Depression in HIV-Infected Patients: Allopathic, Complementary, and Alternative Treatments

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Depression in HIV-infected patients
Allopathic, complementary, and alternative treatments

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Abstract

Objectives: The purpose of this review article is to synthesize the current knowledge related to depression and HIV disease.
Methods: The research literature was critically evaluated for several selected therapies that are prescribed for HIV-infected persons to treat depression. These therapies included pharmacotherapy, psychotherapy, alternative, and complementary therapies.
Results: Several therapies are currently available for the treatment of depression in HIV disease. When prescribing treatments, clinicians should be aware of problems associated with diagnoses, drug–drug interactions, and the benefits of some of the new therapies that are now available. Treatment regimes should be carefully designed to meet the individual needs of the patient and will optimally include a combination of approaches including psychotherapy, pharmacotherapy, education, and/or complementary therapies.
Conclusions: Although HIV is now a treatable disease, the prevalence of depression in the HIV population remains high and should be continually addressed.

Keywords: Acupuncture; Antidepressant; Diagnosis; Massage therapy; Psychotherapy; Treatment

Introduction

Not only does HIV/AIDS elicit detrimental physical manifestations, but psychological health is also negatively affected in individuals living with HIV/AIDS. In the 1980s and 1990s, an abundance of research focused on the psychological aspects of HIV/AIDS. However, since the discovery of the new anti-HIV treatment [e.g., highly active antiretroviral therapy (HAART)], this area of research has diminished. Although HIV disease is now treatable, this does not mean that the psychological issues afflicting HIV-seropositive individuals are solved. Given the magnitude of potential problems associated with being HIV seropositive, it is not surprising that individuals living with these conditions are faced with several different psychosocial conditions, including stigmatization, social isolation, discrimination, and violence [1]. Among individuals with HIV disease, major depression is a frequently observed psychiatric disorder. However, the relationships between HIV and depression are very complex and difficult to assess.

Depression

Major depression is a common form of unipolar depression and is a major public health problem, with a lifetime risk of 10–25% for women and 5–12% for men and prevalence rates of 5–9% for women and 2–3% for men [2]. According to the standard classification criteria stated in the Diagnostic and Statistical Manual of Mental Disorders (DSM-IV), a person may be diagnosed with major depression if he/she experiences one of the first two symptoms and at least five of the remaining symptoms listed in Table 1, almost daily for a period of at least 2 weeks [2].

Depression in HIV infection

HIV disease and depression often display a complex, multifactorial comorbidity. However, given that the
prevalence of depression is high in this population, it is necessary for health care providers to diagnose and treat each patient accordingly.

Studies examining the effects of depression on HIV disease progression have demonstrated significant relationships between depression and disease progression in men [3] and also between depression and mortality in women [4]. In the San Francisco Men’s Health Study, a 9-year longitudinal study of HIV-seropositive men, higher levels of depression at the beginning of the study were associated with faster progression to AIDS [5]. A recent report suggests that HIV-seropositive individuals are more likely to experience depression than their uninfected counterparts. This study reported that HIV-seropositive women had a significantly higher rate of depression and more depressive symptoms than a HIV-seronegative control group [6]. Conversely, Hintz et al. [7] reported that rates of depression were equal between HIV-seropositive and HIV-seronegative homosexual men. While it is unknown whether a gender difference exists in the relationship between HIV and depression, it is possible that HIV-infected women are more likely to suffer from depression given the fact that non-HIV-infected women are twice as likely to suffer from depression than their male counterparts.

Whether or not depression is more prevalent in the HIV-infected population, it is a serious and debilitating mental health problem frequently associated with HIV disease. Causes of depression in HIV disease include a history of preexisting mental illness [8], psychosocial factors [9], and neuropsychiatric disturbances [10].

While the diagnostic criteria for major depression are the same in all populations, certain symptoms may be more prevalent in individuals with HIV disease. Specifically, appetite and sleep disturbances are more frequently reported in HIV-seropositive subjects as compared to HIV-seronegative subjects [7]. Therefore, it may be beneficial for clinicians to pay close attention to neurovegetative symptoms when diagnosing and treating depression in HIV-seropositive patients.

Table 1

<table>
<thead>
<tr>
<th>Symptoms of major depression</th>
</tr>
</thead>
<tbody>
<tr>
<td>According to DSM-IV criteria [2], a person may be diagnosed with major depression if he or she experiences one of the first two symptoms and at least five of the remaining symptoms almost daily for a period of at least 2 weeks</td>
</tr>
<tr>
<td>Depressed mood most of the day, nearly every day</td>
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<tr>
<td>Reduced or loss of interest or pleasure in almost all activities (anhedonia)</td>
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<td>Significant weight loss or gain without dieting</td>
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<tr>
<td>Insomnia or hypersomnia</td>
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<tr>
<td>Feelings of lethargy or restlessness</td>
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<tr>
<td>Fatigue or loss of energy</td>
</tr>
<tr>
<td>Psychomotor retardation or agitation</td>
</tr>
<tr>
<td>Feelings of worthlessness or excessive guilt</td>
</tr>
<tr>
<td>Reduced ability to think or concentrate</td>
</tr>
<tr>
<td>Recurrent thoughts of death or suicide</td>
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</tbody>
</table>

Prevalence of depression in HIV infection

As the number of persons living with HIV continues to grow, it is essential to explore the prevalence of HIV-related depression, as well as the factors that contribute to the depression. Studies indicate a large range of prevalence rates of depression in HIV disease, with reports ranging from 5% to 20% [11–14]. Epidemiological data associated with the prevalence of depression in individuals with HIV infection are conflicting, and this is likely due to differences among reports including patient samples, disease stage, treatment status, and assessment techniques and instrumentation.

Most of the prevalence studies of depression in HIV disease have primarily focused on the male population. In general, it appears that depression rates are higher in HIV-seropositive homosexual men compared to HIV-seropositive heterosexual men; however, rates of depression are similar between HIV-seropositive homosexual men and HIV-seronegative homosexual men [15]. Therefore, depression rates are high in the male homosexual population, independent of HIV serostatus.

Prevalence studies of HIV-infected women have large variations with reported prevalence rates ranging from 1.9% to 35% [16–19] in clinical samples and 30–60% in community samples [20,21]. A prevalence rate of 42% was found in a larger scale study in 765 HIV-seropositive women [4]. Morrison et al. [6] observed a prevalence rate of 19.4% in a population of 93 HIV-seropositive women.

Diagnostic difficulties

The diagnosis and treatment of depression in HIV-infected individuals can be problematic and difficult [10]. The signs and symptoms of depression listed in Table 1 may be confused with the signs and symptoms of HIV disease itself. For example, weight loss, fatigue, insomnia, and anorexia are associated with depression or HIV infection [22]. In addition, depression is more often unrecognized and underdiagnosed in the HIV-infected population [23].

To further complicate accurate diagnosis, depressive symptoms, such as depressed mood, agitation, and insomnia, have been associated with medications frequently used to treat HIV disease [24]. It is quite difficult to discern the etiology of the symptom when several different etiologies are possible (i.e., depression or medication).

Another factor contributing to inconsistent diagnoses of major depression in HIV-infected individuals involves the use of different measurement instruments (self-reports or more structured diagnostic tools) [25]. Upon reviewing the literature, it is crucial to identify whether the study utilized patient self-reports or more structured diagnostic instruments. Self-reports are not the most effective tool for diagnosing depression, especially when other tools are available that have been tested for validity and reliability.
The most common instruments used for diagnosing depression in people living with HIV/AIDS are the Beck Depression Inventory (BDI), the Hamilton Rating Score for Depression (HRSD), and the Center for Epidemiological Studies Depression Scale (CESD) [24].

Major depression also commonly co-occurs with dementia in HIV disease [26]. Therefore, distinguishing neuropsychological dysfunction from depression can be very challenging because of symptom overlap. However, trained clinicians should be able to discern features of dementia from those of depression by examining specific characteristics of the patient’s responses. For example, examining a patient’s responses to questions requiring concentration and memory can help differentiate between features of depression and dementia. Depressed patients are more likely to respond with silence or answering “I don’t know,” whereas patients with dementia attempt to answer questions, frequently with inconsistencies [27].

Additionally, close attention should be given to somatic symptoms in the early phases of disease in relation to depression. Fukunishi et al. [28] administered the Structured Clinical Interview for the DSM-III-R for depression diagnoses and the Profile of Mood States (POMS) to 50 Japanese HIV-seropositive patients. None of the patients fulfilled the criteria for the diagnoses of depression by the DSM-III-R; however, scores of depressive symptoms measured by POMS were significantly higher in the HIV-seropositive subjects, as compared to the control subjects. The HIV-seropositive subjects also reported somatic complaints including, chest pain, abdominal distress, sleep disturbance, numbness, or chills. The authors of the study concluded that although the depressive symptoms were not robust enough to elicit a depression diagnosis, the HIV-seropositive subjects were more likely to experience depressive symptoms. They further concluded that depressive symptoms may accompany somatic problems in this population. Clinicians may want to consider assessing somatic symptoms in HIV-seropositive patients in attempts for earlier diagnosis and treatment for depression and/or depressive symptoms.

Overall, diagnosing depressive disorders in HIV disease proves to be challenging given the comorbidity of major depression and symptoms of HIV disease itself, mediations associated with HIV disease, discrepancies in diagnostic instrumentation, and other neuropsychiatric disorders. It has been recommended that clinicians, knowledgeable in both depression and HIV disease, diagnose depression by focusing on cognitive and affective symptoms that solely reflect mood state (i.e., anhedonia, depressed feelings, feelings of worthlessness). It is also important to recognize that depressive symptoms alone do not necessarily warrant a diagnosis of major depression (for diagnostic criteria, see Table 1). Although major depression is still underdiagnosed in HIV disease [29], accurate diagnoses can be obtained using appropriate diagnostic instruments (BDI, HRSD, and CESD).

**Risk factors**

HIV-infected individuals who are at greatest risk for developing depression are those with a history of depression, homosexual men, women, or intravenous drug users (IVDUs) [30]. One of the strongest predictors of future depressive episodes is a history of major depression. Therefore, HIV-seropositive persons who have suffered from major depression at any time point in the past are at increased susceptibility to future recurrences [31].

Other risk factors associated with developing major depression in HIV-seropositive persons include social stigmatization, isolation, lack of social support, death of friends as a result of HIV/AIDS, and gender [7]. A recent study showed that depression is more common in HIV-seropositive women when compared to their HIV-seronegative counterparts [6]. Depression prevalence rates appear to be higher in HIV-seropositive women than HIV-seropositive men. Overall, these data suggest that being HIV-seropositive in itself is a risk factor for developing major depression in women compared to demographically matched HIV-seronegative women. The fact that HIV-infected women are at a greater risk for developing major depression seems logical since women in non-HIV populations are more likely to experience major depression than men.

It is not clear whether the risk for major depression increases with the stage of HIV disease, but it is evident that patients with increased psychiatric morbidity are at greater risk for poor adherence to antiretroviral medications and at high risk for treatment failure. A study by Gordillo et al. [32] found that depressed patients were less likely to adhere to antiretroviral treatment. Therefore, for individuals with HIV disease and major depression who are taking antiretroviral medications, it is very important for clinicians to effectively treat major depression in an attempt to increase antiretroviral adherence rates.

**Allopathic treatment of major depression in HIV disease**

Managing depression in HIV-infected individuals is made considerably more difficult with the numerous considerations that have to be made in choosing the best treatment strategy. Symptoms of major depression, HIV illness, potential for adverse effects, drug interactions, and potential for abuse are all items that require consideration. There are several different options available for the treatment of major depression in HIV-seropositive individuals, including pharmacotherapy, psychotherapy, and complementary and alternative therapies. Pharmacologic treatment is generally the standard line of treatment, but new and alternative treatments are currently being utilized. Each HIV-seropositive person living with depression must be treated as a unique case, and only after careful assessment...
of symptoms and accurate diagnosis can a treatment protocol be chosen.

Pharmacotherapy

Upon choosing an appropriate antidepressant treatment in HIV-infected persons, it is important to consider potential drug interactions. The effects of several antiretroviral medications are reduced or altered by coadministration of an antidepressant. Conversely, medications prescribed to treat HIV infection may alter the effects of antidepressant medications. For example, the dosages of antidepressants that are metabolized through the CYP3A4 system (nefazodone, sertraline, escitalopram) are found consequently to be higher systemically due to medications that inhibit CYP3A4 metabolism, including protease inhibitors and the nonnucleoside reverse-transcriptase inhibitor (NNRTI) delavirdine [33]. Therefore, coadministration of nefazodone and ritonavir (a protease transcriptase inhibitor) will elicit elevated systemic concentrations of nefazodone. This elevation may produce several unwanted side effects including disorientation, confusion, and dizziness [34].

HIV-related drug interactions with psychoactive drugs are very complex and extensive. For example, not only does ritonavir exert effects on the CYP3A4 metabolic pathway, it also acts as an inducer of the CYP1A2 pathway and inhibits CYP2D6 [35], resulting in an increased plasma antidepressant concentration. Therefore, antidepressant metabolism is most likely altered in the presence of certain medications used in treatment of conditions associated with HIV. Patient profiles should be accurate and up-to-date to identify possible drug interactions before appropriate antidepressant medications can be prescribed.

Tricyclic antidepressants

Previously, the first line of antidepressant treatment used by physicians has been tricyclic antidepressants, or TCAs. Imipramine, the most commonly prescribed TCA, is associated with 74–89% response rates in HIV patients [36]. Further, imipramine’s effects are independent of stage of illness [27]. TCA therapy has not been shown to alter CD4 or T cell counts. However, poor adherence may result from imipramine therapy due to the multiple side effects associated with its use. Thirty percent of imipramine responders discontinued use after 6 months of follow-up [37]. Side effects include anticholinergic responses such as constipation, hypotension, headache, weight gain, and sexual dysfunction (see Table 2). However, since TCAs potentially cause constipation, sedation, and weight gain, patients with chronic diarrhea, insomnia, or weight loss may experience symptomatic relief using TCAs. In addition, TCAs have been used successfully to treat neuropathic pain commonly experienced by HIV-infected persons [27]. Overdose of this medication may cause lethal toxicity. Therefore, patients having suicidal ideation or other psychiatric issues should be carefully monitored.

Selective serotonin reuptake inhibitors

More commonly prescribed antidepressants are selective serotonin reuptake inhibitors, or SSRIs. Concerns associated with TCA use have led to a dramatic increase in SSRI prescription over the past decade. Studies indicate that 64–100% of individuals who are prescribed SSRIs show marked decreases in depressive symptoms [38,39]. Additionally, patients have reported less discontinuation of SSRIs than that of TCAs. As with TCA use, SSRIs have not been shown to alter CD4 or T cell counts. Side effects may include nausea, headache, and sexual dysfunction (see Table 2). Overall, SSRIs are better tolerated by HIV-infected individuals than TCAs, and there are less risks associated with them [37]. Further, a more manageable regimen is associated with this type of treatment (one to two daily doses for SSRIs compared to five to six daily doses for TCAs) [40].

New antidepressants

Several new antidepressants are available for the treatment of major depression. Although further controlled studies are needed to examine the efficacy and drug interactions of these newer antidepressants in HIV disease, recent data suggest that these drugs are promising new alternatives to traditional pharmacological antidepressant treatments.

Escitalopram is a new SSRI and is the S-enantiomer of citalopram. While citalopram appears to be ineffective in animal models of anxiety and depression, escitalopram has potent effects in rodent models [41]. Studies have demonstrated the consistent antidepressant efficacy and tolerability of escitalopram in patients with major depressive disorder [42,43]. Recently, Gutierrez et al. [44] examined escitalopram in the context of HIV illness by evaluating potential pharmacokinetic interaction(s) between ritonavir and escitalopram in healthy subjects. This was examined since ritonavir may have potential effects on plasma concentrations of escitalopram because the CYP3A4 pathway is required to convert escitalopram to its principle metabolite, S-demethylcitalopram (S-DCT) [45]. The authors reported no pharmacokinetic interaction between escitalopram and ritonavir; however, the results of this study should be followed up in a group of HIV-seropositive subjects.

Reboxetine is another new antidepressant medication that acts as a norepinephrine reuptake inhibitor (NRI) [46]. Upon comparing the efficacy of reboxetine with TCAs, patients treated with reboxetine had a greater efficacy, with fewer side effects [47]. Reboxetine has also been shown to have fewer side effects than fluoxetine [48]. Additionally, reboxetine is not metabolized by CYP450 [10]. The use of reboxetine to treat major depression in HIV patients may be an advantageous approach considering its low side effect profile. Carvalhal et al. [49] investigated the efficacy and tolerability of reboxetine in HIV-seropositive subjects and found that reboxetine was effective in reducing depressive symptoms. Further, reboxetine was well tolerated in this
population, with insomnia, sweating, and shivering being the most commonly reported side effects.

Nefazodone, venlafaxine, mirtazapine, and bupropion are relatively new antidepressants and are generally well tolerated by HIV-infected individuals. Nefazodone was efficacious in reducing depressive symptoms in 15 HIV-seropositive subjects. Seventy-three percent of the subjects experienced improved symptomatology with relatively few side effects [34]. Although venlafaxine does not appear to interact with the CYP450 isoenzymes, it is metabolized by CYP450 2D6. Therefore, doses of venlafaxine should carefully considered in patients currently taking ritonavir [50]. Mirtazapine is a relatively new antidepressant that may be beneficial for HIV-seropositive patients that experience wasting in that it promotes weight gain [51]. Bupropion is potentially efficacious in treating major depression in HIV-seropositive patients that experience fatigue and lethargy. However, it is crucial to recognize the interactions of

<table>
<thead>
<tr>
<th>Antidepressant</th>
<th>Response rate in HIV-infected persons</th>
<th>Side effects</th>
<th>Complications</th>
<th>Implications</th>
</tr>
</thead>
<tbody>
<tr>
<td>Tricyclics (imipramine, desipramine)</td>
<td>74% [106]</td>
<td>Constipation, dry mouth, dizziness, hypotension, drowsiness, headache, cognitive problems, and sexual dysfunction [107].</td>
<td>Toxicity in cases of overdose, should not be used in patients with dementia. Adverse side effect profile.</td>
<td>May benefit patients with diarrhea, insomnia, and weight loss.</td>
</tr>
<tr>
<td>SSRIs (fluoxetine, sertraline, paroxetine)</td>
<td>70–83% [37,106,108,109]</td>
<td>Nausea, dry mouth, headache, upset stomach, nervousness, and sexual dysfunction [110].</td>
<td>May have an effect on CYP-450 isoenzyme-mediated metabolism of other drugs [27,40].</td>
<td>Fewer, milder, more transient side effects, safe for individuals with suicidal ideation and cognitive impairment. May be beneficial for patients currently taking protease inhibitors.</td>
</tr>
<tr>
<td>Escitalopram (SSRI)</td>
<td></td>
<td>Nausea (wade 2002), insomnia, ejaculation problems, somnolence, sweating, and fatigue [111].</td>
<td></td>
<td>May be beneficial for patients currently taking protease inhibitors.</td>
</tr>
<tr>
<td>Reboxetine (NRI)</td>
<td>75% [49]</td>
<td>Dry mouth, constipation, tachycardia, insomnia, and sweating [112].</td>
<td></td>
<td>May be beneficial for patients currently taking protease inhibitors.</td>
</tr>
<tr>
<td>Nefazodone</td>
<td>&gt;73% [34]</td>
<td>Dizziness, insomnia, dry mouth, constipation, and blurred vision [113].</td>
<td>May produce adverse effects in combination with ritonavir [34].</td>
<td>Favorable side effect profile. May be attractive alternative for patients who withdraw from treatment upon development of adverse effects to other antidepressants.</td>
</tr>
<tr>
<td>Venlafaxine</td>
<td>&gt;70% [63]</td>
<td>Nausea, headache, anxiety, and sexual dysfunction [114].</td>
<td>May cause an increased blood pressure in some patients [115]. Possible drug–drug interaction with indinavir [116].</td>
<td></td>
</tr>
<tr>
<td>Mirtazapine</td>
<td></td>
<td>Sedation, increased appetite, dizziness, dry mouth, constipation, and weight gain [117].</td>
<td></td>
<td>Does not interact with CYP450 system [27]. May be beneficial for patients experiencing loss of appetite or weight loss.</td>
</tr>
<tr>
<td>Bupropion</td>
<td>60% [118]</td>
<td>Weight loss, dry mouth, sweating dizziness, and nausea [114].</td>
<td>Has the potential to cause seizures in high-risk patients [27].</td>
<td>Should not be used in patients with seizure disorders, taking drugs to lower seizure threshold, eating disorders, brain injury, neurological impairment, withdrawal from CNS depressants [27]. Should not be taken by patients experience wasting problems.</td>
</tr>
<tr>
<td>Psychostimulants (methylphenidate, dextroamphetamine)</td>
<td>&gt;70% [119,120]</td>
<td>Over stimulation, insomnia, loss of appetite.</td>
<td>Potential for abuse, weight loss, and increased anxiety is some patients [27].</td>
<td>For rapid relief of depressive symptoms, increases energy and cognition, may improve cognitive dysfunction [60,62]. Used to combat muscle wasting, hypogonadism and associated symptoms [60]. May help prevent bone loss in HIV+ individuals [123].</td>
</tr>
<tr>
<td>Testosterone/androgen therapy</td>
<td>&gt;58% [121]</td>
<td>Irritability, tension, reduced energy, hair loss, and acne [122].</td>
<td>May cause testicular atrophy, decreased volume of, and watery ejaculation [122].</td>
<td></td>
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</table>
nefazodone, venlafaxine, and bupropion with protease inhibitors such as, ritonavir, efavirenz, and nelfinavir since these antidepressants interfere with the CYP450 pathway. Special attention should be given to each patient’s profile when prescribing these drugs given the specific drug–drug interactions, as well as the risks associated with other diseases (non-HIV) that the patient may have.

Highly active antiretroviral therapy
HAART has resulted in profound viral replication suppression, CD4 cell repletion, prolonged survival, and decreased death rates in the treatment of HIV infection [52–54]. However, the use of HAART has not only been effective in the treatment of HIV disease but has also been associated with significant improvements in depressive symptomatology [55]. Brechtl et al. [56] reported that major depression was significantly improved by HAART in patients with advanced HIV infection. Studies suggest a significant contribution by HAART to improved quality of life and maintenance of functioning and well-being [57,58]. Furthermore, it has been suggested that HAART is associated with improvements in neuropsychological functioning and AIDS dementia complex [59]. Although the original intent of HAART was to treat HIV infection, clinicians should also consider HAART as a combination therapy to treat major depression in HIV-infected patients.

Alternative pharmacotherapy

Psychostimulants
The use of psychostimulant therapy (i.e., methylphenidate, dextroamphetamine) has proven to be an effective line of antidepressant treatment in HIV-seropositive individuals, especially in advanced stages of illness when rapid relief is desired. Psychostimulants begin to show clinical effects within 2–3 days of administration in comparison to standard antidepressant therapy, which takes 2–8 weeks [60]. Holmes et al. [61] reported an 85% response rate when administering methylphenidate to 17 men with HIV disease. In a study done by Wagner et al. [60], 19 men infected with HIV showed a 95% response rate to 6 weeks of dextroamphetamine treatment. Patients reported varying side effects such as overstimulation, insomnia, and appetite suppression with psychostimulant use. Reductions in fatigue have been noted, as well as marked increases in mood, cognition, sense of well-being, energy levels, and interaction with peers [62]. Increases in mobility and self-sufficiency have also been noted [60]. However, while no psychostimulant abuse among HIV-seropositive persons under medical supervision has been reported, clinicians should be aware of the potential for abuse with these stimulants, especially in patients who are IVDUs [27]. In addition, it remains to be determined if the effects of this treatment are sustained at levels similar to other antidepressant treatments. Therefore, larger, more controlled trials are needed to compare psychostimulants with other standard antidepressants.

Testosterone therapy
Another form of pharmacologic treatment for major depression in HIV patients is the use of androgens or testosterone therapy. Hypogonadism, a disorder present in 50% of men with symptomatic HIV/AIDS, is associated with depressed mood, fatigue, decreased libido, decreased appetite, and loss of lean body mass [63]. Muscle wasting or lipodystrophy is also present in many HIV-infected individuals [64]. Data indicate that the anabolic effect of testosterone or androgen therapy may hinder progression or onset of lipodystrophy, reduce muscle wasting, and relieve symptoms related to hypogonadism, including depression [60]. With other forms of antidepressant treatment, mood may improve but lethargy, nutritional problems, and sexual dysfunction may still persist, especially in late-stage HIV illness. However, testosterone has the potential to treat fatigue, low appetite, and sexual functioning due to its anabolic effects [60]. In a study by Rabkin et al. [65], 34 HIV-seropositive patients with major depression and low serum levels of testosterone were treated for 8 weeks, followed by a placebo-controlled double-blind discontinuation phase. A 79% response rate was reported for both phases of intervention for those treated with testosterone therapy, whereas the response rate in the placebo group fell to 13%. Potential side effects of testosterone therapy include irritability, tension, reduced energy, hair loss, and acne. It is important to recognize that this type of therapy is different than the dosing allowed for supraphysiologic anabolic effects. However, adverse effects may still occur such as testicular atrophy, and decreased concentration and volume of ejaculate could occur with chronic use. In addition, as with any drug prescribed, there are always risks associated with patient overdose. Additional research is needed to determine if androgen therapy is effective in patients without hypogonadism.

Psychotherapy
The optimal treatment for major depression in HIV disease is a combination of pharmacotherapy and psychotherapy [66]. Behavioral interventions can be used as adjunct treatments to help HIV-infected individuals in areas of stress and disease management, as well as coping, in an effort to improve quality of life and slow disease progression [67]. Studies show that the acquisition of behavioral coping skills can lead to lower total mood disturbances and less depression in persons with HIV disease [39]. Psychotherapy is found to be advantageous at all stages of illness but is especially efficacious at the time of diagnosis and symptom emergence. These particular times are especially traumatic for HIV-infected individuals and are usually accompanied by symptoms of dysphoria, fear, anxiety, and uncertainty [67]. Individual interpersonal therapy, cognitive behavioral therapy, and group and family therapy are all effective therapies that can be used to treat major depression in HIV-infected individuals [67–69].
Interpersonal therapy is designed to help patients relate changes in mood to changes in their environments. This type of treatment is time dependent, usually consisting of 16 weeks of therapy. During this time, HIV-infected depressed patients will be prompted to talk about current life issues and associate their symptoms with maladaptive changes in behavior [70]. The therapist may then categorize the issues into one of four problem areas: grief, role dispute, role transition, or interpersonal deficits. Markowitz et al. [69] reported that 16 weeks of interpersonal therapy produced greater reductions in depression scores in HIV-seropositive individuals when compared to supportive therapy, a non-interpersonal, noncognitive therapy. Additionally, subjects receiving interpersonal therapy demonstrated greater self-efficacy. It has been suggested that the connections made between mood, events, and the person’s environment may contribute to a differentiation in treatment results. Delivery of interpersonal therapy has been standardized for HIV populations [69].

In early stages of illness, active behavioral coping may be a key element in aiding persons living with HIV. Modifications in diet, exercise, and lifestyle may alleviate some stress associated with adjusting to disease status. However, as disease state advances and patients are unlikely to reverse progression, cognitive coping strategies may need to be employed. Cognitive–behavioral therapy (CBT) is a structured, time-dependent, goal-directed intervention focused on the patient’s current cognitions. Originally developed by Beck, this type of therapy seeks to teach patients to modify thoughts or beliefs that may exacerbate depressive symptoms, recruit social support, and adapt behaviors to effectively reduce distress [71]. Themes that emerge from CBT are the prospect of debilitation and early death, anger, frustration, and depression over abandonment by family and loved ones due to associated stigmas, as well as the ramifications of disclosing disease status, and anxiety over adopting attitudes of hope versus pessimism [68]. Emphasis is placed on positively reframing the patient’s maladaptive cognitions in an effort to facilitate adjustment and acceptance of current disease status [67]. Lutgendorf et al. [67] showed that CBT reduced depression, dysphoria, anxiety, and overall mood disturbance in symptomatic HIV-seropositive gay men who received CBT in a group setting. Further, subjects who received CBT showed greater improvements in active coping skills such as acceptance and reframing, as well as social support when compared to controls.

CBT can be delivered individually or in a group setting depending on the needs of the individual. Those who are likely to feel inhibited by their peers, friends, or family may benefit from a more intimate relationship with the therapist. However, group therapy is widely used in chronic disease populations, focusing on perceptions of environmental control and self-efficacy while providing social support [72]. Social support has been shown to be inversely related to major depression [73]. In studies such as the Lutgendorf [67] study mentioned above, it has been suggested that social support acts as a buffer for relationships lost due to disclosure of HIV status. Group settings help to facilitate social support and also aid patients in accepting their disease status. Such issues targeted in group therapy sessions that are related to HIV are isolation, stigma and shame, family/relationship, and medical issues. Feedback and encouragement from members, as well as facilitators, can provide reinforcement and maintenance of positive behavior changes [74]. Targ et al. [39] studied the effects of structured group therapy compared to the combination of group therapy and medication (fluoxetine). Both treatment groups showed reductions in depression scores and no significant differences were reported between these two treatment groups, suggesting that group therapy is as effective as group therapy in combination with antidepressant pharmacotherapy.

In addition, CBT in a group setting has been shown to reduce a specific parameter of HIV disease progression. Mulder et al. [75] examined the rate of decline of immunological parameters following 15 weeks of a cognitive behavioral group intervention and also 24 months post-intervention. While there were no differences in rate of decline of CD4 cells, CD4 count, or T cell responses between the CBT group and control group pre- to post-intervention, the subjects that showed larger reductions in distress also had a smaller decline in CD4 counts.

Several significant studies have examined the effects of psychotherapy and educational programs in treating major depression and emotional distress in HIV-infected individuals. Blanch et al. [76] evaluated the immediate and long-term efficacy of a structured cognitive behavioral group therapy program in HIV-seropositive patients that had been referred to a consultation–liason psychiatry department. The BDI and the state subscale of the State/Trait Anxiety Inventory (STAI) were administered to subjects at four time points: 1 month before therapy sessions began, during the first session, during the last session, and 3 months after the last session. Improvements in BDI and STAI scores were observed during the intervention and also after the 3-month follow-up period. The authors concluded that a structured cognitive–behavioral group psychotherapy regime in HIV-infected individuals has long-term efficacy in patients referred to a consultation–liason psychiatry unit. In another study, Weiss et al. [77] found that providing educational materials to HIV-seropositive subjects was just as effective in reducing distress over time, as measured by the Hopkins Symptom Checklist and BDI, as a supportive–expressive group intervention that also received educational materials. These studies provide insight into the benefits of using education as part of an intervention program to improve major depression and/or other cognitive problems.

Though it is clear that psychotherapy is beneficial in HIV-seropositive populations, it should be noted that there are several limitations to the current research. Most studies that have used psychotherapy to treat major depression in
HIV populations have looked at homosexual, male samples. Therefore, it is unknown if these results generalize to HIV-seropositive females or heterosexual men. Further, larger, more representative sample sizes utilizing clinically diagnosed HIV-seropositive subjects are needed to gain evidence for this type of therapy as an effective treatment for major depression in HIV disease [67]. Larger studies may also produce other significant outcomes. Additionally, biases may make it difficult to determine a causal relationship between psychotherapy and the attenuation of depressive symptoms. For example, those who sign up or are recruited for interventions may already have expectations regarding the benefits of the study. Therefore, blinded randomized controlled trials are needed to optimally explore the effects of various types of psychotherapy. Lastly, evidence that identifies social support as a significant outcome of group psychotherapy may be confounding since the origin of social support cannot be determined [67].

While the bulk of the research has examined homosexual populations, several studies exist in the literature examining psychopathology in HIV-seropositive IVDUs. In fact, the IVDU population is at greater risk of psychopathology than HIV-seropositive heterosexuals, hemophiliacs, and gay men [78], and this population should be specially considered during treatment or the planning of treatment with forms of psychotherapy. Grassi et al. [79] examined suicidal ideation and psychological morbidity in HIV-seropositive IVDUs compared with hepatitis C virus (HCV) IVDUs and found that suicide ideation, psychological morbidity, and anxiety and depression symptoms were not directly influenced by HIV serostatus. However, the authors concluded that psychological symptoms and suicide ideation should be a focus of attention in order to improve quality of care and to reduce the risk of HIV and/or HCV infection among IVDUs. Another study examined the association between depression severity and drug injection HIV risk behaviors (needle sharing) in IVDUs [80]. The results of this study indicate that greater severity of depression is associated with greater frequency of injection risk behaviors in IVDUs suffering from major depression. Therefore, an avenue for the prevention of HIV infection may be risk reduction programs designed specifically for depressed IVDUs.

In addition, IVDUs with HIV disease are at an increased risk for poor adherence to antiretroviral medications and/or psychotherapy [32]. Tucker et al. [81] reported that HIV-seropositive patients with depression, generalized anxiety disorder, or panic disorder were more likely to be non-adherent to antiretroviral medications than those without a psychiatric disorder. The observed nonadherence was also associated with cocaine, marijuana, amphetamine, and sedative use. The authors suggest the need for screening and treatment for both mental health problems and substance use problems in HIV-seropositive individuals in attempts to improve antiretroviral medication adherence.

When choosing a treatment intervention for major depression among HIV-infected individuals, it is important for clinicians to assess the needs of the individual and pay special attention to those needs relating to stage of disease and drug use. An optimal intervention would incorporate aspects of both individual and group therapies prompting individuals to reframe their deleterious beliefs, employ active coping strategies, enhance social support networks, and employ an educational program.

Complementary and alternative treatments of major depression in HIV disease

While many individuals receive benefits from traditional therapies in the treatment of major depression, others have found relief in the utilization of complementary and/or alternative therapies, including exercise, acupuncture, and massage therapy. These therapies may be especially beneficial for those who do not respond or adversely respond to pharmacological treatment.

Exercise

The benefits of exercise are well documented for an array of health problems including diabetes [82], cardiovascular disease [83], dyslipidemia [84], and cancer [85]. Exercise improves parameters in HIV-seropositive individuals as well. For example, aerobic exercise training for 10 weeks improved exercise capacity in HIV-seropositive men and increased CD4 cell counts [86], and 16 weeks of resistance training in 25 HIV-seropositive subjects (three times per week) resulted in an increase in lean body mass of 1.75 kg, with a concomitant reduction in body fat of 0.92 kg [87].

Several lines of evidence suggest that physical activity may reduce a person’s risk for developing depression, may be effective in reducing symptoms in mild to moderate depression, and may be effective as a supplemental treatment to pharmacotherapy and/or psychotherapy for severe depression [88]. MacArthur et al. [89] reported a trend for improvement in anxiety and depression scores in six HIV-seropositive subjects following 24 weeks of aerobic training. Also, high depression/anxiety scores correlated with low CD4 cell counts. LaPerriere et al. [86] showed that exercise training could reduce the anxiety and depression associated with the notification of HIV-seropositive status. Conversely, Terry et al. [90] found no significant changes in depressive scores in 21 HIV-seropositive subjects upon completion of a 12-week exercise training program.

While not specifically measuring depression, other studies have examined the relationship between exercise and other psychological outcomes in HIV disease. For example, LaPerriere et al. [91] reported that aerobically trained HIV-infected men were protected from stress-related immune impairments as compared to sedentary controls. Stringer et al. [92] found that 6 weeks of aerobic training significantly increased quality of life scores as measured in a
validated questionnaire. These findings are important since patients with HIV disease tend to have significantly lower QOL scores than do patients with other chronic medical conditions, such as heart failure, diabetes, or emphysema [58]. In contrast, Birk et al. [93] reported no significant improvement in QOL scores following a combined treatment of exercise and massage therapy. Differences in results between these two studies are likely due to differences in the frequency, duration, and mode of exercise regimens. For example, the exercise regimen utilized in the Stringer et al. [92] study involved two separate exercise groups; one group of moderate intensity exercise (three sessions/week; 1 h/session; 6 weeks) and the second group of heavy exercise (three sessions/week; 30–40 min/session; 6 weeks). All exercise training sessions were performed on a cycle ergometer. Both groups showed improvements in QOL scores following the 6-week period. The Birk et al. [93] study used a combined intervention of massage therapy and exercise. This group received a weekly 45-min massage and performed two aerobic exercise sessions per week for 12 weeks (approximately 45 min/session). The aerobic exercise included walking, stationary bicycling, stair stepping, and rowing. No improvements in QOL scores were found at the completion of the study. Another potential explanation for the discrepancy in results between these two studies is that different QOL instruments were used.

Although the antidepressant effects of exercise have not been well established in the HIV population, it is plausible that improving the underlying symptoms of HIV via regular exercise participation would elicit a reduction in depressive symptoms.

**Acupuncture**

Traditional Chinese Medicine practitioners employ acupuncture in illness and disease based on ancient theories of energy balance [94]. Based on the belief that energy flows through meridians throughout the body and that the imbalance of the energies constitute illness, acupuncturists insert needles at specific points in attempts to normalize the imbalance. However, Western culture acupuncture is considered a complementary therapy, and theories are based on neurophysiological effects. The overall purpose of acupuncture is to restore physiological, psychological, and emotional functioning.

Acupuncture has been shown to have beneficial effects on several conditions including low back pain, face and neck pain, musculoskeletal pain due to arthritis, nausea and vomiting, addiction, and headache [95]. Further, acupuncture has been shown to reduce sleep disturbances in HIV-infected individuals. Acupuncture has further been implicated as an alternative or complementary for major depression and affective disorders. In a small, randomized controlled trial, Allen et al. [96] compared symptoms of depression in an acupuncture group, placebo group, and a waitlist control group. The acupuncture group showed greater improvements in depressive scores than the placebo group and the waitlist control group. Roschke et al. [97] examined the benefits of adding acupuncture to antidepressant treatment and found that the acupuncture group and placebo acupuncture group, in combination with antidepressant treatment, improved the course of depression more than pharmacologic treatment alone. However, no differences were detected between the acupuncture and placebo acupuncture groups.

Electroacupuncture has also been suggested as an alternative or complementary therapy for major depression. Lou et al. [98] reported a significant reduction in depressive scores following 5 weeks of electroacupuncture in depressed patients. Furthermore, upon completion of the study, no significant differences were found in depressive scores between the electroacupuncture group and a group receiving the antidepressant amitriptyline hydrochloride, suggesting that electroacupuncture was just as effective in treating depression as the antidepressant medication.

Acupuncture is a complementary/alternative therapy that is frequently used by HIV-seropositive individuals as a means to reduce symptoms. In fact, it has been reported that 48% of an HIV-infected cohort in the United States were using acupuncture as a component in their treatment regimens [99]. Further research is needed to better establish the effect of acupuncture on major depression in HIV disease.

**Massage therapy**

Massage therapy is the manipulation of soft tissues through manual techniques that involve applying fixed or movable pressure [100]. The use of massage therapy as a means of relaxation and pain reduction has been used for hundreds of years. Before drugs, the “laying on of hands” was the primary form of healing [101].

Several hypotheses exist regarding the mechanisms of the actions of massage. An established mechanism of massage involves an increased blood circulation to an area of pain or tension, thereby increasing oxygen and nutrient supply to that area and aiding in the removal of toxins and metabolic wastes [102]. Increases in blood flow further improve the lymphatic system providing the body with enhanced immune function to better fight infection. Other possible mechanisms of action of massage include decreased neuronal excitability in the lower motor neuron pool (resulting in relaxation), reduced muscular tension via stretching of connective tissue and skeletal muscle, and increased opioid release [103,104].

A study supporting the beneficial effects of massage therapy was recently done in HIV-seropositive adolescents [105]. Subjects were assigned to one of two treatment groups, a massage group, or the progressive muscle relaxation control group. Both groups received treatments twice a week for 12 weeks. Following the 12-week period, adolescents who received massage therapy reported reductions in anxiety and depression and showed enhanced immune function.
fully prescribe a treatment regimen based on the individual's presentation in HIV disease, clinicians should be able to successfully guide treatment options that are effective in treating major depressive disorders, which may include anti-inflammatory and mood-stabilizing medications. By having an understanding of the drug interactions that may arise with any prescribed antidepressant medications, clinicians can monitor for any adverse effects or complications that may arise. Additionally, there are diagnostic difficulties that present challenges to clinicians when assessing depression in an HIV-seropositive patient since many of the symptoms of major depression are also symptoms of HIV infection itself.

Successful treatment regimens for HIV-infected persons with major depression should be addressed and thoroughly evaluated on an individual basis. There are several treatment options available including pharmacotherapy, psychotherapy, alternative, and complementary therapies. Since most HIV-seropositive patients are likely to be on medications for depression, the treatment of depression in HIV disease should be correlated with the previously prescribed medications. By having an understanding of the treatment options that are effective in treating major depression in HIV disease, clinicians should be able to successfully prescribe a treatment regimen based on the individual needs of the patient.

Conclusion and implications for clinical practice

Just as HIV disease itself requires medical attention and treatment, psychological dysfunction in HIV-infected individuals should be adequately assessed and diagnosed as well. While major depression is quite prevalent among patients with HIV infection, it is still underdiagnosed. Additionally, there are diagnostic difficulties that present challenges to clinicians when assessing depression in an HIV-seropositive patient since many of the symptoms of major depression are also symptoms of HIV infection itself.

Successful treatment regimens for HIV-infected persons with major depression should be addressed and thoroughly evaluated on an individual basis. There are several treatment options available including pharmacotherapy, psychotherapy, alternative, and complementary therapies. Since most HIV-seropositive patients are likely to be on medications for depression, the treatment of depression in HIV disease should be correlated with the previously prescribed medications. By having an understanding of the treatment options that are effective in treating major depression in HIV disease, clinicians should be able to successfully prescribe a treatment regimen based on the individual needs of the patient.

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