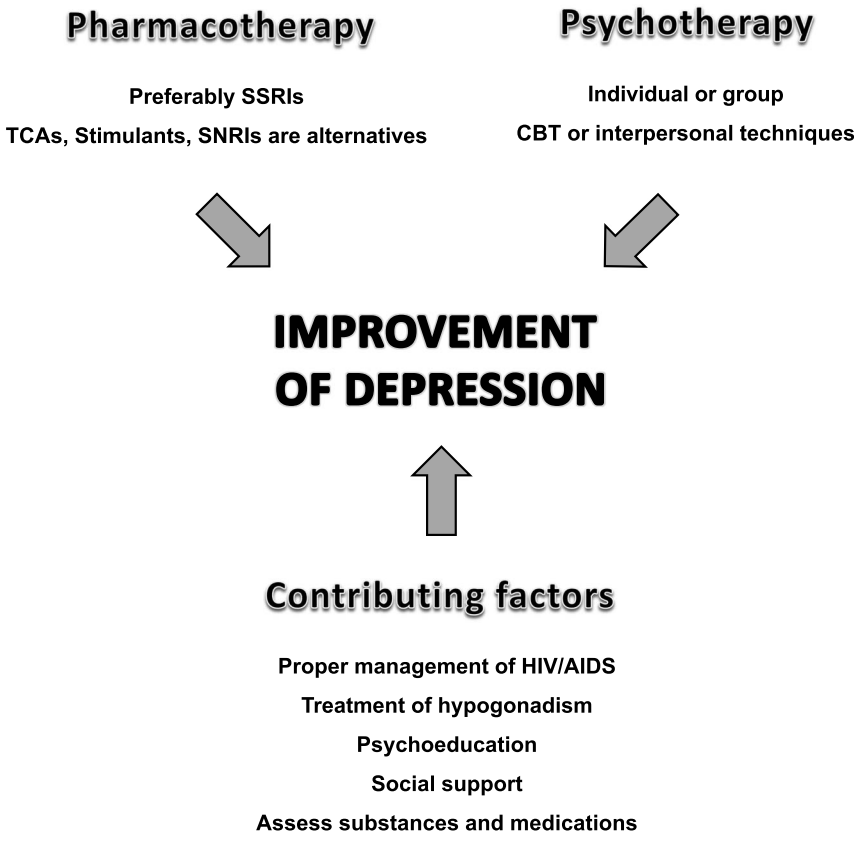

Figure 2. Summary of the treatment of depressive disorders in individuals with HIV/AIDS. CBT, cognitive-behavioral therapy; SNRI, serotonin and noradrenalin reuptake inhibitor; SSRI, selective serotonin reuptake inhibitor; TCA, tricyclics antidepressant.

population.[26,99] Studies with serotonin-norepinephrine reuptake inhibitors such as venlafaxine and duloxetine are limited but suggest efficacy in this population. Given the high rates of neuropathic pain in HIV+ individuals,[100] these agents may be particularly useful.

Though bupropion may be useful for targeting low energy and amotivation in HIV+ persons, it should be used with caution due to the increased seizure risk in HIV.[101] For this reason, doses greater than 300 mg daily are typically not used.[102] Mirtazapine may help with sleep and appetite, but should be used cautiously because of the increased risk of weight gain, as HIV+ persons are already predisposed to metabolic problems.[44,103] Stimulants such as methylphenidate, lisdexamphetamine, and modafinil may be used for cognitive slowing and fatigue associated with MDD, and have specific evidence for improving depressive symptoms in patients with HIV.[11,80,104] Nonetheless, caution is needed with modafinil specifically, given that it is metabolized by CYP 3A4 and may potentially interact with protease inhibitors and other antiretroviral medications.[105]

With respect to augmentation strategies, atypical antipsychotics have been used for depression, but care should again be given to the potential for weight gain and metabolic side effects, as well as the increased risk for extrapyramidal symptoms due to the virus's effects on the basal ganglia.[63,80] Aripiprazole may be a relatively safer option in these regards, though patients on an anti-retroviral therapy regimen that includes cobicistat may need special attention, as levels of aripiprazole can be increased in this setting.[106]

Sleep may be a particularly challenging issue to treat in depressed patients with HIV/AIDS. Cognitive-behavioral therapy for insomnia is the standard of treatment according to the American Academy of Sleep Medicine Clinical Practice Guideline.[107] With respect to pharmacological treatment, melatonin has the potential to suppress the immune system and should therefore be used with caution, though no studies have suggested worsened outcomes in terms of the virus.[108] Despite some relatively mild drug-drug interactions,[80] trazodone is a possible choice for the initial treatment of insomnia.[109] Benzodiazepines may be relatively contraindicated in the setting of a comorbid substance use disorder because of the increased risk of misuse and the potential risk of overdose if benzodiazepines are taken with opioids.[110] Non-benzodiazepine hypnotics are often used with good effect, though prescribers should generally start with lower doses, given the higher rates of side effects such as dizziness, coordination problems, and falls, along with the potential for interaction with protease inhibitors.[78]

Text Box 1 highlights some centrally important considerations to keep in mind when prescribing antidepressants in AIDS/HIV.

Text Box 1
Top Ten Facts About the Use of Antidepressant Medications in HIV/AIDS

1. Patients have higher rates of side effects than the general population, particularly nausea, diarrhea, and dry mouth.[21] Start low doses and increase slowly.
2. SSRIs are the most studied class of antidepressants. They are overall well tolerated and effective.[99–101]
3. Fluoxetine, paroxetine, and fluvoxamine may increase levels of protease inhibitors. Sertraline, citalopram, and escitalopram are the preferred SSRIs.[100,101]
4. TCAs are as effective as SSRIs.[7] Due to the side-effect profile, however, they are generally second- or third-line treatments.
5. SSRIs and TCAs do not have a known impact on the immune system.[99] Very limited data are available for other antidepressants.
6. Studies with SNRIs are limited but suggest that SNRIs are well tolerated and effective. They may also help with neuropathic pain.[103]
7. Use bupropion with caution. It may lower seizure threshold and has potential interactions with protease inhibitors and efavirenz.[105,111]
8. Be careful about using medications that can cause weight gain and metabolic effects, as HIV+ patients are more prone to these side effects.[112]
9. Protease inhibitors may increase levels of fluoxetine, TCAs, and venlafaxine. Ritonavir, which is used to increase levels of some protease inhibitors, inhibits CYP3A4 and can increase trazodone and TCA levels.
10. HIV+ persons have had higher rates of dropout in clinical trials and of nonadherence in clinical practice than the general population.

Psychotherapeutic Interventions

Several studies observed that individual and group psychotherapy is associated with a greater reduction in depression scores (particularly in MDD), improvement of immune status, and reduction of viral load when compared to waitlist or supportive interventions in depressed seropositive individuals.[7,113] The individual or group psychotherapeutic programs are typically based on cognitive-behavioral and interpersonal techniques, including cognitive restructuring, behavioral activation and modification, emotional awareness, assertiveness training, stress management, and encouragement of socialization.[7,113] For patients with comorbid personality disorders or traits, dialectical behavior therapy may also be particularly useful in enhancing coping mechanisms. Some limitations of the current evidence on psychotherapy for depressive disorders in HIV/AIDS are the limited direct comparisons between individual and group psychotherapy and the lack of longer-term follow-up after the end of the intervention, which limits the evidence regarding the sustainability of the improvements.[7,113]

WHAT ARE COMMON CHALLENGES IN TREATING DEPRESSIVE DISORDERS IN HIV/AIDS, AND HOW SHOULD CLINICIANS APPROACH THESE?

Poor adherence to treatment is common and particularly problematic, and may manifest as lack of adherence to medication, missed appointments, and behavioral changes. Additionally, the combination of depression and HIV/AIDS has been strongly linked to suicide.[114,115] Finally, there are particularities related to depression in seropositive children (≤19 years old) and older individuals (≥65 years old) that should be taken into account.

Poor Adherence to Treatment

A robust scientific literature shows that depressive disorders, particularly MDD, in HIV/AIDS are associated with poor adherence to ART.[25,28,29,112,116] In addition, a dose-response relationship is present between severity of depression and nonadherence rates (i.e., severely depressed seropositive individuals are less adherent than those with mild or moderate depression).[112,116] Stigma has also shown an association with avoidance of care and poorer compliance.[117,118] Patients may fear being associated with marginalized populations such as those with substance use disorders and MSM.[118] In addition, some patients might avoid taking medications because doing so triggers painful thoughts and emotions related to shame, self-hatred, and social rejection.

Some interventions may increase adherence to treatment. Prescribing a once-daily regimen of antidepressant at the same time that patients take their ART and other medications can facilitate adherence. Collaborative or co-located models of care using psychiatrists in the same clinic where seropositive individuals receive HIV/AIDS care also seems to facilitate treatment entry and retention.[22] Moreover, adherence is increased by using interactive reminder devices (such as texting), by having case managers contact seropositive individuals who miss appointments or do not fill their prescriptions, and by using trained peer navigators or peer support.[119] Finally, psychosocial interventions to help patients adapt and adjust to life with HIV/AIDS might reduce stigma and improve adherence.[117]

Suicide

Suicide is a major concern when dealing with depressive disorders in HIV/AIDS. The rates of suicide in seropositive individuals are 8 to 10 times higher than in the general population,[115] and depression is the strongest risk factor for suicidality in HIV/AIDS.[114] Though suicide rates have decreased since the introduction of highly active ART in 1996, the risk remains high.[114] Keiser and colleagues[114] evaluated a large Swiss cohort of 15,275 persons with HIV/AIDS and found that 81% of those who died by suicide in the era of highly active ART era had depression. The risk of suicide is higher in the first year after the diagnosis and in advanced phases of the disease.[120,121] Reduced functionality due to HIV/AIDS, multiple contacts with health services, substance use, living single, and low socioeconomic status have also been described as risk factors for suicidality.[10,115,120,121]

Suicidal ideation should be regularly assessed in seropositive persons. Special attention should be given to newly diagnosed individuals and those with advanced and impairing HIV/AIDS. In these two situations, patients tend to have more contacts with health care services, which provides good opportunities to assess and intervene against suicide.[115] Treating the underlying depression, reducing access to lethal means, frequent in-person or phone follow-ups, psychoeducation, and motivational interviewing are possible effective interventions against suicide in HIV/AIDS.[122]

Depression in Seropositive Children and Elderly

When dealing with seropositive children and adolescents, clinicians should be aware of some common challenges. Isolation from peers and poor social support are common concerns in this population, and may lead to truancy and school dropout.[123] Depressed seropositive adolescents also have a higher risk of impulsive behaviors than non-depressed seropositive children—including substance use and risky sexual conduct, all of which increase the risk of transmission of HIV to others.[123] In addition, the relationship between seropositive children and their parents might be fraught in the setting of vertical transmission of HIV or parents who are significantly ill due to their own HIV/AIDS.[123] Dealing with dying or deceased parents may be another challenge. Though antidepressants might be helpful in treating depressed seropositive children, the evidence for psychosocial interventions is overall more robust, and such interventions should be offered, in a noncoercive manner, to all children and adolescents with HIV/AIDS.[124] Community-based groups, such as local AIDS support organizations, may provide helpful psychosocial support.

Depressive disorders in older seropositive individuals may also present unique treatment challenges. First, depressed older adults are more prone to have cognitive problems.[125] Difficulties with executive functioning, memory, and attention may negatively affect compliance to medication and to treatment in general. Second, older patients tend to have more medical comorbidities and to be on polypharmacy. These factors, in combination with poorer drug metabolism, further increase the risk of side effects with neuropsychiatric medication.[125] Third, grief and losses, such as the death of a loved one, are common and may be important contributing factors to the mood disturbance. Older individuals may also be more likely to manifest survivor's guilt as a result of having lived through the early days of the epidemic.

Text Box 2 presents some "clinical pearls" for managing depressive disorders in HIV/AIDS.

LIMITATIONS

Our review should be interpreted in light of its limitations. Although we used several elements of a systematic review such as search strategies and inclusion criteria for the articles, this manuscript was fundamentally a narrative review. Therefore,

Text Box 2
Clinical Pearls on Depressive Disorders in HIV/AIDS

- Never consider depression a normal occurrence in patients with HIV/AIDS. It should be always treated.
- Collaborative care and co-located models are effective in improving access and other outcomes.[22]
- Assess and screen for depression and suicide frequently. Consider the systematic use of validated instruments.[89–93]
- One of the difficulties is the overlap between depression and HIV/AIDS symptoms.[74,82–84] Some of the most specific symptoms for depression are anhedonia and diurnal mood variation.[69]
- Poor compliance to treatment is a common challenge.[11] Monitor adherence to visits and medication refills. Sending reminders and contacting individuals who miss appointments improve treatment adherence.
- Frequent in-person or telephone follow-ups may help in monitoring depressive symptoms, medication side effects, and suicidality.[119]
- One of the most important interventions in addressing depression is to make sure that the patient is receiving proper care for HIV/AIDS.
- Always assess medications and substances that may contribute to depression, such as efavirenz, methamphetamine, cocaine, alcohol, and opioids.[57–63,81]
- Consider depression caused by other medical illnesses such as hypothyroidism, seizures, opportunistic infections, malignancies, and neurosyphilis.[11,17]
- Stigma and shame may negatively affect treatment,[50] and the clinician should approach these issues.
- Groups utilizing cognitive-behavioral techniques, psychoeducation, discussion of stigma, and support seem to be efficacious and cost-effective.[7,117]

some degree of bias may be present in the selection of the articles, and some important reports might have been missed. In addition, this review did not include calculation of quantitative data, such as a meta-analytical component. Finally, this review included studies with somewhat diverse recruitment criteria, distinct instruments to measure depression severity, and samples in different stages of HIV/AIDS. Because of the summary nature of a review, these differences might not be fully described.

CONCLUSIONS

Depressive disorders are common in HIV/AIDS, and MDD is the most frequent psychiatric disorder in seropositive individuals. Despite its negative impact on several HIV/AIDS outcomes, depression is still widely underdiagnosed and undertreated. To better understand and treat depressive disorders, it is important to have a comprehensive view of infectious-immunological, psychosocial, and exogenous factors. Evidence-based recommendations are available for improving the assessment and management of depression in seropositive persons (see summary in Text Box 2), and they should be implemented in real-life practice to improve outcomes.

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REFERENCES

1. James SL, Abate D, Abate KH, et al. Global, regional, and national incidence, prevalence, and years lived with disability for 354 diseases and injuries for 195 countries and territories, 1990–2017: a systematic analysis for the Global Burden of Disease Study 2017. Lancet 2018;392:1789–858.
2. World Health Organization. Global health estimates 2016: 20 leading causes of DALY globally, 2016 and 2000. https://www.who.int/healthinfo/global_burden_disease/GHE2016_DALY_Global_2000_2016_.xls
3. American Psychiatric Association. Diagnostic and statistical manual of mental disorders. 5th ed. Arlington, VA: American Psychiatric Publishing, 2013.
4. World Health Organization. Depression and other common mental disorders: global health estimates. Geneva: WHO, 2017. https://apps.who.int/iris/bitstream/handle/10665/254610/WHO-MSD-MER-2017.2-eng.pdf
5. Bing EG, Burnam MA, Longshore D, et al. Psychiatric disorders and drug use among human immunodeficiency virus-infected adults in the United States. Arch Gen Psychiatry 2001;58:721–8.
6. Nacher M, Adriouch L, Godard Sebillotte C, et al. Predictive factors and incidence of anxiety and depression in a cohort of HIV-positive patients in French Guiana. AIDS Care 2010; 22:1086–92.
7. Olatunji BO, Mimiaga MJ, O'Cleirigh C, Safren SA. Review of treatment studies of depression in HIV. Top HIV Med 2006;14: 112–24.
8. Ciesla JA, Roberts JE. Meta-analysis of the relationship between HIV infection and risk for depressive disorders. Am J Psychiatry 2001;158:725–30.
9. Simoni JM, Safren SA, Manhart LE, et al. Challenges in addressing depression in HIV research: assessment, cultural context, and methods. AIDS Behav 2011;15:376–88.
10. Rabkin JG. HIV and depression: 2008 review and update. Curr HIV/AIDS Rep 2008;5:163–71.
11. Nanni MG, Caruso R, Mitchell AJ, Meggiolaro E, Grassi L. Depression in HIV infected patients: a review. Curr Psychiatry Rep 2015;17:530.
12. Valente SM. Depression and HIV disease. J Assoc Nurses AIDS Care 2003;14:41–51.
13. Patel P, Rose CE, Collins PY, et al. Noncommunicable diseases among HIV-infected persons in low-income and middle-income countries: a systematic review and meta-analysis. AIDS 2018;32 suppl 1:S5–20.
14. Watkins CC, Treisman GJ. Neuropsychiatric complications of aging with HIV. J Neurovirol 2012;18:277–90.
15. Shubber Z, Mills EJ, Nachega JB, et al. Patient-reported barriers to adherence to antiretroviral therapy: a systematic review and meta-analysis. PLoS Med 2016;13:e1002183.

16. Sumari-de Boer IM, Sprangers MA, Prins JM, Nieuwkerk PT. HIV stigma and depressive symptoms are related to adherence and virological response to antiretroviral treatment among immigrant and indigenous HIV infected patients. AIDS Behav 2012;16:1681–9.
17. Leserman J. Role of depression, stress, and trauma in HIV disease progression. Psychosom Med 2008;70:539–45.
18. Carrico AW, Bangsberg DR, Weiser SD, Chartier M, Dilworth SE, Riley ED. Psychiatric correlates of HAART utilization and viral load among HIV-positive impoverished persons. AIDS 2011; 25:1113–8.
19. Miners A, Phillips A, Kreif N, et al. Health-related quality-of-life of people with HIV in the era of combination antiretroviral treatment: a cross-sectional comparison with the general population. Lancet HIV 2014;1:e32–40.
20. Sudfeld CR, Kaaya S, Gunaratna NS, et al. Depression at antiretroviral therapy initiation and clinical outcomes among a cohort of Tanzanian women living with HIV. AIDS 2017; 31:263–71.
21. UNAIDS Programme Coordinating Board. Thematic segment: mental health and HIV/AIDS—promoting human rights, an integrated and person-centred approach to improving ART adherence, well-being and quality of life: country submissions. Geneva: UNAIDS, 2018. https://www.unaids.org/sites/default/files/media_asset/20181128_UNAIDS_PCB43_CRP2.pdf
22. Pence BW, O'Donnell JK, Gaynes BN. Falling through the cracks: the gaps between depression prevalence, diagnosis, treatment, and response in HIV care. AIDS 2012;26:656–8.
23. Psaros C, Geller PA, Aaron E. The importance of identifying and treating depression in HIV infected, pregnant women: a review. J Psychosom Obstet Gynaecol 2009;30:275–81.
24. Schuster R, Bornovalova M, Hunt E. The influence of depression on the progression of HIV: direct and indirect effects. Behav Modif 2012;36:123–45.
25. Nakimuli-Mpungu E, Bass JK, Alexandre P, et al. Depression, alcohol use and adherence to antiretroviral therapy in sub-Saharan Africa: a systematic review. AIDS Behav 2012; 16:2101–18.
26. Arseniou S, Arvaniti A, Samakouri M. HIV infection and depression. Psychiatry Clin Neurosci 2014;68:96–109.
27. Mills JC, Harman JS, Cook RL, et al. Comparative effectiveness of dual vs. single-action antidepressants on HIV clinical outcomes in HIV-infected people with depression. AIDS 2017; 31:2515–24.
28. Gonzalez JS, Batchelder AW, Psaros C, Safren SA. Depression and HIV/AIDS treatment nonadherence: a review and meta-analysis. J Acquir Immune Defic Syndr 2011;58:181–7.
29. Uthman OA, Magidson JF, Safren SA, Nachega JB. Depression and adherence to antiretroviral therapy in low-, middle- and high-income countries: a systematic review and meta-analysis. Curr HIV/AIDS Rep 2014;11:291–307.
30. Mayston R, Kinyanda E, Chishinga N, Prince M, Patel V. Mental disorder and the outcome of HIV/AIDS in low-income and middle-income countries: a systematic review. AIDS 2012; 26 suppl 2:S117–35.
31. Himelhoch S, Medoff DR, Oyeniyi G. Efficacy of group psychotherapy to reduce depressive symptoms among HIV-infected individuals: a systematic review and meta-analysis. AIDS Patient Care STDS 2007;21:732–9.
32. Himelhoch S, Medoff DR. Efficacy of antidepressant medication among HIV-positive individuals with depression: a systematic review and meta-analysis. AIDS Patient Care STDS 2005;19:813–22.
33. Tsai AC. Reliability and validity of depression assessment among persons with HIV in sub-Saharan Africa: systematic review and meta-analysis. J Acquir Immune Defic Syndr 2014;66:503–11.
34. American Psychiatric Association. Practice guideline for the treatment of patients with major depressive disorder. 3rd ed. Washington, DC: APA, 2010. https://psychiatryonline.org/pb/assets/raw/sitewide/practice_guidelines/guidelines/mdd.pdf
35. European AIDS Clinical Society. Guidelines, version 7.1. 2014. https://www.eacsociety.org/files/guidelines-7.1-english.pdf
36. Akena D, Joska J, Obuku EA, Amos T, Musisi S, Stein DJ. Comparing the accuracy of brief versus long depression screening instruments which have been validated in low and middle income countries: a systematic review. BMC Psychiatry 2012; 12:187.
37. Cholera R, Gaynes BN, Pence BW, et al. Validity of the Patient Health Questionnaire–9 to screen for depression in a high-HIV burden primary healthcare clinic in Johannesburg, South Africa. J Affect Disord 2014;167:160–6.
38. Spies G, Kader K, Kidd M, et al. Validity of the K-10 in detecting DSM-IV–defined depression and anxiety disorders among HIV-infected individuals. AIDS Care 2009;21:1163–8.
39. Abas M, Nyamayaro P, Bere T, et al. Feasibility and acceptability of a task-shifted intervention to enhance adherence to HIV medication and improve depression in people living with HIV in Zimbabwe, a low income country in sub-Saharan Africa. AIDS Behav 2018;22:86–101.
40. Capuron L, Pagnoni G, Demetrashvili MF, et al. Basal ganglia hypermetabolism and symptoms of fatigue during interferon-alpha therapy. Neuropsychopharmacology 2007;32:2384–92.
41. Kalichman SC, Rompa D, Cage M. Distinguishing between overlapping somatic symptoms of depression and HIV disease in people living with HIV-AIDS. J Nerv Ment Dis 2000;188:662–70.
42. Endicott J. Measurement of depression in patients with cancer. Cancer 1984;53:2243–8.
43. Dube B, Benton T, Cruess DG, Evans DL. Neuropsychiatric manifestations of HIV infection and AIDS. J Psychiatry Neurosci 2005;30:237–46.
44. Rodriguez-Penney AT, Iudicello JE, Riggs PK, et al. Co-morbidities in persons infected with HIV: increased burden with older age and negative effects on health-related quality of life. AIDS Patient Care STDS 2013;27:5–16.
45. Torrens M, Gilchrist G, Domingo-Salvany A; psyCoBarcelona Group. Psychiatric comorbidity in illicit drug users: substance-induced versus independent disorders. Drug Alcohol Depend 2011;113:147–56.
46. Owe-Larsson B, Sall L, Salamon E, Allgulander C. HIV infection and psychiatric illness. Afr J Psychiatry (Johannesbg) 2009; 12:115–28.
47. Fernandez A, Mendive JM, Salvador-Carulla L, et al. Adjustment disorders in primary care: prevalence, recognition and use of services. Br J Psychiatry 2012;201:137–42.
48. Bachem R, Casey P. Adjustment disorder: a diagnosis whose time has come. J Affect Disord 2018;227:243–53.
49. Tecuta L, Tomba E, Grandi S, Fava GA. Demoralization: a systematic review on its clinical characterization. Psychol Med 2015;45:673–91.
50. Treisman G, Angelino A. Interrelation between psychiatric disorders and the prevention and treatment of HIV infection. Clin Infect Dis 2007;45:S313–7.
51. Jacobsen JC, Maytal G, Stern TA. Demoralization in medical practice. Prim Care Companion J Clin Psychiatry 2007; 9:139–43.
52. Moore DJ, Posada C, Parikh M, et al. HIV-infected individuals with co-occurring bipolar disorder evidence poor antiretroviral and psychiatric medication adherence. AIDS Behav 2012; 16:2257–66.
53. de Sousa Gurgel W, da Silva Carneiro AH, Barreto Reboucas D, et al. Prevalence of bipolar disorder in a HIV-infected outpatient population. AIDS Care 2013;25:1499–503.

54. Blank MB, Himelhoch S, Walkup J, Eisenberg MM. Treatment considerations for HIV-infected individuals with severe mental illness. Curr HIV/AIDS Rep 2013;10:371–9.
55. Bowden CL. A different depression: clinical distinctions between bipolar and unipolar depression. J Affect Disord 2005; 84:117–25.
56. Forty L, Smith D, Jones L, et al. Clinical differences between bipolar and unipolar depression. Br J Psychiatry 2008;192:388–9.
57. Lopes M, Olfson M, Rabkin J, et al. Gender, HIV status, and psychiatric disorders: results from the National Epidemiologic Survey on Alcohol and Related Conditions. J Clin Psychiatry 2012;73:384–91.
58. Harned MS, Pantalone DW, Ward-Ciesielski EF, Lynch TR, Linehan MM. The prevalence and correlates of sexual risk behaviors and sexually transmitted infections in outpatients with borderline personality disorder. J Nerv Ment Dis 2011; 199:832–8.
59. Lieb K, Zanarini MC, Schmahl C, Linehan MM, Bohus M. Borderline personality disorder. Lancet 2004;364:453–61.
60. Wagner EE, Miller AL, Greene LI, Winiarski MG. Dialectical behavior therapy for substance abusers adapted for persons living with HIV/AIDS with substance use diagnoses and borderline personality disorder. Cogn Behav Pract 2004;11:202–12.
61. Goodman M, New AS, Triebwasser J, Collins KA, Siever L. Phenotype, endophenotype, and genotype comparisons between borderline personality disorder and major depressive disorder. J Pers Disord 2010;24:38–59.
62. Saylor D, Dickens AM, Sacktor N, et al. HIV-associated neurocognitive disorder—pathogenesis and prospects for treatment. Nat Rev Neurol 2016;12:234.
63. Watkins CC, Treisman GJ. Cognitive impairment in patients with AIDS—prevalence and severity. HIV AIDS (Auckl) 2015; 7:35–47.
64. Poupard M, Ngom Gueye NF, Thiam D, et al. Quality of life and depression among HIV-infected patients receiving efavirenz- or protease inhibitor-based therapy in Senegal. HIV Med 2007;8:92–5.
65. Udina M, Castellvi P, Moreno-Espana J, et al. Interferon-induced depression in chronic hepatitis C: a systematic review and meta-analysis. J Clin Psychiatry 2012;73:1128–38.
66. International Association of Providers of Aids Care. Fact sheet categories. 2020. http://aidsinfonet.org/categories/
67. Earnshaw VA, Chaudoir SR. From conceptualizing to measuring HIV stigma: a review of HIV stigma mechanism measures. AIDS Behav 2009;13:1160–77.
68. Hatzenbuehler ML, Nolen-Hoeksema S, Erickson SJ. Minority stress predictors of HIV risk behavior, substance use, and depressive symptoms: results from a prospective study of bereaved gay men. Health Psychol 2008;27:455–62.
69. Li L, Lee SJ, Thammawijaya P, Jiraphongsa C, Rotheram-Borus MJ. Stigma, social support, and depression among people living with HIV in Thailand. AIDS Care 2009;21:1007–13.
70. Grassi L, Mezzich JE, Nanni MG, Riba MB, Sabato S, Caruso R. A person-centred approach in medicine to reduce the psychosocial and existential burden of chronic and life-threatening medical illness. Int Rev Psychiatry 2017;29:377–88.
71. Gaida R, Truter I, Grobler C, Kotze T, Godman B. A review of trials investigating efavirenz-induced neuropsychiatric side effects and the implications. Expert Rev Anti Infect Ther 2016; 14:377–88.
72. Treisman GJ, Soudry O. Neuropsychiatric effects of HIV antiviral medications. Drug Saf 2016;39:945–57.
73. Sundberg I, Lannergård A, Ramklint M, Cunningham JL. Direct-acting antiviral treatment in real world patients with hepatitis C not associated with psychiatric side effects: a prospective observational study. BMC Psychiatry 2018;18:157.
74. Deeks SG. HIV infection, inflammation, immunosenescence, and aging. Annu Rev Med 2011;62:141–55.
75. Paxton S. The paradox of public HIV disclosure. AIDS Care 2002;14:559–67.
76. Hartzler B, Dombrowski JC, Crane HM, et al. Prevalence and predictors of substance use disorders among HIV care enrollees in the United States. AIDS Behav 2017;21:1138–48.
77. Berger-Greenstein JA, Cuevas CA, Brady SM, Trezza G, Richardson MA, Keane TM. Major depression in patients with HIV/AIDS and substance abuse. AIDS Patient Care STDS 2007;21:942–55.
78. Omonuwa TS, Goforth HW, Preud'homme X, Krystal AD. The pharmacologic management of insomnia in patients with HIV. J Clin Sleep Med 2009;5:251–62.
79. Bennett DS, Traub K, Mace L, Juarascio A, O'Hayer CV. Shame among people living with HIV: a literature review. AIDS Care 2016;28:87–91.
80. Hill L, Lee KC. Pharmacotherapy considerations in patients with HIV and psychiatric disorders: focus on antidepressants and antipsychotics. Ann Pharmacother 2013;47:75–89.
81. Del Guerra FB, Fonseca JL, Figueiredo VM, Ziff EB, Konkiewitz EC. Human immunodeficiency virus-associated depression: contributions of immuno-inflammatory, monoaminergic, neurodegenerative, and neurotrophic pathways. J Neurovirol 2013;19:314–27.
82. Moran LM, Booze RM, Webb KM, Mactutus CF. Neurobehavioral alterations in HIV-1 transgenic rats: evidence for dopaminergic dysfunction. Exp Neurol 2013;239:139–47.
83. McMichael AJ, Borrow P, Tomaras GD, Goonetilleke N, Haynes BF. The immune response during acute HIV-1 infection: clues for vaccine development. Nat Rev Immunol 2010;10:11–23.
84. Migueles SA, Connors M. Success and failure of the cellular immune response against HIV-1. Nat Immunol 2015;16:563–70.
85. World Health Organization. HIV/AIDS. November 2017. https://www.who.int/features/qa/71/en/
86. Wong N, Levy M, Stephenson I. Hypogonadism in the HIV-infected man. Curr Treat Options Infect Dis 2017;9:104–16.
87. Zarrouf FA, Artz S, Griffith J, Sirbu C, Kommor M. Testosterone and depression: systematic review and meta-analysis. J Psychiatr Pract 2009;15:289–305.
88. Leserman J. The effects of stressful life events, coping, and cortisol on HIV infection. CNS Spectr 2003;8:25–30.
89. Pellowski JA, Kalichman SC, Matthews KA, Adler N. A pandemic of the poor: social disadvantage and the U.S. HIV epidemic. Am Psychol 2013;68:197–209.
90. Williams EC, Joo YS, Lipira L, Glass JE. Psychosocial stressors and alcohol use, severity, and treatment receipt across human immunodeficiency virus (HIV) status in a nationally representative sample of US residents. Subst Abus 2017;38:269–77.
91. Hudson DL, Neighbors HW, Geronimus AT, Jackson JS. The relationship between socioeconomic position and depression among a US nationally representative sample of African Americans. Soc Psychiatry Psychiatr Epidemiol 2012;47:373–81.
92. Chen J, Vargas-Bustamante A, Mortensen K, Ortega AN. Racial and ethnic disparities in health care access and utilization under the Affordable Care Act. Med Care 2016;54:140.
93. Grov C, Golub SA, Parsons JT, Brennan M, Karpiak SE. Loneliness and HIV-related stigma explain depression among older HIV-positive adults. AIDS Care 2010;22:630–9.
94. Nachega JB, Morroni C, Zuniga JM, et al. HIV-related stigma, isolation, discrimination, and serostatus disclosure: a global survey of 2035 HIV-infected adults. J Int Assoc Physicians AIDS Care (Chic) 2012;11:172–8.
95. Brashers DE, Neidig JL, Cardillo LW, Dobbs LK, Russell JA, Haas SM. 'In an important way, I did die': uncertainty and revival in persons living with HIV or AIDS. AIDS Care 1999;11:201–19.

96. O'Connor LE, Berry JW, Weiss J, Gilbert P. Guilt, fear, submission, and empathy in depression. J Affect Disord 2002;71:19–27.
97. Thompson A, Silverman B, Dzeng L, Treisman G. Psychotropic medications and HIV. Clin Infect Dis 2006;42:1305–10.
98. Freudenreich O, Goforth HW, Cozza KL, et al. Psychiatric treatment of persons with HIV/AIDS: an HIV-psychiatry consensus survey of current practices. Psychosomatics 2010; 51:480–8.
99. Eshun-Wilson I, Siegfried N, Akena DH, Stein DJ, Obuku EA, Joska JA. Antidepressants for depression in adults with HIV infection. Cochrane Database Syst Rev 2018;1:CD008525.
100. Ellis RJ, Toperoff W, Vaida F, et al. Smoked medicinal cannabis for neuropathic pain in HIV: a randomized, crossover clinical trial. Neuropsychopharmacology 2009;34:672–80.
101. Watkins CC, Pieper AA, Treisman GJ. Safety considerations in drug treatment of depression in HIV-positive patients: an updated review. Drug Saf 2011;34:623–39.
102. Annamalai A. Neurologic system: seizures. In: Medical management of psychotropic side effects. Cham, Switzerland: Springer, 2017:263–9.
103. Worm SW, Friis-Moller N, Bruyand M, et al. High prevalence of the metabolic syndrome in HIV-infected patients: impact of different definitions of the metabolic syndrome. AIDS 2010; 24:427–35.
104. Hinkin CH, Castellon SA, Hardy DJ, Farinpour R, Newton T, Singer E. Methylphenidate improves HIV-1-associated cognitive slowing. J Neuropsychiatry Clin Neurosci 2001;13:248–54.
105. Rowland A, van Dyk M, Warncken D, Mangoni AA, Sorich MJ, Rowland A. Evaluation of modafinil as a perpetrator of metabolic drug-drug interactions using a model informed cocktail reaction phenotyping trial protocol. Br J Clin Pharmacol 2018;84:501–9.
106. Shah BM, Schafer JJ, Priano J, Squires KE. Cobicistat: a new boost for the treatment of human immunodeficiency virus infection. Pharmacotherapy 2013;33:1107–16.
107. Sateia MJ, Buysse DJ, Krystal AD, Neubauer DN, Heald JL. Clinical practice guideline for the pharmacologic treatment of chronic insomnia in adults: an American Academy of Sleep Medicine clinical practice guideline. J Clin Sleep Med 2017; 13:307–49.
108. Nunnari G, Nigro L, Palermo F, Leto D, Pomerantz RJ, Cacopardo B. Reduction of serum melatonin levels in HIV-1–infected individuals' parallel disease progression: correlation with serum interleukin-12 levels. Infection 2003;31:379–82.
109. Yanofski J, Croarkin P. Choosing antidepressants for HIV and AIDS patients: insights on safety and side effects. Psychiatry (Edgmont) 2008;5:61–6.
110. Weisberg DF, Gordon KS, Barry DT, et al. Long-term prescription opioids and/or benzodiazepines and mortality among HIV-infected and uninfected patients. J Acquir Immune Defic Syndr (1999) 2015;69:223.
111. Barnhofer T, Chittka T. Cognitive reactivity mediates the relationship between neuroticism and depression. Behav Res Ther 2010;48:275–81.
112. Nel A, Kagee A. Common mental health problems and antiretroviral therapy adherence. AIDS Care 2011;23:1360–5.
113. Spies G, Asmal L, Seedat S. Cognitive-behavioural interventions for mood and anxiety disorders in HIV: a systematic review. J Affect Disord 2013;150:171–80.
114. Keiser O, Spoerri A, Brinkhof MW, et al. Suicide in HIV-infected individuals and the general population in Switzerland, 1988–2008. Am J Psychiatry 2010;167:143–50.
115. Jia CX, Mehlum L, Qin P. AIDS/HIV infection, comorbid psychiatric illness, and risk for subsequent suicide: a nationwide register linkage study. J Clin Psychiatry 2012;73:1315–21.
116. Vranceanu AM, Safren SA, Lu M, et al. The relationship of post-traumatic stress disorder and depression to antiretroviral medication adherence in persons with HIV. AIDS Patient Care STDS 2008;22:313–21.
117. Bhatti AB, Usman M, Kandi V. Current scenario of HIV/AIDS, treatment options, and major challenges with compliance to antiretroviral therapy. Cureus 2016;8:e515.
118. Onyebuchi-Iwudibia O, Brown A. HIV and depression in Eastern Nigeria: the role of HIV-related stigma. AIDS Care 2014;26:653–7.
119. Thompson MA, Mugavero MJ, Amico KR, et al. Guidelines for improving entry into and retention in care and antiretroviral adherence for persons with HIV: evidence-based recommendations from an International Association of Physicians in AIDS Care panel. Ann Intern Med 2012;156:817–33, W-284, W-5, W-6, W-7, W-8, W-9, W-90, W-91, W-92, W-93, W-94.
120. Gebremariam EH, Reta MM, Nasir Z, Amdie FZ. Prevalence and associated factors of suicidal ideation and attempt among people living with HIV/AIDS at Zewditu Memorial Hospital, Addis Ababa, Ethiopia: a cross-sectional study. Psychiatry J 2017;2017:2301524.
121. Carrico AW, Johnson MO, Morin SF, et al. Correlates of suicidal ideation among HIV-positive persons. AIDS 2007; 21:1199–203.
122. Mann JJ, Apter A, Bertolote J, et al. Suicide prevention strategies: a systematic review. JAMA 2005;294:2064–74.
123. Zhou E, Qiao Z, Cheng Y, et al. Factors associated with depression among HIV/AIDS children in China. Int J Ment Health Syst 2019;13:10.
124. World Health Organization. Pocket book of hospital care for children: guidelines for the management of common childhood illnesses. Geneva: WHO, 2013.
125. Taylor WD. Depression in the elderly. N Engl J Med 2014;371: 1228–36.