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 (PL WHA) 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 PL WHA. Different treatment modalities, including pharmacological and nonpharmacological therapies, are used for the management of anxiety and depression in PL WHA. 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 PL WHA. However, definitive evidence to decide which nonpharmacological intervention is most beneficial for the management of anxiety and depression in PL WHA 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 ≥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
test for HIV or its components confirmed by a second virological test obtained from a separate determination.\textsuperscript{1,2}

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.\textsuperscript{3}

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

A complex relationship exists between depression and HIV infection. Depression is both a risk factor and a consequence of HIV infection.\textsuperscript{11,12} In PLWA, 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.\textsuperscript{13,14} Depression can easily remain unrecognized and untreated in PLWA.\textsuperscript{15} A meta-analytic study concluded that the development of depression in PLWA was not associated with the sexual orientation of patients or the disease stage of the HIV infection.\textsuperscript{16} However, despite a large number of studies, clear answers are lacking in many areas relating to anxiety and depression in PLWA. This review aims to summarize the recent literature and research related to the prevalence, impact, and management of comorbid depression and anxiety in PLWA. Since there is more literature on depression in PLWA, 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 PLWA reported that the incidence of depression was 2.2 per 100 person years.\textsuperscript{17} Another study reported an incidence of 1.89 per 100 person years for depression and 1.27 per 100 person years for generalized anxiety.\textsuperscript{18}

**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 PLWA.\textsuperscript{19} A psychiatric disorder was present in almost half of the 2,864 PLWA, including 36%
<table>
<thead>
<tr>
<th>Location, reference</th>
<th>Scale used</th>
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<th>Depression prevalence, %</th>
<th>Associated findings</th>
</tr>
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<tbody>
<tr>
<td>Nigeria, Sale and Gadanya</td>
<td>HADS, ICD 10</td>
<td>162</td>
<td>39.9</td>
<td>Depression was associated with the stage of HIV illness, CD4⁺ count level, poverty, low social support, and inability to tolerate ART</td>
</tr>
<tr>
<td>People’s Republic of China, Lu et al</td>
<td>SRDS</td>
<td>102</td>
<td>67.65</td>
<td>Depression and anxiety were associated with low CD4⁺ T-lymphocyte counts</td>
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<tr>
<td>Kenya, Musisi and Kinyanda</td>
<td>ICD 10</td>
<td>82</td>
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<td>Other comorbid disorders included anxiety, somatization, seizures, mania, and HIV-associated progressive encephalopathy</td>
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<td>Tanzania, Marwick and Kaaya</td>
<td>CIS-R</td>
<td>220</td>
<td>15.5</td>
<td>During HIV care, co-morbid psychiatric disorders should be identified and managed</td>
</tr>
<tr>
<td>Jamaica, Clarke et al, (2010)</td>
<td>PHQ-9</td>
<td>63</td>
<td>43</td>
<td>Age, gender, marital status, major stress, living conditions, ART, and CD4⁺ count were not associated with depression</td>
</tr>
<tr>
<td>India, Sivasubramanian et al</td>
<td>M.I.N.I.; DSM–IV</td>
<td>150</td>
<td>29</td>
<td>Depression was associated with low self-esteem and low levels of social support</td>
</tr>
<tr>
<td>Albania, Morrison et al</td>
<td>Semistructured interview</td>
<td>79</td>
<td>62.3</td>
<td>Depression was significantly associated with anxiety, greater number of barriers to care, and greater medical and social needs</td>
</tr>
<tr>
<td>USA, Bhatia et al</td>
<td>CES-D</td>
<td>180</td>
<td>67</td>
<td>Multivariate analysis revealed the association of depression with female gender, low income, history of psychoactive substance abuse, and low access to medical care</td>
</tr>
<tr>
<td>Uganda, Kinyanda et al</td>
<td>M.I.N.I.</td>
<td>618</td>
<td>8.1</td>
<td>Depression was associated with psychosocial impairment, adverse life events, PTSD, GAD, and past history of deliberate self-harm</td>
</tr>
<tr>
<td>India, Agarwal et al</td>
<td>HADS</td>
<td>50</td>
<td>30</td>
<td>46% of PLWHA had low psychological well-being</td>
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<tr>
<td>South Africa, Pappin et al</td>
<td>HADS</td>
<td>716</td>
<td>25.4</td>
<td>Depression was associated with stigma</td>
</tr>
<tr>
<td>Cameroon, L’akoa et al</td>
<td>PHQ-9</td>
<td>100</td>
<td>63</td>
<td>Newly diagnosed HIV-infected patients had higher prevalence of depression, severe immunosuppression, and harmful use of alcohol associated with depression</td>
</tr>
<tr>
<td>People’s Republic of China, Su et al</td>
<td>BDI</td>
<td>258</td>
<td>71.9</td>
<td>Depression was associated with less income and high perceived stress</td>
</tr>
<tr>
<td>India, Talukdar et al</td>
<td>BDI</td>
<td>175</td>
<td>56</td>
<td>Poor QoL was associated with depression and high neuroticism score</td>
</tr>
<tr>
<td>Nigeria, Olagunju et al</td>
<td>SCID-NP</td>
<td>295</td>
<td>14.9</td>
<td>Compared to the general population, PLWHA suffer from more psychiatric disorders</td>
</tr>
<tr>
<td>South Korea, Song et al</td>
<td>BDI</td>
<td>82</td>
<td>21</td>
<td>Depression was associated with poor adherence and anxiety. Comorbidities and unemployment were risk factors for depression.</td>
</tr>
<tr>
<td>People’s Republic of China, Liu et al</td>
<td>BDI</td>
<td>100</td>
<td>39</td>
<td>Depression and anxiety in PLWHA could be reduced by high social support</td>
</tr>
<tr>
<td>India, Chauhan et al</td>
<td>HADS</td>
<td>100</td>
<td>39</td>
<td>Asymptomatic PLWHA had significantly higher prevalence of alcohol dependence, adjustment disorder, and sexual dysfunction compared to control subjects</td>
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<td>Israel, Levy et al</td>
<td>PHQ-9</td>
<td>57</td>
<td>24</td>
<td>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</td>
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<tr>
<td>South Africa, Nel and Kagee</td>
<td>BDI II</td>
<td>101</td>
<td>40.4</td>
<td>ART adherence was significantly related to depressive symptoms on biserial correlations and logistic regression analysis</td>
</tr>
</tbody>
</table>

(Continued)
Depression was associated with low family income, employment status, health status, perceived quality of life; SCID-NP, Structured Clinical Interview for DSM-IV non-patient; SRDS, Self-rating depression scale.

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.4 Prevalence of depression is found to be very high among PLWHA, as compared to general population.20,21 An early meta-analysis reported that the prevalence of depression in PLWHA was ~10% as against 5% in the general population.16

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.22 The different prevalence rates of anxiety disorders may also depend upon the stage of the illness.23 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.24

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<td>Romania, Largu et al</td>
<td>BDI II</td>
<td>146</td>
<td>41 (moderate in 14%; mild in 27%)</td>
<td>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</td>
</tr>
<tr>
<td>Malawi, Kim et al</td>
<td>CDRS-R</td>
<td>562</td>
<td>18.9</td>
<td>7.1% of PLWHA had suicidal ideation</td>
</tr>
<tr>
<td>Germany, Kittner et al</td>
<td>HADS</td>
<td>80</td>
<td>30 (male) and 47 (female)</td>
<td>Guilt for the HIV infection was present in 36% of PLWHA</td>
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<td>India, Bhataia and Munjal</td>
<td>CES-D</td>
<td>160</td>
<td>58.7</td>
<td>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</td>
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<td>People’s Republic of China, Sun et al</td>
<td>CES-D</td>
<td>772</td>
<td>73.1</td>
<td>Depression was associated with health status, perceived social support, job, and gender</td>
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<td>People’s Republic of China, Qiu et al</td>
<td>PHQ-9</td>
<td>370</td>
<td>40.3</td>
<td>Depression was associated with employment status, sexual orientation, resident status, emergence of HIV-related symptoms, stress, and social support</td>
</tr>
<tr>
<td>Haitian females in USA, Glemaud et al</td>
<td>Systematic review</td>
<td>66 original studies</td>
<td>33.60</td>
<td>Low- and middle-income countries had a higher prevalence of depression (41.36%) compared to high-income countries (25.81%)</td>
</tr>
<tr>
<td>Western Europe and Canada, Robertson et al</td>
<td>HADS</td>
<td>2,863</td>
<td>15.7 (14.3% of male and 17.9% of female)</td>
<td>Depression occurred significantly more often in females compared to males</td>
</tr>
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<td>South Korea, Kee et al</td>
<td>BDI</td>
<td>840</td>
<td>36</td>
<td>Both anxiety and depression were associated with persistent symptoms, alcohol and tobacco use, and marital status</td>
</tr>
<tr>
<td>Brazil, Nomoto et al</td>
<td>BDI</td>
<td>59</td>
<td>61</td>
<td>Depression was significantly associated with low income, low social class, and poor QoL</td>
</tr>
<tr>
<td>Denmark, Slot et al</td>
<td>BDI</td>
<td>212</td>
<td>35</td>
<td>Depression was associated with stress, poor health, dissatisfaction with life situation, ART nonadherence, and past history of alcohol abuse or psychiatric treatment</td>
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Table 1 (Continued)
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<td>Anxiety associated with low levels of social support</td>
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<td>Semistructured interview</td>
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<td>82.3</td>
<td>Anxiety significantly associated with depression, first-line ART, recent HIV diagnosis, and greater medical and social needs</td>
</tr>
<tr>
<td>Nigeria, Olagunju et al&lt;sup&gt;37&lt;/sup&gt;</td>
<td>SCAN</td>
<td>4,000</td>
<td>21.7</td>
<td>Anxiety was associated with low family support, lack of employment, and being unmarried</td>
</tr>
<tr>
<td>Canada, Ivanova et al&lt;sup&gt;48&lt;/sup&gt;</td>
<td>HADS (HADS-A ≥11)</td>
<td>361</td>
<td>37</td>
<td>Anxiety was associated with stigma, ART, and worries about reproductive health</td>
</tr>
<tr>
<td>India, Agarwal et al&lt;sup&gt;35&lt;/sup&gt;</td>
<td>HADS</td>
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<td>India, Chauhan et al&lt;sup&gt;43&lt;/sup&gt;</td>
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<td>Italy, Celesia et al&lt;sup&gt;39&lt;/sup&gt;</td>
<td>SRAS</td>
<td>251</td>
<td>47</td>
<td>Anxiety was associated with a high number of ART switches</td>
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<td>Nigeria, Olagunju et al&lt;sup&gt;49&lt;/sup&gt;</td>
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<td>USA, Parhami et al&lt;sup&gt;60&lt;/sup&gt;</td>
<td>NA</td>
<td>7,834</td>
<td>16</td>
<td>53% of the patients had a psychiatric condition, including mood disorder (23%) and substance-related disorder (19%)</td>
</tr>
<tr>
<td>People's Republic of China, Liu et al&lt;sup&gt;42&lt;/sup&gt;</td>
<td>SRAS</td>
<td>320</td>
<td>45.6</td>
<td>Depression and anxiety in PLWHAs could be reduced by high social support</td>
</tr>
<tr>
<td>Israel, Levy&lt;sup&gt;44&lt;/sup&gt;</td>
<td>STAI</td>
<td>57</td>
<td>18</td>
<td>Neurocognitive disturbances and psychiatric illnesses are common in asymptomatic PLWHAs, independent of the time of being positive, immunological status, viral load, or treatment received</td>
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<td>South Africa, Nel and Kagee&lt;sup&gt;45&lt;/sup&gt;</td>
<td>BAI</td>
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<td>28.7</td>
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<td>Western Europe and Canada, Robertson et al&lt;sup&gt;3&lt;/sup&gt;</td>
<td>HADS</td>
<td>2,863</td>
<td>33.3</td>
<td>No significant difference was found between those receiving combination ART and those not receiving it</td>
</tr>
<tr>
<td>Romania, Largu et al&lt;sup&gt;46&lt;/sup&gt;</td>
<td>HAS</td>
<td>146</td>
<td>71 (54% mild, 14% severe, and 3% very severe anxiety)</td>
<td>PLWHAs 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</td>
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<td>772</td>
<td>49</td>
<td>Anxiety was associated with health status, social support, alcohol consumption, and condom use at the last sexual contact</td>
</tr>
<tr>
<td>People's Republic of China, Qiu et al&lt;sup&gt;51&lt;/sup&gt;</td>
<td>GAD-7</td>
<td>370</td>
<td>30.5</td>
<td>Anxiety associated with employment status, sexual orientation, resident status, emergence of HIV-related symptoms, and stress</td>
</tr>
<tr>
<td>Ethiopia, Belete et al&lt;sup&gt;52&lt;/sup&gt;</td>
<td>BAI</td>
<td>436</td>
<td>22.2</td>
<td>Being female, perceived stigma, started ART, and divorced were significantly associated with anxiety</td>
</tr>
<tr>
<td>Haiti females in USA, Glémaud et al&lt;sup&gt;52&lt;/sup&gt;</td>
<td>NA</td>
<td>96</td>
<td>43</td>
<td>12.5% of subjects gave a history of abuse; 34% of subjects had PTSD</td>
</tr>
</tbody>
</table>
Low- and middle-income countries had a higher prevalence (33.92%) compared to high-income countries (25.53%). Both anxiety and depression were associated with persistent symptoms, alcohol and tobacco use, and marital status.

Risk factors associated with depression among HIV patients

The occurrence and severity of depression in PLWHAs 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. 4,30,49,55,61,62 Logistic regression revealed that the predictors of depression in PLWHAs 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. 36

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. 63 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 PLWHAs. 43 As the illness progresses further and CD4+ cell count declines, the prevalence of depression increases. 63,64

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. 65 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. 66 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. 67-69 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 PLWHAs concluded that HIV-positive females had higher levels of anxiety and depression compared to males. 70,71 However, two studies found opposite results. 72,73 The relationship between the gender of the patients and anxiety and depression in PLWHAs therefore needs further detailed evaluation.

Depression and HIV infection

Depression in PLWHAs 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. 74 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. 75

Anxiety and HIV infection

PLWHAs 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. More recent studies have revealed that anxiety and depressive symptoms occur significantly more frequently in PLWHA compared to the general population. The etiological factors to both anxiety and HIV include alcohol and substance abuse, males having sex with males, or males having a bisexual relationship. 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, pain, concurrent substance use disorder, minimal family support, and the spouse having AIDS. 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.

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%. The prevalence of panic disorder is less in PLWHA with resolved grief compared to those with unresolved grief.

GAD and phobic disorder
Prevalence of GAD among PLWHA in various studies ranged between 6.5% and 20%. Longitudinal studies suggested that the passage of time after the initial diagnosis was associated with a significant decrease in the prevalence of GAD. Simple phobia was diagnosed in 9% of 190 PLWHA.

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. 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).

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. There may be some subgroups such as injection drug users, where a high prevalence of depression is found, independent of the HIV status. 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.

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. Various studies and reviews have found a bidirectional association between HIV infection and depression, which involves complex biological and psychosocial interaction. 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. However, ~71% of patients in one study sample were depressed for longer periods than the criterion for adjustment disorder. The incidence of depression also increases with progression of HIV disease.
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. Patients with a stigmatizing illness know how other people view them because of their illness. This is called perceived stigma. 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. Stigma has been related to unsafe sex practices, delay in seeking HIV/AIDS treatment, poor retention in follow-up, poor ART adherence, utilization of HIV voluntary counseling and testing services, and significantly more complaints of anxiety and depression.

Biological model
It has been suggested that symptoms of anxiety and depression in PLWH occur because of biological mechanisms. A recent review 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. 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. Anxiety and depression may also be associated with systemic immune dysregulation.

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

What depression and anxiety do to HIV infection
Depression causes various direct and indirect morbidities, which include suicidal behavior, increased use of health care facilities, and poor QoL. It is important to identify depression among PLWA, as depression is associated with increased chances of HIV transmission and ART nonadherence, resulting in failure to suppress viral load and increased HIV disease progression. There are other mechanisms caused by depression that lead to a faster progression of HIV infection to AIDS, such as elevated cortisol secretion and HIV replication through an increase in norepinephrine secretion. Even AIDS-related death, specifically in females, was associated with chronic depression.

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. It has been suggested that baseline depression does not influence treatment adherence, as it is affected by incident depression during the treatment period. 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 PLWA. Therefore, it is also essential to treat sub-syndromal disorders. Appropriate and adequate management of comorbid depression and anxiety in PLWA will not only result in symptomatic improvement of a psychiatric disorder but also improve ART adherence and their QoL. In addition, improved antiretroviral adherence may reduce depressive symptoms.

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

Anxiolytics and hypnotics
Benzodiazepines (BZDs) are frequently prescribed for anxiety in PLWA despite the lack of studies assessing their anti-anxiety effects in PLWA. In people at risk of
habituation, tolerance, and abuse, BZDs are indicated for short periods of time. Also, PLWH are particularly sensitive to the side effects of BZDs, such as amnesia and paradoxical reactions (dissimulation, confusion, etc).137 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).140,141 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 PLWA receiving protease inhibitors.137,142 Efficacy studies of buspirone on PLWA are lacking. Nonbenzodiazepine 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 PLWA receiving protease inhibitors.141,143

**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.144 Most of the SSRIs have been evaluated in PLWA. Fluoxetine reduced depressive symptoms significantly compared to placebo.51 Significant reduction in depressive symptoms were demonstrated by other SSRIs, but comparative effectiveness of the different SSRIs was yet to be ascertained.137,149 Most SSRIs may be used in HIV-positive adults145,146 since the most common side effects include anxiety, agitation, akathisia, weight loss, and sexual dysfunction.137 However, all SSRIs are metabolized by CYP450 isoenzymes,147 so ARVs may affect their plasma levels. To avoid interactions with ARVs, the better options are sertraline, citalopram, and escitalopram.148,149 However, it should be kept in mind that the chance of serotonin syndrome is increased when SSRIs are given to PLWA who are on ART.150 Depressed PLWA 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.151

**Comparison of TCAs and SSRIs**

Treatment with both paroxetine and imipramine resulted in significantly greater reduction in depression compared to placebo.152 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.153 However, treatment with TCAs is associated with significantly more side effects.152 Considering the fact that dry mouth is a frequent complaint among PLWA,154 TCAs should be used in this population with caution.

**Specific issues with newer antidepressants**

Nefazodone is useful in treating depression in PLWA.155 However, nefazodone-induced hepatitis is a known entity, and hence it should be used with care in PLWA 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.156 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.157 The metabolism of bupropion is interfered by ritonavir, efavirenz, and nefazodine.158,159 A small study reported good tolerance of reboxetine in HIV patients.160

**Psychostimulants**

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

**Hormonal therapies**

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

**Nonpharmacological interventions**

Various techniques and interventions employed in a depressed population were studied in PLWA. 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 PLHWA. A study by Lee et al 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). 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.

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. Another randomized controlled trial involved randomly assigning 101 PLHWA with clinical depression and score ≥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.

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.

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 PLHWA.

Experiential group psychotherapy
A randomized study comparing the effects of experiential group psychotherapy and cognitive–behavioral group psychotherapy on asymptomatic homosexual PLHWA concluded that, while both therapies reduced psychological distress, there was no significant difference between the two therapies.

Cognitive–behavioral stress management
A few studies have reported significant reductions in depression, improved immune control of latent HSV-2 virus, and reduced urinary cortisol levels after CBSM. The reduction in depression was directly related to reduction in cortisol levels in urine. CBSM training of PLHWA taking cART reduces anxiety and depression and improves global psychological functioning and QoL, but does not improve surrogate markers of HIV-1 and self-reported adherence to therapy.

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

Cognitive remediation therapy
In addition to anxiety and depression, PLHWA 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.
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.181

Aerobic and resistance exercise

Exercise produces beneficial physiological changes and also reduces depression and anxiety in PLWHA.182

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. SSRIs 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.

References


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