GUIDELINE WATCH: PRACTICE GUIDELINE FOR THE TREATMENT OF PATIENTS WITH HIV/AIDS

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Since publication in 2000 of APA's *Practice Guideline for the Treatment of Patients With HIV/ AIDS* (1), new evidence has become available that affects the psychiatric care of patients with human immunodeficiency virus (HIV) infection and acquired immune deficiency syndrome (AIDS). This guideline watch highlights this evidence for the following areas: epidemiology, antiretroviral medication regimens, HIV-associated cognitive-motor disorders, treatment of psychiatric disorders and conditions when comorbid with HIV infection, hepatitis C virus (HCV) and HIV coinfection, and metabolic syndrome and lipodystrophy.

▶ EPIDEMIOLOGY

HIV infection remains a global pandemic. According to the Joint United Nations Programme on HIV/AIDS, as of December 2004 more than 39 million people in the world were estimated to be living with HIV/AIDS; 95% of these people lived in low- and middle-income countries (2). Globally, more than 20 million persons have died of AIDS since the disease was first identified in 1981. Worldwide, 14,000 people are newly infected with HIV every day (3). According to the U.S. Centers for Disease Control and Prevention, through 2003, the cumulative

estimated number of diagnoses of AIDS in the United States was 929,985; the cumulative estimated number of deaths of persons with AIDS was 524,060; and an estimated 1,039,000 to 1,185,000 persons in the United States were living with HIV/AIDS, with 24%–27% unaware of their HIV infection (4). In the United States, prevention efforts have been successful at decreasing HIV incidence. New infections, however, remain stabilized at 40,000 per year, with people of color bearing a disproportionate burden of new infections, suggesting that new strategies must be developed for further reducing the spread of HIV.

In recent years, there has been a change in the epidemiology of AIDS in the United States. Initially the epidemic mostly affected men who had sex with men, intravenous drug users, pregnant women, women who were breast-feeding, and recipients of blood products. Data now show an increasing number of individuals infected through unprotected heterosexual intercourse. For men, the majority of infections continues to result from drug use and sex between men. Among women, however, heterosexual intercourse accounts for most HIV infections (4). Recent studies have provided increasing evidence that the main risk factor for women is undisclosed risk behavior of their male partners, especially sex with other men (5). Increasingly, it is important for psychiatrists to assess specific risk behaviors that facilitate HIV transmission rather than making assumptions about risk based on patients' sexual orientation, marital status, or other characteristics. Identifying drug-using and sexual behaviors is an ongoing component of psychiatric practice.

▶ ANTIRETROVIRAL AGENTS

Recommended regimens

Since publication of the APA practice guideline in 2000, changes have occurred in the U.S. Department of Health and Human Services (DHHS) guidelines on antiretroviral therapy for the management of HIV infection (available online at http://aidsinfo.nih.gov). According to the DHHS guidelines, as of October 2005 there were 21 approved antiretroviral agents, belonging to four classes (6). A new class of antiretroviral medications, the fusion/entry inhibitors, is engineered to work by preventing the virus from fusing with a cell membrane and entering the cell, thus preventing infection of cells. Antiretroviral agents are prescribed in combination regimens that are also known as *combination antiretroviral therapy* (CART) (previously termed *highly active antiretroviral therapy* [HAART]) (6). The timing of CART initiation has been debated and may depend on assessment of viral load, CD4 count, and history of associated symptoms. There has been consensus to recommend the following as first-line regimens: 1) efavirenz + (lamivudine or emtricitabine) + (zidovudine or tenofovir) or 2) lopinavir + (lamivudine or emtricitabine) + zidovudine.

Notably, three nonnucleoside reverse transcriptase inhibitors (NNRTIs) (namely, delavirdine, efavirenz, and nevirapine) are currently marketed for use. The NNRTI-based regimens are commonly prescribed as initial therapy for treatment-naive patients. These regimens have the advantage of lower pill burden compared with most protease inhibitor–based regimens. Use of NNRTI-based regimens as initial therapy spares the protease inhibitors for later use, reducing or delaying patient exposure to some of the treatment-limiting adverse effects more commonly associated with the protease inhibitors. The major disadvantage of these regimens is their low genetic barrier for resistance. Only a single mutation need exist to confer resistance to these agents. Moreover, resistance often develops across the entire class. As a result, patients who do not respond to this initial regimen may lose the utility of other NNRTIs and/or may transmit NNRTI-resistant virus to others. Efavirenz is recommended, on the basis of safety data, as the preferred NNRTI in initial therapy. Exceptions are pregnant women (especially during the first trimester), women who are planning to conceive, and women who are not using effective and consistent contraception. For such patients, nevirapine is recommended as the alternative to

efavirenz. Delavirdine has the least potent antiviral activity in this class and is not recommended for initial treatment.

Because of the association of the protease inhibitor class of antiretrovirals with the development of metabolic syndrome (see "Metabolic Syndrome and Lipodystrophy" below), regimens are structured to reserve this class of antiretrovirals for future use in case of treatment failure.

Many new medications to manage HIV infection are in development.

Adherence

In patients receiving antiretroviral treatment, lack of almost perfect adherence to daily regimens continues to be the greatest barrier to sustaining a clinically effective response. Within the community, lack of adherence can also lead to the development of HIV strains resistant to the available antiretrovirals. The prevalence of HIV isolates that demonstrate resistance to antiretroviral agents is increasing, and such isolates can develop despite stable low-level viremia (7). Resistance testing, genotypic or phenotypic, is indicated when patients experience virologic failure (failure to achieve or maintain virologic suppression below 400 HIV RNA copies/mL plasma at 24 weeks or 50 copies/mL plasma at 48 weeks or >400 copies/mL plasma after viral suppression [6, 8]).

Directly observed therapy (DOT), originally used to improve cure rates of tuberculosis in hard-to-reach populations, has been adapted for individuals receiving treatment for HIV to decrease long-term morbidity and mortality. In treatment-experienced HIV-infected substance-using patients, DOT has been successfully used to promote adherence. A study of 69 HIV-infected individuals enrolled in a community-based modified DOT program showed a median decrease of 2.7 log in HIV viral load (9). DOT also provides a way to offer psychosocial support as well as connections to addiction, psychiatric, and social services (10).

Adherence to antiretroviral therapy improves in depressed patients treated with antidepressants. Untreated depression has been associated with medication nonadherence (11).

Drug-drug interactions between new antiretroviral agents and psychotropic medications

Interactions between psychotropic and antiretroviral medications are common in the HIV-infected patient. Drug-drug interactions are too numerous to be listed here in full. Most medications used in the treatment of psychiatric disorders are metabolized by the cytochrome P450 (CYP) enzymes, especially the subgroups 3A4 and 2D6. Of the antiretrovirals, the protease inhibitors tend to pose the greatest risk for changes in drug levels that are significant in the HIV patient. Ritonavir is the most potent of the protease inhibitors, with the greatest impact on the inhibition of 3A4 and to a lesser extent 2D6. Enfuvirtide, the fusion inhibitor, is not an inhibitor of CYP enzymes and does not alter the metabolism of CYP 3A4, CYP 2D6, CYP 2C19, or CYP 2E1 substrates. Thus, it has no significant impact on blood levels of psychiatric medications or other antiretrovirals (12).

Efavirenz has been shown in vivo to induce CYP 3A4 (12). Other compounds that are substrates of CYP 3A4 may have decreased plasma concentrations when coadministered with efavirenz. In vitro studies have demonstrated that efavirenz inhibits 2C9, 2C19, and 3A4 isoenzymes in the range of observed efavirenz plasma concentrations (13). Coadministration of efavirenz with drugs primarily metabolized by these isoenzymes may result in altered plasma concentrations of the coadministered drug. Therefore, appropriate dose adjustments may be necessary for these drugs.

Drugs that induce CYP 3A4 activity (e.g., phenobarbital, rifampin, rifabutin) would be expected to increase the clearance of efavirenz, resulting in lowered plasma concentrations (http://www.rxlist.com/cgi/generic/efaviren_ad.htm).

Antiretrovirals that inhibit or induce the CYP enzymes may increase or decrease methadone levels, leading to acute withdrawal symptoms or excessive dosing in otherwise stabilized methadone maintenance patients, which may lead to unfounded assumptions about opioid relapse (14–16).

TABLE 1. Useful Web Sites for Information on Drug-Drug Interactions

http://hivinsite.ucsf.edu/InSite?page=md-rr-24
http://www.projectinform.org/fs/druginter.html
http://www.rxlist.com/cgi/generic2/ritonavirsol_ad.htm
http://www.atforum.com/SiteRoot/pages/addiction_resources/Drug_Interactions.pdf
http://www.aidsetc.org/pdf/p02-et/et-03-00/pharm2005.pdf

It is important for psychiatrists to remain in contact with other medical providers, maintain updated lists of all medications and substances of abuse, and frequently consult updated web-based information sites regarding potential drug-drug interactions (17). Web sites (Table 1) provide the most up-to-date information about specific drug-drug interactions.

Central nervous system (CNS) side effects

Efavirenz has been reported to produce side effects including sleep disturbances and a transient neurovestibular symptom complex (18–20). Such side effects are common but generally short-term.

One randomized, controlled study of 100 patients supported the addition of efavirenz rather than a second drug from other classes of antiretrovirals for improved quality of life, despite a greater incidence of side effects; the study authors recommended, however, that patients with prior histories of emotional disturbances be monitored carefully over the long term (21). A cross-sectional study of 828 patients determined that factors independently associated with discontinuation of efavirenz were female gender, unemployment, a steady sexual partner, and multiple episodes of depression (22). Another cross-sectional study of 60 patients on regimens that included efavirenz and 60 patients on regimens that included a protease inhibitor found that mild and clinically tolerable neuropsychiatric disorders could persist after 2 years in patients receiving efavirenz; quality of life and psychological status remained good in both study groups (23).

In a study conducted by the AIDS Clinical Trials Group (24), efavirenz was associated not only with having vivid dreams but also with being off balance, having the sensation of falling over, feeling that the room is spinning, being unsteady in walking, feeling lightheaded, and being drowsy. Neuropsychological performance improved with initiation of therapy in an efavirenz-treated group compared with an NRTI-treated control group. Nevertheless, small negative significant correlations between efavirenz levels and neuropsychological performance persisted over time (24). Efavirenz causes subjective symptoms during the first week of treatment that are most consistently described as a vestibular disorder. Overall, sleep quality was not impaired by efavirenz and was improved at week 4 compared with the control group. Transient increases in vivid dreams associated with efavirenz use resolved by week 4 of therapy. No differences in changes of depressed mood or anxiety were detected. Overall, efavirenz-associated toxicities resolved without treatment by week 4 (24).

▶ HIV-ASSOCIATED COGNITIVE-MOTOR DISORDERS

Cognitive-motor disorders in patients with HIV infection are common and may be progressive (25, 26). However, the incidence of HIV-associated dementia in the CART era has been reduced by 50%, and a similar reduction has been reported for minor cognitive-motor disorder. It is not yet clear whether this benefit persists over the long-term course of illness and treatment or which regimens are most effective in sustaining cognitive function. In developed countries, it has been suggested that the prevalence of cognitive disorders has increased because of the increased longevity of the patient population overall. It can be concluded that these disorders continue to be a significant source of morbidity among patients (25, 27, 28).

In many HIV patients with neurocognitive impairment, the impairment probably remains undiagnosed. Patients with HIV-associated cognitive-motor disorder may benefit from early intervention with combination antiretroviral therapy, as well as adjuvant treatments for the pathophysiological factors in the CNS that contribute to neurocognitive impairment. Available antiretroviral agents suppress HIV replication but do not eradicate the virus. The brain can serve as an important reservoir for the virus, contributing to an increased likelihood that a cognitive-motor disorder may develop over time.

Some antiretroviral agents can cross the blood-brain barrier and therefore decrease viral load in the cerebrospinal fluid. Improvements in neurocognitive function, however, have been shown even with regimens not containing cerebrospinal fluid (CSF)–penetrating antiretrovirals. In a study of 31 patients who received new antiretroviral treatment, patients whose regimens included CSF-penetrating agents showed greater reduction in CSF viral load and improved neuropsychological function. Treatment-naive patients had greater improvement in neuropsychological function than treatment-experienced patients (29). Other studies have not shown benefit, and thus the question of whether adding CSF-penetrating agents is beneficial is still controversial. Other immunological factors (i.e., chemokines, cytokines, tumor necrosis factor) are also implicated in the development of neuropathological changes leading to neurocognitive symptoms. Other factors that contribute to progression of cognitive disorders include age, concurrent methamphetamine use, and hepatitis coinfection (29–32).

► CHANGES IN CLASSIFYING NEUROCOGNITIVE IMPAIRMENT

A June 13, 2005, conference (sponsored by the National Institute of Mental Health and the National Institute of Neurological Disorders and Stroke) on CNS disorders associated with HIV in developed and resource-limited settings included a meeting on revising the American Academy of Neurology criteria for HIV-associated cognitive-motor disorders (33). This conference identified and defined the diagnostic criteria for HIV-associated dementia and minor cognitive-motor disorder and added a condition: asymptomatic neurocognitive impairment. The proposed new criteria, described below, are expected to be published in early 2006.

Asymptomatic neurocognitive impairment occurs without any associated decrement in functional status. The presence of asymptomatic neurocognitive impairment poses a risk for progression to a cognitive-motor disorder, now to be termed *neurocognitive disorder.*

Mild neurocognitive disorder, previously termed *HIV-associated minor cognitive-motor disorder,* will now require neurocognitive impairment at least one standard deviation below the mean (normed for specific populations) in at least two neurocognitive domains, one of which must be primarily cognitive. This change from the criteria for minor cognitive-motor disorder reflects prioritization of deficits observed in the neurocognitive sphere over those observed in the motor and behavioral spheres. The criteria for mild neurocognitive disorder are determined by specific neuropsychological tests. In addition, a systematic exclusion of confounding conditions (e.g., opportunistic CNS disease, systemic illness, psychiatric illness, substance use disorders, or medications with CNS effects) is recommended. Where neuropsychological testing is unavailable, the criteria may also be determined by using an alternative clinical method (such as the HIV Dementia Scale or the International HIV Dementia Scale). Functional impairment is a necessary finding for a diagnosis of neurocognitive disorders.

HIV-associated dementia, previously termed *AIDS dementia complex,* is defined (for persons with moderate or severe impairment) as impairment within at least two cognitive domains that is greater than or equal to two standard deviations below the mean, or impairment within at least one cognitive domain that is greater than or equal to one standard deviation below the mean and impairment within one other domain that is greater than or equal to 2.5 standard deviations below the norm. Like the criteria for mild neurocognitive disorder, these criteria re-

flect prioritization of deficits observed in the neurocognitive sphere over those observed in the motor and behavioral spheres. The criteria are determined by specific neuropsychological tests that sample each of the neuropsychological domains as well as by a more systematic assessment of functional status and exclusion of confounding conditions. HIV dementia is more subcortical than cortical, and therefore clinical symptoms tend to involve motor functions, memory, mood with flattening of emotional range, apathy, and coarsening of personality. The HIV Dementia Scale is more sensitive to subcortical deficits than the Folstein Mini-Mental State Examination, which is directed mostly at cortical deficits and may not detect impairment until very late in the course of HIV dementia. Other tests directed at assessing psychomotor speed and subcortical processing, such as the grooved pegboard or Trail Making Test Part B, may be clinically useful. In resource-limited settings, alternative clinical methods may determine the criteria, after careful ruling out of other processes in the CNS that might account for the changes in mental status scores.

▶ DEPRESSION

It has been established that depressive disorders among people with HIV infection may approach nearly 50% and that depression is associated with accelerated HIV disease progression, nonadherence to antiretroviral treatment, and mortality (34–37). Major depression remains underdiagnosed and undertreated in persons with HIV, especially African Americans, but using screening instruments can enhance detection (38, 39). In a double-blind, randomized, controlled trial of 25 patients infected with HIV, treatment of depression had a beneficial influence on health-related quality of life (40).

Psychotherapeutic or psychopharmacological treatments shown to be effective in other populations are useful also in the HIV-infected patient with co-occurring psychiatric disorders. Guidelines for the treatment of the major psychiatric disorders are available from APA (41).

To date, no specific antidepressant has been shown to be preferable or not to work in HIV patients, provided attention is paid to drug-drug interactions and sides effects that are more likely in the medically ill population. There are small studies of specific antidepressants and other agents. Mirtazapine, sustained-release bupropion, and venlafaxine seem to be effective, have at least equivalent tolerability to tricyclics and selective serotonin reuptake inhibitors, and do not have significant drug-drug interactions. Further studies to investigate these medications in a placebo-controlled fashion are still lacking (42–44).

A recent review described selective serotonin reuptake inhibitors as being safe and effective for the treatment of depression in patients with HIV and having better tolerability than tricyclic antidepressants (45). There is one report of serotonin syndrome occurring when antidepressants are used with some antiretrovirals (46).

There is also emerging evidence for other agents. A small, uncontrolled, open-label pilot study showed encouraging results for the use of modafinil to treat depressive symptoms and fatigue in patients with HIV (47). A small randomized, placebo-controlled trial showed significant improvement in mood and energy of HIV-infected men treated with dextroamphetamine (48). A large randomized, controlled trial did not support use of testosterone as a first-line treatment for depressive disorders in HIV-positive men; however, it was suggested that with additional study, testosterone may be indicated as a useful option for medically ill men experiencing significant fatigue as well as depression (49).

Cognitive behavior therapy groups, educational programs, and stress management techniques have also been shown to improve depression in patients with HIV (50–52). Psychodynamic, cognitive behavior, and interpersonal therapies are also applicable to the HIV population. A study by Nemeroff et al. (53) reported that in depressed patients with a history of early psychological trauma, psychotherapy alone was superior to psychopharmacology alone. Despite the methodological difficulties in such research, several studies have demonstrated the

effectiveness of psychodynamic psychotherapy in depression (54–56) and in other psychiatric disorders, including personality disorders, which often co-occur with HIV and depression (57–60).

► ## BIPOLAR DISORDERS AND PSYCHOSIS

There is a strong association between psychosis and HIV-related mood disorders (61). A retrospective review of the charts of 15 patients infected with HIV and receiving antiretroviral therapy suggested that the mood stabilizer divalproex sodium is well tolerated and does not increase viral load (62). In fact, new studies suggest that valproic acid might over time help to eradicate HIV from latent cells (63–65). Psychiatrists should closely monitor hepatic function and serum levels of valproic acid in the HIV patient, given the number of hepatically metabolized medications most patients with HIV have to take.

A study of 46 patients with HIV syndrome and mental illness showed that bipolar disorder was associated with nonadherence to antiretroviral therapy (66). A study of 2,459 New Jersey Medicaid beneficiaries found that patients with schizophrenia were not significantly less persistent in their use of antiretroviral therapy than those without serious mental illness, but patients with severe affective disorders were less persistent (67).

Primary psychosis can occur in HIV-positive patients, as can secondary psychoses associated with infectious, systemic, and cerebral complications of HIV infection (68). Case reports of psychosis, with or without manic features, have been associated with the use of efavirenz and other antiretroviral regimens, corticosteroids, antivirals such as ganciclovir and interferon-α, antimicrobials such as sulfadiazine and dapsone, and buspirone (69–72). One case of reversible coma associated with the use of ritonavir with risperidone has been reported (73). Concerns have grown about the metabolic complications associated with the use of second-generation (atypical) antipsychotics (see "Metabolic Syndrome and Lipodystrophy" below), although they remain better tolerated than first-generation antipsychotics in patients with HIV/AIDS (74).

► ## HEPATITIS C VIRUS AND HIV INFECTION

HCV infection has become more prevalent in the general population and in the HIV-infected population. Overall, approximately 30% of all HIV-positive patients are HCV positive (75, 76). A recent study found a high prevalence of HCV among crystal methamphetamine users (77). Current evidence suggests that in patients treated with combination antiretroviral therapy, HCV infection may not increase HIV replication, but HIV infection appears to increase HCV replication, leading to more patients with coinfection having symptoms and medical illness related to their HCV infection. Studies have also shown that although HCV infection does not significantly change viral load or CD4 parameters in HIV-infected individuals, the survival time of such individuals is shortened (78, 79). Laboratory evidence suggests that HIV may facilitate HCV replication in monocytes, explaining the extrahepatic consequences of HCV in coinfected individuals (80).

Significant rates of HCV are found in patients with psychiatric disorders because of the high lifetime rates of intravenous drug use in the population with severe mental illness (81, 82). Psychiatric disorders are also prevalent in HCV-infected patients, as shown in Figure 1.

HIV, HCV, and cognitive impairment

Studies suggest that HCV may be able to replicate in the brain, and HCV has been associated with cognitive impairment independently of hepatic compromise. HCV viral load can be measured in the blood and CSF. HCV can cause cognitive impairment in the absence of systemic illness, elevated liver enzymes, or liver failure, and there appears to be an additive effect of HCV
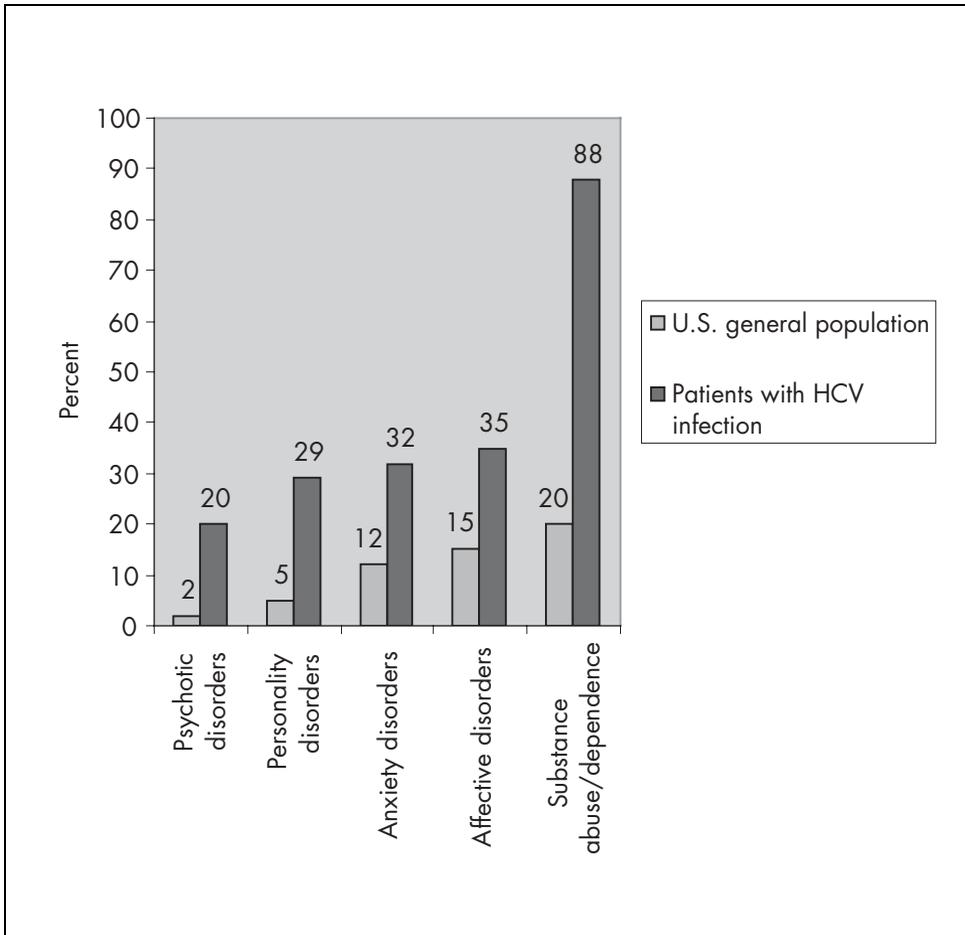
FIGURE 1. Prevalence of DSM-IV-TR Psychiatric Disorders in Patients With Hepatitis C, Compared With U.S. General Population.

Source. Reprinted with permission from Rifai and Rosenstein (83); data from Epidemiologic Catchment Area study (84, 85).

and HIV on cognitive dysfunction (86–88). Several studies have shown HCV infection to be a predictor of impairments in learning, abstraction, and motor skills in the HIV-negative population as well (77, 89, 90). In one study, 46% of HIV-positive/HCV-positive patients met criteria for HIV-associated dementia, as opposed to 10% of HIV-positive/HCV-negative patients; however, 45% of HIV-positive/HCV-negative patients met criteria for minor cognitive-motor disorder, as opposed to 23% of HIV-positive/HCV-positive patients (30). In advanced HCV disease, increasing ammonia levels can also lead to CNS impairment, usually reversible with appropriate treatment (77, 91).

Management of psychiatric consequences of HCV treatment

Psychiatrists are often asked to evaluate patients who have a current episode or history of mood disorders before the initiation of treatment for HCV. Depression is the most common side effect of interferon treatment with ribavirin for HCV infection. Current evidence of the value of antidepressant treatment in the non-HIV population suggests that antidepressant medication should be continued in those already being treated for depression and should be considered as

prophylaxis in those with a prior history of depression (92, 93). A double-blind, randomized, controlled trial of 40 patients with malignant melanoma who received interferon treatment suggested that prophylactic treatment with paroxetine is an effective strategy for minimizing depression induced by interferon (94). A small open-label study suggested citalopram may be effective for depression in patients with HCV infection (95).

▶ METABOLIC SYNDROME AND LIPODYSTROPHY

Since the 1990s, clinicians have observed changes in body morphology and metabolic parameters that appeared to be related to the combination antiretroviral treatment regimens that were prolonging and improving quality of life for people with HIV infection. Numerous factors contribute to body morphological changes, including antiretroviral therapy, HIV infection itself, and perhaps immune reconstitution occurring in the context of ongoing disease (96–100).

People with HIV present with body changes, including what is now called *lipoatrophy* and/or *lipohypertrophy* (also known together as the *lipodystrophy syndrome*). The associated profound metabolic abnormalities, such as hyperglycemia, hyperinsulinemia, hyperlipidemia, and hypertension, are now commonly referred to as the *metabolic syndrome.*

One of the reasons for the wide range of prevalence rates of metabolic syndrome reported in patients on protease inhibitor regimens (2%–84%) (96, 101–103) has been the lack of uniformity of definitions, criteria, and assessment methodology.

Risk factors for lipodystrophy include exposure to protease and nucleoside reverse transcriptase inhibitors, duration of use of a protease inhibitor or a nucleoside reverse transcriptase inhibitor, duration and severity of HIV disease, viral load, time since reversal of clinical progression of HIV infection, increasing age, female gender, and extreme changes in body mass index (104). Fat accumulation is correlated with female gender, low viral load, and high body mass index. Fat depletion is associated with low body mass index and the use of the nucleoside reverse transcriptase inhibitor stavudine (105).

A retrospective cohort study showed that 13% of 221 patients treated with protease inhibitor therapy for 5 years developed lipodystrophy, suggesting that the effect of antiretroviral medication may be an important contributor to the development of the syndrome (106).

Males are reported to be at greater risk of developing metabolic abnormalities, including hypertriglyceridemia, hypercholesterolemia, and hyperglycemia. Another study has suggested that mixed fat redistribution (concurrent fat wasting and fat accumulation) may be related to effective HIV suppression by combination antiretroviral therapy (107). The greatest risk factor identified thus far has been protease inhibitor use. Data from one study (96) showed that 64% of patients (74 of 116) receiving protease inhibitor therapy suffered from lipodystrophy, as opposed to only 3% of patients (1 of 32) who had never received protease inhibitor therapy.

Lipoatrophic changes are characterized by subcutaneous fat depletion in the face, arms, legs, and gluteal region. Muscles of the extremities may appear more pronounced, and veins may appear more prominent in fat-depleted regions. (The fat wasting observed in this syndrome is distinguished from other wasting conditions associated with HIV infection, including the AIDS wasting syndrome, malnutrition, cachexia, adrenal insufficiency, and severe chronic infections.) Lipohypertrophy is characterized by truncal obesity, dorsocervical fat accumulation (buffalo hump), and breast enlargement (108–112).

The lipodystrophy syndrome appears to increase risk in HIV-positive patients for cardiovascular and cerebrovascular disease (113). The hypercholesterolemia may predispose individuals to accelerated atherosclerosis and premature coronary artery disease (114–117). One retrospective study (118) of more than 1,300 patients demonstrated an increased frequency of myocardial infarction in HIV-infected patients receiving protease inhibitor therapy (119, 120).

Many HIV-infected patients may exhibit more than one risk factor for the development of coronary artery and cerebrovascular disease: hypertriglyceridemia, low high-density lipoprotein

cholesterol, increased low-density lipoprotein cholesterol, elevated diastolic blood pressure, decreased tissue plasminogen activator levels, and increased plasminogen activator inhibitor–1 levels. The median time to the development of hypercholesterolemia may precede that of lipodystrophy by 3–6 months (121, 122).

It is important to consider a diagnosis of metabolic syndrome in patients receiving antiretroviral therapy who manifest insulin resistance, particularly if fat redistribution, dyslipidemia, or hyperglycemia is present. Second-generation antipsychotic medications, often prescribed for late-stage HIV-associated dementia, delirium, and psychotic disorders, can increase the risk of metabolic syndrome. Second-generation antipsychotics less associated with metabolic syndrome are ziprasidone and aripiprazole (123). Clozapine and olanzapine have been implicated in a greater risk for development of metabolic syndrome (123–126).

Currently, there are no medications or treatments approved by the U.S. Food and Drug Administration for metabolic syndrome, although the statin drugs are being used and specifically tested. There are controlled studies to suggest effective interventions to reverse the development of lipodystrophy syndrome; rosiglitazone (127) and pioglitazone are being used and specifically tested. However, use of psychiatric medications least likely to affect the metabolic parameters described above may reduce patients' risk for developing a metabolic syndrome.

The changes in body morphology may have significant psychological effects on people with HIV who are already living with a stigmatized illness. Development of lipodystrophy may contribute to nonadherence to antiretroviral medications or exacerbate mood and anxiety disorders. Psychiatrists can help patients with HIV whose treatments may adversely affect quality of life balance the competing wishes to sustain health and well-being.

▶ ACKNOWLEDGMENT

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