

# Prevalence, impact, and management of depression and anxiety in patients with HIV: a review

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**Abstract:** The prevalence of depression and anxiety in people living with HIV/AIDS (PLWHA) ranges from 7.2% to 71.9% and 4.5% to 82.3%, respectively. This wide variation is attributed to differences in sample size and characteristics, and methodology for assessment of anxiety and depression. Moreover, anxiety and depression increase the morbidity of HIV by poor adherence to treatment and various other significant mechanisms. Early identification and effective management of these disorders is associated with improved antiretroviral adherence and improved quality of life in PLWHA. Different treatment modalities, including pharmacological and nonpharmacological therapies, are used for the management of anxiety and depression in PLWHA. Benzodiazepines are indicated for short periods of time. Clonazepam and lorazepam are safe in terms of drug–drug interactions and may be preferred. Selective serotonin reuptake inhibitors are safer than tricyclic antidepressants. Though the different selective serotonin reuptake inhibitors are supposed to be equally effective, to avoid interactions with antiretrovirals, the better options are sertraline, citalopram, and escitalopram. Various nonpharmacological therapies, including cognitive behavior therapy, interpersonal therapy, supportive psychotherapy, cognitive–behavioral-oriented group psychotherapy, experiential group psychotherapy, cognitive–behavioral stress management, stress management interventions, cognitive remediation therapy, mindfulness-based therapy, and aerobic and resistance exercise have been reported to be useful in treating depression among PLWHA. However, definitive evidence to decide which nonpharmacological intervention is most beneficial for the management of anxiety and depression in PLWHA is still required.

**Keywords:** tricyclic antidepressants, benzodiazepines, SSRI, CBT, interpersonal therapy, mindfulness based therapy

## Introduction

The human immunodeficiency virus (HIV) is transmitted through sexual intercourse (unprotected anal or vaginal) and blood contamination, as well as during pregnancy, childbirth, and breastfeeding from the mother. The virus infects cells of the immune system, thereby weakening it, as a result of which the individual becomes more susceptible to various infections. The World Health Organization (WHO) states that the infection can advance to a final stage in 10–15 years (antiretroviral drugs can slow down the process even further), known as the acquired immunodeficiency syndrome (AIDS). The diagnosis of HIV infection in people  $\geq 18$  months is defined by WHO as:

positive HIV antibody testing, which is confirmed by a second HIV antibody test relying on different antigens or of different operating characteristics; and/or positive virological

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test for HIV or its components confirmed by a second virological test obtained from a separate determination.<sup>1,2</sup>

Once a person's HIV-positive status is confirmed, he or she has to make some life-changing decisions. First, they have to make the important decision about whether to inform their significant other of their HIV-positive status. Second, they have to decide about undergoing treatment and continuing it regularly. Finally, they have to decide about future sexual relations and whether they should have children. As a result of their decision, they may become isolated with reduced social support, may refuse treatment, or even develop psychiatric illnesses such as anxiety and depression.<sup>3</sup>

The most common neuropsychiatric disorder in people living with HIV/AIDS (PLWHA) is depression.<sup>4</sup> Similarly, the prevalence of an anxiety disorder in PLWHA is more common than in the general population.<sup>5</sup> Depression and anxiety are associated with an increase in morbidity and mortality in PLWHA and adversely affect the adherence to antiretroviral therapy (ART), quality of life (QoL), and health-related QoL.<sup>6-8</sup> Improvement in overall functioning of PLWHA and adherence to ART may follow effective treatment of depression and anxiety.<sup>9,10</sup>

A complex relationship exists between depression and HIV infection. Depression is both a risk factor and a consequence of HIV infection.<sup>11,12</sup> In PLWHA, contributory factors for depression include comorbidities, coping with the prospects of illness and death, neurobiological changes related to persistent central nervous system (CNS) infections due to HIV, social stigma, sexual dysfunction, and side effects of ART.<sup>13,14</sup> Depression can easily remain unrecognized and untreated in PLWHA.<sup>15</sup> A meta-analytic study concluded that the development of depression in PLWHA was not associated with the sexual orientation of patients or the disease stage of the HIV infection.<sup>16</sup> However, despite a large number of studies, clear answers are lacking in many areas relating to anxiety and depression in PLWHA. This review aims to summarize the recent literature and research related to the prevalence, impact, and management of comorbid depression and anxiety in PLWHA. Since there is more literature on depression in PLWHA, this review reflects that bias.

## Methodology

Literature was searched for any articles that related to HIV, depression, anxiety prevalence, impact and treatment during February and May 2015. A PubMed search strategy was used with the following paired phrases: "HIV Depression Anxiety", "HIV Depression Anxiety Prevalence", "HIV

Depression Anxiety Impact", and "HIV Depression Anxiety Treatment". A Google search was done with the search term "HIV Depression Anxiety, Prevalence, Impact and Treatment". Only full articles were downloaded and included for this review. During the PubMed search, using the term "HIV Depression Anxiety prevalence" returned 336 articles; similarly, "HIV Depression Anxiety impact" returned 140 articles and "HIV Depression Anxiety treatment" returned 482 articles. This initial search was done without any restrictions on the year of publication or the type of article. All publications containing information on any of the following endpoints in relation to HIV patients were shortlisted: depression, anxiety, prevalence, impact, and management (treatment), and abstracts of the articles were read to screen them. Thereafter, the full text of the selected articles were reviewed; recently published articles were preferred over older ones, and many cross-references were also checked and the articles found. Articles were excluded if they were not written in English, were related to child and adolescent population, or were of unrelated findings. Official documents from the WHO were also screened; in addition, some other articles were identified through Google and from the personal knowledge of the authors. In total, the findings of ~150 articles were reviewed.

## Results

### Incidence

There were very few results relating to studies estimating the incidence of depression or anxiety. A study that analyzed a sample of 2,737 PLWHA reported that the incidence of depression was 2.2 per 100 person years.<sup>17</sup> Another study reported an incidence of 1.89 per 100 person years for depression and 1.27 per 100 person years for generalized anxiety.<sup>18</sup>

### Prevalence

In contrast to the few studies estimating the incidence, there were abundant studies estimating the prevalence of depression and anxiety. We scrutinized ~40 and 30 studies, respectively, for depression and anxiety prevalence. There was a wide range of differences on the prevalence across these studies, as summarized in Tables 1 and 2 for depression and anxiety, respectively. There was a problem regarding the use of different methodologies and different definitions. In a recent Nigerian study, depressive symptoms were present in at least 49% of PLWHA.<sup>19</sup> A psychiatric disorder was present in almost half of the 2,864 PLWHA, including 36%

**Table I** Prevalence rate of depression in patients with HIV

Location, reference	Scale used	Sample size	Depression prevalence, %	Associated findings
Nigeria, Sale and Gadanya <sup>25</sup>	HADS, ICD 10	162	39.9	Depression was associated with the stage of HIV illness, CD4 <sup>+</sup> count level, poverty, low social support, and inability to tolerate ART
People's Republic of China, Lu et al <sup>26</sup>	SRDS	102	67.65	Depression and anxiety were associated with low CD4 <sup>+</sup> T-lymphocyte counts
Kenya, Musisi and Kinyanda <sup>27</sup>	ICD 10	82	40.8	Other comorbid disorders included anxiety, somatization, seizures, mania, and HIV-associated progressive encephalopathy
Thailand, Nüesch et al <sup>28</sup>	HADS	251	7.2	ART improved mental health and QoL
Tanzania, Marwick and Kaaya <sup>29</sup>	CIS-R	220	15.5	During HIV care, co-morbid psychiatric disorders should be identified and managed
Jamaica, Clarke et al, (2010) <sup>30</sup>	PHQ-9	63	43	Age, gender, marital status, major stress, living conditions, ART, and CD4 <sup>+</sup> count were not associated with depression
India, Sivasubramanian et al <sup>31</sup>	M.I.N.I.; DSM-IV	150	29	Depression was associated with low self-esteem and low levels of social support
Albania, Morrison et al <sup>32</sup>	Semistructured interview	79	62.3	Depression was significantly associated with anxiety, greater number of barriers to care, and greater medical and social needs
USA, Bhatia et al <sup>33</sup>	CES-D	180	67	Multivariate analysis revealed the association of depression with female gender, low income, history of psychoactive substance abuse, and low access to medical care
Uganda, Kinyanda et al <sup>34</sup>	M.I.N.I.	618	8.1	Depression was associated with psychosocial impairment, adverse life events, PTSD, GAD, and past history of deliberate self-harm
India, Agarwal et al <sup>35</sup>	HADS	50	30	46% of PLWHA had low psychological well-being
South Africa, Pappin et al <sup>36</sup>	HADS	716	25.4	Depression was associated with stigma
Cameroon, L'akoa et al <sup>37</sup>	PHQ-9	100	63	Newly diagnosed HIV-infected patients had higher prevalence of depression, severe immunosuppression, and harmful use of alcohol associated with depression
People's Republic of China, Su et al <sup>38</sup>	BDI	258	71.9	Depression was associated with less income and high perceived stress
India, Talukdar et al <sup>39</sup>	BDI	175	56	Poor QoL was associated with depression and high neuroticism score
Nigeria, Olagunju et al <sup>40</sup>	SCID-NP	295	14.9	Compared to the general population, PLWHA suffer from more psychiatric disorders
South Korea, Song et al <sup>41</sup>	BDI	82	21	Depression was associated with poor adherence and anxiety. Comorbidities and unemployment were risk factors for depression.
People's Republic of China, Liu et al <sup>42</sup>	CES-D	320	66.3	Depression and anxiety in PLWHA could be reduced by high social support
India, Chauhan et al <sup>43</sup>	HADS	100	39	Asymptomatic PLWHA had significantly higher prevalence of alcohol dependence, adjustment disorder, and sexual dysfunction compared to control subjects
Israel, Levy et al <sup>44</sup>	PHQ-9	57	24	Neurocognitive disturbances and psychiatric illnesses were common in asymptomatic PLWHA, but were independent of the time of being positive, immunological status, viral load, or treatment received
South Africa, Nel and Kagee <sup>45</sup>	BDI II	101	40.4	ART adherence was significantly related to depressive symptoms on biserial correlations and logistic regression analysis

(Continued)

**Table 1** (Continued)

Location, reference	Scale used	Sample size	Depression prevalence, %	Associated findings
Romania, Largu et al <sup>46</sup>	BDI II	146	41 (moderate in 14%; mild in 27%)	PLWHA were afraid (of death, complications, other people's reaction to the diagnosis), confused (in terms of diagnosis, the mode of infection, the future), angry (against the source of infection, themselves, God), felt guilty and blamed themselves
Malawi, Kim et al <sup>47</sup>	CDRS-R	562	18.9	7.1% of PLWHA had suicidal ideation
Germany, Kittner et al <sup>48</sup>	HADS	80	30 (male) and 47 (female)	Guilt for the HIV infection was present in 36% of PLWHA
India, Bhatia and Munjal <sup>49</sup>	CES-D	160	58.7	Depression was associated with low family income, unemployment, low education, not married, migration, poor relationship with spouse, poor social support, and visiting commercial sex workers
People's Republic of China, Sun et al <sup>50</sup>	CES-D	772	73.1	Depression was associated with health status, perceived social support, job, and gender
People's Republic of China, Qiu et al <sup>51</sup>	PHQ-9	370	40.3	Depression was associated with employment status, sexual orientation, resident status, emergence of HIV-related symptoms, stress, and social support
Haitian females in USA, Glémaud et al <sup>52</sup>		96	49	12.5% of subjects gave a history of abuse; 34% of subjects had PTSD
Lowther et al <sup>53</sup>	Systematic review	66 original studies	33.60	Low- and middle-income countries had a higher prevalence of depression (41.36%) compared to high-income countries (25.81%)
Western Europe and Canada, Robertson et al <sup>5</sup>	HADS	2,863	15.7 (14.3% of male and 17.9% of female)	Depression occurred significantly more often in females compared to males
South Korea, Kee et al <sup>54</sup>	BDI	840	36	Both anxiety and depression were associated with persistent symptoms, alcohol and tobacco use, and marital status
Brazil, Nomoto et al <sup>55</sup>	BDI	59	61	Depression was significantly associated with low income, low social class, and poor QoL
Denmark, Slot et al <sup>56</sup>	BDI	212	35	Depression was associated with stress, poor health, dissatisfaction with life situation, ART nonadherence, and past history of alcohol abuse or psychiatric treatment

**Abbreviations:** AIDS, acquired immunodeficiency syndrome; ART, antiretroviral therapy; BDI, Beck Depression Inventory; CDRS-R, Children's Depression Rating Scale-Revised; CES-D, Center for Epidemiologic Studies Depression Scale; CIS-R, Clinical Interview Schedule-Revised; DSM, *Diagnostic and Statistical Manual of Mental Disorders*; GAD, generalized anxiety disorder; HADS, Hospital Anxiety and Depression Scale; HIV, human immunodeficiency virus; ICD, International Classification of Diseases; M.I.N.I., Mini International Neuropsychiatric Interview; PHQ-9, Patient Health Questionnaire; PLWHA, persons living with HIV/AIDS; PTSD, post-traumatic stress disorder; QoL, quality of life; SCID-NP, Structured Clinical Interview for DSM-IV non-patient; SRDS, Self-rating depression scale.

having depression and 16% with generalized anxiety disorder (GAD). Nearly 40% of subjects were using an illicit substance and 12% were drug dependent.<sup>4</sup> Prevalence of depression is found to be very high among PLWHA, as compared general population.<sup>20,21</sup> An early meta-analysis reported that the prevalence of depression in PLWHA was ~10% as against 5% in the general population.<sup>16</sup>

The prevalence of depression and anxiety among people with HIV infection was quite variable across different recent studies. The prevalence rate of depression in HIV patients in different studies varied from 7.2% to 71.9% (Table 1). The studies were from various countries and had varying sample sizes, different methodologies, and used different depression rating scales or questionnaires.

While treating PLWHA, comorbid anxiety is often missed and not treated. Anxiety is higher among PLWHA than in the general population. In studies conducted across the world, the prevalence of anxiety varied from 4.5% to 82.3% (Table 2). Newly diagnosed HIV patients who feel socially stigmatized or are under excessive stress because of their disease had a higher prevalence of anxiety.<sup>22</sup> The different prevalence rates of anxiety disorders may also depend upon the stage of the illness.<sup>23</sup> While unipolar depressive disorders are the most common mental disorder among PLWHA, the majority also suffered from comorbid psychiatric disorders, which most frequently included anxiety disorders, dysthymia, and substance use disorder.<sup>24</sup>

**Table 2** Prevalence of anxiety in patients with HIV

Location, reference	Scale	Sample size	Anxiety prevalence, %	Associated findings
People's Republic of China, Lu et al <sup>26</sup>	SRAS	102	43.13	Anxiety and depression were associated with low CD4 <sup>+</sup> T-lymphocyte counts
Kenya, Musisi and Kinyanda <sup>27</sup>	ICD 10 criteria	82	45.6	Other comorbid disorders included depression, somatization, seizures, mania, and HIV-associated progressive encephalopathy
Thailand, Nüesch et al <sup>28</sup>	HADS	251	16.3	ART improved mental health and QoL
Tanzania, Marwick and Kaaya <sup>29</sup>	CISR	220	4.5	During HIV care, comorbid psychiatric disorders should be identified and managed
India, Sivasubramanian et al <sup>31</sup>	M.I.N.I.; DSM-IV	150	24	Anxiety associated with low levels of social support
Albania, Morrison et al <sup>32</sup>	Semistructured interview	79	82.3	Anxiety significantly associated with depression, first-line ART, recent HIV diagnosis, and greater medical and social needs
Nigeria, Olagunju et al <sup>57</sup>	SCAN	4,000	21.7	Anxiety was associated with low family support, lack of employment, and being unmarried
Canada, Ivanova et al <sup>58</sup>	HADS (HADS-A $\geq 11$ )	361	37 had high anxiety	Anxiety was associated with stigma, ART, and worries about reproductive health
India, Agarwal et al <sup>35</sup>	HADS	50	54	46% of PLWHA had low psychological well-being
South Africa, Pappin et al <sup>36</sup>	HADS	716	30.6	Anxiety was associated with ART side effects, avoidant coping, and stigma
India, Chauhan et al <sup>43</sup>	HADS	100	19	Asymptomatic PLWHA had significantly higher prevalence of alcohol dependence, adjustment disorder, and sexual dysfunction compared to control subjects
Italy, Celesia et al <sup>59</sup>	SRAS	251	47	Anxiety was associated with a high number of ART switches
Nigeria, Olagunju et al <sup>40</sup>	SCID-NP	295	8.1	Compared to the general population, PLWHA suffer from more psychiatric disorders
USA, Parhami et al <sup>60</sup>	NA	7,834	16	53% of the patients had a psychiatric condition, including mood disorder (23%) and substance-related disorder (19%)
People's Republic of China, Liu et al <sup>42</sup>	SRAS	320	45.6	Depression and anxiety in PLWHA could be reduced by high social support
Israel, Levy <sup>44</sup>	STAI	57	18	Neurocognitive disturbances and psychiatric illnesses are common in asymptomatic PLWHA, independent of the time of being positive, immunological status, viral load, or treatment received
South Africa, Nel and Kagee <sup>45</sup>	BAI	101	28.7	–
Western Europe and Canada, Robertson et al <sup>5</sup>	HADS	2,863	33.3	No significant difference was found between those receiving combination ART and those not receiving it
Romania, Largu et al <sup>46</sup>	HAS	146	71 (54% mild, 14% severe, and 3% very severe anxiety)	PLWHA were afraid (of death, complications, other people's reaction to the diagnosis), confused (in terms of diagnosis, the mode of infection, the future), angry (against the source of infection, themselves, God), felt guilty and blamed themselves
Germany, Kittner et al <sup>48</sup>	HADS	80	40 (male) and 73 (female)	Guilt for the HIV infection was present in 36% of PLWHA
People's Republic of China, Sun et al <sup>50</sup>	SRAS	772	49	Anxiety was associated with health status, social support, alcohol consumption, and condom use at the last sexual contact
People's Republic of China, Qiu et al <sup>51</sup>	GAD-7	370	30.5	Anxiety associated with employment status, sexual orientation, resident status, emergence of HIV-related symptoms, and stress
Ethiopia, Belete et al <sup>22</sup>	BAI	436	22.2	Being female, perceived stigma, started ART, and divorced were significantly associated with anxiety
Haitian females in USA, Glémaud et al <sup>52</sup>	NA	96	43	12.5% of subjects gave a history of abuse; 34% of subjects had PTSD

(Continued)



**Table 2** (Continued)

Location, reference	Scale	Sample size	Anxiety prevalence, %	Associated findings
Lowther et al <sup>53</sup>	Systematic review	66 original studies	28.38	Low- and middle-income countries had a higher prevalence (33.92%) compared to high-income countries (25.53%)
South Korea, Kee et al <sup>54</sup>	STAI	840	32	Both anxiety and depression were associated with persistent symptoms, alcohol and tobacco use, and marital status

**Abbreviations:** AIDS, acquired immunodeficiency syndrome; ART, antiretroviral therapy; BAI, Beck Anxiety Inventory; CISR, Clinical Interview Schedule-Revised; DSM, *Diagnostic and Statistical Manual of Mental Disorders*; GAD-7, Generalized Anxiety Disorder Scale; HADS, Hospital Anxiety and Depression Scale; HAS, Hamilton Anxiety Scale; HIV, human immunodeficiency virus; ICD, International Classification of Diseases; M.I.N.I., Mini-International Neuropsychiatric Interview; PLWHA, persons living with HIV/AIDS; PTSD, post-traumatic stress disorder; QoL, quality of life; SCAN, Schedule for clinical assessment in neuropsychiatry; SCID-NP, Structured Clinical Interview for DSM-IV non-patient; SRAS, Zung Self-Rating Anxiety Scale; STAI, State-Trait Anxiety Inventory; NA, not available.

## Risk factors associated with depression among HIV patients

The occurrence and severity of depression in PLWHA are associated with various factors, which include problems in accepting that they have a deadly illness, HIV-related symptoms, substance use disorders, stigma, stress, disability, lower education, loss of job, lower socioeconomic status, disturbances in body image, social isolation, migration, death of family members, unmarried status, poor relationship with spouse, and frequenting commercial sex workers.<sup>4,30,49,55,61,62</sup> Logistic regression revealed that the predictors of depression in PLWHA include stress, dissatisfaction with life situation, poor health, belief that all aspects of life are affected by HIV infection, ART, nonadherence, past history of alcohol abuse, and past history of psychiatric treatment.<sup>56</sup>

### Stage of illness

There may be various stages of disease progression in the HIV infection and HIV/AIDS care continuum: diagnosis establishment, contact with HIV medical care, undergoing treatment, at the start of ART, and during adherence to ART.<sup>63</sup> Asymptomatic stage is less distressing, and a low prevalence may be attributable to this stage of HIV infections. A recent study on asymptomatic HIV patients found relatively low prevalence of only 6% and 7%, respectively, for depression and anxiety. This study also found significantly increased prevalence of adjustment disorder, alcohol dependence, and sexual dysfunction in asymptomatic PLWHA.<sup>43</sup> As the illness progresses further and CD4<sup>+</sup> cell count declines, the prevalence of depression increases.<sup>63,64</sup>

### Gender of the patients

There are various direct and indirect factors linked to the susceptibility of females in the transmission of HIV/AIDS. The problem is further compounded with females of developing countries having poor education, health, and

hygiene. In one study, female sex workers in Bangladesh reported their inability to convince their sexual partner to have safe sex.<sup>65</sup> The rates of depression in females in the general population as well as among HIV patients with injectable drug use are higher than those in males.<sup>66</sup> There are also gender differences in the symptoms of depression. During depressive episodes, females more frequently reported somatic symptoms of anxiety, easy fatigability, hypochondriac symptoms, poor appetite, and insomnia.<sup>67–69</sup> The presence or absence of these items in any rating scales influences depression ratings across the genders. Two studies focusing on the gender of the patients and psychiatric disorders in PLWHA concluded that HIV-positive females had higher levels of anxiety and depression compared to males.<sup>70,71</sup> However, two studies found opposite results.<sup>72,73</sup> The relationship between the gender of the patients and anxiety and depression in PLWHA therefore needs further detailed evaluation.

## Depression and HIV infection

Depression in PLWHA may be a result of CNS involvement by HIV; prior history of mood disorders may not have been present. On the other hand, in an individual newly diagnosed as HIV-positive, the resulting stigma and emotional effects may precipitate an episode or relapse of depression.<sup>74</sup> A 2-year longitudinal study concluded that the risk of depression in the intermediate term is increased by symptomatic HIV disease but not by HIV infection. However, strong predictors of future vulnerability were either a past history of depression or past history having two or more psychiatric disorders.<sup>75</sup>

## Anxiety and HIV infection

PLWHA may experience anxiety at the time of detection, onset, or progression of HIV infection, ranging across the full spectrum of anxiety disorders. A previous study found

that anxiety symptoms were common in HIV patients, but the prevalence of syndromal anxiety disorders is similar to that in the general population.<sup>76</sup> More recent studies have revealed that anxiety and depressive symptoms occur significantly more frequently in PLWHA compared to the general population.<sup>54</sup> The etiological factors to both anxiety and HIV include alcohol and substance abuse, males having sex with males, or males having a bisexual relationship.<sup>77</sup> Increased anxiety symptoms in PLWHA were associated with being a former smoker, HIV infection detected within the past year, persistent symptoms presenting for >7 days in the past 6 months,<sup>54</sup> pain, concurrent substance use disorder, minimal family support, and the spouse having AIDS.<sup>78</sup> In a study based in India, anxiety disorders were detected in 36% PLWHA, the majority of whom had GAD. The prevalence of anxiety disorders in this study was higher than that found in studies conducted in developed countries.<sup>78</sup>

### Panic disorder

Panic disorder is a frequent comorbid diagnosis with other psychiatric disorders as well as in association with HIV infection. Various studies report that the prevalence of panic disorder in patients with HIV ranged from 11% to 16%.<sup>4,79–81</sup> The prevalence of panic disorder is less in PLWHA with resolved grief compared to those with unresolved grief.<sup>82</sup>

### GAD and phobic disorder

Prevalence of GAD among PLWHA in various studies ranged between 6.5% and 20%.<sup>4,80,81,83–85</sup> Longitudinal studies suggested that the passage of time after the initial diagnosis was associated with a significant decrease in the prevalence of GAD.<sup>81</sup> Simple phobia was diagnosed in 9% of 190 PLWHA.<sup>83</sup>

### Post-traumatic stress disorder

In a review of various studies, the prevalence rates of post-traumatic stress disorder (PTSD) were found to vary between 10.4% and 42.2% in PLWHA.<sup>86</sup> The reasons for the occurrence of comorbid PTSD and other anxiety disorders in PLWHA include the trauma of having a potentially fatal illness, stigma related to HIV/AIDS, and the high rates of exposure to traumatic events (physical or sexual assault, the death of a friend or close family member).<sup>12,87–93</sup>

## Methodological issues

The 7.2%–71.9% prevalence for depression and 4.5%–82.3% for anxiety represent significant heterogeneity across various studies. This variance is probably due to the methodological

and conceptual factors that differ across studies and the differences in various measuring tools to quantify depression and anxiety (Tables 1 and 2).

There are various methodological issues related to the prevalence studies of anxiety and depression in PLWHA: difficulty in finding homogenous segments of the HIV population; defining depression or anxiety as symptoms or syndromal diagnosis; different diagnostic criteria used such as *Diagnostic and Statistical Manual* or International Classification of Diseases and their versions; and use of a rating scale that varies from self-reported symptom checklists to clinician-administered psychiatric ratings.<sup>20</sup> There may be some subgroups such as injection drug users, where a high prevalence of depression is found, independent of the HIV status.<sup>94</sup> Different studies have also included samples of different age ranges and gender and at different stages of the illness. Some studies enquired for the presence of any depressive symptoms cross-sectional or in the past 2 weeks, or past month, or past year, or lifetime. It is expected that the prevalence of depression will increase as the time frame is lengthened.<sup>20</sup>

## Impact

HIV infection and psychiatric illness are significant related risk factors, as PLWHA suffer from psychiatric symptoms and disorders more frequently than the general population. On the other hand, in people with a severe psychiatric disorder, HIV infection occurs more often than in the general population. Studies indicate that prior psychiatric history and symptomatic HIV disease, but not asymptomatic HIV disease, are predictors of vulnerability for depression.<sup>75</sup> Various studies and reviews have found a bidirectional association between HIV infection and depression, which involves complex biological and psychosocial interaction.<sup>95</sup> This leads to two questions: 1) why does HIV infection lead to depression and anxiety; and 2) what does depression and anxiety do to HIV infection.

### Why HIV infection leads to depression and anxiety

Various factors have been identified across studies that can be grouped as psychosocial and biological factors causing depression and anxiety among patients with HIV. Immediately after being diagnosed with HIV, patients show an increase in psychological distress. Adjustment problems were expected among newly diagnosed HIV patients.<sup>96</sup> However, ~71% of patients in one study sample were depressed for longer periods than the criterion for adjustment disorder.<sup>97</sup> The incidence of depression also increases with progression of HIV disease.<sup>98,99</sup>

## Stigma

Researchers have identified the stigma of HIV/AIDS as an important factor since stigma is found frequently with HIV/AIDS and is correlated with depression, anxiety, and other psychosocial problems.<sup>100–103</sup> Patients with a stigmatizing illness know how other people view them because of their illness. This is called perceived stigma.<sup>104</sup> Stigmatization leads to restricted social activities, and because of their status, they may start to agree with the negative stereotypes associated with the condition. This process is referred to as internalized stigma,<sup>105</sup> which ultimately leads to psychosocial distress, depression, and anxiety.<sup>101,106,107</sup> Stigma has been related to unsafe sex practices,<sup>106</sup> delay in seeking HIV/AIDS treatment,<sup>108</sup> poor retention in follow-up,<sup>109</sup> poor ART adherence,<sup>110</sup> poor utilization of HIV voluntary counseling and testing services,<sup>111</sup> and significantly more complaints of anxiety and depression.<sup>102</sup>

## Biological model

It has been suggested that symptoms of anxiety and depression in PLWHA occur because of biological mechanisms.<sup>112</sup> A recent review<sup>113</sup> described how HIV can predispose infected individuals to depression by several interrelated mechanisms. These include inducing chronic elevation of cytokines through activation of microglia and astrocytes; decreasing monoaminergic function; inducing neurotoxicity, especially in dopaminergic neurons; and reducing brain-derived neurotrophic factor. These viral pathways interact with psychosocial factors to create the depressive state.<sup>113</sup> These mechanisms, which may be caused directly by the virus or by the psychological stress related to negative psychosocial impact of HIV diagnosis, may also induce the activation of hypothalamic–pituitary–adrenal axis and the sympathetic nervous system, which activate cell-mediated immunity both in the periphery and the CNS.<sup>114,115</sup> Anxiety and depression may also be associated with systemic immune dysregulation.<sup>116</sup>

## Effects of antiretroviral drugs

Depression and anxiety have also been attributed to antiretroviral drugs. A systematic review revealed that compared to the general population, PLWHA on ART have a higher prevalence of anxiety and depression.<sup>53</sup> Neuropsychiatric symptoms attributed to antiretroviral drugs (mainly efavirenz) improved significantly following substitution with another drug (eg, nevirapine).<sup>117,118</sup>

## What depression and anxiety do to HIV infection

Depression causes various direct and indirect morbidities, which include suicidal behavior,<sup>119</sup> increased use of health

care facilities,<sup>120</sup> and poor QoL.<sup>80</sup> It is important to identify depression among PLWHA, as depression is associated with increased chances of HIV transmission<sup>121</sup> and ART nonadherence,<sup>122–124</sup> resulting in failure to suppress viral load<sup>125</sup> and increased HIV disease progression.<sup>126–129</sup> There are other mechanisms caused by depression that lead to a faster progression of HIV infection to AIDS, such as elevated cortisol secretion<sup>13</sup> and HIV replication through an increase in norepinephrine secretion.<sup>130</sup> Even AIDS-related death, specifically in females, was associated with chronic depression.<sup>64,131</sup>

## Depression and disease progression

HIV infection and the disease progression have altered significantly since the beginning of highly active ART and combination ART (cART). A good outcome depends on the patient's adherence to the medication regimen. Presence of depression is associated with medication nonadherence, resulting in a poor HIV disease outcome.<sup>132–134</sup> It has been suggested that baseline depression does not influence treatment adherence, as it is affected by incident depression during the treatment period.<sup>135</sup> This indicates that impaired treatment adherence is due to the acute depression, which occurs as a reactive phenomenon rather than a preexisting or past history, or a predisposition for depression.

## Management

After recognizing, measuring, and understanding depression and anxiety associated with HIV, treating these comorbid disorders is the next focus. It is important to remember that subsyndromal presentation is associated with poor self-care and adverse health outcomes in PLWHA. Therefore, it is also essential to treat sub-syndromal disorders.<sup>125</sup> Appropriate and adequate management of comorbid depression and anxiety in PLWHA will not only result in symptomatic improvement of a psychiatric disorder but also improve ART adherence and their QoL.<sup>136,137</sup> In addition, improved antiretroviral adherence may reduce depressive symptoms.<sup>138</sup>

## Pharmacological intervention

Anxiolytics, hypnotics, antidepressants, psychostimulants, and hormones have been used for in the treatment of depression and anxiety in PLWHA.

### Anxiolytics and hypnotics

Benzodiazepines (BZDs) are frequently prescribed for anxiety in PLWHA<sup>139</sup> despite the lack of studies assessing their anti-anxiety effects in PLWHA.<sup>136</sup> In people at risk of



habituation, tolerance, and abuse, BZDs are indicated for short periods of time. Also, PLWHA are particularly sensitive to the side effects of BZDs, such as amnesia and paradoxical reactions (disinhibition, confusion, etc).<sup>137</sup> Both clonazepam and lorazepam lack active metabolites and are safe in terms of drug–drug interactions. These drugs are probably the BZDs of choice for HIV patients receiving antiretrovirals (ARVs).<sup>140,141</sup> Unlike BZDs, buspirone shows no potential for dependence and tolerance, and sexual dysfunction and weight gain are rare. However, it is metabolized by CYP3A4 and is best avoided in PLWHA receiving protease inhibitors.<sup>137,142</sup> Efficacy studies of buspirone on PLWHA are lacking. Non-benzodiazepine hypnotics (eszopiclone, zopiclone, zolpidem, and zaleplon) have low dependence potential and avoid daytime sedation that may occur with BZDs, but are also metabolized by CYP3A4 and should be avoided in PLWHA receiving protease inhibitors.<sup>141,143</sup>

## Antidepressants

### Selective serotonin reuptake inhibitors

Though slightly less effective than tricyclic antidepressants (TCAs), selective serotonin reuptake inhibitors (SSRIs) are better tolerated and therefore, are more suitable for long-term therapy.<sup>144</sup> Most of the SSRIs have been evaluated in PLWHA. Fluoxetine reduced depressive symptoms significantly compared to placebo.<sup>61</sup> Significant reduction in depressive symptoms were demonstrated by other SSRIs, but comparative effectiveness of the different SSRIs was yet to be ascertained.<sup>137,149</sup> Most SSRIs may be used in HIV-positive adults<sup>145,146</sup> since the most common side effects include anxiety, agitation, akathisia, weight loss, and sexual dysfunction.<sup>137</sup> However, all SSRIs are metabolized by CYP450 isoenzymes,<sup>147</sup> so ARVs may affect their plasma levels. To avoid interactions with ARVs, the better options are sertraline, citalopram, and escitalopram.<sup>148,149</sup> However, it should be kept in mind that the chance of serotonin syndrome is increased when SSRIs are given to PLWHA who are on ART.<sup>150</sup> Depressed PLWHA who are compliant with SSRIs not only show a reduction in symptoms of depression but also better adherence to highly active ART and improved laboratory parameters.<sup>151</sup>

### Comparison of TCAs and SSRIs

Treatment with both paroxetine and imipramine resulted in significantly greater reduction in depression compared to placebo.<sup>152</sup> In a double-blind comparison in the treatment of depressed women with advanced HIV disease, the response rate was 63% and 50%, respectively, for fluoxetine and desipramine.<sup>153</sup> However, treatment with

TCAs is associated with significantly more side effects.<sup>152</sup> Considering the fact that dry mouth is a frequent complaint among PLWHA,<sup>154</sup> TCAs should be used in this population with caution.

### Specific issues with newer antidepressants

Nefazodone is useful in treating depression in PLWHA.<sup>155</sup> However, nefazodone-induced hepatitis is a known entity, and hence it should be used with care in PLWHA because of the frequent occurrence of viral hepatitis. Mirtazapine is also an effective antidepressant with the added benefit of decreasing nausea and increasing weight, and can be useful in HIV wasting disease.<sup>156</sup> Venlafaxine has minimal interaction with CYP450 enzymes, reducing the chances of interaction with antiretroviral drugs; however, when used alongside ritonavir, its dose should be decreased.<sup>157</sup> The metabolism of bupropion is interfered by ritonavir, efavirenz, and nelfinavir.<sup>158,159</sup> A small study reported good tolerance of reboxetine in HIV patients.<sup>160</sup>

## Psychostimulants

In an observational study, depressed PLWHA were randomly assigned to two groups and treated with either desipramine or methylphenidate. Treatment response was observed in 40% and 43% of subjects, respectively.<sup>161</sup> A similar study reported that 73% of those assigned to dextroamphetamine responded to treatment.<sup>162</sup> A specific indication for psychostimulants is neglect of self-care and nutrition in advanced HIV patients.<sup>161,162</sup>

## Hormonal therapies

Testosterone is reduced in HIV infection, and this may lead to anorexia, anergia, depression, and sexual dysfunction. Based on this hypothesis, hormonal therapies have been advocated to treat depression in PLWHA with some success.<sup>163</sup> However, this type of therapy is likely to be useful in PLWHA with decreased testosterone level.

## Nonpharmacological interventions

Various techniques and interventions employed in a depressed population were studied in PLWHA. The major interventions employed were cognitive behavior therapy (CBT), interpersonal therapy (IPT), supportive psychotherapy, cognitive–behavioral-oriented group psychotherapy, experiential group psychotherapy, cognitive–behavioral stress management (CBSM), stress management interventions, cognitive remediation therapy, mindfulness-based therapy, and aerobic and resistance exercise.

### Cognitive behavior therapy

There is considerable evidence in the form of randomized controlled studies, meta-analysis, and systematic analysis attesting the efficacy of CBT in treating anxiety and depressive disorders in PLWHA.<sup>164–166</sup> A study by Lee et al<sup>164</sup> evaluated the feasibility and effectiveness of group CBT in combination with medication in 13 patients with HIV and depression. The authors found an overall positive response in terms of improvement in depression, and cognitive restructuring was the most helpful psychotherapeutic process of CBT. In a meta-analysis of 15 controlled trials, significant effects were found for improving symptoms of depression ( $d=0.33$ ), anxiety ( $d=0.30$ ), anger ( $d=1.00$ ), and stress ( $d=0.43$ ).<sup>165</sup> Similarly, a recent systemic review including 2,173 participants from 20 studies suggested that cognitive-behavioral intervention may be effective in the treatment of depression and anxiety in individuals living with HIV/AIDS. Effect sizes ranged from 0.02 to 1.02 for depression and 0.04 to 0.70 for anxiety.<sup>166</sup>

### Interpersonal therapy

A randomized clinical trial reported that IPT resulted in significantly lower scores on the Hamilton Rating Scale for Depression (HAM-D) and the Beck Depression Inventory (BDI) compared to supportive psychotherapy.<sup>167</sup> Another randomized controlled trial involved randomly assigning 101 PLWHA with clinical depression and score  $\geq 15$  on the HAM-D to various treatment modalities. Results indicated that a significantly greater reduction in HAM-D scores occurred after IPT and supportive psychotherapy plus imipramine compared to CBT and supportive psychotherapy without imipramine.<sup>168</sup>

### Supportive psychotherapy

Supportive psychotherapy was primarily based on teaching coping skills. A comparative study of CBT and supportive therapy reported clinically significant changes in depression in both groups, which were maintained at follow-up after 3 months. An important finding was that the occurrence of unprotected anal intercourse was reduced after supportive therapy.<sup>167</sup>

### Cognitive-behavioral-oriented group psychotherapy

Two small studies found cognitive-behavioral-oriented group psychotherapy to be effective in improving psychosocial adjustment and reducing psychological distress in PLWHA.<sup>169,170</sup>

### Experiential group psychotherapy

A randomized study comparing the effects of experiential group psychotherapy and cognitive-behavioral group psychotherapy on asymptomatic homosexual PLWHA concluded that, while both therapies reduced psychological distress, there was no significant difference between the two therapies.<sup>170</sup>

### Cognitive-behavioral stress management

A few studies have reported significant reductions in depression,<sup>171–175</sup> improved immune control of latent HSV-2 virus,<sup>174</sup> and reduced urinary cortisol levels after CBSM.<sup>174,175</sup> The reduction in depression was directly related to reduction in cortisol levels in urine.<sup>174,175</sup> CBSM training of PLWHA taking cART reduces anxiety and depression<sup>176,177</sup> and improves global psychological functioning<sup>180</sup> and QoL<sup>176,177</sup> but does not improve surrogate markers of HIV-1 and self-reported adherence to therapy.<sup>176</sup>

### Stress management interventions

A meta-analysis revealed that, in PLWHA, stress management resulted in significant improvements in anxiety, depression, distress, fatigue, and QoL, but had no effect on immune function (CD4<sup>+</sup> counts and viral load) or hormone functions, indicating the need for further studies.<sup>178</sup> A recent study concluded that, while both group stress management and group CBT were effective in PLWHA, the former was more effective than the latter to decrease depression and anxiety.<sup>179</sup>

### Cognitive remediation therapy

In addition to anxiety and depression, PLWHA continue to have cognitive impairments despite receiving cART. These cognitive and emotional impairments adversely affect occupational and driving performance, contribute to poor emotional processing, increase cognitive complaints, reduce QoL, and increase caregiver burden. Speed-of-processing training, a type of cognitive remediation therapy, may help to improve cognitive performance on measures of visual attention, speed of processing, and timed-task performances. A few studies also suggest that speed-of-processing training could also improve mood functions (depression and anxiety). The benefits of the improvement in these cognitive and emotional systems are a decrease or slowing in cognitive decline along with the potential to protect against clinically significant depressive symptoms. Further investigation into the benefits of this type of training as a behavioral adjunct for the pharmacologically burdened HIV population is needed.<sup>180</sup>

## Mindfulness-based therapy

Mindfulness-based treatment improves the well-being and QoL of PLWHA. In addition, it contributes to enhanced immunity, telomerase activity, and plasma levels of serotonin and melatonin. At the same time, it diminishes autonomic nervous system reactivity.<sup>181</sup>

## Aerobic and resistance exercise

Exercise produces beneficial physiological changes and also reduces depression and anxiety in PLWHA.<sup>182</sup>

## Conclusion

There is enormous variation in the reported prevalence rates of depression, which ranges from 16% to 72%, and in the prevalence for anxiety, which ranges from 16% to 47%, among HIV patients. Various factors associated with and causative for this wide variation across studies include sample composition, diagnostic issues, different rating scales, gender of the patients, staging of HIV illness, etc. Moreover, depression increases the morbidity of HIV by poor adherence to treatment and various other significant mechanisms. Early identification and effective management of these disorders improves the QoL and adherence to ARV in PLWHA. Different treatment modalities including pharmacological and nonpharmacological psychotherapies have been used for the management of depression and anxiety in PLWHA. BZDs are indicated for short periods of time. Clonazepam and lorazepam are safe in terms of drug–drug interactions and may be preferred. SSRI are safer than TCAs. While differences in the efficacy of various SSRIs have not been established, to avoid interactions with ARVs, the better options are sertraline, citalopram, and escitalopram. Nonpharmacological therapies, including various psychotherapies and aerobic and resistance exercises, are effective in treating depression among PLWHA. However, definitive evidence to decide which nonpharmacological intervention is most beneficial for the management of depression in PLWHA is still awaited.

## Disclosure

The authors report no conflicts of interest in this work.

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