# NEUROPSYCHIATRIC MANIFESTATIONS OF HIV-1 INFECTION AND AIDS

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By 1999, the United Nations estimated that more than 33 million people worldwide had been infected by HIV-1 and more than 16 million had died of AIDS. Approximately 90% of these infections occurred in developing countries, particularly in sub-Saharan Africa, which accounts for 65% of HIV cases (1). In the United States and Canada, more than 920,000 adults and children were living with HIV/ AIDS by the end of 1999, and more than 400,000 had died. Initially, HIV-1 infection primarily affected men, but today, women comprise more than 16% of all AIDS cases in the United States. Among U.S. women with AIDS, the proportion of African-Americans and other minorities has been rising faster than the proportion of women in other segments of the population. By the end of 1997, African-American women accounted for 56% of AIDS cases among women in the United States. Another change in the demographics of the epidemic is seen in the mode of transmission. In the United States, homosexual transmission has stabilized or declined while infection via heterosexual transmission (5% to 18%) and injection drug use (15% to 23%) has increased significantly.

Neuropsychiatric and neurologic signs and symptoms have been described since the earliest reports on AIDS. The neuropsychiatric manifestations described in these early reports included progressive dementia, depression with pronounced apathy and psychomotor slowing, manic symptoms, and atypical psychosis. Initially, these mental disturbances were attributed to psychological reactions to a systemic illness, the effects of psychosocial stressors associated with the disease, or the consequences of opportunistic

immunosuppression, cerebrovascular disease, systemic toxicity, and complications of antiretroviral therapy. As understanding of the broad range of neuropsychiatric manifestations of HIV infection has grown, new classification and diagnostic criteria have replaced the earlier, more inexact terms, such as HIV encephalopathy and AIDS dementia complex, terms that combined diverse cognitive, motor, and affective—behavioral complications. The following sections review neurocognitive functioning in HIV-1 infection and the neuropsychiatric manifestations of such infection and their management.

infections or neoplasms within the central nervous system

(CNS). It is now recognized that the neuropsychiatric mani-

festations of HIV infection can result from the direct effects

of HIV on the brain and CNS or from indirect effects,

such as opportunistic infections or tumors associated with

### NEUROPSYCHOLOGICAL MANIFESTATIONS OF HIV-1 INFECTION

### Neurocognitive Functioning in HIV Infection

HIV-related neurocognitive deficits are manifestations of the direct and indirect effects of HIV on the CNS and can range from subtle changes in attention and psychomotor processing to full-blown dementia (2). Postmortem neuropathologic examination of HIV-seropositive patients has implicated both cortical and subcortical structures, specifically the frontal lobes, subcortical white matter, and basal ganglia (3–5). The caudate nucleus and basal ganglia are primary areas of HIV pathogenesis (6,7).

Neuropsychological assessment has played a crucial role in the identification of patterned impairment in HIVinfected persons. It has proved useful in the diagnosis of

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HIV-related cognitive disturbances and is used widely to quantify changes in cognitive processes associated with treatment. A battery of neuropsychological tests designed to cover the cognitive and behavioral domains affected by HIV-1 infection has been widely used to assess neurocogni-

tive functioning in HIV-infected persons (8).

Although it is generally agreed that patients in the symptomatic stages of HIV infection and those in whom AIDS has developed exhibit deficits in a variety of cognitive domains (9–13), the question of whether significant neurocognitive deficits occur in the asymptomatic stages of infection or in those who are mildly symptomatic remains controversial. Some investigators have found neuropsychological deficits in asymptomatic HIV-seropositive persons (14–21,22). However, a large number of studies have found subtle or no differences in neuropsychological functioning between asymptomatic HIV-seropositive and HIV-seronegative subjects (23–33).

It has been argued that a subgroup of asymptomatic HIV-seropositive patients may show cognitive deficits (12, 16,20,34,35). In other words, HIV may have a deleterious effect on brain function in certain asymptomatic HIVinfected persons. Evaluating group differences in overall impairment ratings may be the most sensitive and accurate method of assessing neurocognitive impairment in asymptomatic persons (9). In a review of 57 studies that examined neuropsychological functioning in asymptomatic persons, the median percentage of impaired test performances in asymptomatic persons was 35%, and in seronegative persons it was 12% (36). In another review of 36 cross-sectional studies and nine longitudinal studies, about half the reviewed studies indicated no significant difference in neuropsychological test performance between symptomatic and nonsymptomatic participants (37). In the majority of longitudinal studies (66.6%), no cognitive impairment in HIVpositive persons was found at baseline or at subsequent follow-up visits (37). Methodologic differences in study design and analysis probably account for discrepancies between studies.

Asymptomatic persons at risk for neurocognitive impairment have been found to display one of two patterns of deficits: (a) depression, psychomotor slowing, and diminished verbal memory or (b) lowered verbal and nonverbal cognitive functioning in the absence of a mood disturbance (38). Current research indicates that cognitive impairment is uncommon in asymptomatic HIV-seropositive persons (22,37), is not associated with deficits in social or occupational functioning (9,11), and, when present, is subtle and limited to a few cognitive domains.

It has been estimated that 55% to 86% of persons in the AIDS stages of HIV infection demonstrate significant neurocognitive deficits (9,16). Objective impairments in HIV disease include psychomotor slowing, forgetfulness, and difficulties with attention and concentration. In the later stages of HIV infection (symptomatic HIV and

AIDS), executive skills and motor speed may also become impaired.

#### Attention/Concentration

HIV infection has been associated with deficits in attention (9,39–41). Specifically, HIV-infected persons show deficits in dual-task or divided-attention paradigms (41,42). It has been argued that cognitive slowing may be at the root of the attentional deficits seen in many symptomatic persons (41). Additional work is needed to examine whether other components of attention (e.g., switching, engagement/disengagement, spatial attention) are also disrupted.

#### Working Memory

One critical cognitive function is "working memory," the ability to hold information "on line" in the service of performing an impending task (43,44). Evidence suggests that persons with HIV infection demonstrate deficits in working memory because of the affinity of HIV-1 for frontal—subcortical circuits (45). Given the anatomic evidence for involvement of frontal and related subcortical structures in executive functioning and HIV infection, it is not surprising that executive processes are affected by HIV infection. In fact, recent studies have found evidence for the *selective* impairment of verbal and spatial working memory processes in HIV-seropositive persons (13,45–49). Deficits of working memory tend to be observed in the later stages of HIV infection (i.e., after AIDS has been diagnosed) (45).

#### Learning and Memory

Patients with subcortical disorders (e.g., Parkinson disease, Huntington disease, basal ganglia disease) typically demonstrate deficits of recall in the context of relatively spared recognition memory but show fewer false-positive errors than are typically seen in patients with cortical dysfunction (50,51). This pattern, which supposedly reflects a problem with the retrieval of information rather than difficulties with encoding, is also seen in patients with HIV infection (5,7, 12,51).

#### Motor/Psychomotor Speed

Psychomotor slowing appears to be the most common HIV-related neurocognitive deficit and may underlie deficits in higher-order cognitive processes (52). Slowed complex cognitive processing may occur independently of peripheral nerve compromise, basic motor impairment, or psychiatric status (10). Psychomotor and motor impairment in HIV-infected persons has been well documented (5,53) and may be evident even in the earliest stages of HIV infection (31, 39). Reaction time tasks have been particularly helpful in detecting HIV-related cognitive slowing because they allow

for a more precise analysis of the effects of HIV on psychomotor processing (42).

#### Progression of Neurocognitive Deficits

The progression of HIV disease is associated with neurologic deficits (54) and deteriorating neurocognitive performance (9,14,36,55). Neurocognitive impairment is a proximal predictor of AIDS and mortality in HIV-infected persons (56-58). Slowed information processing and memory deficits before the development of AIDS have been associated with mortality independently of Centers for Disease Control and Prevention (CDC) clinical stage, CD4+ T-lymphocyte count, hemoglobin level, antiretroviral treatment, or sociodemographic variables such as age, education, and socioeconomic status (58). Patients with advanced HIV disease who are neurocognitively impaired are at higher risk for death than those at the same stage of infection without cognitive disturbance (56). In addition, prominent psychomotor slowing has been associated with more rapid neurologic progression in persons with HIV-associated dementia (59).

#### **HIV-1-Associated Dementia Complex**

In 1986, Navia et al. (60) described a triad of clinical symptoms that were later categorized as AIDS dementia complex (ADC). These symptoms included cognitive impairment, motor dysfunction, and behavioral changes in the context of a diagnosis of AIDS. In this landmark study of 70 patients with AIDS subjected to autopsy, 46 were characterized as demented. The majority of the patients with ADC (63%) had a preexisting diagnosis of AIDS. However, in 37% of the cases, ADC had developed before clinical evidence of AIDS. This finding led to problems with the ADC label because it was evident from the Navia study that a subgroup of patients who did not meet diagnostic criteria for AIDS displayed cognitive symptoms associated with HIV infection. In addition, certain patients displayed some, but not all, of the symptoms necessary to be classified as having ADC.

In 1990, the World Health Organization (WHO) recommended a new diagnostic term, *HIV-1-associated dementia* (HAD), to replace ADC (61). The American Academy of Neurology also adopted this new term for research purposes (62) (Table 90.1). Today, the two terms are often used interchangeably. However, because the progression of HIV infection to AIDS can now be delayed with aggressive antiretroviral therapy, a focus on HIV rather than on AIDS may be a more appropriate way to classify neurocognitive impairment.

HIV-associated dementia complex is the most common neurologic disorder in HIV infection, affecting 6% to 30% of all infected persons (11,63–65). It has an insidious onset, although persons with HAD may experience an acceleration

### TABLE 90.1. CRITERIA FOR A CLINICAL DIAGNOSIS OF HIV-1-ASSOCIATED DEMENTIA<sup>a</sup>

- I. Sufficient for diagnosis of AIDS
  - A. HIV-1-associated dementia complex

Probable (must have each of the following):

- Acquired abnormality in at least two of the following cognitive abilities (present for at least 1 month): attention/concentration, speed or processing of information, abstraction/reasoning visuospatial skills, memory/learning, and speech/language
  - The decline should be verified by reliable history and mental status examination. In all cases, when possible, history should be obtained from an informant, and examination should be supplemented by neuropsychological testing.
- 2. At least one of the following:
  - a. Acquired abnormality in motor function or performance verified by clinical examination (e.g., slowed rapid movements, abnormal gait, limb incoordination, hyperreflexia, hypertonia, or weakness), neuropsychological tests (e.g., fine motor speed, manual dexterity, perceptual motor skills) or both.
  - b. Decline in motivation or emotional control or change in social behavior. This may be characterized by any of the following: change in personality with apathy, inertia, irritability, emotional lability, or new onset of impaired judgment characterized by socially inappropriate behavior or disinhibition.
- 3. Absence of clouding of consciousness during a period long enough to establish the presence of #1.
- 4. Evidence of another etiology, including active central nervous system opportunistic infection or malignancy, psychiatric disorders (e.g., depressive disorder), active alcohol or substance use, or acute or chronic substance withdrawal; must be sought from history, physical and psychiatric examination, and appropriate laboratory and radiologic investigation (e.g., lumbar puncture, neuroimaging). If another potential etiology (e.g., major depression) is present, it is *not* the cause of the above cognitive, motor, or behavioral symptoms and signs.

Possible (must have one of the following):

- 1. Other potential etiology present (must have *each* of the following):
  - a. As above (see Probable #1, 2, and 3).
  - Other potential etiology is present but the cause of #1 above is uncertain.
- Incomplete clinical evaluation (must have each of the following):
  - a. As above (see Probable #1, 2, and 3).
  - Etiology cannot be determined (appropriate laboratory or radiologic investigations not performed).

of symptomatology. Before the introduction of highly active antiretroviral therapy (HAART), the median survival time for patients with late-stage HAD was 6 months (60,65). HAD affects cognitive, motor, and behavioral functioning, and patients often exhibit apathy, cognitive and motor slowing, and impaired memory, abstract reasoning, and judg-

<sup>&</sup>lt;sup>a</sup>From the Working Group of the American Academy of Neurology Task Force, 1991.

### TABLE 90.2. DIAGNOSTIC CRITERIA FOR DEMENTIA DUE TO HIV DISEASE

1284

- A. The development of multiple cognitive deficits manifested by both
  - memory impairment (impaired ability to learn new information or to recall previously learned information) and
  - 2. one (or more) of the following cognitive disturbances:
    - a. aphasia (language disturbance)
    - b. apraxia (impaired ability to carry out motor activities despite intact motor function)
    - c. agnosia (failure to recognize to identify objects despite intact sensory function)
    - d. disturbance in executive functioning (i.e., planning, organizing, sequencing, abstracting)
- B. The cognitive deficits in criteria A1 and A2 each cause significant impairment in social or occupational functioning and represent a significant decline from a previous level of functioning.
- C. Evidence from the history and physical examination or laboratory findings indicate that the disturbance is the direct physiologic consequence of HIV infection affecting the central nervous system.
- D. Deficits do not occur exclusively during the course of a delirium.

ment. HAD represents the more severe end of a continuum of HIV-related cognitive deficits; the milder end is represented by the presence of a single cognitive impairment, such as psychomotor slowing. The deficits observed in this disorder result in impaired social and occupational functioning.

A diagnosis of HAD requires laboratory evidence of HIV-1 infection and the exclusion of other CNS conditions (e.g., toxoplasmosis, CNS lymphoma, cytomegalovirus ventriculitis, cryptococcal meningitis, meningitis associated with syphilis, progressive multifocal leukoencephalopathy). Other causes, such as depression and delirium, which can manifest as cognitive impairment, must also be ruled out.

The American Psychiatric Association has defined dementia due to HIV disease as a dementia that is judged to be the direct pathophysiologic consequence of HIV disease and has outlined its own diagnostic criteria (Table 90.2).

### HIV-Associated Dementia and HIV Disease Progression

Price and Brew (66) argued that it is not enough simply to characterize HIV-infected persons as demented or not. Diagnosis should also involve staging of the severity of dementia and a description of specific impairments. Therefore, ADC was divided into different stages to differentiate levels of neurocognitive and neuropsychiatric functioning in HIV-infected persons (Table 90.3).

The course of HAD is highly variable. HAD begins with subtle deficits in cognitive processes (e.g., difficulties with concentration, forgetfulness, mental slowing). In some patients, HAD progresses rapidly after the diagnosis has been made (within weeks to months), whereas other patients show cognitive stability for months or years or very slow neurologic and neurocognitive progression (5,50,60). Persons in the early stages of HAD often complain of poor concentration, psychomotor retardation, and forgetfulness (60). They typically present with significantly less impairment in functions of daily living, cognition, and social and occupational functioning than is seen in the later stages of HAD. Hallmark symptoms of early-stage dementia are apathy, lethargy, poor concentration, and social withdrawal. Psychotic symptoms are not typically observed at this stage.

The later stage of HAD corresponds to ADC as originally

### TABLE 90.3. AIDS DEMENTIA COMPLEX STAGING SCHEME

ADC Stage	Characteristics
Stage 0 (normal) Stage 0.5	Normal mental and motor function.
(equivocal/	Either minimal or equivocal symptoms
subclinical)	of cognitive or motor dysfunction
	characteristic of ADC, or mild signs
	(snout response, slowed extremity
	movements), but without impairment of work or capacity to perform ADL; gait
	and strength are normal.
Stage 1 (mild)	Unequivocal evidence (symptoms, signs, neuropsychological test performance) of functional intellectual or motor
	impairment characteristic of ADC, but
	able to perform all but the more
	demanding aspects of work or ADL; can walk without assistance.
Stage 2 (moderate)  Stage 3 (severe)	Cannot work or maintain the more
	demanding aspects of daily life, but
	able to perform basic activities of
	self-care; ambulatory, but may require
	a single prop.  Major intellectual incapacity (cannot
	follow news or personal events,
	cannot sustain complex conversation,
	considerable slowing of all output) or
	motor disability (cannot walk unassisted,
	requiring walker or personal support,
	usually also with slowing and clumsiness
	of arms).
Stage 4 (end stage)	Nearly vegetative; intellectual and social
	comprehension and responses are at a
	rudimentary level; nearly or absolutely mute; paraparetic or paraplegic with
	double incontinence.

ADC, AIDS dementia complex; ADL, activities of daily living. From Price R, Brew B. The AIDS dementia complex. *J Infect Dis* 1988;158:1079–1083, and Sidtis JJ, Gatsonis C, Price RW, et al. Zidovudine treatment of the AIDS dementia complex: results of a placebo-controlled trial. *Ann Neurol* 1993;33:343–349.

defined, and survival expectancy at this stage may be 6 months or less. Features includes global cognitive dysfunction, significant functional impairment, and psychotic symptoms. Late-stage symptoms also may include aphasia, confusion, disorientation, delusions, hallucinations, seizures, and muscular weakness and paralysis (particularly in the lower limbs). Advanced dementia may result in disinhibition, mutism, catatonia, and incontinence (5,60). Neuropsychiatric complications of late-stage HAD include depression, mania, and psychosis.

The introduction of HAART has altered the course of HIV infection and AIDS and has diminished the CNS manifestations of HIV, even though protease inhibitors exhibit relatively poor penetration of the blood-brain barrier.

#### Prevalence of HIV-Associated Dementia

An early prospective study of HIV infection in the United States revealed that HAD develops in approximately 15% of patients with AIDS (65). The WHO cross-cultural study examining the neuropsychiatric consequences of HIV infection represents the best study of the prevalence of HAD based on a diverse clinical sample. This study examined persons at five sites around the world (Bangkok, Thailand; Kinshasa, Zaire; Munich, Germany; Nairobi, Kenya; and Sao Paulo, Brazil). The prevalence rates for dementia in patients with AIDS ranged from 4.4% to 6.9% and did not differ between four of the five recruitment centers (in Bangkok, no cases of HAD were recorded). In addition, no patients met the criteria for HAD while in the asymptomatic stage (11). In 1997, the CDC reported that 5% of adults with an AIDS-defining opportunistic illness had HIV encephalopathy (dementia) (67).

#### Early HIV-1-Associated Cognitive Motor Impairment

To classify appropriately HIV-1-seropositive persons who do not meet the criteria for dementia, the American Academy of Neurology AIDS Task Force introduced the term *HIV-1-associated minor cognitive/motor disorder* (MCMD) (62) (Table 90.4), a correlate of the WHO diagnosis of HIV-1-associated minor cognitive/motor disorder (61). In comparison with HAD, MCMD involves subtler neurocognitive difficulties that may not necessarily affect a patient's activities of daily living or occupational functioning.

The American Academy of Neurology AIDS Task Force specified that persons with HIV could be given this diagnosis regardless of their medical status. In other words, patients who are otherwise asymptomatic according to the CDC definitions may meet the criteria for MCMD. MCMD and HAD may represent areas along a common continuum of cognitive impairment, but they may also exist as distinct elements (62). However, the pattern of deficits observed in

## TABLE 90.4. CRITERIA FOR A CLINICAL DIAGNOSIS OF HIV-1-ASSOCIATED COGNITIVE/MOTOR COMPLEX<sup>a</sup>

- II. Not sufficient for diagnosis of AIDS
  - A. HIV-1-associated minor cognitive/motor disorder *Probable* (must have *each* of the following):
    - Cognitive/motor behavioral abnormalities (must have each of the following):
      - a. At least two of the following acquired cognitive, motor, or behavioral symptoms (present for at least 1 month) verified by reliable history, when possible, from an informant):
        - (1) Impaired attention or concentration
        - (2) Mental slowing
        - (3) Impaired memory
        - (4) Slowed movements
        - (5) Incoordination
        - (6) Personality change, or irritability or emotional lability
    - b. Acquired cognitive/motor abnormality verified by clinical neurologic examination or neuropsychological testing (e.g., fine motor speed, manual dexterity, perceptual motor skills, attention/concentration, speed of processing of information, abstraction/ reasoning, visuospatial skills, memory/learning, or speech/ language)
    - Disturbance from cognitive/motor/behavioral abnormalities (see #1) causes mild impairment of work or activities of daily living (objectively verifiable or by report of a key informant).
    - 3. Does not meet criteria for HIV-1-associated dementia complex or HIV-1-associated myelopathy.
    - 4. No evidence of another etiology, including active central nervous system opportunistic infection or malignancy, or severe systemic illness determined by appropriate history, physical examination, and laboratory and radiologic investigation (e.g., lumbar puncture, neuroimaging). The above features should not be attributable solely to the effects of active alcohol or substance use, acute or chronic substance withdrawal, adjustment disorder, or other psychiatric disorders.
    - 5. Criteria for minor cognitive motor disorder include at least two of the following acquired cognitive, motor, or behavioral symptoms, generally assessed with neuropsychological evaluation:
      - a. Impaired attention or concentration
      - b. Mental slowing
      - c. Impaired memory
      - d. Slowed movements
      - e. Incoordination
      - f. Personality change, irritability, or emotional lability

both disorders is characteristic of patients with dysfunction of frontal–subcortical neuronal circuitry (68), which means that persons with HAD or MCMD demonstrate differential deficits in the retrieval of information relative to the encoding or storage of information (51). HIV seropositivity with

<sup>&</sup>lt;sup>a</sup>From the Working Group of the American Academy of Neurology Task Force, 1991.

MCMD has been associated with a poorer prognosis relative to HIV seropositivity without MCMD (56), which suggests that MCMD may be a precursor of HAD.

#### Confounding Variables

To diagnose HIV-related cognitive deficits in patients (i.e., to conceptualize cognitive impairment in these patients as specifically related to the HIV virus), other potential causes of neurocognitive impairment must be ruled out. Depression, anxiety, and substance abuse are conditions seen in HIV disease that may contribute to neurocognitive impairment (69,70).

#### Depression and Apathy

Significant depressive symptomatology has been reported in patients with HIV-1 infection (71–74). Clinical assessments of persons with HIV infection can be confounded by the overlap of symptoms of HIV infection and somatic symptoms of depression (e.g., lack of motivation, low levels of energy, fatigue, weight loss, poor sleep patterns) (75), so that the severity of depression in HIV-seropositive persons is potentially overestimated (76,77). Therefore, cognitive and affective symptoms may be more accurate indicators of an underlying mood disorder in persons with HIV/AIDS because somatic symptoms may reflect advanced stages of disease and be unrelated to depression.

Although symptoms of depression and neuropsychological impairment may occur together in many HIV-infected persons, most studies have demonstrated that neuropsychological abnormalities observed in HIV infection are distinct and cannot be attributed to depression *per se* (18,35,73,77–84). It has been shown that depressed patients with HIV-1 infection may exhibit deficits in learning and memory (79,81,85), but the contributions of depression to the development and degree of these impairments appear to be minimal.

Apathy and reduced motivation are frequently observed in HIV-seropositive patients (45,60). Apathy, but not depression, also has been associated with deficits of working memory in HIV-seropositive patients, which suggests that both are manifestations of dysfunction in frontal—subcortical circuitry (45).

#### **Substance Abuse**

It is well known that HIV infection can be contracted through the intravenous administration of drugs with shared needles. The persistent use of drugs through other routes (e.g., inhaling crack/cocaine) may also increase the risk for HIV infection; drug abusers may practice prostitution to support their habit or engage in risky sexual behavior while under the influence of drugs or alcohol. The use of drugs such as crack/cocaine has been significantly associated with earlier progression to AIDS in HIV-seropositive persons (86). Injection drug use has also been associated with

more rapid progression of HAD (59), and recreational drug use has been found to diminish overall neuropsychological performance and reduce visuomotor processing, executive functioning, motor speed and strength, and sensorimotor perception in persons in the early stages of HIV infection (87).

Many investigators have postulated that drug use may increase the risk of HIV-seropositive persons for cognitive impairment (19); possibly, drug use induces CNS impairment independent of that caused by HIV infection. For example, it is known that chronic cocaine use can result in seizures, cerebrovascular accidents, and movement disorders. Deficits in attention, learning and memory (88-90), word production, visuomotor integration (90), and executive function (91) are specifically affected by cocaine use. These deficits have been related to dysfunction in prefrontal brain regions, the orbitofrontal cortex, and the anterior cingulate gyrus (91) and to cerebral hypoperfusion in the frontal, periventricular, and temporal-parietal areas (90). Although this is a plausible hypothesis, most studies have found that substance abuse does not independently contribute to neuropsychological dysfunction after HIV seropositivity is taken into account (92). The interaction of HIV infection and drug use does not appear to produce additional cognitive deficits (26,27,80,93-96).

#### Other Cofactors

Other factors may potentially confound the neuropsychological functioning of HIV-infected persons, including gender, ethnicity, level of education, and medication regimen.

#### Gender and Ethnicity

Racial and ethnic minorities have been disproportionately affected by HIV/AIDS, and women constitute one of the most rapidly increasing groups at risk for AIDS in the United States (96,97). Although neuropsychological assessment has been helpful in elucidating patterns of impairment in persons with HIV/AIDS, most of the study participants have been well-educated, Caucasian, homosexual men. It remains unclear whether neuropsychological instruments are equally valid in assessing HIV-related neurocognitive functioning in populations who differ in terms of ethnicity/culture, language, educational background, and socioeconomic status. Neuropsychological tests and batteries, in addition to being sensitive to the presence of cerebral pathology, are also sensitive to demographic factors, including gender, ethnicity, socioeconomic status, education, and age.

Neuropsychological tests may overdiagnose organic impairment in neurologically intact African-Americans (98); thus, clinicians must be cautious about reporting increased neurocognitive impairment among HIV-infected members of minorities. Ideally, separate norms for specific ethnic subgroups (e.g., African-Americans) should be established. Studies that examined the effect of ethnicity on neuro-

psychological performance in the context of HIV infection have found that after correction for education, ethnicity accounts for additional variance (99). One possible explanation for these findings is that matching for grade level does not always resolve the effects of disparate educational experiences of test subjects. Also, within the African-American population, the incidence of poverty and homelessness is higher, situations that can have a pervasive influence on the interactions of persons with their environment and thus their performance on neuropsychological tests. Also, many tests ignore the fact that African-Americans display ideals, values, beliefs, and cultural traditions that contribute to unique psychological processes not often tapped by mainstream neuropsychological instruments (100).

African-Americans who were HIV-seropositive and matched for age, education, gender, and HIV disease stage obtained lower scores than their Caucasian counterparts on neurocognitive measures (101). However, acculturation level accounts for the vast majority of these differences in performance. Acculturation level refers to the degree to which a person's beliefs, values, and behaviors are consistent with European-American culture, the dominant cultural basis for most standardized neuropsychological measures. Therefore, it is important to examine acculturation level to improve the accuracy with which HIV-related neurocognitive deficits are diagnosed in ethnic minorities. Manly et al. (101) suggest that measures that assess attention, psychomotor speed, and retention may be of greater utility in assessing HIV-associated cognitive deficits across cultural groups.

African-Americans show a pattern of performance deficits in neuropsychological functioning that are similar to those reported in majority populations. For example, studies have found deficits in verbal and nonverbal memory in symptomatic men (77) and women (102). As in ethnic minority populations, the incidence of HIV-1 infection in women has continued to rise. However, few studies have explored the neuropsychological sequelae of HIV infection in women. It has been reported that HIV-infected women report more psychological symptoms than HIV-infected men (103,104) and that the early signs of HIV infection in women are often overlooked and underrecognized in comparison with the symptoms of men (105). HIV disease progression does not appear to differ according to sex (86). Gender does not appear to be related to rates of CD4<sup>+</sup> cell decline, first CD4+ count below 200/mm3, clinical progression to clinical AIDS, or mortality (86).

However, neurocognitive functioning does appear to differ between HIV-seropositive men and women. Whereas HIV-infected men and women show similar vulnerability to cognitive dysfunction, AIDS in women is associated with a poorer neuropsychological test performance (52). Also, the degree of impairment in symptomatic HIV-seropositive women has been found to be greater than that in either HIV-seropositive homosexual men or HIV-seropositive intravenous drug users (106). These differences do not appear

to be secondary to differences in age, education, or mood, which suggests that neuropsychological impairment may become apparent earlier in HIV-seropositive women than in HIV-seropositive men.

Few studies have examined neurocognitive functioning solely in HIV-seropositive women. The studies that have been conducted seem to demonstrate a similar pattern of deficits in both women and men. In a longitudinal study, HIV-seropositive women demonstrated slower reaction times and motor speed and less improvement in verbal memory than did seronegative women at 6-month followup (107). Cross-sectional analyses have found no differences between asymptomatic women and seronegative controls (30,102). However, with progression to AIDS, deficits in attention and memory became evident (102). In a preliminary investigation, Costa et al. (108) found no differences between asymptomatic HIV-seropositive and HIV-seronegative women in quantitative EEG activity during various conditions, nor between the two groups on any of the neurocognitive or neuropsychiatric measures administered.

#### **Psychosocial Variables**

Fewer years of education, lower estimated premorbid intelligence, lower occupational attainment, and lower socioeconomic status may put patients at particular risk for HIVrelated neurocognitive impairment (38,109,110). Satz (109) found the rate of impairment in asymptomatic HIVseropositive participants to be comparable with that of seronegative controls among participants with more than 12 years of education. The rate of impairment in asymptomatic HIV-seropositive participants with 12 or fewer years of education was more than twice that of seronegative controls (38% vs. 17%). Stern et al. (110) found that HIV-seropositive participants with a low cognitive reserve (based on measures of education level, occupational attainment, and vocabulary) performed worse on neuropsychological measures than did HIV-seronegative and HIV-seropositive participants with a high cognitive reserve. According to the cognitive reserve theory, the threshold for neuropsychological symptoms of persons with a greater cognitive or brain reserve may be higher after acquired brain injury (109). These studies suggest that a low cognitive reserve increases one's risk for cognitive dysfunction and underscore the need to consider demographic variables in any evaluation of neuropsychological function in HIV infection.

# Clinical Significance of Early Cognitive/Motor Disturbance and Its Relationship to Future Disease

The identification of HIV-related neurocognitive and neuropsychiatric disturbances has potential medical and vocational implications for patients. In particular, cognitive disturbances can affect the ability to adhere to antiretroviral

medication regimens and can affect occupational functioning.

#### Adherence to Medication Regimen

1288

The administration of protease inhibitors in combination with nucleoside analogues has successfully suppressed HIV replication in many persons with HIV-1 infection. However, the long-term effectiveness of medication regimens that include protease inhibitors depends on strict adherence to the prescribed drug regimen. Poor adherence can lead to changes in plasma levels of HIV RNA and the development of treatment-resistant viral mutations (111). In other words, resistance to a particular drug and cross-resistance to drugs within a particular class can develop in persons who comply poorly with their medication regimen. Understanding the various factors that contribute to medication adherence is critical to optimizing the treatment of persons with HIV/AIDS.

Factors affecting adherence may include relationships with health care providers, complexity of antiretroviral regimens, depression, substance abuse, cultural beliefs, and neurocognitive functioning. Factors affecting medication adherence may vary across HIV disease stage. For example, it is well established that persons in the later stages of HIV infection exhibit neuropsychological deficits associated with frontal-subcortical brain dysfunction. Therefore, in more advanced HIV infection, poor compliance may be related to neurocognitive compromise. Poor adherence to antiviral medication has been associated with poor performance on measures of divided attention, learning and memory, executive function, and psychomotor ability (42,112,113). Hinkin et al. (42) examined the relationship between neurocognitive and neuropsychiatric symptoms, substance abuse, medication complexity and side effects, and a variety of psychosocial factors in predicting adherence to antiretroviral medication. Medication adherence was assessed by computerized monitoring (medication event monitor system, or MEMS), in which a computer chip embedded in the cap of a pill bottle records the date and time when the bottle is opened. Preliminary data from this group revealed that medication adherence is associated with executive function and prospective memory. Apathy, but not depression, was also found to predict poor adherence.

#### **Employment**

It has been proposed that neurocognitive impairment is clinically significant when it affects everyday functioning (114). For some HIV-infected persons, cognitive difficulties result in occupational problems even in the early stages of infection, when cognitive impairment is mild (114–116). When employed persons rated their job performance relative to that before their HIV diagnosis, self-perceived decreases in work abilities were five times more prevalent in those with neurocognitive impairment (114). Impaired persons also performed worse on standardized work samples

and displayed more discrepancies between expected levels of functioning (based on work history) and observed levels (based on work samples), which suggested an acquired decrease in vocational abilities (117). Furthermore, HIV-sero-positive persons who demonstrated neurocognitive impairment were two to three times more likely to be unemployed than were those without cognitive impairment, even after control for medical status (114,115). A poorer performance on tasks of learning and executive functioning seems to be a good predictor of loss of employment status (115).

#### Pharmacologic Treatment of HIV Infection

Highly active antiretroviral therapy has changed the epidemiology of HIV disease progression. In 1996, the annual AIDS incidence decreased for the first time in the United States. In 1997, this pattern continued as the number of new AIDS diagnoses decreased (97). However, AIDS prevalence increased from 1996 to 1997, probably because of longer survival times after diagnosis. This decline in the incidence of AIDS and AIDS deaths and the observed delay in progression to AIDS are in part a consequence of HAART. In a HAART regimen, three or more antiretroviral drugs, such as a nucleoside analogue reverse transcriptase inhibitor, a protease inhibitor, and a non-nucleoside reverse transcriptase inhibitor, are usually combined.

Before the advent of HAART, monotherapy with zidovudine (AZT) was reported to improve neurocognitive functioning, slow progression to dementia (118–120), decrease neuropathologic features of AIDS (4), and prevent mild cognitive impairment associated with HIV (121).

In a patient population largely comprising persons on monotherapy (81%), treated patients showed superior information processing on a reaction time task (a sensitive measure of HIV-related cognitive slowing) in comparison with untreated participants (48). High doses of AZT are reportedly more effective in improving neurocognitive functioning (120), and long-term use of AZT has been associated with improved cognitive performance in subjects with early symptomatic HIV infection and AIDS (122).

The introduction of protease inhibitors has resulted in new approaches to the treatment of HIV infection. Patients on an HAART regimen perform better than do those treated with less intensive antiretroviral therapy (e.g., regimens that do not include a protease inhibitor) (116). However, persons on combined antiretroviral therapy, regardless of whether a protease inhibitor is included, have shown improved psychomotor speed in comparison with antiretroviral-naïve patients and patients treated with monotherapy (123). Improvement in neurocognitive functioning has been associated with a reduction in viral load (116). HAART has resulted in undetectable levels of HIV in the blood. Even though the CNS penetration of protease inhibitors is poor, multiple drug regimens lower serum viral load,

slow disease progression, and in some cases improve HIV-associated cognitive motor complex, reverse HIV encephalopathy, and improve cognitive impairment (124,125). Future research will focus on the mechanisms of HAART-associated improvement in neuropsychological functioning and the possibility that the CNS may act as a reservoir for HIV.

### PSYCHIATRIC MANIFESTATIONS OF HIV-1 INFECTION

#### **Psychiatric Symptoms in HIV-1 Infection**

Major depression is the most common psychiatric disease among HIV-1-infected persons (74) Earlier controlled studies showed that the prevalence of major depression and other mood disorders is higher in asymptomatic HIV-1-infected homosexual men than in the general population (126,127) but is similar to the prevalence in HIV-1-seronegative homosexual men (71,128,129). In several early studies, from 4% to 9% of both HIV-1-infected and uninfected homosexual men reported a major depression in the month before study evaluation, and in the study of Perkins and colleagues (73), a major depression developed in 6% of both HIV-1infected and uninfected subjects during a 6-month followup period. Evidence also indicates that similar proportions (from zero to 5%) of HIV-1-infected and uninfected persons meet DSM-III-R criteria for current anxiety disorders (73). Thus, after more than 15 years of research, the available data suggest that the prevalence of major depression is high in asymptomatic HIV-1-infected gay men in comparison with the prevalence in men of similar age in the population at large, but no higher than that in seronegative gay men of similar age and somewhat lower than that in patients with serious medical illnesses, such as cancer and heart disease (130-133). These findings underscore the issue that mood disorders should not be considered a "normal" phenomenon in HIV-1-infected persons. Rather, they should be assessed carefully and treated appropriately.

Diagnosing major depression in HIV-1-infected patients can be complicated because several symptoms of major depression (i.e., fatigue, sleep disturbance, and weight loss) are also common symptoms of progression of HIV-1 disease (134,135). However, although complaints of fatigue and insomnia in asymptomatic HIV-1-infected homosexual men are significantly associated with depressed mood and other symptoms of major depression, they are not associated with low CD4<sup>+</sup> counts or decreased neuropsychological functioning (136,137). Thus, complaints of fatigue and insomnia in otherwise asymptomatic HIV-1-infected patients are highly suggestive of an underlying mood disorder, and patients with such complaints should be assessed routinely for major depression.

Factors that influence the development of major depression in HIV-1-infected persons have not been well studied.

However, several studies suggest that the prevalence of a past history of major depression is relatively high in HIVinfected persons and may be a risk factor for the development of major depression (74). The first of these was the study of Perkins and colleagues (73), who found a relationship between major depression in asymptomatic HIV-1infected homosexual men and a prior history of major depression. Coping with the threat of AIDS also may be related to the overall level of depressed and dysphoric mood. Leserman and colleagues (138) reported that a depressed and anxious mood was less frequent in asymptomatic HIV-1-infected men using active coping strategies to deal with the threat of AIDS (e.g., fighting spirit, reframing stress to maximize personal growth, planning a course of action, seeking social support) than in those using passive coping strategies (denial or feeling helpless). Like the studies of persons with other potentially life-threatening diseases, early studies of HIV-1-seropositive persons found that they usually are able to adjust successfully to their infection and that most are able to maintain hope over time. More recently, the availability of HAART has led to a still greater sense of hope. Therefore, coping strategies in HIV-infected persons may influence the development of depression or anxiety.

Studies of psychiatric and psychosocial factors in HIVinfected women are emerging as the demographics of the HIV epidemic change. Early studies are difficult to interpret because study methodology and populations differed considerably (74). A high rate of major depression was found in women using intravenous drugs, but this rate did not differ from that of men using intravenous drugs (139,140); high rates of major depression were found in both seropositive and seronegative men and women using intravenous drugs. However, a gender difference was found; the prevalence of depressive and anxiety symptoms, but not syndromes, was higher in women than in men. This finding held for both seropositive and seronegative subjects. In a related study of Boland et al. (141), HIV status was not related to depressive symptoms at baseline in a large, multicenter, prospective sample of U.S. women. Both seronegative and seropositive women had a high prevalence of depressive symptoms on the Center for Epidemiological Studies Depression Scale (CES-D); however, diagnoses of depressive disorder were not obtained. In the study of Morrison et al. (142), who examined the prevalence of depressive and anxiety disorders in a large cohort of rural U.S. women, the prevalence of major depressive disorder and anxiety symptoms was significantly higher in seropositive women without active substance abuse than in seronegative controls

As reviewed earlier, the effects of HIV-1 on the CNS may result in a variety of neurocognitive and related psychiatric symptoms in the later stages of illness. In addition, persons infected with HIV-1 may be at further risk for the development of psychiatric symptoms because of diseases secondary to AIDS that also have CNS effects and because of medica-

tions used to treat HIV-1 infection. Although psychiatric symptoms in HIV-1-infected persons in the later stages of illness may represent new-onset psychiatric disorders, it is more likely that these symptoms reflect the direct CNS effects of HIV-1, HIV-1-related CNS disturbances, and CNS effects of medications used in the treatment of AIDS. Thus, although Leserman and colleagues (138) found an increase in depressive symptoms approximately 1.5 years before the onset of AIDS, in the study of Rabkin et al. (140), the onset of syndromal depression and anxiety did not increase despite worsening HIV infection during a 4-year period.

Evidence from earlier stages of the epidemic suggests that HIV-1 may cause organic mood disturbance. In a 17-month retrospective chart review of patients with AIDS, Lyketsos and colleagues examined associated historical and clinical features in an attempt to separate organic and functional symptoms (145). They used a family history of mood disorder as a "marker" for functional mood disorders. They further assumed that coexisting dementia and a low CD4<sup>+</sup> count are "markers" of HIV-1-related mood disorders. None of the patients with a personal or family history of mood disorder had coexistent dementia, and all but one of the patients without a personal or family history of mood disorder had coexistent dementia. In addition, among the 8% of patients who experienced manic episodes, the CD4<sup>+</sup> count was significantly higher in those without a personal history of mood disorder. Although these findings suggest that mania may be a consequence of the direct or indirect effects of HIV-1 on the brain, controlled studies have yet to find this relationship (74). Vitamin B<sub>12</sub> deficiency may also place HIV-1-infected patients at risk for organic mood disturbance. Between 20% and 30% of patients with AIDS and 7% of asymptomatic HIV-1-infected patients have been reported to have a vitamin B<sub>12</sub> deficiency. Furthermore, vitamin B<sub>12</sub> deficiency has previously been shown to be associated with depression and can occur in the absence of hematologic or neurologic signs (146). Although the relationship between vitamin B<sub>12</sub> level and depressive symptomatology in HIV-1-infected patients is not clear (147), it is prudent that the medical evaluation of depressive symptoms in HIV-1-infected patients include an assessment of serum  $B_{12}$  levels.

Although relatively uncommon, psychosis may result from HIV-1 involvement of the CNS. Earlier case studies of symptomatic HIV-1-infected persons have reported psychotic symptoms, including delusions, bizarre behavior, and hallucinations. Mood disturbances, including euphoria, irritability, and labile or flat affect, have often accompanied psychotic symptoms in these patients. Similarly, anxiety and agitation were reported in almost half of the reported cases. In addition, some evidence indicates that psychosis may be a symptom of the terminal stages of AIDS; half of the patients described had a progressively worsening course, with dementia or death occurring within a few months after the onset of psychotic symptoms. Psychosis may be more fre-

quently found in patients with significant AIDS-related neurocognitive impairment than in patients in earlier stages of the disease. In one retrospective chart review of 46 patients identified with HIV-1-associated dementia, Navia and Price (148) found that psychotic symptoms had developed in 15%. Relatedly, data from the San Diego HIV Neurobehavioral Research Center (149) suggest that HIV-1-infected patients with psychosis trend toward greater neurocognitive impairment than do nonpsychotic HIV-infected controls. Thus, new-onset psychosis may be secondary to HIV-related encephalopathy. Accordingly, a complete organic workup should be considered for HIV-1-infected patients with significant disturbance of mood or psychosis.

### Treatment of Psychiatric Disorders in HIV-1 Infection

Available evidence suggests that mood symptoms and syndromes in the asymptomatic stage of HIV-1 infection are not secondary to the effects of HIV-1 on the brain and should be evaluated and treated as in the general population. Although confirmatory data are lacking, this probably also holds true in the symptomatic stages of the disease.

#### Controlled Studies with Antidepressant Drugs

Only a small proportion of the published studies of the treatment of mood disorders in patients with HIV-1 infection have been double-blinded, randomized, placebo-controlled studies. In the study of Rabkin et al. (150), imipramine was effective in 97 HIV-infected patients. At 6 weeks, they found a response rate of 74% in the imipramine group versus 26% in the placebo group. No changes in CD4+ helper/inducer cell counts were found in the imipraminetreated subjects. However, adverse anticholinergic side effects led to discontinuation of imipramine within 6 months in more than one-third of the responders. Elliott and coworkers (151) blindly and randomly assigned 75 HIV-seropositive patients to treatment with imipramine, paroxetine, or placebo. Of the 75 enrolled subjects, 75% completed 6 weeks of treatment; only 45% completed the full 12-week trial. The two antidepressants were found to be equally efficacious at 6, 8, and 12 weeks, and both were significantly more efficacious than placebo. Side effects of the tricyclic antidepressants markedly influenced attrition. The dropout rate in the imipramine group was 48%, 20% in the paroxetine group, and 24% in the placebo group. Zisook and colleagues (152) reported that fluoxetine was more effective than group therapy in a randomized, double-blinded, placebo-controlled study of 47 HIV-seropositive men with major depression. Rabkin and colleagues (153) recently completed a double-blinded, placebo-controlled, 8-week trial with fluoxetine in 120 HIV-seropositive subjects. Among the subjects who completed the 8-week trial, 74% of the fluoxetine group responded to treatment, in comparison with 47% of the placebo group. When intention-to-treat analysis was used, the differences between the treatment groups were less remarkable (57% of the fluoxetine-treated subjects responded compared with 41% of the placebo group). Drug treatment did not alter levels of CD4+ cell counts. Thus, the available data suggest that the selective serotonin re-uptake inhibitors (SSRIs) are effective and well tolerated in the treatment of HIV-associated major depression.

#### Open Trials with Antidepressant Drugs

In a study related to the one described above, Rabkin and colleagues (154) enrolled HIV-infected subjects with depression who had failed imipramine treatment (i.e., they had relapsed, could not tolerate the side effects, or did not respond to the drug) in a 12-week open-label trial of fluoxetine. Although depression at baseline as measured on the Hamilton Depression Scale (HAM-D) was more severe in this sample (12.5) than in the imipramine study sample (15.8), 83% of subjects treated with fluoxetine (at doses of 15 to 60 mg/d) responded and exhibited significant reductions in their HAM-D scores. Fluoxetine treatment did not alter CD4+ counts. Fluoxetine was tolerated better than imipramine. In an open-label trial of 28 depressed HIVinfected subjects, Rabkin et al. (155) found a 70% response rate among subjects who had 8 weeks of treatment with sertraline. Side effects resulted in a loss of 18% of the total sample. Sertraline did not alter the counts of either CD4+ cells or natural killer cells.

Ferrando and colleagues (156) conducted a 6-week openlabel, parallel-group trial of the SSRIs paroxetine, fluoxetine, and sertraline in 33 symptomatic HIV-infected patients with depression. Seventy-three percent of subjects completed the trial, and of these, 83% responded to their assigned treatment. Most of the subjects who dropped out did so because of complaints of agitation, anxiety, and insomnia during weeks 1 through 3. Both depression and somatic symptoms perceived to be related to HIV infection improved with SSRI treatment. Differences in efficacy between the three SSRIs could not be ascertained reliably because of the study design and small sample size. More recently, these authors performed a small open trial comparing fluoxetine (n = 21) and sertraline (n = 9) in HIV-infected women (157). Sixty percent of the women completed the trial, and of these, 78% were responders (e.g., HAM-D score decreased 50% or more). Grassi et al. (158) performed a 6-week open trial of the efficacy of paroxetine in 10 HIV-seropositive patients with major depression. Significant improvement in HAM-D scores was noted between weeks 2 through 6 of the study. Recently, a 73% response rate was demonstrated with nefazodone in a small open trial of 15 outpatients. Few adverse side effects were noted (159). As discussed in the next section, clinicians must be aware of the potential for drug interactions between antidepressants that potentially inhibit the CPY450 3A4 isoenzyme system and protease inhibitors and for adverse effects of herbal therapy. Although the outcomes of the open-label studies have generally been consistent with those of the available double-blinded, randomized, placebo-controlled trials, these findings must nonetheless be interpreted cautiously.

#### Effects of Psychostimulants and Novel Agents

Fernandez et al. (160) compared desipramine with methylphenidate in a treatment trial of 15 subjects. With either agent, subjects showed a response rate of approximately 50%; however, subjects treated with desipramine experienced more adverse events, including dry mouth, anxiety, and insomnia. In the open trial of Wagner et al. (161) of 24 patients with AIDS, debilitation, low levels of energy, and a DSM-III-R diagnosis of depressive disorder, the response rate to dextroamphetamine treatment was 75%. Improvements in mood and energy coincided, and analysis revealed significant reductions in HAM-D scores after as little as 2 weeks of treatment. Although systematic followup evaluations were not conducted, anecdotal evidence suggested that the treatment effect (improved mood and energy) was maintained for up to 2 years in some subjects. In a small treatment series of Rabkin et al. (154), all seven patients treated with a combination of fluoxetine and dextroamphetamine (5 to 25 mg/d) responded during the 12week course of treatment, another preliminary observation that warrants further study. Placebo-controlled trials are necessary to confirm these promising observations.

HIV-associated reductions in testosterone levels have been found to correlate with changes in mood, appetite, and energy and with sexual dysfunction. In a double-blinded, placebo-controlled trial (6-week trial followed by 12-week open-label maintenance), testosterone injections were effective in improving both mood and libido, energy, and body muscle mass in 70 HIV-seropositive men with hypogonadal symptoms who completed the trial (162). The authors also found that exercise may augment improvement in psychological and nutritional status in HIV-seropositive patients receiving testosterone therapy (163). In an 8-week openlabel pilot study of 45 HIV-positive subjects, the adrenal steroid dihydroepiandrosterone (DHEA) appeared promising for improving mood in addition to anabolic and androgenic parameters (153).

### Treatment Considerations for Mood Disorder and Other Psychiatric Conditions

Antidepressant therapy is effective and can improve the quality of life of HIV-infected persons. SSRIs and newer agents may be particularly well suited for use in depressed HIV-seropositive patients because these agents do not pro-

1292

duce the significant side effects (e.g., anticholinergic,  $\alpha$ -adrenergic, histaminergic, and cardiac effects) caused by the tricyclic agents and other older classes of antidepressants (164). Further study is required.

Pain is frequently undertreated in patients with HIV infection (165), although it is well established that antidepressants are effective agents for the treatment of chronic pain, particularly antidepressants with noradrenergic properties (132). However, patients with AIDS experience adverse effects more frequently with tricyclic antidepressants than do patients with AIDS-related complex and asymptomatic HIV-seropositive patients (166). Better-tolerated antidepressants with effects on serotoninergic and noradrenergic neurotransmitter systems include venlafaxine, mirtazepine, and paroxetine; these may prove useful and are awaiting controlled studies. Finally, placebo-controlled clinical trials have not demonstrated that stimulants are effective in treating primary depression (167), but they may be useful adjunctive agents in depressed patients with HIV infection, as noted above.

#### Treatment of Psychotic Symptoms

The treatment of psychotic disorders in HIV-infected patients has been less well studied than the treatment of mood disorders. Several reports have noted that HIV-seropositive patients may be more sensitive to the extrapyramidal side effects associated with dopamine-receptor antagonists (149, 168). This is thought to be related to the subcortical motor slowing associated with HIV infection. In a case series of 21 patients with psychotic symptoms (12 had mania with psychotic features), risperidone was found to be efficacious and caused fewer side effects than did conventional antipsychotic drugs (169), although some anecdotal data suggest that the sensitivity of AIDS patients to both older and newer antipsychotic agents may be increased (170). Controlled studies are needed in this area.

In general, the same strategies used to treat the general population with psychotropic drugs are appropriate in HIVinfected patients with psychotic symptoms or mood disorders. Pharmacologic knowledge can be used to therapeutic advantage and to avoid potential untoward effects. Factors such as drug interactions related to psychotropic drug metabolism and protein binding, half-life, and effects on appetite require careful consideration, particularly in more debilitated HIV-infected patients. Potential interactions between psychotropic drugs and the antiretroviral agents used in HIV therapy with multiple drugs warrant consideration by the clinician because a potential for drug interactions exists. Psychotropic drugs, non-nucleoside reverse transcriptase inhibitors, and protease inhibitors may serve as substrates for various cytochrome P-450 enzymes in the liver. Each of these classes of compounds may possess enzyme-inducing or enzyme-inhibiting properties, and drugs such as the protease inhibitor ritonavir may simultaneously modify a number of isoenzymes (171).

The nontraditional herbal psychotropic agents used to treat psychiatric syndromes must also be monitored closely in HIV-positive patients. An open-label study recently revealed that the efficacy of the protease inhibitor indinavir (which is a metabolized by the 3A4 isoenzyme system) is markedly reduced by the concomitant administration of St. John's wort (a potent inducer of the 3A4 system) (172). The reduction in indinavir levels was estimated to be sufficient to cause drug resistance and treatment failure. Finally, given that psychotropic drugs such as antidepressants can improve the quality of life of HIV-positive persons, further research is needed to determine whether effective treatment can improve medical outcomes in selected subsets of HIV-infected patients.

### Psychoneuroimmunology of HIV-1 Infection

The multifactorial nature of HIV infection has led researchers to examine the influence of stress, depression, and other psychosocial factors on the course of this disease. A growing literature points to the potentially harmful effects of stress and depression on cellular immunity (173–176), and to the potentially negative impact of these psychosocial factors on the course of several types of cancer (177–180). Among patients with breast cancer, severe life stress has been associated with a greater probability of relapse (179), and psychosocial interventions to improve coping skills have resulted in increased numbers and function of natural killer cells and longer survival in patients with breast cancer or melanoma (177,178,181). These studies await replication.

Early findings on the significance of depression in predicting a decline in immune status and disease progression were inconsistent. Investigators found no relationship between psychosocial and psychiatric factors such as depressive disorders, distress, and stressors, on the one hand, and measures of HIV-1 disease progression, including CD4<sup>+</sup> and CD8+ cell counts, on the other. However, a relationship was noted between the number and severity of HIV-related symptoms and levels of depressive disorders, distress, and stressors (182-184). In a 1996 metaanalysis, Zorilla et al. (185) found that depressive symptoms were longitudinally related to self-reported symptoms of HIV infection, but not to changes in CD4+ T-lymphocyte counts or other commonly accepted markers of HIV disease progression. The mixed findings of this metaanalysis may have resulted from the inclusion of studies in which cross-sectional designs and relatively brief follow-up periods were used.

Prospective studies conducted for longer time intervals have found that depression may significantly predict HIV disease progression. In the San Francisco Men's Health Study, a 9-year longitudinal study of 395 seropositive gay men, researchers found that subjects classified as depressed

at study entry on the CES-D (186) progressed more rapidly to AIDS (187). The median time to first AIDS diagnosis was 6.2 years for subjects who were depressed at study entry and 7.6 years for nondepressed subjects. This finding held after control for baseline demographic variables, CD4<sup>+</sup> T-lymphocyte count, HIV-related medical symptoms, and health habits. At 5 years, this cohort showed no significant association of baseline depression with AIDS diagnosis; however baseline depression was associated with a decline in CD4<sup>+</sup> T lymphocytes (188). After 7 years of follow-up, subjects with elevated depressive symptoms at every visit had a 1.7 times greater risk of mortality than did those who had never had an elevated depression score (189).

Initial analysis of 1,809 HIV-seropositive gay men in the Multicenter AIDS Cohort (MAC) study found no relationship between baseline depression, measured by the CES-D, and progression of HIV infection during 8 years of followup (190). Disease progression was defined as time to AIDS, death, or decline in CD4<sup>+</sup> T lymphocytes. In a subsequent report on years 2 through 6, a robust increase of 30% to 104% above baseline levels (depending on CES-D depression cut point) was noted in self-reported depressive symptoms beginning 1.5 years before a clinical diagnosis of AIDS and continuing beyond the diagnosis of AIDS (191). The authors interpreted these findings as an indication that depression may increase toward the later stages of HIV infection and thus be a manifestation of the HIV disease process. However, a subsequent survival analysis of these data, in which the level of depressive symptoms during the 6 months before AIDS diagnosis was used, showed no relationship between depression and time to death (144). A limitation of both these prospective cohort studies is the method of ascertainment of depression. The CES-D is not a clinical diagnostic tool; its sensitivity for DSM-III major depression is 80% to 90%, and its specificity is 70% to 80% (192).

The Coping in Health and Illness Project (CHIP) is a prospective study of initially asymptomatic HIV-infected gay men who are followed every 6 months; extensive clinical interviews are used to define depression and stressful life events. An analysis of this cohort at study entry showed a significant effect of stress on parameters of cellular immunity (143); furthermore, depressive symptoms, especially in the presence of severe stress, were related to declines in several lymphocyte subsets (e.g., CD16 and CD56 natural killer cells and CD8 cytotoxic suppressor cells) during a 2year period (193). At 5.5 years, an increased risk for AIDS was associated with a higher cumulative level of depressive symptoms, measured by a modified Hamilton Depression Rating Scale (HDRS) excluding somatic symptoms that could be related to HIV disease. For every increase of one severe depressive symptom (3-point increment on the HDRS), the risk for AIDS doubled (194). This result, however, lost statistical significance after control for stressful life events and social support, which overlapped with depressive symptoms. The small number of subjects with elevated scores may partially account for this outcome.

The CHIP investigators are also directly investigating the effect of stressful life events on clinical outcome. Evans et al. (195) found that for each severe stressful event per 6month study interval, the risk for early HIV disease progression doubled in men studied for up to 3.5 years. At 5.5 years (194) and 7.5 years (196) of follow-up of the CHIP cohort, Leserman et al. reported that more cumulative stressful events were associated with faster progression to AIDS. At both time points in follow-up, every increase in cumulative average stress equivalent to one severe stressor or two moderate stressors doubled the risk for AIDS. At 7.5 years, 47% of those above the median for stressful life events had progressed to AIDS, versus 27% of those below the median. Higher levels of serum cortisol were also associated with faster progression to AIDS, but variations in cortisol did not account for the stress findings (196).

Other studies also lend support to the hypothesis that stressful events may hasten the progression of HIV infection. In the study of Kemeny and Dean (197), the stress of bereavement before study entry was associated with a more rapid decline in CD4+ count during 3 to 4 years of follow-up in 85 gay men. Bereavement did not predict progression to AIDS or mortality rate. Ironson et al. (198) found that in men with whose distress was greater at the time of HIV serostatus notification, the likelihood for the development of HIV-related clinical symptoms at 2-year follow-up was greater. In a recent study of 67 asymptomatic HIV-infected African-American women, trauma (e.g., death of child, assault, rape), particularly among those with posttraumatic stress disorder, was associated with a greater decrease in the CD4<sup>+</sup>/CD8<sup>+</sup> ratio during 1 year of followup (199).

It is noteworthy that studies in which relatively short follow-up periods and questionnaire methods are used to assess life stress have generally not shown an association of stress with reduction in CD4<sup>+</sup> T-lymphocyte counts. Studies that examine actual stressors (e.g., bereavement) or interview-based contextual ratings of cumulative stressful events are more likely to show such results than studies based on questionnaire assessments of stress.

Other psychosocial variables (social support and coping) have been linked to HIV disease progression. Recently, Leserman and colleagues reported faster progression to AIDS during 5.5 and 7.5 years of follow-up in men with less cumulative average social support satisfaction and more cumulative average denial (194,196). These findings echo those of some earlier research showing potentially harmful effects of denial and potentially beneficial effects of social support (200–202). In the study of Antoni and colleagues (203), HIV-infected gay men scoring above, rather than below, the median on passive coping strategies (e.g., denial, behavioral and mental disengagement) had lower CD4<sup>+</sup>/CD8<sup>+</sup> ratios and lymphocyte proliferative responses to

phytohemagglutinin at 3 weeks and 1 year after serostatus notification. An increase in denial from before to after serostatus notification was also associated with a greater probability of development of symptoms and AIDS during a 2-year follow-up study of gay men (198). In the study of Solano and colleagues (201) of 100 male and female HIV-infected subjects, those who became symptomatic after 1 year had shown more denial and less "fighting spirit" at baseline.

The findings of other studies regarding the effects of social support have been less consistent. Larger social networks and greater emotional support predicted longer survival during 5 years in men who were symptomatic or had AIDS; however, larger social networks were associated with faster progression to AIDS in those who were asymptomatic at entry (202). Loneliness was associated with a more rapid decline in CD4<sup>+</sup> levels but was unrelated to AIDS or mortality during 3 years of follow-up in 205 symptomatic HIV-infected men (204). Other prospective studies have reported no significant associations of social support with HIV disease progression or decline in CD4<sup>+</sup> T lymphocytes (205).

In summary, the evidence is substantial that psychosocial factors such as depression and stressful life events may adversely affect disease progression in persons infected with HIV. It must be noted that most of the cited studies of psychosocial moderators of HIV infection have been conducted in men, primarily before the advent of protease inhibitors. Therefore, we need additional studies of women and patients currently on HAART.

#### **CONCLUSION**

Considerable preclinical and clinical research has been conducted in an effort to describe the neuropsychiatric manifestations of HIV-1 disease and increase our understanding of its underlying neuropathologic mechanisms. The virus enters the CNS early in the course of disease and causes both direct and indirect CNS effects. Subtle abnormalities can be detected on pathologic, neuroimaging, and neuropsychological studies before the onset of AIDS-defining illnesses, although the clinical significance of these findings continues to be unclear. In symptomatic AIDS, neuropsychiatric and neurologic complications are prevalent, and these can often be among the first manifestations of AIDS.

Since the earliest years of the HIV epidemic, most persons infected with HIV-1 have coped well. Major depression continues to be the most prevalent common psychiatric diagnosis in HIV-1-seropositive men; the prevalence is high compared with epidemiologic estimates in the general population, but it is similar to that in seronegative gay men and no higher than that in patients with other serious medical illnesses. The interrelationships between the CNS, endocrine system, and immune system are being actively investigated. Moreover, recent studies suggest that stress and

depression may adversely affect immune function and accelerate the progression of HIV-1 disease. However, these studies require confirmation by comprehensive, longitudinal investigations in which similar methodologies are used. Future study is also necessary to increase our understanding of the neuropsychiatric manifestations of HIV-1 infection in women and its special effects on neurologic development in infants and children.

Recent controlled trials of psychopharmacologic treatment have yielded positive results for the alleviation of depression, and preliminary evidence also indicates a reduction in neurocognitive impairment. Future neuropsychopharmacologic approaches will likely focus on both direct and indirect effects of HIV-1 in the brain in an effort to develop novel interventions that may alter the course of disease and symptomatic treatments to improve clinical outcome and quality of life. The long-term impact of HAART on HIV-related CNS disease and associated neuropsychiatric manifestations will also be extensively studied.

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