Human Immunodeficiency Virus and Depression in Primary Care: A Clinical Review

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Background: Human immunodeficiency virus (HIV)–infected individuals are at increased risk of developing depression. Depressive syndromes in these patients pose a challenge both diagnostically and therapeutically. These syndromes reflect both the presence of preexisting mood disorders and the development of depressive syndromes subsequent to HIV infection.

Data Sources: A search of the literature to 2005 was performed using the PubMed and Ovid search engines. English- and Portuguese-language articles were identified using the following keywords: *HIV* or *AIDS* and *depression, mental illness, suicide, fatigue, psychiatry,* and *drug interactions*. Additional references were identified through bibliography reviews of relevant articles.

Data Synthesis: The clinical presentation and differential diagnosis of depressive symptoms in HIV illness and the role of HIV in the development of these conditions are reviewed. Management issues including suicide assessment and treatment options are then discussed, and potentially important pharmacokinetic interactions are reviewed.

Conclusions: Individuals with HIV show higher rates of depression. This phenomenon may be due to a preexisting psychiatric disorder or to the HIV infection. Untreated depression symptoms may lead to noncompliance with drug regimens or increased high-risk behaviors. Given the adverse sequelae of untreated depressions in HIV illness, identification and management of depression are integral components of comprehensive HIV care.

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Individuals with human immunodeficiency virus (HIV) are at increased risk of developing depression.[1,2] Prevalence rates of depression in HIV patients have ranged from 5% to 20% due to possible heterogeneity of patient samples.[3] These prevalence rates for depression are not dissimilar from those observed in other serious chronic medical conditions. Sadly, diminished quality of life, treatment nonadherence, increased substance use, and suicide are all potential outcomes of untreated depression. Depression may also predispose patients to other high-risk behaviors and have a direct effect on immunologic markers,[4] potentially even influencing disease progression and survival.[5] With rates of depression as high as 20%[6] among patients presenting for HIV treatment, and the significant impact of untreated depression on the transmission of HIV, clinicians treating HIV illness have a critical role in the recognition, triage, and management of depression in persons with HIV/acquired immunodeficiency syndrome (AIDS).

A search of the literature to 2005 was performed using the PubMed and Ovid search engines. English- and Portuguese-language articles were identified using the following keywords: *HIV* or *AIDS* and *depression, mental illness, suicide, fatigue, psychiatry,* and *drug interactions*. Additional references were identified through bibliography reviews of relevant articles.

DIFFERENTIAL DIAGNOSIS AND CLINICAL CORRELATES

Depressive episodes are characterized by a broad range of neurovegetative symptoms (e.g., changes in appetite, sleep, sexual function, initiative, and energy) and cognitive-affective symptoms (e.g., feelings of guilt, hopelessness, helplessness, anhedonia, negative view of self or others, and suicidal ideation). Though a depressed mood is often present, it is not necessary for the diagnosis of a major depressive episode; some patients more readily endorse a loss of interest and feeling "stressed" or "nervous."

Clinicians may find themselves normalizing depressive symptoms, perhaps thinking that the patient should be depressed in this given situation. Yet, the presence of prominent anhedonia, uncharacteristic emotional responses, and persistent neurovegetative symptoms all

Table 1. Differential Diagnosis of Depression in HIV Illness

Major depressive disorder
Bipolar disorders
Adjustment disorders
Bereavement
Secondary depressive syndromes
Primary HIV encephalopathy
Other CNS infections (toxoplasma encephalitis, cryptococcal meningitis, CNS syphilis, and other opportunistic infections)
CNS neoplasms
Medications (interferon, sulfonamides, isoniazid, efavirenz)
Substance abuse

Abbreviations: CNS = central nervous system, HIV = human immunodeficiency virus.

point to the diagnosis of a major depressive episode that is qualitatively distinct from a normal stress response.

A stress-vulnerability model of depression posits that a given individual will respond to a psychological or physical stressor in ways that are determined by his or her biological vulnerabilities, psychological makeup, and social circumstances. HIV infection may be construed as an accelerator in such a model. Thus, identifying underlying vulnerabilities by evaluating psychiatric history, substance abuse, family psychiatric history, and previous adverse stress responses is important. The presence of vulnerability factors strengthens a diagnosis of major depressive disorder when equivocal or nonspecific depressive symptoms are present. Notably, the majority of individuals with HIV pursuing treatment for depression or developing a major depressive episode have had prior depressive episodes.[7,8]

Diagnosing depression in the context of HIV illness presents significant diagnostic challenges (Table 1).[9] Depressive syndromes in persons with HIV may represent a primary mood disorder (major depressive disorder or bipolar disorder), medication effects, substance abuse, or other medical conditions. Depression can result from direct central nervous system (CNS) invasion by HIV, the effect of antiretroviral drugs (efavirenz) and other pharmacologic treatments (e.g., interferon), or HIV-related complications such as opportunistic infections and intracranial tumors.

While a full discussion of the various diagnostic approaches (etiologic, inclusive, exclusive, and substitutive) and their relative advantages and disadvantages[10–12] is beyond the scope of this review, a brief summary of common approaches follows. DSM-IV adopts an etiologic approach. Symptoms such as weight loss or fatigue are counted toward a diagnosis of depression, except when they seem to be clearly caused by a general medical condition. An exclusive approach, on the other hand, would simply drop symptoms such as anorexia and fatigue due to their low specificity in the medically ill patient (compromising diagnostic sensitivity). The substitutive approach advocated by Endicott[11] would eliminate weight loss, impaired concentration, psychomotor changes, and loss of energy and substitute them with cognitive-affective symptoms. However, there is no universal agreement as to which specific symptoms should replace the ones that have been eliminated. The diagnostic model chosen may depend on the goals of the individual clinician. If the consequences of missing a diagnosis of depression are serious, one may choose to adopt an inclusive diagnostic framework in which neurovegetative changes count toward a diagnosis of depression regardless of their cause (medical or psychiatric). Other authors, however, have suggested that alternative diagnostic schemes offer little, if any advantage over the current DSM approach.[13] Because HIV-related symptoms can mimic the neurovegetative symptoms of depression, we find the diagnostic value of classic depression indicators (changes in sleep, appetite, and energy) to vary with the stage of HIV illness; neurovegetative symptoms are of less consistent value during later stages of the disease (i.e., Centers for Disease Control and Prevention [CDC] category B or C).[14–16]

Fatigue is a nonspecific symptom common both to HIV illness and depression. Ferrando et al.[17] reported fatigue in 14% of HIV-infected patients with CD4+ counts less than 500. Capaldini[18] differentiated among physical fatigue caused by anemia, chronic diarrhea, chronic pain, or HIV treatment; motivational fatigue; inability to experience pleasure (true anhedonia); mental fatigue due to neurocognitive deficits; and fatigue secondary to hypogonadism.[19]

A study by Millikin et al.[20] highlighted the diagnostic conundrum presented by fatigue. The investigators found fatigue to be correlated with depressive symptoms, but not with AIDS diagnosis or medication status. Fatigue also correlated with subjective neurocognitive complaints, but not with objective neuropsychological performance. In contrast, apathy, which is often mistaken for fatigue, has more of a dulled emotional tone and a sense of detachment or indifference. Apathy may be a more reliable marker for subcortical neurocognitive decline and possibly direct involvement of striatal structures.[21]

When significant neurocognitive changes are present, consideration of possible HIV-associated dementia or HIV1-associated minor cognitive motor disorder (HMCMD) is necessary. Memory impairment, reduced ability to concentrate, disturbances in complex attentional tasks and executive functioning, motor retardation, and behavioral abnormalities may occur in both depression and neurodegenerative processes.

An underlying mood disorder in HIV-seropositive individuals can lead to complaints of cognitive decline that are not seen during a neuropsychological evaluation,[22] with depression appearing to be independent of neuropsychological functioning.[23]

When there is question, neurocognitive testing[24,25] and a full neurologic examination can assist in differentiating

Table 2. Symptoms Suggestive of Bipolar Disorders

Decreased need for or ability to sleep
Excessive energy
Physical overactivity, increased goal-directed behaviors
Increased impulsive and sexual behaviors
Overactive thoughts, inability to "shut off" one's brain
Increased talking and pressured speech
Expansiveness or elation
Heightened irritability
Grandiosity

between cognitive difficulties due to depression and impairment caused by a neurodegenerative processes. If other symptoms of depression are present, an antidepressant trial may be warranted; cognitive function can then be assessed again after the depressive symptoms have lessened.

Finally, hepatitis C coinfection, which is fairly prevalent in HIV-infected patients,[26] may also contribute to CNS dysfunction.[27,28] Aside from cognitive decline, the treatment of hepatitis C carries important diagnostic implications, as interferon therapy can lead to depressive symptomatology. While preexisting depression is not an absolute contraindication for interferon therapy, depression should be treated before interferon treatment is started, and patients should be closely followed for the development of a mood disorder.[29]

Determining the cause of depressive symptoms requires careful consideration of both the nature and course of the individual symptoms, with awareness that concurrent processes may occur. In addition to the history of the present illness, evaluation includes a complete review of systems and personal and family histories of psychiatric illness, substance abuse, and suicide attempts. Pertinent laboratory evaluation includes total and serum free testosterone levels and assessment for subclinical and clinical hypothyroidism, which are prevalent in HIV-infected individuals, especially males.[30,31] Particular attention should be paid to recent medication changes that may have acted as precipitants of psychiatric symptoms.

Assessment for comorbidities such as anxiety disorders and substance abuse is essential, as clinical presentations often represent comorbid conditions rather than a single process. The prevalence of anxiety disorders was found to be as high as 38.2% in an urban community health clinic sample of HIV-infected patients.[32] Posttraumatic syndromes, which may become exacerbated during depressions, are of particular relevance,[33] as preexisting posttraumatic stress syndrome may be associated with high-risk behaviors that increase the likelihood of infection; predisposing risk behaviors for HIV may also facilitate the exposure to traumatic events. Finally, emotional and physical trauma resulting from the sequelae of an HIV diagnosis may lead to a plethora of psychiatric phenomena.[34]

The differential diagnosis for any depressed patient must include possible bipolar disorders (Table 2). Assessment for bipolarity should occur prior to starting antidepressant therapy to avoid worsening of the condition, leading to a more agitated or manic state. Agitation, emotional lability, irritability, and restlessness are all clues to possible bipolarity that may be masked by concurrent depressive symptoms. If there is uncertainty regarding the presence of underlying bipolar disorder, we recommend obtaining a psychiatric consultation, if possible, prior to initiating antidepressant treatment. When manic symptoms are present, precipitants of secondary mania[35] need to be considered. HIV itself, infections such as cryptococcal meningitis, and agents such as corticosteroids,[36] androgens,[37] zidovudine,[38] didanosine,[39] and possibly efavirenz[40] have all been associated with induction of mania. Initial assessment of mania should include a careful history of the present illness with particular attention devoted to recent medication additions or adjustments, as well as underlying risk factors for bipolar illness including family history of bipolarity or psychotic illnesses.

Table 3. Individual Clinical Risk Factors for Suicide

Previous suicide attempts
Substance abuse
Fixed hopelessness
Agitation
Severe anxiety and panic
Complete loss of pleasure
Uncontrolled physical pain
Social isolation
Poor social support
Occupational or financial problems
Recent loss of relationship
Inadequate coping skills
Insomnia
History of impulsive behavior

SUICIDE

Risk and Assessment

As in patients with any chronic medical illness, the potential for suicide should be evaluated in all patients with HIV illness and reassessed at routine intervals if any suicide risk factors are present. A recent study found that 26% of HIV-seropositive patients in an HIV mental health clinic sample reported suicidal ideation within a month of admission. Of these patients, 49% had a suicidal plan and 48% expressed a suicidal intent.[41] Table 3 summarizes individual clinical risk factors for suicide. Contrary to a widely held assumption, asking about suicide does not increase the risk of suicidal behavior.

Predictors of suicide attempts in HIV-seropositive patients are psychiatric comorbidities, substance use, and previous suicide attempts.[42] A patient with advanced AIDS but no prior psychiatric history might not consider suicide, while an asymptomatic seropositive patient who has a history of drug abuse, impulsiveness, or suicide attempts predating HIV infection could be at markedly increased risk for suicide.

HIV-infected individuals with recent losses, occupational problems, social isolation, poor social support, or the experience of stigmatization seem to be at increased risk.[43–45] Hopelessness and despair also convey increased risk for completed suicide in the general population,[46] as do high levels of anxiety, agitation, panic attacks, and severe loss of interest or pleasure.[47] One important caveat, however, is that although these risk factors for suicide are important to identify, they are not highly predictive, and their absence does not assure one that the patient is completely safe.

It is unclear to what degree the progression of HIV illness influences suicidal ideation.[48] The time periods immediately after HIV diagnosis[49,50] and just before AIDS develops[50] may be of particularly high risk for the occurrence of suicidal behavior. Later in the course of the illness, suicidality may be exacerbated by HIV dementia, which is associated with labile mood, behavioral disinhibition, impaired judgment, and increased impulsivity.[51] Exacerbation of suicidality can occur even if the patient had good premorbid functioning without family or personal psychiatric history.

In some cases, the "option" of suicide in the distant future is an adaptational mechanism.[52] Patients with such thoughts often do not actually desire hastened death at the present moment, but reserve the option of suicide to be used at an adverse landmark in the future; this landmark ultimately gets pushed further out as patients acquire a greater sense of mastery in living with their illness. Patients should be encouraged to share with their clinicians any change in the immediacy or nature of their thoughts of death. Even for these patients, the risk of completed suicide may become greater in the context of acute distress; thus, continued reevaluation is essential.

An open inquiry regarding thoughts, fears, or desire for death can reassure patients that the clinician is comfortable with discussing these difficult realities and may reduce feelings of guilt or shame that inhibit patients from acknowledging such thoughts. Questions regarding thoughts of or desire for death can be prefaced by noting that persons living with HIV often find themselves having thoughts of death at times of distress. Questioning begins broadly and then becomes more specific with questions regarding desire, intent, plans, access to means, and immediacy—and what, if anything, has kept them from acting upon the thoughts to date. Suicidal ideation as a "coping strategy" to counter dependency fears or anxiety over loss of control should always be distinguished from the result of acute impulsive activity that is sometimes precipitated by the loss of executive function or comorbid psychiatric disorders.

Interventions to reduce acute suicide risk should focus on reversible risk factors, with the clinician assuring the patient that distressing factors such as uncontrolled pain, severe anxiety, and insomnia will be addressed and, if necessary, consultations will be obtained. These interventions should be accompanied by an assessment of available supports and, if appropriate, the enlistment of significant others, trusted family members, or friends in the overall care plan. When suicidal ideation is used as a coping strategy, a psychotherapy referral may be recommended.

For patients with limited social supports, an explicit reassurance of continued support and concern from the treatment team may lessen feelings of isolation and alienation. Active problem-solving with identification of alternatives helps patients focus on the present and lessens the sense of helplessness.

Special Considerations

Persons in the terminal stages of AIDS generally do not desire hastened death through suicide. Rather, a request for clinician-assisted suicide may be a response to psychic distress coming from uncontrolled physical pain, severe depression, and other reversible causes of distress. Attitudes of HIV patients toward physician-assisted suicide seem to be mainly a function of psychological distress.[53] For patients with any physical discomfort, early initiation of palliative care (which does not imply a terminal status) and a commitment to aggressive pain management are essential, as the fears of persistent pain and of painful death can both lead to the development of suicidal thoughts.[54]

TREATMENT OF DEPRESSION

As can be concluded from the preceding discussion, treatment of depression in HIV illness can have multiple positive outcomes: enhanced quality of life, improved adherence to medication, reduction of high-risk behaviors and suicidality, and potentially enhanced immune function.[55,56] Given the complex interplay among biological predispositions, neuropathologic involvement, personality factors, and life circumstances that characterizes HIV disease, the treatment of depression should be multimodal and involve both pharmacologic and psychosocial interventions.

Selecting and Using Antidepressants

General clinical considerations. Psychotropic medication selection is determined by demonstration of efficacy for depression and comorbid conditions, relevance of pharmacodynamic and pharmacokinetic properties for a particular patient, patient history of treatment response, ease of use, and safety considerations. Antidepressant selection requires consideration of side effects that may interfere with treatment adherence or lead to worsening of other disease states; this is especially important for HIV-seropositive individuals, who often have a heightened sensitivity to drugs, are burdened with complex

treatment regimens, and need to maintain antiretroviral levels within suppressive ranges. Notably, side effects also may be exploited for therapeutic purposes, as in the selection of a sedating antidepressant that can immediately address insomnia. If a psychiatrist is already treating the patient, coordination of care with that provider can further enhance the patient's recovery from depression and lessen iatrogenic complications related to pharmacologic management.

In general, treatment with antidepressants is best started at lower doses and with slower titration in patients with HIV illness, especially in those with advanced illness or complex medication regimens. However, clinicians still should strive to attain an optimal dose that brings about complete remission of depressive symptoms. Remission of depression symptoms, minimization of side effects, and avoidance of drug-illness and drug-drug interactions are all goals of effective antidepressant treatment. It is also important to remind patients that antidepressants may take several weeks to achieve full efficacy and that patients should continue taking the medication after the desired effect in order to maintain remission of depressive symptoms. Similarly, antidepressants should not be discontinued or have dosages altered without physician supervision.

Given the relative tolerability of selective serotonin reuptake inhibitors (SSRIs), their safety in overdose, and their efficacy,[57–59] these agents have been widely used in the treatment of depression. Side effects of the SSRI class include insomnia, anxiety, agitation, sexual dysfunction, irritability, decreased or increased appetite, and nausea. Many of these side effects subside during the first few weeks of treatment, though sexual dysfunction tends to persist. One slight pharmacologic difference among SSRIs is paroxetine's mild anticholinergic activity,[60] suggesting that paroxetine should be used with some caution if significant cognitive impairment is present.

SSRIs primarily differ from one another by their pharmacokinetic profiles. Fluoxetine and its active metabolite have especially long half-lives, making fluoxetine a less appealing choice than other SSRIs, particularly in cases of decreased clearance due to organ failure. Paroxetine's pharmacologic profile is associated with the potential for a discontinuation syndrome if the drug is abruptly stopped. The syndrome is characterized by a flu-like picture with symptoms of cholinergic rebound, paresthesias, heightened depressive symptoms, affective lability, deterioration of mood state, dizziness, insomnia, nausea, nervousness, and agitation.[61] Although especially prominent with abrupt paroxetine discontinuation, the potential for a discontinuation syndrome is also a concern for all shorter half-life SSRIs and serotonin and norepinephrine reuptake inhibitors (SNRIs). Among the SSRIs, citalopram[62] and its *S*-enantiomer, escitalopram, are generally well tolerated; they have intermediate half-lives and favorable pharmacokinetic profiles. Sertraline also has a favorable kinetic profile in comparison to fluoxetine and paroxetine.

Venlafaxine is an SNRI with a side effect profile similar to those of SSRIs, though venlafaxine is also associated with increases in diastolic blood pressure at higher doses. Similar to paroxetine, venlafaxine should not be interrupted abruptly because of the possibility of a discontinuation syndrome, which can include severe dysphoria and recurrence of suicidal ideation. Duloxetine, a recently released antidepressant, is an SNRI that appears to have benefits in treating some forms of pain.[63–65] However, no data regarding duloxetine use in HIV illness are available at this time.

Bupropion is a drug with both noradrenergic and dopaminergic actions. Given its potential activating effects, bupropion can be useful for those patients for whom anergia is a significant problem. A recent prospective trial of sustained release bupropion in depressed patients with HIV demonstrated the drug's efficacy and tolerability in this patient population.[66] However, because it can lower seizure threshold, bupropion is not recommended for individuals suffering from intracranial pathologies such as toxoplasmosis, lymphomas, and cytomegalovirus. Bupropion use is also not recommended for patients with eating disorders or severe electrolyte disturbances.

Mirtazapine is thought of as a broad-spectrum antidepressant, with antagonism of α_2, 5-HT_2, and 5-HT_3 receptors. It can increase appetite, leading to weight gain, and promote sleep through antihistaminic effects; it also potentially lessens nausea through its 5-HT_3 antagonism.[67] Notably, the drug is more sedating at lower than at higher doses. Early experience with the drug found that 3 of 2796 patients developed severe neutropenia.[68] However, case reports from more than 10 million patients exposed to mirtazapine found the incidence of agranulocytosis to be rare.[68]

Nefazodone is an atypical antidepressant with prominent anxiolytic and sleep-normalizing properties. As is true for mirtazapine and bupropion, nefazodone has minimal adverse effect on sexual functioning, in contrast to the SSRIs and SNRIs. Unfortunately, nefazodone has been associated with rare cases of hepatotoxicity and hepatic failure and the potential for important drug-drug interactions.

Trazodone, a medication chemically similar to nefazodone, is frequently used to treat insomnia and to augment therapy with SSRIs. Side effects include postural hypotension, xerostomia (though less than is seen with the use of tricyclic antidepressants [TCAs]), and priapism (rare). The possibility of sedation or hypotension limits trazodone use at doses high enough to be therapeutic for treatment of depression.

We do not recommend the use of TCAs as first-line agents. Although TCAs and in particular imipramine have

been shown to be effective in placebo-controlled trials,[69] they are accompanied by several side effects to which patients with HIV appear particularly sensitive. TCAs have pronounced anticholinergic properties, which can cause delirium, orthostatic hypotension, neurocognitive impairment, urinary retention, exacerbation of conduction delays, narrow angle glaucoma, and oral thrush by means of decreased salivation. Nevertheless, TCAs are sometimes used to treat pain associated with HIV neuropathy. In our opinion, the use of TCAs should be reserved for HIV-asymptomatic patients in whom neurocognitive impairment has been ruled out, due to the fact that even patients who are medically asymptomatic may still exhibit mild HMCMD. When TCAs are used, secondary TCAs such as desipramine and nortriptyline, which have lower anticholinergic and orthostatic liability, are preferred.[70]

Similarly, the use of monoamine oxidase inhibitors (MAOIs) in primary care settings is not recommended. Dietary restrictions may constitute an additional burden in patients already plagued by complex pharmacologic regimens, and MAOIs may not be a feasible alternative. If initiation of an MAOI seems a reasonable course of action, referral to an experienced psychopharmacologist should be arranged. The same holds true for augmentation strategies when patients have not responded to first-line antidepressant agents.

Further pharmacokinetic considerations. While assessment of possible pharmacokinetic interactions is required whenever prescribing multiple medications in HIV illness, the complexity and number of potential medication combinations make it impractical for any clinician to memorize all potential interactions. Therefore, a general understanding of the underlying kinetic principles can greatly assist in identifying potential interactions, with the help of references such as Table 4[71–75] and the *Physicians' Desk Reference*.[76]

Oxidative enzymes responsible for the metabolism of drugs are divided into families and subfamilies named according to the cytochrome P450 variants (1A2, 2D6, 3A4, etc.). Drugs metabolized by a particular enzyme are substrates of that enzyme; a drug can be a substrate for more than 1 enzyme. Drugs can also induce or inhibit P450 enzymatic systems as well as other metabolic pathways (e.g., hydroxylation, glucuronidation). Moreover, a drug can inhibit (e.g., paroxetine, fluoxetine, nefazodone) or induce (carbamazepine) the enzyme or enzymes responsible for its own metabolism.

Protease inhibitors and nonnucleoside reverse transcriptase inhibitors (NNRTIs) are primarily metabolized through the hepatic enzymatic system P450 3A family and secondarily through P450 2D6. Protease inhibitors, and to some degree NNRTIs, may affect P450 systems through induction or inhibition. Among protease inhibitors, ritonavir is the strongest inhibitor of P450 isoenzymes (3A3/4, 2D6, 2C19, and 2C9), followed by

Table 4. Selected Pharmacokinetic Interactions[a]

Cytochrome	Substrates	Inhibitors	Inducers
1A2	Amitriptyline Caffeine Duloxetine Fluvoxamine Imipramine Methadone Mirtazapine Olanzapine Zolpidem	Fluvoxamine Ritonavir	Ritonavir Smoking
2B6	Bupropion Efavirenz Nevirapine	Efavirenz Nelfinavir Ritonavir	Nevirapine
2C9/19	Amitriptyline Citalopram Escitalopram Fluoxetine Imipramine	Ritonavir Efavirenz Modafinil Nelfinavir	Rifampin
2D6	Amitriptyline Amphetamines Aripiprazole Atomoxetine β-Blockers Codeine Desipramine Duloxetine Trazodone Haloperidol Imipramine Indinavir Mirtazapine Nelfinavir Nortriptyline Oxycodone Paroxetine Perphenazine Risperidone Ritonavir Thioridazine Tramadol Venlafaxine	Bupropion Duloxetine Fluoxetine Paroxetine Perphenazine Ritonavir Sertraline	
3A3/4	Alprazolam Amprenavir Aripiprazole Buspirone Carbamazepine Clonazepam Dexamethasone Diazepam Eszopiclone Indinavir Itraconazole Midazolam Modafinil Nefazodone Nelfinavir Nevirapine Quetiapine Ritonavir Saquinavir Sildenafil Triazolam Ziprasidone	Delavirdine Grapefruit juice Indinavir Itraconazole Ketoconazole Nefazodone Norfluoxetine Ritonavir Saquinavir Fluvoxamine Amprenavir Efavirenz	Carbamazepine Dexamethasone Efavirenz Modafinil Nevirapine Rifabutin Rifampin St. John's wort

[a]Based on references 71–76.

indinavir (2D6 and 3A3/4) and then by 2 weak inhibitors of the isoenzymes 3A3/4 and 2C9, saquinavir and nelfinavir. Amprenavir also inhibits P450 3A3/4. Finally, the NNRTIs nevirapine and efavirenz are 3A family substrates and inducers (efavirenz is also an inhibitor of 3A3/4).

Coadministration of a psychotropic and an antimicrobial may cause alterations in levels of either or both drugs. Examples of kinetic interactions include those of protease inhibitors, especially ritonavir, inhibiting the metabolism of antidepressants, antipsychotics, methadone, and 3,4-methylenedioxymethamphetamine (MDMA). Ritonavir coadministered with fluoxetine may lead to accumulation of both fluoxetine and its metabolite norfluoxetine, which may account for reports of serotonin syndrome, characterized by myoclonus, hyperpyrexia, and agitation, observed in patients using antiretrovirals with fluoxetine.[77] It is therefore advisable to start treatment with an SSRI at a low dose and to carefully monitor for side effects when SSRIs and protease inhibitors are coadministered.

Other interactions include interference of trazodone metabolism by 3A3/4 inhibition from coadministration of ketoconazole, ritonavir, and indinavir.[78] Even short coadministration with ritonavir impairs trazodone clearance and can increase the likelihood of trazodone-related adverse side effects such as hypotension.[79] Lastly, ritonavir, efavirenz, and nelfinavir may interfere with the metabolism of bupropion by inhibition of cytochrome P450 2B6, through which bupropion is metabolized[80]; given bupropion's potential for lowering seizure threshold, caution is warranted when these medications are combined.

Nefazodone and fluvoxamine are both potent inhibitors of P450 3A3/4, complicating their use in patients with complex drug regimens. Paroxetine, fluoxetine, and duloxetine are potent inhibitors of P450 2D6 and may raise the levels of several protease inhibitors metabolized through the 2D6 pathway; this increased inhibition could be viewed as either a desirable or an undesirable effect. Alternatively, the concurrent use of indinavir and venlafaxine can lead to reduced indinavir levels[81]; the clinical significance of this finding is not clearly established. Table 4 summarizes other potentially significant interactions.

Protein binding of psychotropic drugs should also be considered as a potential source of pharmacokinetic interactions. Among the commonly used antidepressants, duloxetine, fluoxetine, paroxetine, and sertraline show protein binding greater than 90%. Mirtazapine (85%), bupropion (84%), citalopram (80%), and fluvoxamine (77%) have intermediate protein binding, and escitalopram (56%) and venlafaxine (27%) have the lowest binding.[76]

In summary, complex treatment regimens require awareness of potential interactions before treatment with new medications is begun and further require ongoing monitoring of interactions that can significantly alter dosing strategies. Furthermore, clinicians need to anticipate possible dose adjustments whenever a potent inhibitor or inducer is removed from a patient's drug regimen. In light of the above considerations, citalopram, escitalopram, mirtazapine, and venlafaxine all seem to be reasonable first-line agents, provided that a careful risk-benefit analysis is performed for each patient prior to starting treatment with any medication.

Other Somatic Treatments of Depression

Psychostimulants such as methylphenidate and amphetamine have been successfully used in the management of depressive symptoms and in ameliorating symptoms of cognitive decline in patients with HIV illness.[82–85] Stimulants have been shown to improve apathy, fatigue, anorexia, self-care, and suicidal ideation in medically ill patients.[86] They can be especially useful when rapid amelioration of severe anergia is desired. Obviously, caution should be exercised in individuals with recent cocaine or stimulant abuse, because all stimulants have an abuse potential. However, there are few, if any, published reports of abuse of stimulants prescribed under medical supervision.[70] In all cases, a detailed record of stimulant prescriptions should be kept by the clinician to avoid the possibility of diversion, and, when necessary, cross-checking of prescriptions filled with the dispensing pharmacies should be done. A careful baseline assessment of target symptoms with an objective evaluation of cognitive impairment may also be helpful in tracking symptom improvement.

An alternative to stimulants in patients with substance abuse history is modafinil, a schedule II drug used in narcolepsy and other medical disorders such as Parkinson's disease. Although modafinil is a promising agent for the treatment of fatigue,[87] its use in HIV patients and its possible pharmacokinetic interactions[88] have not yet been adequately studied. Therefore, we recommend that modafinil be used in consultation with an experienced psychopharmacologist after a careful assessment of possible pharmacologic interactions.

Spurred by the recognition of testosterone deficiency with signs of hypogonadism in many men and women with symptomatic HIV illness, investigators studying androgen replacement therapies have reported the benefit of such treatment in reducing fatigue and depressive symptoms in HIV-infected men (using dehydroepiandrosterone or testosterone)[19,89–91] and most recently women,[92] though results in the latter group have been mixed.[93] Transdermal testosterone replacement (patches or gel) may offer some advantage compared with intramuscular formulations, as transdermal formulations may be characterized by a more physiologic pharmacokinetic profile.[94,95]

Benzodiazepines, when used judiciously for short periods of time in selected populations, may be useful

adjuncts in treating acute physical anxiety and panic symptoms, especially while waiting for primary treatments, such as SSRIs, to become effective. Those drugs with intermediate half-lives and less complex metabolic pathways, such as lorazepam or oxazepam, are recommended. The ongoing use of benzodiazepines is generally discouraged, especially in patients with substance abuse potential or cognitive dysfunction. The persistence of anxiety symptoms requires diagnostic reevaluation and consideration of other treatment options.

St. John's wort (*Hypericum*) is a botanical preparation used by some patients as an antidepressant alternative. However, it has questionable efficacy[96] and is not recommended in patients taking protease inhibitors due to the potential reduction of protease inhibitor levels.[97,98]

Electroconvulsive therapy may be an option for those severely depressed patients not responsive to pharmacologic interventions. Recent studies have pointed to its efficacy[99] and possible use in HIV-induced stupor.[100]

Psychosocial Treatments and Consultations

Psychosocial interventions are important components of the overall treatment for any depressed patient. Interpersonal therapy[101] and cognitive-behavioral therapy, especially in a group format,[102,103] have demonstrated effectiveness in studies of depressed HIV-seropositive individuals. Contracts that outline expectations and goals of treatment and relapse prevention techniques have been found to be effective for extroverts with unstable behavioral patterns.[104] Couples or family therapy may be useful when significant difficulties emerge in negotiating disclosure of HIV status or when family support is critical for a patient's treatment compliance. Psychodynamic approaches may assist HIV-infected individuals in elaborating the meaning of their illness and address fears of rejection, isolation, dependency, and loss of control. In all cases, a supportive stance with a focus on reducing high-risk behaviors is essential.

Patients with past or current alcohol and substance abuse require ongoing monitoring for alcohol/substance use, with a relapse prevention focus. If the patient is using substances or is at risk for substance use, a referral to a chemical dependency group or community resource such as Narcotics Anonymous or Alcoholics Anonymous is advised. Unfortunately, some peer-led substance use groups are critical of psychotropic medication, regardless of the severity or nature of the disorder being treated, and patients may need encouragement in finding a group that is supportive regarding the appropriate use of antidepressants.

While any patient with depression should be considered at risk for possible bipolar illness, clinicians need to be especially alert for possible bipolarity in depressed patients who abuse substances. Patients often use alcohol and other substances to self-medicate emerging bipolar symptoms. An increase in alcohol, benzodiazepine, or marijuana use after starting antidepressant treatment may be a clinical indicator of emerging manic-spectrum symptoms. Such a patient requires immediate evaluation and treatment to prevent further exacerbation of manic-spectrum symptoms. Similarly, psychiatric consultation should be considered whenever patients develop unusual clinical presentations while on treatment with psychotropic medications. As summarized in Table 5, psychiatric consultation is also indicated for more complicated cases and for cases in which safety issues are of concern.

Table 5. When to Refer Patients to Mental Health Providers

Disabling depressive symptoms
Suicidal thoughts with plan or intent
Severe hopelessness and negativism
Persistent agitation
Psychotic symptoms
Pronounced affective instability
Suspected bipolar disorder
Nonresponse to 3 or more antidepressant trials
Complicated psychopharmacologic regimens
Maladaptive social functioning

CONCLUSIONS

Evidence to date suggests that individuals with HIV illness have increased rates of depression, often reflecting both the presence of preexisting mood disorders and the development of depressive syndromes subsequent to HIV infection. Depressions are treatable, and their treatment improves quality of life and adherence to medication regimens with potential for enhanced survival. Treating depression may also reduce high-risk behaviors in HIV-infected patients, conceivably diminishing the risk of co-infection with resistant HIV strains or other pathogens such as hepatitis C virus, and a reduction of high-risk behaviors can also help reduce HIV secondary transmission. Given the adverse sequelae of untreated depression in HIV illness, identification and management of depression are integral components of comprehensive HIV care.

Drug names: alprazolam (Xanax, Niravam, and others), amphetamine (Adderall and others), amprenavir (Agenerase), aripiprazole (Abilify), atomoxetine (Strattera), bupropion (Wellbutrin and others), buspirone (BuSpar and others), carbamazepine (Carbatrol, Equetro, and others), citalopram (Celexa and others), clonazepam (Klonopin and others), delavirdine (Rescriptor), desipramine (Norpramin and others), dexamethasone (Mymethasone, Hexadrol, and others), diazepam (Valium and others), didanosine (Videx and others), duloxetine (Cymbalta), efavirenz (Sustiva), escitalopram (Lexapro), eszopiclone (Lunesta), fluoxetine (Prozac and others), haloperidol (Haldol and others), imipramine (Tofranil and others), indinavir (Crixivan), isoniazid (Nydrazid, Laniazid, and others), itraconazole (Sporanox and others), ketoconazole (Ketozole and others), lorazepam (Ativan and others), methadone (Methadose and others), methylphenidate (Ritalin, Metadate, and others), mirtazapine (Remeron and others), modafinil (Provigil), nelfinavir (Viracept), nevirapine (Viramune), nortriptyline (Pamelor, Aventyl, and others), olanzapine (Zyprexa), oxycodone (OxyContin, Roxicodone, and others), paroxetine (Paxil, Pexeva, and others), quetiapine (Seroquel), rifabutin (Mycobutin), rifampin

(Rimactane, Rifadin, and others), risperidone (Risperdal), ritonavir (Norvir), saquinavir (Invirase), sertraline (Zoloft), sildenafil (Revatio and Viagra), testosterone (Androderm, Testim, and others), tramadol (Ultram and others), trazodone (Desyrel and others), triazolam (Halcion and others), venlafaxine (Effexor), zidovudine (Retrovir and others), ziprasidone (Geodon), zolpidem (Ambien).

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REFERENCES

1. Rabkin JG, Ferrando SJ, Jacobsberg LB, et al. Prevalence of axis I disorders in AIDS cohort: a cross-sectional, controlled study. Compr Psychiatry 1997;38:146–154
2. Ciesla JA, Roberts JE. Metanalysis of the relationship between HIV infection and risk for depressive disorders. Am J Psychiatry 2001;158: 725–730
3. Cruess DG, Evans DL, Repetto MJ. Prevalence, diagnosis and pharmacological treatment of mood disorders in HIV disease. Biol Psychiatry 2003:54:307–316
4. Evans DL, Ten Have TR, Douglas SD. Association of depression with viral load, CD8 T lymphocytes and natural killer cells in women with HIV infection. Am J Psychiatry 2002;159:1752–1759
5. Ickovics JR, Hamburger ME, Vlahov D. Mortality, CD4+ cell count decline, and depressive symptoms among HIV-seropositive women: longitudinal analysis from the epidemiological research study. JAMA 2001;285:1466–1474
6. Lyketsos CG, Hanson A, Fishman M, et al. Screening for psychiatric morbidity in a medical outpatient clinic for HIV infection: the need for a psychiatric presence. Int J Psychiatry Med 1994;24:103–113
7. Khouzam HR, Donnelly NJ, Ibrahim NF. Psychiatric morbidity in HIV patients. Can J Psychiatry 1998;43:51–56
8. Leserman J. HIV disease progression: depression, stress, and possible mechanisms. Biol Psychiatry 2003;54:295–306
9. Penzak SR, Reddy YS, Grimsley SR. Depression in patients with HIV infection. Am J Health Syst Pharm 2000;57:376–386
10. Koenig HG, George LK, Peterson BL. Depression in medically ill hospitalized older adults: prevalence, characteristics, and course of symptoms according to six diagnostic schemes. Am J Psychiatry 1997;154: 1376–1383
11. Endicott J. Measurements of depression in patients with cancer. Cancer 1984;53(suppl 10):2243–2249
12. Bukberg J, Penman D, Holland JC. Depression in hospitalized cancer patients. Psychosom Med 1984;46:199–212
13. Koenig HG, Pappas P, Holsinger T. Assessing diagnostic approaches to depression in medically ill older adults: how reliably can mental health professionals make judgments about the cause of symptoms? J Am Geriatr Soc 1995;43:472–478
14. Malbergier A. Tratamento de depressao em individuos infectados pelo HIV. Rev Bras Psiquiatr 2001;23:160–167
15. Perkins DO, Leseman J, Stern RA, et al. Somatic symptoms of HIV infection: relationship to depressive symptoms and indicators of HIV disease. Am J Psychiatry 1995;152:1776–1781
16. Baker J, Ruiz-Rodriguez R, Whitfeld M, et al. Bacillary angiomatosis: a treatable cause of acute psychiatric symptoms in human immunodeficiency virus infection. J Clin Psychiatry 1995;56:161–166
17. Ferrando S, Evans S, Goggin K, et al. Fatigue in HIV illness: relationship to depression, physical limitations, and disability. Psychosom Med 1998;60:759–764
18. James JS. Fatigue and HIV: interview with Lisa Capaldini M.D. AIDS Treatment News 1998;291:1–6
19. Wagner GJ, Rabkin JG, Rabkin R. Testosterone as a treatment for fatigue in HIV+ men. Gen Hosp Psychiatry 1998;20:209–213
20. Millikin CP, Rourke SB, Halman MH, et al. Fatigue in HIV/AIDS is associated with depression and subjective neurocognitive complaints but not neuropsychological functioning. J Clin Exp Neuropsychol 2003;25: 201–215
21. Paul RH, Brickman AM, Navia B. Apathy associated with volume of the nucleus accumbens in patients infected with HIV. J Neuropsychiatry Clin Neurosci 2005;17:167–171
22. Moore LH, Van Gorp WG, Hinken CH, et al. Subjective complaints versus actual cognitive deficits in predominantly symptomatic HIV seropositive individuals. J Neuropsychiatry Clin Neurosci 1997;9:37–44
23. Richardson MA, Satz PF, Myers HF, et al. Effects of depressed mood versus clinical depression on neuropsychological test performance among African American men impacted by HIV/AIDS. J Clin Exp Neuropsychol 1999;21:769–783
24. Bornstein RA, Pace P, Rosenberger P. Depression and neuropsychological performance in asymptomatic HIV infection. Am J Psychiatry 1993; 150:922–927
25. Hinkin CH, van Gorp WG, Satz P, et al. Depressed mood and its relationship to neuropsychological test performance in HIV-1 seropositive individuals. J Clin Exp Neuropsychol 1992;14:289–297
26. Brau N, Bini EJ, Shahidi A. Prevalence of hepatitis C and co-infection with HIV among United States veterans in the New York City metropolitan area. Am J Gastroenterol 2002;97:2071–2078
27. Ryan EL, Morgello S, Isaacs K, et al. Neuropsychiatric impact of hepatitis C on advanced HIV. Neurology 2004;62:957–962
28. Brew BJ. Evidence for a change in AIDS dementia complex in the era of highly active antiretroviral therapy and the possibility of new forms of AIDS dementia complex. AIDS 2004;18(suppl 1):S75–S78
29. Schaefer M, Schwaiger M, Garkisch AS, et al. Prevention of interferon-alpha associated depression in psychiatric risk patients with chronic hepatitis C. J Hepatol 2005;42:788–789
30. Beltran S, Lescure FX, Desailloud R, et al. Increased prevalence of hypothyroidism among human immunodeficiency virus infected patients: a need for screening. Clin Infect Dis 2003;37:579–583
31. Quirino T, Bongiovanni M, Ricci E, et al. Hypothyroidism in HIV-infected patients who have or have not received HAART [letter]. Clin Infect Dis 2004;38:596–597
32. Berg MB, Mimiaga MJ, Safren SA. Mental health concerns of HIV-infected gay and bisexual men seeking mental health services: an observational study. AIDS Patient Care STDS 2004;18:635–643
33. Martinez A, Israelski D, Walker C, et al. Posttraumatic stress disorder in women attending human immunodeficiency virus outpatient clinic. AIDS Patient Care STDS 2002;16:283–291
34. Kelly B, Raphael B, Judd F, et al. Posttraumatic stress disorder in response to HIV infection. Gen Hosp Psychiatry 1998;20:345–352
35. Ellen SR, Judd FK, Mijch AM, et al. Secondary mania in patients with HIV infection. Aust N Z J Psychiatry 1999;33:353–360
36. Wada K, Yamada N, Suzuki H. Recurrent cases of corticosteroid-induced mood disorder: clinical characteristics and treatment. J Clin Psychiatry 2000;61:261–267
37. Markowitz JS, Carson WH, Jackson CW. Possible dehydroepiandrosterone-induced mania. Biol Psychiatry 1999;45:241–242
38. Maxwell S, Schefftner WA, Kessler HA. Manic syndrome associated with zidovudine treatment [letter]. JAMA 1988;259:3406–3407
39. Brouillette MJ, Choiunard G, Lalonde R. Didanosine-induced mania in HIV infection [letter]. Am J Psychiatry 1994;151:1839–1840
40. Shah MD, Balderson K. A manic episode associated with efavirenz therapy for HIV infection [letter]. AIDS 2003;17:1713–1714
41. Haller DL, Miles DR. Suicidal ideation among psychiatric patients with HIV: psychiatric morbidity and quality of life. AIDS Behav 2003;7: 101–108
42. James ME, Rubin CP, Willis SE. Drug abuse and psychiatric findings in

HIV-seropositive pregnant patients. Gen Hosp Psychiatry 1991;13:4–8
43. Rundell JR, Kyle KM, Brown GR, et al. Risk factors for suicide attempts in a human immunodeficiency virus screening program. Psychosomatics 1992;33:24–27
44. Kalichman SC, Heckman T, Kochman A, et al. Depression and thoughts of suicide among middle-aged and older persons living with HIV-AIDS. Psychiatr Serv 2000;51:903–907
45. Rajs J, Fugelstad A. Suicide related to human immunodeficiency virus infection in Stockholm. Acta Psychiatr Scand 1992;85:234–239
46. Hirschfeld RM, Russel JM. Assessment and treatment of suicidal patients. N Engl J Med 1997;337:910–915
47. Fawcett J, Scheftner WA, Fogg L, et al. Time-related predictors of suicide in major affective disorder. Am J Psychiatry 1990;147:1189–1194
48. Komiti A. Suicidal behavior in people with HIV/AIDS: a review. Aust N Z J Psychiatry 2001;35:747–757
49. Rundell JR, Kyle KM, Brown GR, et al. Risk factors for suicide attempts in a human immunodeficiency virus screening program. Psychosomatics 1992;33:24–27
50. Gala C, Pergami A, Catalna J, et al. Risk of deliberate self-harm and factors associated with suicidal behaviour among asymptomatic individuals with human immunodeficiency virus infection. Acta Psychiatr Scand 1992;86:70–75
51. Alfonso CA, Cohen MA. HIV-dementia and suicide. Gen Hosp Psychiatry 1994;16:45–46
52. Rabkin JG, Remien R, Katoff L, et al. Suicidality in AIDS long-term survivors: what is the evidence? AIDS Care 1993;5:401–411
53. Breitbart W, Rosenfeld BD, Passik SD. Interest in physician assisted suicide among ambulatory patients. Am J Psychiatry 1997;154:294–295
54. Massie MJ, Gagnon P, Holland JC. Depression and suicide in patients with cancer. J Pain Symptom Manage 1994;9:325–340
55. Antoni MH. Stress management effects on psychological, endocrinological, and immune functioning in men with HIV infection: empirical support for a neuropsychoendocrinological model. Stress 2003;6:173–188
56. Ho WZ, Douglas SD. Substance P and neurokinin-1 receptor modulation of HIV. J Neuroimmunol 2004;157:48–55
57. Rabkin JG, Rabkin R, Wagner G. Effects of fluoxetine on mood and immune status in depressed patients with HIV illness. J Clin Psychiatry 1994;55:92–97
58. Ferrando SJ, Goldman JD, Charness WE. Selective serotonin reuptake inhibitor treatment of depression in symptomatic HIV infection and AIDS: improvements in affective and somatic symptoms. Gen Hosp Psychiatry 1997;19:89–97
59. Zisook S, Peterkin J, Goggin KJ, et al, and the HIV Neurobehavioral Research Center Group. Treatment of major depression of HIV-seropositive men. J Clin Psychiatry 1998;59:217–224
60. Fujishiro J, Imanishi T, Onozawa K, et al. Comparison of the anticholinergic effects of the serotoninergic antidepressants, paroxetine, fluvoxamine and clomipramine. Eur J Pharmacol 2002;454:183–188
61. Rosenbaum JF, Fava M, Hoog SL, et al. Selective serotonin reuptake inhibitor discontinuation syndrome: a randomized clinical trial. Biol Psychiatry 1998;44:77–87
62. Currier MB, Molina G, Kato M. Citalopram treatment of major depressive disorder in Hispanic HIV and AIDS patients: a prospective study. Psychosomatics 2004;45:210–216
63. Nelson JC, Wohlreich MM, Mallinckrodt CH, et al. Duloxetine for the treatment of major depressive disorder in older patients. Am J Geriatr Psychiatry 2005;13:227–235
64. Maizels M, McCarberg B. Antidepressant and antiepileptic drugs for chronic non-cancer pain. Am Fam Physician 2005;71:483–490
65. Bomholt SF. Antinociceptive effects of antidepressants amitriptyline, duloxetine, mirtazapine and citalopram in animal models of acute persistent and neuropathic pain. Neuropharmacology 2005;48:252–263
66. Currier MB. A prospective trial of sustained release bupropion for epression in HIV seropositive and AIDS patients. Psychosomatics 2003;44:120–125
67. Kast RE. Mirtazapine may be useful in treating nausea and insomnia of cancer chemotherapy [letter]. Support Care Cancer 2001;9:469–470
68. Remeron (mirtazapine). Physicians' Desk Reference. 59th ed. Montvale, NJ: Thomson PDR; 2005
69. Rabkin JG, Rabkin R, Harrison W, et al. Effect of imipramine on mood and enumerative measures of immune status in depressed patients with HIV illness. Am J Psychiatry 1994;151:516–523
70. Ferrando SJ, Wapenyi K. Psychopharmacological treatment of patients with HIV and AIDS. Psychiatr Q 2002;73:33–49
71. Robinson MJ, Qaqish RB. Practical psychopharmacology in HIV-1 and acquired immunodeficiency syndrome. Psychiatr Clin North Am 2002; 25:149–175
72. Gillenwater DR, McDaniel JS. Rational psychopharmacology for patients with HIV infection and AIDS. Psychiatr Ann 2001;311:28–34
73. Riesenman C. Antidepressant drug interactions and the cytochrome P450 system: a critical appraisal. Pharmacotherapy 1995;15(6 pt 2):84S–99S
74. Nemeroff CB, Devane CL, Pollock BG. Newer antidepressants and the cytochrome P450 system. Am J Psychiatry 1996;153:311–320
75. Skinner MH, Kuan HY, Pan A, et al. Duloxetine is both an inhibitor and a substrate of cytochrome P4502D6 in healthy volunteers. Clin Pharmacol Ther 2003;73:170–177
76. Physicians' Desk Reference. 59th ed. Montvale, NJ: Thompson PDR; 2005
77. DeSilva KE, Le Flore DB, Marston BJ, et al. Serotonin syndrome in HIV infected individuals receiving antiretroviral therapy and fluoxetine. AIDS 2001;15:1281–1285
78. Zalma A, von Moltke LL, Granda BW, et al. In vitro metabolism of trazodone by CPY3A: inhibition by ketoconazole and human immunodeficiency viral protease inhibitor. Biol Psychiatry 2000;47:655–661
79. Greenblatt DJ, Von Moltke LL, Harmatz JS, et al. Short term exposure to low dose ritonavir impairs clearance and enhances adverse effects of trazodone. J Clin Pharmacol 2003;43:414–422
80. Hesse LM, von Moltke LL, Shader RI, et al. Ritonavir, efavirenz and nelfinavir inhibit CYP2B6 activity in vitro: potential drug interactions with bupropion. Drug Metab Dispos 2001;29:100–102
81. Levin GM. A pharmacokinetic drug-drug interaction study of venlafaxine and indinavir. Psychopharmacol Bull 2001;35:62–71
82. Brown GR. The use of methylphenidate for cognitive decline associated with HIV disease. Int J Psychiatry Med 1995;25:21–37
83. Fernandez F, Levy JK, Samley HR, et al. Effects of methylphenidate in HIV-related depression: a comparative trial with desipramine. Int J Psychiatry Med 1995;25:53–67
84. Breitbart W, Rosenfeld B, Kaim M, et al. A randomized, double-blind, placebo controlled trial of psychostimulants for the treatment of fatigue in ambulatory patients with human immunodeficiency virus disease. Arch Intern Med 2001;161:411–420
85. Hinkin CH, Castellon SA, Hardy DJ. Methylphenidate improves HIV-associated cognitive slowing. J Neuropsychiatry Clin Neurosci 2001;13:248–254
86. Masand PS, Tesar GE. Use of stimulants in the medically ill. Psychiatr Clin North Am 1996;19:515–547
87. Rabkin JG, McElhiney MC, Rabkin R, et al. Modafinil treatment for fatigue in HIV+ patients: a pilot study. J Clin Psychiatry 2004;65: 1688–1695
88. Roberston P Jr, Hellriegel ET, Arora S, et al. Effect of modafinil on the pharmacokinetics of ethynil estradiol and triazolam in healthy volunteers. Clin Pharmacol Ther 2002;71:46–56
89. Rabkin JG, Wagner GJ, Rabkin R. Testosterone therapy for human immunodeficiency virus-positive men with and without hypogonadism. J Clin Psychopharmacol 1999;19:19–27
90. Rabkin JG, Ferrando SJ, Wager GJ, et al. DHEA treatment for HIV+ patients: effects on mood, androgenic and anabolic parameters. Psychoneuroendocrinology 2000;25:53–68
91. Rabkin JG, Wagner GJ, McElhiney MC, et al. Testosterone versus fluoxetine for depression and fatigue in HIV/AIDS patients: a placebo controlled trial. J Clin Psychopharmacol 2004;24:379–385
92. Miller K, Corcoran C, Amstrong C, et al. Transdermal testosterone administration in women with acquired immunodeficiency syndrome wasting: a pilot study. J Clin Endocrinol Metab 1998;83: 2717–2725
93. Choi HH, Gray PB, Storer TW. Effects of testosterone replacement in human immunodeficiency virus-infected women with weight loss. J Clin Endocrinol Metab 2005;90:1531–1541
94. Basaria S, Dobs AS. New modalities of transdermal testosterone replacement. Treat Endocrinol 2003;2:1–9
95. Cutter CB. Compounded percutaneous testosterone gel: use and effects in hypogonadal men. J Am Board Fam Pract 2001;14:22–32
96. Linde K, Berner M, Egger M, et al. St John's wort for depression: meta-analysis of randomised controlled trials. Br J Psychiatry 2005; 186:99–107

97. James JS. St John's wort warning: do not combine with protease inhibitors, NNRTIs. AIDS Treat News 2000;337:3–5
98. Mannel M. Drug interactions with St John's wort: mechanisms and clinical implications. Drug Saf 2004;27:773–797
99. Schaerf FW, Miller RR, Lipsey JR, et al. ECT for major depression in four patients infected with human immunodeficiency virus. Am J Psychiatry 1989;146:782–784
100. Kessing L, LaBianca JH, Bolwig TG. HIV-induced stupor treated with ECT. Convuls Ther 1994;10:232–235
101. Markowitz JC, Kocsis JH, Fishman B, et al. Treatment of depressive symptoms in human immunodeficiency virus-positive patients. Arch Gen Psychiatry 1998;55:452–457
102. Lee MR, Cohen L, Hadley SW, et al. Cognitive-behavioral group therapy with medication for depressed gay men with AIDS or symptomatic HIV infection. Psychiatr Serv 1999;50:948–952
103. Lechner SC, Antoni MH, Lydston D, et al. Cognitive-behavioral interventions improve quality of life in women with AIDS. J Psychosom Res 2003;54:253–261
104. della Penna DL, Treisman GJ. HIV/AIDS. In: Levenson JL, ed. The American Psychiatric Publishing Textbook of Psychosomatic Medicine. 1st ed. Arlington, Va: American Psychiatric Publishing, Inc; 2005: 613–615

For the CME Posttest for this article, see pages 252–253.