

*Practitioner's Guide  
to the Neuropsychiatry  
of HIV/AIDS*

Edited by

WILFRED G. VAN GORP  
and  
STEPHAN L. BUCKINGHAM

THE GUILFORD PRESS  
New York London

© 1998 The Guilford Press

# *Neuropsychological Features of HIV Disease*

CHARLES H. HINKIN  
STEVEN A. CASTELLON  
WILFRED G. VAN GORP  
PAUL SATZ

## **INTRODUCTION**

In the last decade, a tremendous amount of research effort and clinical care has been devoted to understanding the neuropsychological changes associated with HIV-1 infection. From the first case reports of unexpected cognitive decline in AIDS (Navia, Cho, Petito, & Price, 1986b) to the impressively large studies of hundreds and thousands of infected patients that were ultimately performed (Miller et al., 1990; Heaton et al., 1995), our knowledge of the natural history of HIV-1-related dementia, our ability to accurately evaluate and diagnose HIV-infected patients, and (encouragingly) our increasing ability to treat neuropsychological deficits in patients with AIDS have all increased significantly.

Given the prevalence of HIV-1-associated cognitive impairment, neuropsychological evaluation is frequently a critical part of the diagnosis and treatment of HIV-1-infected individuals. Making decisions on important issues related to differential diagnosis (e.g., "worried well" status vs. subclinical cognitive decline; depression vs. dementia), and

tracking medication response over time, are but two of the important roles the clinical neuropsychologist is called upon to play. This chapter provides an overview of the typical cognitive and behavioral sequelae of HIV-1 infection; it also covers such issues as the epidemiology of HIV-associated dementia, neuroimaging findings, the relationship between cognition and depression, and the accuracy of patients' self-reported cognitive status.

### CASE STUDY

The following is a case study of an individual who exemplifies the characteristic cognitive and behavioral deficits seen in HIV-1-associated dementia complex. It should be noted that although this is not an uncommon presentation, many HIV-infected individuals do not develop neuropsychological deficits of the severity of those affecting this patient. We refer to this relatively prototypical case to illustrate various issues throughout the chapter.

Mr. Smith, a 42-year-old, partnered white male with 16 years of education, presented for neuropsychological evaluation with complaints of trouble concentrating, forgetfulness, and difficulty doing two things at a time. His partner, who accompanied him, added that Mr. Smith was also increasingly apathetic and occasionally overly irritable. Medically, the patient was first diagnosed HIV-1-seropositive 8 years ago. Two years ago he suffered an episode of *Pneumocystis carinii* pneumonia (PCP), thus meeting diagnostic criteria for AIDS. His current CD4 T-cell count was 50. Current medications included zidovudine and saquinavir, 2'-deoxy-3'-thiacytidine, as well as a number of anti-opportunistic-infection agents. The patient was administered a comprehensive battery of neuropsychological tests, which revealed the following profile of strengths and deficits. On the Wechsler Adult Intelligence Scale-Revised (WAIS-R), Mr. Smith's Full Scale IQ was 110, with his Verbal IQ slightly higher than his Performance IQ. He encountered greatest difficulty on WAIS-R subtests sensitive to attentional difficulty, such as Digit Span and Arithmetic, as well as on timed measures such as the Digit Symbol subtest. In contrast, his best performances were on the Vocabulary and Information subtests—two WAIS-R tasks that are relatively resistant to the deleterious effects of HIV. Other areas of cognitive impairment observed on neuropsychological testing included (1) poor divided attention; (2) memory impairment for both verbal and nonverbal material that was "forgetful" in nature;

and (3) psychomotor slowing, seen as a difficulty in performing speeded tasks where thought is wedded to action. In addition, Mr. Smith also reported a significant degree of depressive symptomatology, as measured by both the Beck Depression Inventory (BDI) and the Minnesota Multiphasic Personality Inventory-2 (MMPI-2). In contrast, Mr. Smith performed well within normal limits on measures of language, visual-spatial ability, praxis, and calculation. Although aware of his difficulties, Mr. Smith reported that they had not yet had adverse impact upon his ability to perform most activities of daily living. However, because he was now having difficulty with the most demanding of his job responsibilities, he decided to go on disability leave from his job as a public accountant. (See Table 1.1 for a summary of Mr. Smith's neuropsychological test scores.)

### TERMINOLOGY AND DIAGNOSTIC CRITERIA

There remains considerable confusion among both mental health professionals and the lay public about the appropriate terminology to use in describing the cognitive changes attendant upon HIV-1 infection. A number of different diagnostic labels have been employed over the years, including "AIDS dementia complex," which was first introduced by Navia, Jordan, and Price (1986b) to identify the constellation of cognitive, behavioral, and motor symptoms that can occur alone or in combination in HIV-affected individuals. Soon thereafter, Price and Brew (1988) proposed a scaling system in which the severity of AIDS dementia complex could be graded (e.g., stage 0 = absent, stage 1 = mild, stage 3 = severe), to capture the sometimes obvious differences in degree of cognitive impairment seen in HIV-infected individuals. Following these earliest attempts at developing meaningful nomenclature, labels such as "HIV-related encephalopathy," "HIV-1-associated cognitive/motor complex," and "dementia due to HIV disease" have also been used to describe essentially the same syndrome.

Some of the historically most important attempts to codify criteria for the diagnosis of HIV-related cognitive impairment are reviewed below.

#### Centers for Disease Control

In 1987 the Centers for Disease Control (CDC) published diagnostic criteria for HIV-related encephalopathy, which in some ways closely resembled Navia et al.'s (1986b) description of AIDS dementia complex. HIV-related encephalopathy was considered a condition that

TABLE 1.1. Neuropsychological Data for Mr. Smith

|  |  |
|--|--|
| Age: 42                                    | Education: 16 years  |
| Presenting concerns:                       | Concentration difficulty, forgetfulness, trouble "doing two things at once"; more apathetic and irritable (according to informant)   |
| CD4 count: 50                              | History of opportunistic infections: <i>Pneumocystis carinii</i> pneumonia (one bout 2 years ago)  |
| Current medications:                       | Zidovudine, 2'-deoxy-3'-thiacytidine, saquinavir   |
| Wechsler Adult Intelligence Scale-Revised: | Full Scale IQ: 110, Verbal IQ: 112, Performance IQ: 105<br>Best subtests: Vocabulary (91st percentile), Information (91st percentile)<br>Worst subtests: Digit Span (16th percentile), Digit Symbol (9th percentile)   |
| Attention:                                 | Simple attn.: Intact, although digits backward somewhat low<br>Divided attn.: Poor (Auditory Consonant Trigrams: 4th percentile)   |
| Memory:                                    | California Verbal Learning Test: Immediate Recall: 7/16<br>Delayed Recall: 6/16<br>Immediate Cued Recall: 10/16<br>Delayed Recognition: 14/16<br>Wechsler Memory Scale-Revised: Logical Memory I: 50th percentile<br>Logical Memory II: 23rd percentile<br>Visual Reproduction I: 43rd percentile<br>Visual Reproduction II: 20th percentile   |
| Other test data:                           | Trail Making Test, Part B: 4th percentile: Suggestive of psychomotor slowing<br>Stroop task, Part A: 13th percentile: Also suggestive of psychomotor slowing<br>Wisconsin Card Sorting Test: 6/6 categories but higher than usual number of perseverative errors<br>Finger Tapping Test: Dominant hand, 35th percentile; nondominant hand, 29th percentile<br>Beck Depression Inventory: 19 (suggestive of moderate level of depressive symptomatology)<br>Minnesota Multiphasic Personality Inventory-2: Scale 2 (Depression) elevated ( $T = 75$ ) |

could qualify an otherwise asymptomatic person for a diagnosis of AIDS and was defined as follows:

Clinical findings of disabling cognitive and/or motor dysfunction interfering with occupation or activities of daily living, or loss of behavioral developmental milestones affecting a child, progressing over weeks to months, in the absence of a concurrent illness or other condition than HIV infection that could explain the findings. Methods to rule out such concurrent illness and conditions must include cerebrospinal fluid examination and either brain imaging (computed tomography or magnetic resonance) or autopsy.

Although this definition represented a significant step forward by providing a consensual definition and label for an HIV-related encephalopathy or dementia, it was nonetheless criticized as being ambiguous and imprecise, with certain key terms not adequately defined (e.g., "clinical findings," "disabling cognitive and/or motor dysfunction").

The CDC, also in 1987, developed the first system for HIV disease staging, primarily for the purposes of surveillance and classification. This earliest staging system consisted of four main groups. Group I included people with time-limited medical symptoms appearing at or shortly following initial seroconversion; group II included individuals who were medically asymptomatic; group III contained those with progressive generalized lymphadenopathy (enlarged lymph nodes), but without any other notable symptoms of infection; and group IV included people with AIDS or AIDS-related complex, including people with symptoms of constitutional disease (persistent fever, weight loss, and diarrhea). This staging system emphasized individuals with AIDS, the last stage of the disease, and was eventually criticized on that grounds as being insufficient for predicting disease progression prior to the appearance of AIDS.

In 1993, the CDC published a revised classification system for HIV infection, which is currently widely used for describing the stage of HIV infection in a given patient (Mapou & Law, 1994). This two-factor staging system groups patients on the basis of type and degree of physical symptoms present (asymptomatic, mildly symptomatic, or AIDS-defining opportunistic infection), as well as on the basis of degree of immunosuppression present (CD4 count of  $>500$  cells/mm<sup>3</sup>, 200-499 cells/mm<sup>3</sup>, or  $<200$  cells/mm<sup>3</sup>). This revised staging system responded to the important observation that a high CD4 count can occur in medically symptomatic patients and a low count can occur in asymptomatic patients. The CDC 1993 classification system is shown in Table 1.2.

### American Academy of Neurology

An AIDS Task Force from the American Academy of Neurology (AAN, 1991) attempted to further clarify and define diagnostic criteria for AIDS-related dementia and to make these criteria more objective. The AAN criteria recognize that cognitively impaired HIV-infected individuals may present with either a full-blown dementia syndrome or more mild and selective cognitive abnormalities. For this reason, HIV-1-associated cognitive/motor complex has been divided into two subgroups: HIV-1-associated dementia complex and HIV-1-associated minor cognitive/motor disorder. In HIV-1-associated minor cogni-

**TABLE 1.2. Centers for Disease Control and Prevention (CDC) 1993 Revised Classification System for HIV Infection, and Expanded AIDS Surveillance Case Definition for Adolescents and Adults**

| CD4+ T-cell categories                        | Clinical categories                          |  |                               |
|---|--|--|-------------------------------|
|   | (A) Asymptomatic, acute (primary) HIV or PGL | (B) Symptomatic, not (A) or (C) conditions | (C) AIDS indicator conditions |
| (1) $\geq 500/L$                              | A1   | B1   | C1                            |
| (2) 200-499/L                                 | A2   | B2   | C2                            |
| (3) $<200/L$<br>(AIDS indicator T-cell count) | A3   | B3   | C3                            |

Note. Clinical categories C1-C3, B3, and A3 constitute the expanded AIDS surveillance case definition.

**Category C: AIDS-defining illnesses or infections**

- (1) PCP (*Pneumocystis carinii* pneumonia)
- (2) Cryptosporidium
- (3) Tuberculosis
- (4) Coccidiomycosis
- (5) Recurrent pneumonia in the past year (other than PCP)
- (6) Candidiasis (only pulmonary, esophageal, or bronchial)
- (7) Wasting syndrome—diarrhea with loss of 15 lbs. or greater than 10% of body weight
- (8) CMV (cytomegalovirus)
- (9) Cryptococcus
- (10) K.S. (Kaposi's sarcoma) or lymphoma
- (11) Dementia due to HIV disease
- (12) MAC (*Mycobacterium avium* complex)
- (13) PML (progressive multifocal leukoencephalopathy)

**Category B: Symptomatic non-AIDS conditions**

- (1) Oral candidiasis
- (2) Vulvovaginal candidiasis
- (3) Cervical dysplasia, moderate or severe
- (4) Severe unexplained diarrhea, fever for over 1 month
- (5) Oral hairy leukoplakia
- (6) Herpes zoster (two distinct episodes or more than one site)
- (7) Idiopathic thrombocytopenic purpura
- (8) Pelvic inflammatory disease, severe

**Category A: Asymptomatic**

- (1) PGL (persistent generalized lymphadenopathy)
- (2) No symptoms

Note. From CDC (1992).

tive/motor disorder, activities of daily living and occupational performance are less severely impaired than in HIV-1-associated dementia complex, with the individual able to perform all but the most demanding aspects of work or activities of daily living. Table 1.3 provides the AAN criteria for HIV-1-associated cognitive/motor complex.

**TABLE 1.3. American Academy of Neurology (AAN) Criteria for HIV-1-Associated Cognitive/Motor Complex**

All of the following diagnoses require laboratory evidence for systemic HIV-1 infection (enzyme-linked immunosorbent assay [ELISA] test confirmed by Western blot, polymerase chain recreation, or culture).

**I. Sufficient for diagnosis of AIDS**

**HIV-1-Associated Dementia Complex\***

**Probable (must have each of the following):**

1. Acquired abnormality in at least *two* of the following cognitive abilities (present for at least 1 month): attention/concentration, speed of information processing, abstraction/reasoning, visuospatial skill, memory/learning, and speech/language.
  - a) 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.
  - b) Cognitive dysfunction causing impairment of work or activities of daily living. The impairment should not be attributable solely to severe systemic illness.
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, hypertonía, or weakness), neuropsychological test (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 changes in personality such as apathy, inertia, irritability, emotional lability, or new onset of impaired judgment characterized by socially inappropriate behavior or disinhibition.
3. Absence of clouding of consciousness (delirium) during a period long enough to establish the presence of #1.
4. Evidence of another etiology, including active CNS 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 radiological investigation (e.g., lumbar puncture, neuroimaging). If another potential etiology (e.g., major depressive disorder) 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.
  - b) Other potential etiology is present but the cause of #1 above is uncertain.
2. Incomplete clinical evaluation (must have each of the following):
  - a) As above (see **Probable**) #1, 2, 3.
  - b) Etiology cannot be determined (appropriate laboratory or radiological investigations not performed).

(continued)

TABLE 1.3. (cont.)

**I. Not sufficient for diagnosis of AIDS****HIV-1-Associated Minor Cognitive/Motor Disorder****Probable (must have each of the following):**

1. 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):
  - a) Impaired attention or concentration
  - b) Mental slowing
  - c) Impaired memory
  - d) Slowed movements
  - e) Incoordination
  - f) Personality change, or irritability or emotional lability

Acquired cognitive/motor abnormality verified by clinical neurological 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).
2. 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 CNS opportunistic infection or malignancy, or severe systemic illness determined by appropriate history, physical examination, and laboratory and radiological 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.

*Note.* From AAN (1991). Copyright 1991 by the American Academy of Neurology. Reprinted by permission.

\*For research purposes, HIV-1-associated dementia complex can be coded to describe the major features:

HIV-1-associated dementia complex requires criteria 1, 2a, 2b, 3, and 4.

HIV-1-associated dementia complex (motor) requires criteria 1, 2a, 3, and 4.

HIV-1-associated dementia complex (behavior) requires criteria 1, 2b, 3, and 4.

**American Psychiatric Association**

Finally, the fourth edition of the *Diagnostic and Statistical Manual of Mental Disorders* (DSM-IV; American Psychiatric Association, 1994) has for the first time included dementia due to HIV disease in the psychiatric nosology. As detailed in Table 1.4, to meet DSM-IV diagnostic criteria for dementia due to HIV disease, patients must have memory impairment as well as impairment in at least one other neuropsychological domain, such as language or executive function.

Furthermore, these deficits cannot occur solely in the context of a delirium and must be of sufficient severity to result in a decrement in occupational or social functioning.

**Comment**

Although arguments can be made in favor of any of these diagnostic schemes, it is our opinion that the AAN criteria best capture the neuropsychological sequelae of HIV infection, whereas the CDC classification is best for staging the physical status of infected patients. The CDC criteria would be applied as follows to Mr. Smith: Since he had already contracted an AIDS-defining opportunistic infection and had a CD4 count of less than 200/mm<sup>3</sup>, his physical status would be staged as CDC category C3. Neuropsychological testing documented the presence of moderate memory impairment, psychomotor slowing, poor divided attention, mild executive dysfunction, and depressed and irritable mood—deficits that led Mr. Smith to take disability leave from his job. Although relatively mild, these symptoms would nonetheless warrant a DSM-IV diagnosis of dementia due to HIV disease. Since his cognitive symptoms had only affected the more demanding aspects of

TABLE 1.4. American Psychiatric Association Criteria for Dementia Due to HIV Disease

- A. The development of multiple cognitive deficits manifested by both:
    - (1) memory impairment (impaired ability to learn new information or to recall previously learned information)
    - (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 or identify objects despite intact sensory information)
      - (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 represents a significant decline from a previous level of functioning.
  - C. There is evidence from the history, physical examination, or laboratory findings that the disturbance is the direct physiological consequence of HIV infection.
  - D. The deficits do not occur exclusively during the course of a delirium.
- Coding note:** Also code 043.1 HIV infection affecting central nervous system on Axis III.

*Note.* Reprinted with permission from the *Diagnostic and Statistical Manual of Mental Disorders*, Fourth Edition. Copyright 1994 American Psychiatric Association.

his daily life, he would meet AAN criteria for HIV-1-associated minor cognitive/motor disorder.

## INCIDENCE/PREVALENCE

### HIV/AIDS

The CDC report that through December of 1996, approximately 580,000 cases of AIDS had been diagnosed in the United States, and more than one million individuals in the United States were HIV seropositive. Provisional data provided by the CDC in September 1997 showed a decline in AIDS incidence during 1996 compared with 1995 and a continued decline (23% drop) in the number of AIDS deaths. These figures reflect increased success with the medical care of HIV/AIDS including the development and increased utilization of antiretroviral combination therapy regimens.

While surveillance data are beginning to show encouraging trends, HIV infection remains one of the leading causes of death in the United States among persons aged 15 to 44 (Ventura, Peters, Martin, & Maurer, 1997). Additionally, ethnic minorities and women are being especially hard hit by HIV/AIDS in the U.S. (Green, Karon, & Nwan-yawu, 1992; Kalichman & Sikkema, 1994). For example, while the overall incidence of AIDS opportunistic infections among Black and Latino men and among Black women who had heterosexual risk factors (CDC, 1997).

### Neuropsychological Deficits in HIV-1 Infection

Cognitive impairment is a frequent concomitant of HIV infection. This impairment, in its most severe form, presents as a dementia syndrome with symptoms severe enough to cause severe occupational impairment and to disrupt even the most basic activities of daily living. The annual incidence of HIV-associated dementia following the development of AIDS was recently estimated at 7% (McArthur et al., 1993), but it can vary considerably, depending on the referral population studied and the selection criteria used. Estimates of the prevalence of HIV-associated dementia range from 6% to 66%, with a consensus building that between 10% and 30% of patients with AIDS will eventually develop dementia (McArthur et al., 1993; Maj et al., 1994; Heaton et al., 1995). The survival times of patients who develop HIV-associated dementia can vary markedly, with one study estimating the median time of survival following a diagnosis of dementia at 6 months (McArthur et al., 1993).

The prevalence rates of less severe but significant cognitive impairment in medically symptomatic patients (those in CDC categories B and C) vary widely, again seemingly in part because of population characteristics and the impairment criteria used. The literature shows prevalence rates ranging from 12% (Miller et al., 1990) to 86% (Grant et al., 1987), with a recent well-done, large-scale study showing approximately 55% of all AIDS (CDC category C) patients and 44% of all mildly symptomatic (CDC category B) patients showing some degree of cognitive impairment (Heaton et al., 1995). Among symptomatic HIV-seropositive patients, cognitive deficits have been reported in almost all neuropsychological domains, including memory (Lunn et al., 1991; McKegney et al., 1990; Poutiainen, Iivanainen, Elovaara, Valle, & Lahdevirta, 1988), motor speed and control (Bornstein et al., 1991; Dunbar, Perdices, Grunseit, & Cooper, 1992; Lunn et al., 1991), abstraction ability (McKegney et al., 1990), verbal fluency (Stern et al., 1991), and self-regulation (Krikorian, Wrobel, Meinecke, Liang, & Kay, 1990).

At one point there was considerable debate about the frequency and degree of cognitive impairment in medically asymptomatic HIV-seropositive individuals. An early study of a small sample of asymptomatic subjects reported neuropsychological abnormalities in 44% of these patients, relative to HIV-seronegative controls (Grant et al., 1987). This study received widespread attention and led to suggestions that patients with early, asymptomatic HIV infection should not be allowed to perform certain government sector jobs. However, in a much larger study of neuropsychological functioning in asymptomatic individuals, Miller et al. (1990) found that asymptomatic subjects performed no worse than noninfected controls when matched for age and level of education. In fact, a number of cross-sectional and longitudinal studies have concluded that HIV-1-seropositive asymptomatic patients do not differ neuropsychologically from HIV-1-seronegative controls (Boccellari et al., 1993; Franzblau et al., 1991; Mauri et al., 1993; McAllister et al., 1992). On the other hand, some investigators *have* found differences on a group level between asymptomatic and control subjects (Bornstein et al., 1992; McKegney et al., 1990), or have found a higher frequency of neuropsychologically "abnormal" patients among asymptomatic patients relative to seronegative controls (Lunn et al., 1991; Wilkie, Eisdorfer, Morgan, Loewenstein, & Szapocznik, 1990). Capturing the inconsistency of the findings regarding cognitive impairment in asymptomatic HIV-infected patients, White, Heaton, Monsch, and the HNRC Group (1995) reviewed 75 neuropsychological studies of such subjects. They found that 32% of these studies showed significant neuropsychological differences between asymptomatic HIV-positive subjects and

controls, whereas 47% of the studies found no significant group differences. In a well-done study using both a large sample and a thorough neuropsychological assessment battery, Heaton et al. (1995) found approximately that 30% of their asymptomatic subjects showed some evidence of cognitive impairment. Bornstein et al. (1992) found that approximately 10–20% of asymptomatic patients suffered from neuropsychological impairment to a degree that influenced their daily lives.

In conclusion, there is a steady increase in cognitive abnormalities as the disease progresses into the symptomatic stages, with the prevalence rate of significant neuropsychological impairment increasing markedly as a patient begins to show symptoms of AIDS (Heaton et al., 1995). Neuropsychological impairment is less obvious and prevalent in asymptomatic HIV infection, but there is a subset of patients who will show at least mild cognitive compromise. Research to date suggests that it is more the exception than the rule to see severe functional disruption in the earliest stages of HIV infection.

## SECONDARY NEUROLOGICAL ILLNESSES IN HIV INFECTION

It is clear that HIV can be detected in the central nervous system (CNS) of infected patients (Navia et al., 1986a). Nearly half of all seropositive but asymptomatic individuals show evidence of HIV in their cerebrospinal fluid (Resnick et al., 1985) and nearly 90% of all patients who die of AIDS show evidence of neuropathological abnormalities of the CNS on autopsy (Collier, Gayle, & Bahls, 1987; Navia et al., 1986a).

Because opportunistic infections of the CNS occur frequently in immunosuppressed patients, when a patient is being evaluated for HIV-related dementia, the presence of secondary neurological illnesses must first be ruled out. In the United States, the most frequent CNS opportunistic infections leading to neuropsychological deterioration are cerebral toxoplasmosis, cryptococcal meningitis, and progressive multifocal leukoencephalopathy (PML) (McArthur, Selnes, Glass, Hoover, & Bacellar, 1994).

Cerebral toxoplasmosis is the most common HIV-related opportunistic neurological illness, affecting approximately 10–15% of all HIV-infected patients. Necrotic abscesses appear that are often multifocal and scattered throughout the cerebral hemispheres, with an affinity for the basal ganglia and frontal lobes (McArthur et al., 1994). Structural neuroimaging depicts toxoplasmosis as ring-enhancing mass lesions that may be difficult to differentiate from CNS lymphoma (as

discussed below). Because it can produce one or more cerebral lesions, toxoplasmosis frequently has a focal presentation with neurobehavioral sequelae, dependent on the site(s) of lesion(s). Cerebral toxoplasmosis is often responsive to treatment, with approximately 80% of cases responding clinically within 1–4 weeks following initiation of pyrimethamine and sulfadiazine treatment (McArthur et al., 1994).

CNS lymphomas are another leading cause of secondary neurological illness in HIV-infected individuals. Like toxoplasmosis, a primary lymphoma often begins with a focal presentation, with one or more cortical regions differentially affected. Specific neurobehavioral syndromes (such as aphasia, agraphia, and ataxia) may be seen, depending on the site of the lesion, and focal neurological signs will develop in approximately 40% of all cases (McArthur et al., 1994). The typical presentation of CNS lymphomas includes a slowly progressive neurological deterioration, with death usually occurring within 3–4 months.

PML results from a papovavirus infection, which leads to a demyelinating disorder that affects the hemispheric white matter and causes patchy foci of demyelination. Typically, subcortical areas are the first sites of involvement, but the gray matter may also be affected—occasionally before any subcortical lesions are evident (McArthur et al., 1994). The cognitive changes associated with PML are typically related to the specific, often multiple brain regions affected by the virus. As with the CNS lymphomas, specific focal neurobehavioral syndromes may be present in the early stages of PML. Aphasia, apraxia, hemiparesis, hemineglect, and visual-field defects are commonly seen in PML. Following the diagnosis of PML, the patient usually deteriorates rapidly, with death often occurring within weeks to months after initial diagnosis.

## NEUROIMAGING AND HIV INFECTION

### Structural Neuroimaging

Computerized tomography (CT) studies in HIV-1 infection reveal generalized cerebral atrophy, with widened cortical sulci and enlarged ventricles, in the majority of patients with AIDS. Structural abnormality is much more frequently found in the later stages of HIV infection, with nearly 70% of all patients with AIDS showing some degree of atrophy (Raininko et al., 1992). Regardless of the stage of infection, central and cortical atrophy is the most frequently reported finding when CT is used.

Magnetic resonance imaging (MRI) is assuming an increasingly important role in the diagnostic workup of HIV-infected patients, with

T<sub>2</sub>-weighted images most sensitive in detecting the brain abnormalities associated with HIV. MRI is better than CT for assessing the white matter pathology often found in HIV infection. MRI scans indicate that in addition to sulcal widening and ventricle enlargement, the white matter, particularly the periventricular white matter, is often abnormal in HIV-infected patients (McArthur et al., 1989; Elovaara et al., 1990).

Interestingly, most studies using structural neuroimaging techniques have failed to find a convincing association between degree of CT or MRI abnormality and neuropsychological deficit. (However, see Hall, Whaley, Robertson, & Hamby, 1996). A sizeable minority of HIV-infected patients show normal CT and MRI scans well into the middle and even late stages of HIV infection.

In conclusion, because structural neuroimaging yields largely non-specific findings and is not strongly associated with behavioral change, it is perhaps most useful in ruling out the presence of focal lesions due to secondary opportunistic infection.

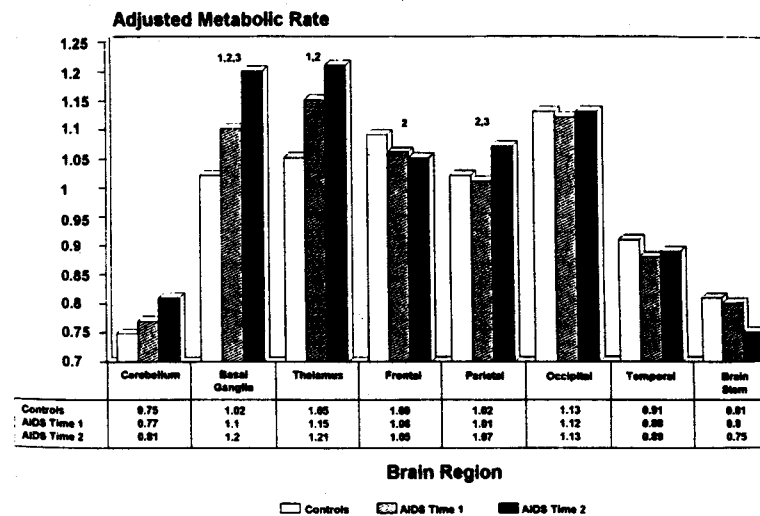
### Functional Neuroimaging

Functional neuroimaging employs techniques such as positron emission tomography (PET), single-photon emission computerized tomography (SPECT), and functional MRI (fMRI). Unlike structural imaging techniques such as X-rays, CT, and MRI, which provide a picture of the brain's structure, these newer techniques provide a picture of the brain's function—that is, which parts of the brain are working normally and which parts are not. Several studies (Hinkin et al., 1995a; Rottenberg et al., 1987; van Gorp et al., 1992) have employed PET scans using fluorodeoxyglucose, a radioactively labeled sugar that the brain uses as fuel. Those parts of the brain that are most active utilize the most glucose; the brain structures that are least active use less. This glucose metabolism can then be imaged. We have published two PET studies of cerebral metabolic abnormalities in HIV infection. Our first study (van Gorp et al., 1992) compared patients with AIDS to uninfected controls and found that the patients with AIDS demonstrated basal ganglia hypermetabolism (i.e., the subcortical structures that control psychomotor function, among other behaviors, were overly active in these patients). We also found that the subjects who were most demented had decreased metabolism of the temporal lobes, the brain area that is actively involved in memory. In an effort to understand how cerebral metabolism changes over time, we next looked at these patients' PET scans 6 months later (Hinkin et al., 1995a). As shown in Figure 1.1, we found that the subjects with AIDS demonstrated even greater hypermetabolism of the basal ganglia—a finding that may reflect

increased effort expended by the brain in order to maintain its neuropsychological integrity.

### NATURAL HISTORY AND CLINICAL COURSE

There is considerable individual variability in the clinical course of HIV-associated cognitive/motor complex. Although it is not possible to predict the exact course of illness in any one HIV-infected person, we are increasingly able to suggest a *typical* course of cognitive deterioration, from the first signs of CNS involvement to end-stage dementia. Some (but not all) patients report experiencing headaches, photophobia, and flu-like symptoms within the first few weeks of initial infection, similar to an aseptic meningitis. After these symptoms abate, the clinical course is frequently characterized by months or even years of latent, asymptomatic infection. The asymptomatic stage may last an average of 10 years before overt symptoms arise. Changes in cognitive functioning are often first observed concurrently with the appearance



**FIGURE 1.1.** Ratios of local cerebral metabolic activity to whole-brain metabolic activity in the seronegative control subjects at time 1 and the AIDS group at time 1 and time 2. 1, significant difference, AIDS time 1 versus control subjects; 2, significant difference, AIDS time 2 versus control subjects; 3, significant difference, AIDS time 1 versus time 2. From Hinkin et al. (1995a). Copyright 1995 by the American Psychiatric Press. Reprinted by permission.

of constitutional symptoms. A recent study found relatively little cognitive decline prior to the onset of an AIDS-defining illness unless an overt dementia was present. Following onset of an AIDS-defining illness, cognitive decline was most pronounced in the area of fine motor skills, but relatively mild in other cognitive domains (Selnes et al., 1995). Other commonly observed cognitive changes include difficulty concentrating and paying attention (e.g., losing one's train of thought), as well as psychomotor slowing.

Although most clinicians have assumed that patients with HIV-related dementia will show a relatively steady decline in mental status once the initial cognitive signs are present, it appears that some patients instead have relatively stable periods of plateau, which are later followed by a more precipitous drop in intellectual functioning. Still others never evidence any overt signs of cognitive decline. The modal clinical course in HIV-1 infection, however, is generally believed to progress gradually through the following stages of cognitive impairment, which are based in part upon the AAN staging scheme for an AIDS-related dementia.

- *Subclinical.* Patients report decreased concentration, attention problems and loss of their train of thought. Mild forgetfulness, such as "double booking" of appointments, may also be seen. Work, unless especially demanding, may not be affected; commonly, basic activities of daily living are unimpaired. It is important to consider whether dysphoria or clinical depression is contributing to (or is even primarily responsible for) the self-reports of cognitive inefficiency.

- *Mild.* Individuals may report more pronounced cognitive changes, including psychomotor slowing, forgetfulness, and a decline in work performance. Modest changes in the more challenging activities of daily living are present, including personal finances (e.g., balancing checkbook, keeping track of bills). Also, patients often report experiencing difficulty keeping track of multiple appointments.

- *Moderate.* By this stage, patients are frequently unable to work at any but the most basic of occupational tasks, and may be unable to perform rapid psychomotor tasks such as driving. Memory is now impaired. Patients may need assistance with more demanding activities of daily living, such as housecleaning and cooking.

- *Severe.* At this stage, patients need assistance with most or all activities of daily living and are totally dependent upon others. Global cognitive impairment is present and obvious.

- *End-stage.* Patients are mute, bed-bound, incontinent, and globally cognitively impaired.

## NEUROPSYCHOLOGICAL PERFORMANCE BY DOMAIN IN HIV INFECTION

Numerous research studies have described how HIV-infected persons perform on neuropsychological testing (for reviews, see Grant & Martin, 1994; Kelly et al., 1997; Hinkin, van Gorp, & Satz, 1995b; van Gorp et al., 1993). Although some debate remains, a general consensus has been reached regarding which neuropsychological functions appear particularly susceptible to the effects of HIV infection (Butters et al., 1990; Bornstein, 1994). Once again, we need to stress that many infected patients never experience any significant cognitive impairment, and that generally the patients with more advanced illness (patients diagnosed with AIDS, with a CD4 count less than 200/mm<sup>3</sup>) are particularly likely to develop cognitive impairment (Grant et al., 1993; Heaton et al., 1995; Stern et al., 1995). Below, we describe which cognitive domains are most likely to decline and which tests of those behaviors appear best suited to detect such decline. Table 1.5 summarizes the findings regarding the domains.

### Mental Status/Intelligence

Mental status screening tests usually consist of a brief series of questions that can be asked of a patient at bedside and that do not require any test materials other than paper and pencil. Patients are asked to engage in activities such as providing the date and the season, counting backward by 7's, repeating phrases such as "No ifs, ands, or buts," and remembering several words for a brief period of time.

Although of great utility in the examination of cortical dementias such as Alzheimer's disease, mental status screening examinations such as the Mini-Mental State Exam (MMSE; Folstein, Folstein, & McHugh, 1975), the Blessed Dementia Rating Scale (Blessed, Tomlinson, & Roth, 1968), and the Neurobehavioral Cognitive Status Examination (Schwamm et al., 1987) are of limited usefulness in detecting early signs of HIV-associated cognitive decline (Grant & Atkinson, 1995; Hinkin et al., 1995b). Generally, it is not until the moderate stage of HIV-associated dementia that patients score below suggested cutoff scores (e.g., MMSE  $\leq$  24).

Intelligence, as operationalized by the IQ and as assessed by the WAIS-R (Wechsler, 1981), is commonly affected in HIV-1 infection. This is particularly true for the Performance subtests of the WAIS-R, in which subjects receive bonus points for rapid completion of tasks such as the Block Design, Object Assembly, and Digit Symbol tests (Hinkin et al., 1995b). Digit Symbol is perhaps the most sensitive of all

**TABLE 1.5. Neuropsychological Effects of HIV-1 Infection by Stage of Infection**

| Neuropsychological deficit/domain  | Early, middle: Affected? | Late (dementia): Affected? | End-stage: Affected? |
|------------------------------------|--------------------------|----------------------------|----------------------|
| Abstraction                        | No                       | +/-                        | +/-                  |
| Agraphia                           | No                       | No                         | +/-                  |
| Calculation                        | No                       | +/-                        | Yes                  |
| Concentration                      | +/-                      | Yes                        | Yes                  |
| Digit span                         | No                       | +/-                        | Yes                  |
| Divided attention                  | +/-                      | Yes                        | Yes                  |
| Executive/frontal system functions | +/-                      | Yes                        | Yes                  |
| Expressive language                | No                       | No                         | +/-                  |
| Judgment                           | No                       | +/-                        | +/-                  |
| Motoric functions                  | +/-                      | +/-                        | Yes                  |
| Mood                               |                          |                            |                      |
| Agitation                          | No                       | +/-                        | +/-                  |
| Anxiety                            | +/-                      | +/-                        | +/-                  |
| Depression                         | +/-                      | +/-                        | +/-                  |
| Mania                              | No                       | No                         | No                   |
| Naming                             | No                       | No                         | Yes                  |
| Psychomotor speed                  | +/-                      | Yes                        | Yes                  |
| Recent memory                      | +/-                      | Yes                        | Yes                  |
| Receptive language                 | No                       | No                         | +/-                  |
| Remote memory                      | No                       | No                         | No                   |
| Sensory functions                  | No                       | +/-                        | +/-                  |
| Verbal fluency                     | No                       | Yes                        | Yes                  |
| Visual construction                | No                       | +/-                        | Yes                  |
| Visual perception                  | No                       | No                         | +/-                  |

the WAIS-R subtests to the effects of HIV infection (Hinkin et al., 1995b). Because the Verbal subtests are largely untimed, HIV-1-infected subjects tend to perform better on these tasks. Of WAIS-R Verbal subtests, HIV-infected patients frequently have the greatest difficulty on the digits backward portion of Digit Span and Arithmetic, two measures sensitive to attentional disruption. Generally, patients perform adequately on the Vocabulary and Information subtests.

In addition to providing a measure of global intelligence and information regarding component cognitive processes such as visual construction or attention, the WAIS-R can also be of some assistance in detecting a focal opportunistic infection of the CNS. Should clinicians note more than a 15- to 20-point discrepancy between Verbal and Performance IQs, follow-up neuropsychological testing and referral for neurological testing and/or neuroimaging are indicated.

### Attention/Concentration

Adequate attention is a requisite basis for virtually every higher-level cognitive function, since if patients are unable to pay attention, they will certainly have difficulty engaging in any additional cognitive processing. Accordingly, careful assessment of attention and concentration in the workup of HIV-1-infected patients is critical, especially given the myriad potential causes of diminished attention in HIV-infected patients. The detrimental effects of acute physical illness and/or chronic debilitation on attentional functioning must be considered. Along these lines, poor attention may also be caused by the effects of medication, prescribed or otherwise, and/or psychiatric distress.

One common cause of pronounced attentional impairment is delirium, also known as "acute confusional state." Delirium is a relatively common condition in HIV-infected patients, with published studies suggesting that nearly half of hospitalized HIV-infected patients sustain a delirium at some point during their inpatient hospitalization. Acute confusional state has many causes, including toxic or metabolic disorders, adverse medication response, hypoxia, systemic infection, or focal CNS opportunistic infections and neoplasms. Because delirium can reflect a potentially life-threatening underlying disease, it is crucial that immediate referral for medical care be initiated.

The clinical assessment of attention and concentration commonly includes evaluation of simple attention, sustained concentration, and divided attention. Of these, divided attention is most likely to be impaired in HIV-1 infection (E. M. Martin et al. 1995; Law et al., 1994; Sorenson, Martin, & Robertson, 1994). From a clinical perspective, two tasks have proven to be sensitive measures of divided attention: (1) the Auditory Consonant Trigrams (ACT) test, also known as the Brown-Peterson procedure, and (2) the Paced Auditory Serial Addition Task (PASAT). Both tests require patients to allocate attentional focus simultaneously to two activities. On the ACT, patients are provided with consonant triplets, and then must engage in an "interference" task, counting backward by 3's for varying periods of time (usually 3, 9, 18, and 36 seconds). Following completion of this interference task, the subject must then recall the original three letters. The PASAT requires patients to add the last two numbers from a continuous string of numbers presented at increasingly rapid rates. Trouble engaging in two such activities at the same time is one of the more common complaints of HIV-infected patients.

Difficulties with sustained concentration may underlie patients' complaints of trouble reading, despite an absence of actual reading

impairment. Alternatively (or conjunctively), fatigue or affective disturbance may account for subjective complaints of reading difficulty (van Gorp et al., 1991). Although computerized measures of sustained attention such as a continuous-performance test are best suited to detect such impairment, clinical measures requiring patients to engage continuously in a behavior can also be employed. Our group has found that Parts A and B of the Stroop task, which require subjects to read and/or name 100-item lists of either color words (e.g., "red," "blue," "green") or color blocks, assess this domain adequately. In general, HIV-infected individuals as a group perform as well as seronegative control subjects on tasks of sustained attention (Stern et al., 1991).

Finally, simple attention is generally within normal limits in early HIV-associated dementia (Heaton et al., 1995). Usually only the most demented, delirious, or acutely physically ill patients will demonstrate severely impaired basic attention. As such, mental control tasks such as counting backward or saying the alphabet are usually unimpaired. On the WAIS-R Digit Span subtest and other digit span tests (also putative measures of simple attention), most HIV-infected subjects perform within normal limits, especially on digits forward (Grant et al., 1987; Tross et al., 1988; van Gorp, Miller, Satz, & Visscher, 1989). When patients are required to repeat strings of digits in the reverse direction (i.e., digits backward), they are more likely to show slightly depressed performance (Stern et al., 1991).

### Speech and Language

Speech, which can be conceptualized as the mechanical production of language, is frequently affected by HIV infection. Diminished volume of speech, or "hypophonia," is common, as is "dysarthria" or reduced intelligibility of speech. Not infrequently, speech is slowed among HIV-infected patients when compared to premorbid levels.

In contrast, language is generally spared in HIV infection unless individuals are severely demented, delirious, or suffering from a focal CNS opportunistic infection affecting language areas of the brain. Both expressive and receptive language abilities, as well as repetition, are usually normal. Although patients frequently complain of difficulty reading, this is almost always secondary to impaired concentration rather than to alexia per se. Similarly, although many patients complain of word-finding difficulty, performance on confrontation naming tests—for example, the Boston Naming Test, in which patients must provide the names for pen-and-ink drawings—is usually within normal limits (Heaton et al., 1995; Janssen et al., 1989; Stern, Sano, Williams, & Gorman, 1989; van Gorp et al., 1989). Writing, however, may be

adversely affected because of poorer penmanship. Among the typical neuropsychological tests of language, measures of verbal fluency are the only tasks on which HIV-infected individuals encounter difficulty (Hinkin et al., 1995b; Saykin et al., 1988). An example of a verbal fluency task is the Controlled Oral Word Association Test (Benton & Hamsher, 1989), in which patients must rapidly name as many words as possible that begin with certain letters of the alphabet. If HIV-infected patients demonstrate symptoms consistent with a frank aphasia, such as an inability to repeat, paraphasic errors, or an inability to produce or understand speech, this is almost always a cause for alarm; prompt medical treatment of the underlying cause (often a CNS opportunistic infection) is required.

### Visual-Spatial Function

Visual-spatial abilities include such behaviors as visual construction, visual perception, visual scanning/tracking, and geographic/topographic orientation. Although early studies suggested that symptomatic subjects performed more poorly on neuropsychological tests of visual-spatial ability, such as the WAIS-R Block Design subtest (van Gorp et al., 1989; Tross et al., 1988), most researchers and clinicians now agree that visual-spatial abilities are largely spared in HIV infection (Poutiainen et al., 1988; Saykin et al., 1988; Stern et al., 1991). However, since many neuropsychological tests of visual-spatial ability (e.g., the Block Design subtest) are timed, psychomotor slowing may lead to a lowered score because patients do not receive bonus points for speed. Completion of complicated, unstructured visual-constructive tasks, such as the Copy portion of the Rey-Osterrieth Complex Figure Test, can also be affected. This is generally secondary to poor planning and problem solving rather than to visual-spatial impairment.

### Memory

Impaired memory is common in HIV infection and is in fact required for the DSM-IV diagnosis of dementia due to HIV disease. The memory deficit in HIV infection is primarily one of retrieval rather than encoding or storage, although these stages can also be affected (Bornstein et al., 1993a; Hinkin et al., 1995b). Patients with AIDS may have difficulty with free recall (e.g., recall of story details or word lists), but when they are provided with cues or multiple-choice options, their performance often improves dramatically. Learning of new information may also be affected in HIV disease, but this generally does not resemble the amnesic quality of Alzheimer's disease. Frequently, be-

cause of attentional difficulty, patients have difficulty attending to and thus encoding new material to be learned; moreover, because of executive dysfunction, they may employ ineffective strategies to guide the encoding process.

In assessing infected patients' memory function, one should test both verbal memory (e.g., memory for word lists) and nonverbal memory (e.g., memory for designs). Verbal and nonverbal memory are equally susceptible to the effects of HIV infection (Stern et al., 1991); although several early studies suggested that nonverbal memory was perhaps more sensitive to the effects of HIV infection, this apparent sensitivity was more likely to have been due to the increased difficulty of typical nonverbal tasks.

Typically, neuropsychology has focused on "declarative memory," or memory for "knowing that." Another type of memory process has been termed "procedural memory," or "knowing how," and is exemplified by such activities as typing, playing a musical instrument, or riding a bike. The ability to learn new procedures, though commonly affected in other subcortical diseases such as Huntington's disease, appears to be affected in only a subgroup of patients with AIDS. Dr. Alex Martin and his colleagues (A. Martin et al., 1992) demonstrated that although on a group level patients with AIDS performed as well as seronegative controls did on a measure of procedural learning/memory, there was a subgroup of patients who clearly performed much worse. Interestingly, these researchers found that this subgroup of poor performers also evidenced higher levels of an excitatory neurotoxin (quinolinic acid) in their cerebrospinal fluid (A. Martin et al., 1992), strengthening the conclusion that impaired procedural learning is associated with CNS disease in patients with AIDS.

Working memory is that aspect of cognition that controls the simultaneous processing and active manipulation of information. For example, a working memory task might require subjects to complete a string of simple mental arithmetic problems (e.g.,  $5 + 3 = \_$ ,  $9 - 4 = \_$ ,  $6 + 7 = \_$ , etc.) while simultaneously asking them to remember the last digit of each problem (in the example above, 3, 4, 7). There is compelling evidence suggesting that working memory is mediated by prefrontal structures and circuits that are intimately connected with subcortical regions (Baddeley, Della Sala, Papagno, & Spinnler, 1997; Gabrieli, Singh, Stebbins, & Goetz, 1996; Goldman-Rakic & Friedman, 1991). Recent studies of working memory in HIV-1 infection have shown that at least a subgroup of seropositive individuals show working memory deficits (Bartok et al., 1997; Sahakian et al., 1995; Stout et al., 1995).

## Executive Functions

"Executive functions," or "frontal systems functions," are that behaviors which monitor, direct, and control other behaviors; they include such skills as problem solving, sequencing, judgment, inhibition, and divided attention. Although a clear consensus has yet to be reached (Claypoole et al., 1990; Stern et al., 1989; Poutiainen et al., 1988; Grant et al., 1987; Rubinow, Berettini, Brouwers, & Lane, 1988), it appears that only certain executive functions are significantly affected by HIV (see Sahakian et al., 1995). One such area of impairment is the ability to engage simultaneously in several tasks at once. An example of this is driving while talking on a car phone or engaging in conversation while watching television. In a minority of patients with AIDS, difficulties with inhibition and judgment also arise (Saykin et al., 1988). In such cases, patients may underestimate the degree of impairment they have actually suffered. In the vast majority of patients, problem solving is spared. This latter contention is strongly supported by studies using the Wisconsin Card Sorting Test (WCST), a putative measure of hypothesis formation, set shifting, and nonverbal problem solving; the majority of these studies have found HIV-infected subjects to be unimpaired (on this test Stern et al., 1989; Claypoole et al., 1988). In our own laboratory, we compared the performance of patients with AIDS and uninfected controls on the WCST and found that the two groups performed virtually identically.

## Motor Functions

With advanced disease, HIV-1-infected patients become increasingly slow. This slowing takes two basic forms: (1) slowing of motor movements and (2) slowing of cognition. Motor slowing is measured by tasks such as the Finger Tapping Test, a measure requiring patients to tap a key rapidly on a teletype-like machine, using the index finger. Some studies have found that patients with AIDS tend to perform worse (more slowly) on this task than do uninfected controls (Saykin et al., 1988), while others have not found this difference (Claypoole et al., 1990; Franzblau et al., 1991; Olo, Johnson, & Grafman 1991). Although it is caused in part by central slowing, upper-extremity motor slowing may also be caused by myelopathy and myopathy, peripheral neuropathy, or simply the effects of physical illness. It is important to note that neuropathies and myopathies can occur as direct effects of HIV infection or as side effects of pharmacological treatment (Brew, 1993).

Slowing of cognition, especially when speed of thought is linked

to action (psychomotor slowing), is considered the cardinal sign of HIV-associated dementia (Hinkin et al., 1995), with the majority of studies to date having found differences between HIV-infected patients and noninfected controls on measures of psychomotor speed (Miller et al., 1990; Poutiainen et al., 1988; van Gorp et al., 1989). Clinical measures, such as the Digit Symbol subtest of the WAIS-R and the Trail Making Test, are particularly well suited for detecting psychomotor slowing. Slowed cognition, or "bradyphrenia," can also be sensitively detected via computerized measures of speeded information processing (Miller & Wilkie, 1994), which are discussed next.

### Mr. Smith's Neuropsychological Performance Pattern

To return to Mr. Smith's case, inspection of his performance on neuropsychological testing revealed that his pattern of neuropsychological strengths and deficits was fairly typical of HIV-1 infection. He encountered the greatest difficulty on measures of memory. A comparison of his ability to recognize information with his free recall suggested that his memory problem was based more in retrieval than in encoding or storage. After a 20-minute delay, Mr. Smith was only able to recall 6 of the 16 words on the California Verbal Learning Test, but was able to accurately recognize 14 of the 16 words when he was presented with multiple-choice options. As can be seen in Table 1.1, other notable findings from his neuropsychological examination included the presence of marked psychomotor slowing. Tasks such as the Digit Symbol subtest of the WAIS-R and Part B of the Trail Making test posed considerable difficulty for him. Comparing those scores with his average performance on the Finger Tapping Test, a measure of pure motor speed, suggested that his slowing was more cognitive than motoric in nature. His difficulty on the ACT test, on which he scored at the 4th percentile, reflected his problems in dividing attention between two simultaneous activities. Equally important was consideration of the neuropsychological tasks on which Mr. Smith performed well. No evidence of language or visual-spatial impairment was observed. Had major deficits been seen in these domains, this would have suggested that an additional disease process, such as a CNS opportunistic infection, was present.

### COMPUTERIZED ASSESSMENT IN HIV-1 INFECTION

As mentioned above, both motor slowing and psychomotor slowing are considered hallmarks of HIV-related cognitive impairment; both are

also quite amenable to computer assessment. In fact, in the early stages of HIV-1 infection, conventional neuropsychological measures may lack the necessary sensitivity to detect the often subtle cognitive changes that occur in a subset of patients (Miller & Wilkie, 1994). Computerized assessment measures may be more sensitive than are conventional neuropsychological tasks in demonstrating cognitive impairment (Miller & Wilkie, 1994), especially during the earlier stages of HIV infection.

The majority of studies using computerized assessment tools have measured reaction time and early-stage information-processing efficiency. Many of these instruments, which were developed according to the tenets of cognitive and experimental psychology, have shown promise in identifying deficits in a sizeable minority of HIV-infected patients (A. Martin et al., 1992; E. M. Martin, Sorensen, Edelstein, & Robertson, 1992b; Miller, Satz, van Gorp, Visscher, & Dudley, 1989; Law et al., 1993). Clearly, the sometimes subtle decrements in reaction time or information-processing speed do not always correlate with functional impairment, but it may be that these deficits are indicative of the onset of brain disease or an impending dementing process (Miller & Wilkie, 1994). Obviously, the ability to identify at-risk individuals as early in the disease process as possible could be of tremendous value.

As defined in most studies, "reaction time" is a composite measure of motor speed and the time required for such mental events as perception, stimulus processing, and decision making (Miller & Wilkie, 1994). "Simple reaction time" (SRT) is the time it takes an individual to respond to a single stimulus, such as the appearance of a visual cue or of an auditory tone. SRT, as it is generally conceptualized, does not involve higher cognitive processing (i.e., decision making) and is thought to measure mainly stimulus registration and motor speed. "Choice reaction time" (CRT) is the time it takes an individual to respond to one of at least two distinct stimuli that may occur, with each stimuli associated with a different response (e.g., "Push the button if you see a blue stimulus; don't push it if you see a red stimulus"). CRT, as the name implies, involves higher cognitive processing (i.e., making a decision about the status of a given stimulus) and can vary considerably in difficulty or in the information-processing demands required. The difference between SRT and CRT for any individual represents the speed of information processing for a particular choice decision and has been referred to as "decision-making time" (Miller & Wilkie, 1994). A limitation of much of the computerized reaction time research is that investigators have used different computerized measures of SRT and CRT, which make comparisons across groups more difficult.

Most reaction time studies have concluded that CRT is more likely than SRT to be impaired in HIV-1 infection. Perdices and Cooper (1989) found that asymptomatic patients performed similarly to seronegative controls on measures of both SRT and CRT, whereas symptomatic patients were significantly slower on measures of CRT but not SRT compared with controls. Although some investigators have found no differences between asymptomatic subjects and HIV-seronegative controls on either SRT or CRT tasks (Martin, Robertson, Edelstein, Jagust, & Sorensen, 1992a; Miller, Satz, & Visscher, 1991; Perdices & Cooper, 1989), others have found both asymptomatic and symptomatic subjects to be significantly slower than control subjects on measures of CRT (E. M. Martin et al., 1992b). It appears that SRT is less affected in HIV infection, or that if it is, this occurs in the later, symptomatic stages of the disease (A. Martin et al., 1992).

A study conducted by Alex Martin's group (1992) studied reaction time in both asymptomatic and symptomatic HIV-seropositive subjects, as well as HIV-seronegative psychiatric patients with adjustment disorders and HIV-seronegative controls with no medical or psychiatric illness. They found that both seropositive groups were slower on SRT and CRT measures than were both seronegative groups. Also, at a 6-month follow-up, on average, both seropositive groups were significantly slower than they were previously. Interestingly, there was a significant correlation between slowing of reaction time over time and cerebrospinal fluid levels of an endogenous neurotoxin, quinolinic acid.

Although some debate exists, a consensus is beginning to emerge that most symptomatic HIV-seropositive patients show signs of slowing on computerized measures of reaction time, relative to seronegative controls. This slowing may be more pronounced on measures of CRT (Perdices & Cooper, 1989), but it has also been observed on measures of SRT as well (Miller et al., 1990; A. Martin et al., 1992). With regards to asymptomatic patients, there is some evidence that they may show slowing on measures of CRT when compared with seronegative controls (E. M. Martin et al., 1992b; but also see Miller et al., 1991); however, they show roughly comparable performance on measures of SRT.

## DEPRESSION AND HIV INFECTION

Considering the chronic and life-threatening nature of HIV, it is probably not surprising that HIV-infected individuals show high rates of depressed mood. The prevalence of depressed mood has been reported at nearly 80% in some studies (Boccellari, Dilley, & Shore, 1988; Perry & Tross, 1984), while the prevalence of a clinical syndrome

of major depression in HIV-infected individuals has been reported at between 10% and 15% (Boccellari et al., 1988; Dilley, Ochitill, Perl, & Volberding, 1985). These elevated rates of depression are seen regardless of whether self-report measures (Cleary et al., 1993; Kelly et al., 1993) or interactive diagnostic interviews (Atkinson et al., 1988; Bornstein et al., 1993b) are used to ascertain depressive symptomatology. Clearly, these rates exceed those found in the general population.

As suggested above, depressive symptomatology in HIV-infected individuals may be a reaction to the life-altering, chronic, and ultimately terminal nature of the illness. Studies have found higher rates of depression and psychiatric disturbance immediately after patients learn that they have tested HIV-positive (Bix et al., 1995; Cleary, Singer, & Rogers, 1988; Ostrow et al., 1989). Also, immediately prior to HIV testing and while awaiting testing results, patients may show prominent symptoms of mood disturbance. Psychiatric support and, if necessary, crisis intervention may be most required at these times. Although psychiatric distress generally tends to lessen over time (Fell et al., 1993), some studies have suggested that depression may reemerge at transitional points of the disease (Grant & Atkinson, 1990). These transitions are often identified by physical symptoms (e.g., advent of AIDS-defining illness), with research suggesting that patients with the most HIV-related medical complications are more likely to be anxious and depressed (Gorman et al., 1991; Fell et al., 1993). Such issues as social stigmatization and marginalization are also important to consider as potential contributors to feelings of isolation and depression.

Certainly depression may be directly related to the involvement of subcortical brain structures (Cummings, 1993). Increased rates of depression have been reported in several neurological disorders that differentially affect subcortical structures (e.g., Parkinson's disease, Huntington's disease), suggesting that the presence of depression in some HIV-infected patients may relate, at least in part, to actual CNS changes. There is considerable overlap between the symptomatology characteristic of unipolar major depression and the presentation of various subcortical dementias; in fact, researchers have suggested that major depression is causally related to subcortical pathology (King & Caine, 1990; Cummings, 1993). Accordingly, depression and cognitive decline are perhaps best conceptualized as dual-pronged manifestations of an underlying disease process.

## Issues Involved in Assessing Depression

Several issues concerning the measurement of depression in patients with HIV or AIDS warrant consideration. A primary complication in

assessing depression in HIV-infected patients is the often considerable overlap between symptoms of depression and physical illness. Such signs and symptoms as fatigue, diminished sleep and appetite, weight loss, and somatic complaints may be diagnostically ambiguous. When somatic symptoms occur independently of affective distress, they may not be indicative of the vegetative signs of a mood syndrome, but instead simply signs of physical illness (Drebing, van Gorp, Hinkin, et al., 1994). Research with medical populations (Volk, Pace, & Parchman, 1993) in general, and HIV patients specifically (Drebing et al., 1994; Harker et al., 1995), has shown that the inclusion of somatic items in the measurement of depression often leads to increased rates of false positives. Clinicians and researchers working with HIV-infected patients should therefore use caution when interpreting measures containing somatic items, such as the BDI (Beck & Steer, 1987), the Hamilton Rating Scale for Depression Scale (Hamilton, 1960), and the MMPI-2. It is perhaps more prudent to emphasize cognitive and affective symptoms and signs of depression, especially with patients in the later, symptomatic stages of HIV disease. One such measure that minimizes the influence of physical symptoms in the assessment of depression is the Geriatric Depression Scale, a test originally designed for the elderly, which omits questions assessing neurovegetative symptomatology.

It is well established that severe depression can lead to cognitive impairment, especially in the elderly (Cassens, Wolfe, & Zola, 1990; La Rue, 1992). This phenomenon, which has been termed "pseudodementia," is more properly termed the "dementia syndrome of depression." Given the high prevalence of depression in HIV-1 infected individuals, it is reasonable to wonder whether depression is leading to potentially reversible dementias in this population. Studies that have addressed this question have almost uniformly concluded that, *on a group level*, depressed HIV-1 infected patients do not perform significantly poorer on more poorly on neuropsychological testing than do HIV-1 patients without depression (Atkinson et al., 1988; Bix et al., 1995; Grant et al., 1993; Hinkin et al., 1992; Pace, Rosenberger, Nasrallah & Bornstein, 1993). This is not meant to suggest that, *on an individual basis*, depression cannot result in a significant decrement in cognition.

### Subjective Complaints of Cognitive Decline

Among the common manifestations of depression are hypersensitivity to and exaggeration of difficulties real or imagined. From a clinical perspective, we have observed that many HIV-infected patients will complain of cognitive deficits that cannot be detected on a thorough neuropsychological evaluation. Conversely, we have also encountered

a subgroup of patients who, despite incontrovertible signs of severe neuropsychological impairment, will nevertheless deny that they have suffered any cognitive decline. The relationship between patients' complaints of self-perceived cognitive decline and performance on neuropsychological testing has also been empirically studied (Hinkin et al., 1996; Mapou et al., 1993; Poutiainen & Elovaara, 1996; van Gorp et al., 1991). This issue is of considerable importance to practicing clinicians, in that many treatment decisions (e.g., altering medication regimens) are based in large part on patients' self-report. Several studies have found that medically asymptomatic subjects' complaints of functional decline are indeed associated with poorer performance on objective neuropsychological testing (Mapou et al., 1993; Poutiainen & Elovaara, 1996). In contrast, several other studies have found that subjects who complain of cognitive decline do *not* perform worse on neuropsychological testing (Hinkin et al., in press; van Gorp et al., 1991; Wilkins et al., 1991). Rather, in a study of 223 HIV-infected asymptomatic subjects, we (van Gorp et al., 1991) found that subjects who complained of cognitive impairment tended instead to be more depressed. Since patient complaint of cognitive decline is often at variance with objective neuropsychological findings and instead tends to be related to level of depression, clinicians should obtain correlative data (e.g., interviews with significant others) prior to making diagnostic and treatment decisions.

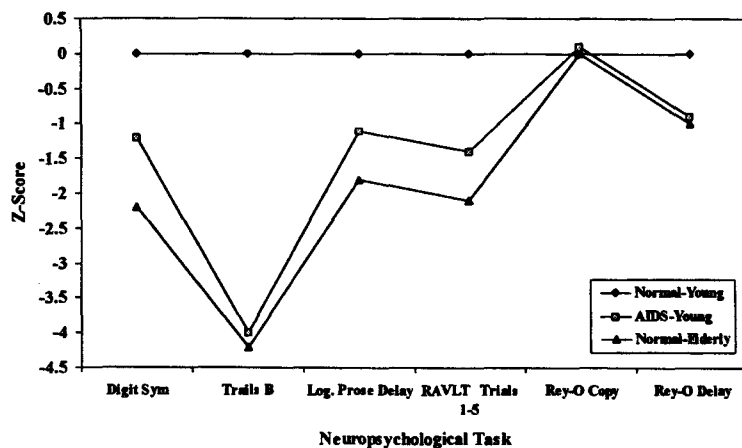
### HIV-RELATED COGNITIVE DECLINE COMPARED WITH THE NORMAL AGING PROCESS

Clinicians not formally trained in neuropsychology may experience some understandable difficulty incorporating the information detailed in this chapter in their own work with HIV-infected patients. A helpful heuristic for better understanding the neuropsychological effects of HIV infection is to view the cognitive sequelae of HIV/AIDS as similar to the neuropsychological changes associated with the normal aging process. In both instances, individuals may become both motorically and cognitively slower; similarly, both the elderly and patients with AIDS may become forgetful and have difficulty engaging in several tasks at once. Because both groups may face a foreshortened life span, similar psychodynamic issues may also arise. Noting the overlapping symptomatology between the normal elderly and younger patients with AIDS, we (Hinkin et al., 1990) compared the neuropsychological performance of three groups of individuals: (1) uninfected younger males with a mean age of 36; (2) older uninfected males with a mean

age of 70; and (3) a group of younger men (mean age = 36) diagnosed with AIDS. As can be seen in Figure 1.2, the younger subjects with AIDS performed virtually identically to the elderly, uninfected group. Those tasks that were problematic for the older subjects (e.g., Part B of the Trail Making Test) also proved difficult for the younger subjects with AIDS, whereas those tasks which were normal in the elderly cohort were also within normal limits for the AIDS subjects. These data suggest that clinicians seeking to gain insight into the cognitive changes caused by HIV-1 infection can utilize the normal aging process as a useful heuristic model.

### WHEN SHOULD A PATIENT BE REFERRED FOR EVALUATION?

One critical question that practicing clinicians must address is "When should I refer my patient for a neuropsychological evaluation?" Although no hard and fast answer can be provided, several guiding principles exist. Should a patient's family and/or friends complain of changes in the patient's thinking or behavior, this is almost always cause



**FIGURE 1.2.** Pattern of neuropsychological performance for three groups: AIDS patients, normal elderly, and normal young. Digit Sym, Wechsler Adult Intelligence Scale—Revised, Digit Symbol subtest; Log Prose, Wechsler Memory Scale, Logical Prose subtest; RAVLT, Rey Auditory Verbal Learning Test; Rey-O, Rey-Osterrieth Complex Figure. From Hinkin et al. (1990). Copyright 1990 by *Canadian Journal on Aging*. Reprinted by permission.

for further workup and referral. In contrast, as discussed above, the validity of patients' self-complaint is often debatable. A conservative and prudent course is to take a patient's self-report at face value and refer for testing. Another clear reason for referral for neuropsychological testing is evidence that the patient's ability to perform at work or to discharge higher-level activities of daily living (e.g., balancing a checkbook) is beginning to suffer. Neuropsychological evaluation can also be helpful in establishing legal competence such as the ability to enter into contracts or execute a will, as well as in providing medical evidence to support a disability claim.

Resources permitting, neuropsychological testing concurrent with important disease milestones such as patient's CD4 count dropping below 200/mm<sup>3</sup>, viral load climbing above 20,000–30,000 copies/mm<sup>3</sup>, onset of AIDS, or the institution of antiretroviral therapies—has also been proven to be a useful adjunct.

### NEUROPSYCHOLOGICAL BATTERIES FOR THE ASSESSMENT OF DEMENTIA DUE TO HIV DISEASE

There has been considerable debate regarding what measures are most appropriate for investigating HIV-related cognitive dysfunction. Practical considerations such as patient tolerance, test administration costs, and fatigue effects must be balanced against the goal of thoroughly assessing all relevant cognitive domains. Some studies have used brief screening batteries lasting less than 1 hour (e.g., McArthur et al., 1989; Miller et al., 1990), while others have used assessment batteries requiring up to 7–9 hours of testing (Saykin et al., 1988; Heaton et al., 1995). Not surprisingly, the likelihood of identifying a problem appears to be related to the length of the battery administered. Brief screening batteries, developed out of necessity for large-scale longitudinal research, run the risk of increased false negatives or the failure to detect actual deficits. On the other hand, patients' inability to tolerate day-long testing frequently precludes using more lengthy assessment batteries.

Assigned with the task of constructing an ideal assessment battery for evaluating HIV-infected individuals, a National Institute of Mental Health (NIMH) working group chaired by the late Nelson Butters proposed the following 10 areas of examination: (1) premorbid intelligence, (2) attention, (3) speed of processing, (4) memory, (5) abstraction, (6) language, (7) visual perception, (8) constructional abilities, (9) motor abilities, and (10) psychiatric symptoms (Butters et al., 1990). The battery recommended by this group takes between 7 and 9 hours to administer,

with additional time required for scoring, interpretation, and report preparation. A shortened version of the original NIMH battery, requiring between 1 and 2 hours of patient contact, has also been suggested. Table 1.6 lists the neuropsychological tests recommended by Butters et al. (1990) for the assessment of HIV-infected persons.

The Multicenter AIDS Cohort Study (MACS), assigned the task of testing large number of subjects longitudinally, used a multistage approach to develop a brief screening neuropsychological assessment battery (see Selnes & Miller, 1994, for details). Initially, they determined which measures from among 24 originally given to HIV-infected (asymptomatic and symptomatic) patients and seronegative controls best discriminated the performance of patients with AIDS from control subjects. Next, they identified major domains of cognitive functioning

**TABLE 1.6. Neuropsychological Tests Recommended by the NIMH Working Group**

*Intelligence*

Wechsler Adult Intelligence Scale—Revised (WAIS-R)  
National Adult Reading Test—Revised

*Simple and divided attention and sustained concentration*

WAIS-R Digit Span  
Paced Auditory Serial Addition Task  
Trail Making test (Parts A and B)

*Language*

Boston Naming Test  
Verbal fluency tests

*Visual-spatial function*

WAIS-R Block Design

*Verbal memory*

California Verbal Learning Test

*Nonverbal memory*

Wechsler Memory Scale—Revised, Visual Reproductions I and II

*Motor speed*

Finger Tapping Test  
Grooved Pegboard Test

*Psychomotor speed and speed of information processing*

Trail Making Test  
WAIS-R Digit Symbol  
Sternberg Search Task  
Simple and choice reaction time

*Executive and frontal systems functions*

Category Test

*Mood, affect, and personality*

Beck Depression Inventory or Hamilton Rating Scale for Depression  
State-Trait Anxiety Inventory  
Diagnostic Interview Schedule

*Note.* Adapted from Butters et al. (1990, p. 966). Copyright 1990 by Swets & Zeitlinger. Adapted by permission.

by performing factor analyses on the 24 original measures. They then eliminated any redundancy by selecting the one measure from each cognitive domain that showed the greatest power to discriminate AIDS patients from seronegative controls. The resulting assessment battery is both brief, taking approximately 45 minutes to administer, and sensitive to the earliest cognitive symptoms of HIV infection. Table 1.7 contains the MACS neuropsychological screening battery.

## SUMMARY

To summarize, some degree of cognitive decline will occur in the majority of HIV-1-infected patients. This decline can range from very subtle psychomotor slowing and forgetfulness to profound dementia. Although the types of cognitive problems seen in HIV-infected individuals vary, the most common deficits are forgetfulness, psychomotor slowing, and trouble dividing attention between competing activities. Depression, apathy, anxiety, and irritability are also common. Should practicing clinicians suspect the presence of neuropsychological decline, they should screen for incipient cognitive decline, if they are appropriately trained to do so. Positive findings on screening should then trigger referral for a more comprehensive neuropsychological evaluation.

**TABLE 1.7. MACS Neuropsychological Screening Battery**

1. Trail Making Test, Parts A and B
2. Grooved Pegboard Test (dominant and nondominant hands)
3. Symbol Digit Modalities
  - Raw score
  - Paired recall
4. Rey Auditory Verbal Learning Test
  - Trials 1-5
  - Interference
  - Recall after interference
  - Delayed recall
  - Delayed recognition
5. Rey-Osterrieth Complex Figure Test
  - Copy
  - Immediate recall
  - Delayed recall
6. Stroop Task
7. California Computerized Assessment Package
  - Simple reaction time
  - Choice reaction time
  - Serial pattern matching (sequential reaction time)

*Note.* Adapted from Selnes and Miller (1994). Copyright 1994 by Oxford University Press. Adapted by permission.

## REFERENCES

- American Academy of Neurology (AAN). (1991). Nomenclature and research case definitions for neurological manifestations of human immunodeficiency virus—type 1 (HIV-1) infection: Report of a working group of the American Academy of Neurology AIDS Task Force. *Neurology*, *41*(6), 778–785.
- American Psychiatric Association. (1994). *Diagnostic and statistical manual of mental disorders* (4th ed.). Washington, DC: Author.
- Atkinson, J. H., Grant, I., Kennedy, C. J., et al. (1988). Prevalence of psychiatric disorders among men infected with human immunodeficiency virus. *Archives of General Psychiatry*, *45*, 859–864.
- Baddeley, A. D., Della Sala, S., Papagno, C., & Spinnler, H. (1997). Dual-task performance in dysexecutive and nondysexecutive patients with a frontal lesion. *Neuropsychology*, *11*, 187–194.
- Bartok, J. A., Martin, E. A., Pitrak, D. L., Novak, R. M., Pursell, K. J., Mullane, K. M., & Harrow, M. (1997). Working memory deficit in HIV-seropositive drug users. *Journal of the International Neuropsychological Society*, *3*, 451–456.
- Beck, A. T., & Steer, R. A. (1987). *Beck Depression Inventory: Manual*. San Antonio, TX: Psychological Corporation.
- Benton, A. L., & Hamsher, K. (1989). *Multilingual Aphasia Examination*. Iowa City: AJA Associates.
- Bix, B. C., Glosser, G., Holmes, W., Ballas, C., Meritz, M., Hutelmyer, C., & Turner, J. (1995). Relationship between psychiatric disease and neuropsychological impairment in HIV seropositive individuals. *Journal of the International Neuropsychological Society*, *1*, 581–588.
- Blessed, G., Tomlinson, B. E., & Roth, R. (1968). The association between quantitative measures of dementia and of senile change in the cerebral grey matter of elderly subjects. *British Journal of Psychiatry*, *114*, 797–811.
- Boccellari, A., Dilley, J. W., Chambers, D. B., Yingling, C. D., Tauber, M. A., Moss, A. R., & Osmond, D. H. (1993). Immune function and neuropsychological performance in HIV-1 infected homosexual men. *Journal of Acquired Immune Deficiency Syndromes*, *6*, 592–601.
- Boccellari, A., Dilley, J. W., & Shore, M. D. (1988). Neuropsychiatric aspects of AIDS dementia complex: A report on a clinical series. *Neurotoxicology*, *9*, 381–390.
- Bornstein, R. A. (1994). Methodological and conceptual issues in the study of cognitive change in HIV infection. In I. Grant & A. Martin (Eds.), *Neuropsychology of HIV infection* (pp. 3–19). New York: Oxford University Press.
- Bornstein, R. A., Nasrallah, H. A., Para, M. F., Fass, R. J., et al. (1991). Rate of CD4 decline and neuropsychological performance in HIV infection. *Archives of Neurology*, *48*, 704–707.
- Bornstein, R. A., Nasrallah, H. A., Para, M. F., Whitacre, C. C., et al. (1992). Neuropsychological performance in asymptomatic HIV infection. *Journal of Neuropsychiatry and Clinical Neurosciences*, *4*, 386–394.
- Bornstein, R. A., Nasrallah, H. A., Para, M. F., Whitacre, C. C., Rosenberger, P., & Fass, R. J. (1993a). Neuropsychological performance in symptomatic and asymptomatic HIV infection. *AIDS*, *7*, 519–524.
- Bornstein, R. A., Pace, P., Rosenberger, P., Nasrallah, H. A., Whitacre, C. C., & Fass, R. J. (1993b). Depression and neuropsychological performance in asymptomatic HIV infection. *American Journal of Psychiatry*, *150*, 922–927.
- Brew, B. J. (1993). HIV-1 related neurological disease. *Journal of Acquired Immune Deficiency Syndromes*, *6*(Suppl. 1), S10–S15.
- Butters, N., Grant, I., Haxby, J., Judd, L. L., Martin, A., McClelland, J., Pequegnat, W., Schacter, D., & Stover, E. (1990). Assessment of AIDS related cognitive changes: Recommendations of the NIMH Workshop on Neuropsychological Assessment Approaches. *Journal of Clinical and Experimental Neuropsychology*, *12*, 963–978.
- Cassens, G., Wolfe, L., & Zola, M. (1990). The neuropsychology of depressions. *Journal of Neuropsychiatry*, *2*, 202–213.
- Centers for Disease Control (CDC). (1987). Revision of the CDC surveillance case definition for acquired immunodeficiency syndrome. *Morbidity and Mortality Weekly Report*, *36*(Suppl.), 1S–16S.
- Centers for Disease Control and Prevention. (1992). Centers for Disease Control 1993 revised classification system for HIV infection and expanded surveillance case definition for AIDS among adolescents and adults. *Morbidity and Mortality Weekly Report*, *41*, 1–10.
- Centers for Disease Control and Prevention. (1997). Update: Trends in AIDS incidence—United States, 1996. *Morbidity and Mortality Weekly Report*, *46*(37), 861–867.
- Claypoole, K., Townes, B., Collier, A., et al. (1990). *Neuropsychological aspects of early HIV infection*. Paper presented at the Eighteenth Annual Conference of the International Neuropsychological Society, Orlando, FL.
- Cleary, P. D., Singer, E., & Rogers, T. F. (1988). Sociodemographic and behavioral characteristics of HIV antibody-positive blood donors. *American Journal of Public Health*, *78*, 953–957.
- Cleary, P. D., Van Devanter, N., Rogers, T., Singer, E., Shipton-Levy, R., Steilen, M., Stuart, A., Avorn, J., & Pindyck, J. (1993). Depressive symptoms in blood donors notified of HIV infection. *American Journal of Public Health*, *83*, 534–539.
- Collier, A. C., Gayle, T. C., & Bahls, F. H. (1987). Clinical manifestations and approach to management of HIV infection and AIDS. *AIDS: A Guide for the Primary Physician*, *13*, 27–33.
- Cummings, J. L. (1993). The neuroanatomy of depression. *Journal of Clinical Psychiatry*, *54*(Suppl.), S14–S20.
- Dilley, J. W., Ochitill, H. N., Perl, M., & Volberding, P. (1985). Findings in psychiatric consultation with patients with acquired immune deficiency syndrome. *American Journal of Psychiatry*, *142*, 82–86.
- Drebing, C. E., van Gorp, W. G., Hinkin, C. H., Miller, E. N., Satz, P., Kim, D. S., Holston, S., & D'Elia, L. F. (1994). Confounding factors in the measurement of depression of HIV. *Journal of Personality Assessment*, *62*, 68–83.
- Dunbar, N., Perdices, M., Grunseit, A., & Cooper, D. A. (1992). Changes in

- neuropsychological performance of AIDS-related complex patients who progress to AIDS. *AIDS*, 6, 691-700.
- Elovaara, I., Poutiainen, E., Raininko, R., Valanne, L., Vira, A., Valle, S.-L., Lahdevirta, J., & Iivanainen, M. (1990). Mild brain atrophy in early HIV infection: The lack of association with cognitive deficits and HIV-specific intrathecal immune response. *Journal of the Neurological Sciences*, 99, 121-136.
- Fell, M., Newman, S., Hems, M., Durrance, P., et al. (1993). Mood and psychiatric disturbance in HIV and AIDS: Changes over time. *British Journal of Psychiatry*, 162, 604-610.
- Folstein, M. F., Folstein, S. E., & McHugh, P. R. (1975). Mini-Mental State. *Journal of Psychiatric Research*, 12, 189-198.
- Franzblau, A., Letz, R., Hershman, D., Mason, P., Wallace, J. I., & Bekesi, J. G. (1991). Quantitative neurologic and neurobehavioral testing of persons infected with human immunodeficiency virus type 1. *Archives of Neurology*, 48, 263-268.
- Gabrieli, J. D., Singh, J., Stebbins, G. T., & Goetz, C. G. (1996). Reduced working memory span in Parkinson's disease: Evidence for the role of a frontal-striatal system in working and strategic memory. *Neuropsychology*, 10, 322-332.
- Goldman-Rakic, P. S., & Friedman, H. R. (1991). The circuitry of working memory revealed by anatomy and metabolic imaging. In H. S. Levin, H. M. Eisenberg, & A. L. Benton (Eds.), *Frontal lobe function and dysfunction* (pp. 72-91). New York: Oxford University Press.
- Gorman, J. M., Kertzner, R., Cooper, T., et al. (1991). Glucocorticoid level and neuropsychiatric symptoms in homosexual men with HIV infection. *American Journal of Psychiatry*, 148, 41-45.
- Grant, I., & Atkinson, J. H. (1990). The evolution of neurobehavioral complications of HIV infection. *Psychological Medicine*, 20, 747-754.
- Grant, I., & Atkinson, J. H. (1995). Psychiatric aspects of acquired immune deficiency syndrome. In H. I. Kaplan & B. J. Sadock (Eds.), *Comprehensive textbook of psychiatry* (Vol. 6, pp. 1644-1668). Baltimore: Williams & Wilkins.
- Grant, I., Atkinson, J. H., Hesselink, J. R., Kennedy, C. J., Richman, D. D., Spector, S. A., & McCutchan, J. A. (1987). Evidence for early central nervous system involvement in the acquired immunodeficiency syndrome (AIDS) and other human immunodeficiency virus (HIV) infections. *Annals of Internal Medicine*, 107, 828-836.
- Grant, I., & Martin, A. (1994). Neurocognitive disorders associated with HIV-1 infection. In I. Grant & A. Martin (Eds.), *Neuropsychology of HIV infection* (pp. 3-19). New York: Oxford University Press.
- Grant, I., Olshen, R. A., Atkinson, J. H., Heaton, R. K., Nelson, J., McCutchan, J. A., & Weinrich, J. D. (1993). Depressed mood does not explain neuropsychological deficits in HIV-infected persons. *Neuropsychology*, 7, 53-61.
- Green, T. A., Karon, J. M., & Nwanyanwu, D. C. (1992). Changes in AIDS incidence trends in the United States. *Journal of Acquired Immune Deficiency Syndromes*, 5, 547-555.
- Hall, M., Whaley, R., Robertson, K., & Hamby, S. (1996). The correlation between neuropsychological and neuroanatomic changes over time in asymptomatic and symptomatic HIV-1 infected individuals. *Neurology*, 46, 1697-1702.
- Hamilton, M. (1960). A rating scale for depression. *Journal of Neurology, Neurosurgery and Psychiatry*, 23, 56-62.
- Harker, J. O., Satz, P., Jones, F. D., Verma, R. C., Gan, M. P., Poer, H. L., Gould, B. D., & Chervinsky, A. B. (1995). Measurement of depression and neuropsychological impairment in HIV-1 infection. *Neuropsychology*, 9, 110-117.
- Heaton, R. K., Grant, I., Butters, N., White, D. A., Kirson, D., Atkinson, J. H., McCutchan, J. A., Taylor, M. J., et al. (1995). The HNRC 500: Neuropsychology of HIV infection at different disease stages. *Journal of the International Neuropsychological Society*, 1, 231-251.
- Hinkin, C. H., Cummings, J. L., van Gorp, W. G., Satz, P., Mitrushina, M., & Freeman, D. (1990). Frontal/subcortical features of normal aging: An empirical analysis. *Canadian Journal on Aging*, 9, 104-119.
- Hinkin, C. H., van Gorp, W. G., Mandelkern, M. A., Gee, M., Satz, P., Holston, S., Marcotte, T. D., Evans, G., Paz, D. H., Ropchan, J. R., Quinones, N., Khonsary, A., & Blahd, W. H. (1995a). Cerebral metabolic change in patients with AIDS: Report of a six-month follow-up using positron-emission tomography. *Journal of Neuropsychiatry and Clinical Neurosciences*, 7, 180-187.
- Hinkin, C. H., van Gorp, W. G., & Satz, P. (1995b). Neuropsychological and neuropsychiatric aspects of HIV infection in adults. In H. I. Kaplan & B. J. Sadock (Eds.), *Comprehensive textbook of psychiatry* (Vol. 6). Baltimore: Williams & Wilkins.
- Hinkin, C. H., van Gorp, W. G., Satz, P., Marcotte, T., Durvasula, R. S., Wood, S., Campbell, L., & Baluda, M. (1996). Actual versus self-reported cognitive dysfunction in HIV-1 infection: Memory-metamemory dissociations. *Journal of Clinical and Experimental Neuropsychology*, 18, 431-443.
- Hinkin, C. H., van Gorp, W. G., Satz, P., Weisman, J. D., Thommes, J., & Buckingham, S. (1992). Depressed mood and its relationship to neuropsychological test performance in HIV-1 seropositive individuals. *Journal of Clinical and Experimental Neuropsychology*, 14, 289-297.
- Janssen, R., Saykin, J., Cannon, L., Campbell, J., Pinsky, P. F., Hessol, N. A., O'Malley, P. M., Lifson, A. R., Doll, L. S., & Rutherford, G. W. (1989). Neurological and neuropsychological manifestations of human immunodeficiency virus (HIV-1) infection: Association with AIDS-related complex but not asymptomatic HIV-1 infection. *Annals of Neurology*, 26, 592-600.
- Kalichman, S. C., & Sikkema, K. J. (1994). Psychological sequelae of HIV infection and AIDS: Review of empirical findings. *Clinical Psychology Review*, 14, 611-632.
- Kelly, J. A., Murphy, D. A., Bahr, G. R., Koop, J., Morgan, M., Kalichman, S. C., Stevenson, L. Y., Brasfield, T. L., Bernstein, B., & St. Lawrence, J. (1993). Factors associated with severity of depression and high-risk sexual behavior among persons diagnosed with human immunodeficiency virus (HIV) infection. *Health Psychology*, 12, 215-219.
- Kelly, M. D., Grant, I., Heaton, R. K., Marcotte, T. D., et al. (1997). Neuropsychological findings in HIV infection and AIDS. In I. Grant & K. Adams (Eds.), *Neuropsychological assessment of neuropsychiatric disorders* (2nd ed., pp. 403-422). New York: Oxford University Press.
- King, D. A., & Caine, E. D. (1990). Depression. In J. L. Cummings (Ed.), *Subcortical dementia* (pp. 218-230). New York: Oxford University Press.

- Krikorian, R., Wrobel, A. J., Meinecke, C., Liang, W. M., & Kay, J. (1990). Cognitive deficits associated with human immunodeficiency virus encephalopathy. *Journal of Neuropsychiatry and Clinical Neurosciences*, 2, 256-260.
- La Rue, A. (1992). *Aging and neuropsychological disorders*. New York: Plenum Press.
- Law, W. A., Martin, A., Mapou, R. L., Roller, T. L., Salazar, A. M., Temoshok, L. R., & Rundell, J. R. (1994). Working memory in individuals with HIV infection. *Journal of Clinical and Experimental Neuropsychology*, 16, 173-182.
- Lunn, S., Skydsjerg, M., Schulsinger, H., Parnas, J., Pedersen, C., & Mathiesen, L. (1991). A preliminary report on the neuropsychologic sequelae of human immunodeficiency virus. *Archives of General Psychiatry*, 48, 139-142.
- Maj, M., Satz, P., Janssen, R., Zaudig, M., Starace, F., D'Elia, L., Sughondbabirom, B., Mussa, M., Naber, D., Ndeti, D., Schulte, G., & Sartorius, N. (1994). WHO Neuropsychiatric AIDS Study, Cross-Sectional Phase II: Neuropsychological and neurological findings. *Archives of General Psychiatry*, 51, 51-61.
- Mapou, R. L., & Law, W. A. (1994). Neurobehavioral aspects of HIV disease and AIDS: An update. *Professional Psychology: Research and Practice*, 25, 132-140.
- Mapou, R. L., Law, W. A., Martin, A., Kampen, D., Salazar, A. M., & Rundell, J. R. (1993). Neuropsychological performance, mood, and complaints of cognitive and motor difficulties in individuals infected with the human immunodeficiency virus. *Journal of Neuropsychiatry and Clinical Neurosciences*, 5, 86-93.
- Martin, A., Heyes, M. P., Salazar, A. M., Kampen, D. L., Williams, J., Law, W. A., Coats, M. E., & Markey, S. P. (1992). Progressive slowing of reaction time and increasing cerebrospinal fluid concentrations of quinolinic acid in HIV-infected individuals. *Journal of Neuropsychiatry and Clinical Neurosciences*, 4, 270-279.
- Martin, E. M., Pitrak, D. L., Robertson, L. C., Novak, R. M., et al. (1995). Global-local analysis in HIV-1 infection. *Neuropsychology*, 9, 102-109.
- Martin, E. M., Robertson, L. C., Edelstein, H., Jagust, W., Sorensen, D. J., et al. (1992a). Performance of patients with early HIV-1 infection on the Stroop task. *Journal of Clinical and Experimental Neuropsychology*, 14, 857-868.
- Martin, E. M., Sorensen, D. J., Edelstein, H. E., & Robertson, L. C. (1992b). Decision-making speed in HIV-1 infection: A preliminary report. *AIDS*, 6, 109-113.
- Mauri, M., Sinfioriani, E., Muratori, S., et al. (1993). Three-year neuropsychological follow-up in a selected group of HIV-infected homosexual/bisexual men. *AIDS*, 7, 241-245.
- McAllister, R. H., Hems, M. V., Harrison, M. J. G., et al. (1992). Neurological and neuropsychological performance in HIV seropositive men without symptoms. *Journal of Neurology, Neurosurgery and Psychiatry*, 55, 143-148.
- McArthur, J. C., Cohen, B. A., Selnes, O. A., Kumar, A. J., et al. (1989). Low prevalence of neurological and neuropsychological abnormalities in otherwise healthy HIV-1 infected individuals: Results from the Multicenter AIDS Cohort Study. *Annals of Neurology*, 26, 601-611.
- McArthur, J. C., Hoover, D. R., Bacellar, H., Miller, E. N., Cohen, B. A., Becker, J. T., Graham, N. M., McArthur, J. H., Selnes, O. A., Jacobsen, L. P., et al.

- (1993). Dementia in AIDS patients: Incidence and risk factors, Multicenter AIDS Cohort Study. *Neurology*, 43, 2245-2252.
- McArthur, J. C., Selnes, O. A., Glass, J. D., Hoover, D. R., & Bacellar, H. (1994). HIV dementia: Incidence and risk factors. In R. W. Price & S. Perry III (Eds.), *Research publications of the Association for Research in Nervous and Mental Disease: Vol. 72. HIV, AIDS and the brain* (pp. 251-272). New York: Raven Press.
- McKegney, F. P., O'Dowd, M. A., Feiner, C., et al. (1990). A prospective comparison of neuropsychologic function in HIV-seropositive and seronegative methadone-maintained patients. *AIDS*, 4, 565-569.
- Miller, E. N., Satz, P., van Gorp, W. G., Visscher, B., & Dudley, J. (1989). Computerized screening for HIV-related cognitive decline in gay men: Cross-sectional analyses and one-year follow-up. *Abstract of the International Conference on AIDS*, 5, 465.
- Miller, E. N., Satz, P., & Visscher, B. (1991). Computerized and conventional neuropsychological assessment of HIV-1 infected homosexual men. *Neurology*, 41, 1608-1616.
- Miller, E. N., Selnes, O. A., McArthur, J. C., Satz, P., Becker, J. T., Cohen, B. A., Sheridan, K., Machado, A. M., van Gorp, W. G., & Visscher, B. (1990). Neuropsychological performance in HIV-1-infected homosexual men: The Multicenter AIDS Cohort Study (MACS). *Neurology*, 40, 197-203.
- Miller, E. N., & Wilkie, F. L. (1994). Computerized testing to assess cognition in HIV-positive individuals. In R. W. Price & S. Perry III (Eds.), *Research publications of the Association for Research in Nervous and Mental Disease: Vol. 72. HIV, AIDS and the brain* (pp. 161-175). New York: Raven Press.
- Navia, B., Cho, E. S., Petito, C., & Price, R. (1986a). The AIDS dementia complex: II. Neuropathology. *Annals of Neurology*, 19, 525-535.
- Navia, B. A., Jordan, B. D., & Price, R. W. (1986b). The AIDS dementia complex: I. Clinical features. *Annals of Neurology*, 19, 517-524.
- Olo, C., Johnson, R., & Grafman, J. (1991). Signs of cognitive change in HIV disease: An event-related brain potential study. *Neurology*, 41, 209-215.
- Ostrow, D. G., Monjan, A., Joseph, J., Van Raden, M., Fox, R., Kingsley, L., Dudley, J., & Phair, J. (1989). HIV-related symptoms and psychological functioning in a cohort of homosexual men. *American Journal of Psychiatry*, 146, 737-742.
- Pace, P. L., Rosenberger, P., Nasrallah, H. A., & Bornstein, R. A. (1993). Depression and neuropsychological performance in symptomatic HIV infection. *Journal of Clinical and Experimental Neuropsychology*, 15, 95.
- Perdices, M. A., & Cooper, D. A. (1989). Simple and choice reaction time in patients with human immunodeficiency virus infection. *Annals of Neurology*, 25, 460-467.
- Perry, S. W., & Tross, S. (1984). Psychiatric problems of AIDS inpatients at a New York hospital: Preliminary report. *Public Health Reports*, 99, 20-25.
- Poutiainen, E., & Elovaara, I. (1996). Subjective complaints of cognitive symptoms are related to psychometric findings of memory deficits in patients with HIV-1 infection. *Journal of the International Neuropsychological Society*, 2, 219-225.
- Poutiainen, E., Iivanainen, M., Elovaara, I., Valle, S., & Lahdevirta, J. (1988).

- Cognitive changes as early signs of HIV infection. *Acta Neurologica Scandinavica*, 78, 49-52.
- Price, R. W., & Brew, B. J. (1988). The AIDS dementia complex. *Journal of Infectious Diseases*, 158, 1079-1083.
- Raininko, R., Elovaara, I., Vira, A., Valanne, L., Haltia, M., & Valle, S. L. (1992). Radiological study of the brain at various stages of human immunodeficiency virus infection: Early development of brain atrophy. *Neuroradiology*, 34, 190-196.
- Resnick, L., de Marzio-Veronese, F., Schupbach, J., Tourtellotte, W., Ho, D., Muller, F., Shapshak, P., Vogt, M., Groopman, J., Markham, P., & Gallo, R. (1985). Intra-blood-brain-barrier synthesis of HTLV-III specific IgG in patients with neurological symptoms associated with AIDS or ARC. *New England Journal of Medicine*, 313, 1498-1504.
- Rottenberg, D. A., Moeller, J. R., Strother, S. C., et al. (1987). The metabolic pathology of the AIDS dementia complex. *Annals of Neurology*, 22, 700-706.
- Rubinow, D., Berettini, C., Brouwers, P., & Lane, H. (1988). Neuropsychiatric consequences of AIDS. *Annals of Neurology*, 23(Suppl.), S24-S26.
- Sahakian, B. J., Elliot, R., Low, N., Mehta, M., Clark, R. T., & Pozniak, A. L. (1995). Neuropsychological deficits in tests of executive function in asymptomatic and symptomatic HIV-1 seropositive men. *Psychological Medicine*, 25, 1233-1246.
- Saykin, A., Janssen, R., Sprehn, G., et al. (1988). Neuropsychological dysfunction in HIV-infection: Characterization in a lymphadenopathy cohort. *International Journal of Clinical Neuropsychology*, 10, 81-95.
- Schwamm, L. H., Van Dyke, C., Kiernan, R. J., et al. (1987). The Neurobehavioral Cognitive Status Examination. *Annals of Internal Medicine*, 107, 486-491.
- Selnes, O. A., Galai, N., Bacellar, H., Miller, E. N., Becker, J. T., Wesch, J., van Gorp, W. G., & McArthur, J. C. (1995). Cognitive performance after progression to AIDS: A longitudinal study from the Multicenter AIDS Cohort Study. *Neurology*, 45, 267-275.
- Selnes, O. A., & Miller, E. N. (1994). Development of a screening battery for HIV-related cognitive impairment: The MACS experience. In I. Grant & A. Martin (Eds.), *Neuropsychology of HIV infection* (pp. 176-187). New York: Oxford University Press.
- Sorenson, D. J., Martin, E. M., & Robertson, L. C. (1994). Visual attention in HIV-1 infection. *Neuropsychology*, 8, 424-432.
- Stern, Y., Liu, X., Marder, K., Todak, G., Sano, M., Ehrhardt, A., & Gorman, J. (1995). Neuropsychological changes in a prospectively followed cohort of homosexual and bisexual men with and without HIV infection. *Neurology*, 45, 467-472.
- Stern, Y., Marder, K., Bell, K., Chen, J., Dooneief, G., Goldstein, S., Mindry, D., Richards, M., Sano, M., Williams, J., Gorman, J., Ehrhardt, A., & Mayeux, R. (1991). Multidisciplinary baseline assessment of homosexual men with and without human immunodeficiency virus infection: III. Neurologic and neuropsychological findings. *Archives of General Psychiatry*, 48, 131-138.
- Stern, Y., Sano, M., Williams, J., & Gorman, J. (1989). Neuropsychological

- consequences of HIV infection. *Journal of Clinical and Experimental Neuropsychology*, 11, 78.
- Stout, J. C., Salmon, D. P., Butters, N., Taylor, M., Peavy, G., Heindel, W. C., Delis, D. C., Ryand, L., Atkinson, J. H., Chandler, J. L., Grant, I., & the HNRC Group. (1995). Decline in working memory associated with HIV infection. *Psychological Medicine*, 25, 1221-1232.
- Tross, S., Price, R., Navia, B., et al. (1988). Neuropsychological characterization of the AIDS dementia complex: A preliminary report. *AIDS*, 2, 81-88.
- van Gorp, W. G., Hinkin, C. H., Satz, P., Miller, E. N., Weisman, J., Holston, S., Drebing, C., Marcotte, T. D., & Dixon, W. (1993). Subtypes of HIV-related neuropsychological functioning: A cluster analysis approach. *Neuropsychology*, 7, 62-72.
- van Gorp, W. G., Mandelkern, M. A., Gee, M., et al. (1992). Cerebral metabolic dysfunction in AIDS: Findings in a sample with and without dementia. *Journal of Neuropsychiatry and Clinical Neurosciences*, 4, 280-287.
- van Gorp, W. G., Miller, E. N., Satz, P., & Visscher, B. (1989). Neuropsychological performance in HIV-1 immunocompromised patients: A preliminary report. *Journal of Clinical and Experimental Neuropsychology*, 11, 763-773.
- van Gorp, W. G., Satz, P., Hinkin, C. H., Selnes, O. A., Miller, E. N., McArthur, J. C., Cohen, B., Paz, D., & the Multicenter AIDS Cohort Study (MACS). (1991). Metacognition in HIV-1 seropositive asymptomatic individuals: Self-ratings versus objective neuropsychological performance. *Journal of Clinical and Experimental Neuropsychology*, 13, 812-819.
- Ventura, S. J., Peters, K. D., Martin, J. A., & Maurer, J. D. (1997). Births and deaths: United States, 1996. *Monthly Vital Statistics Report*, 45(12) (Suppl.).
- Volk, R. J., Pace, T. M., & Parchman, M. L. (1993). Screening for depression in primary care patients: Dimensionality of the short form of the Beck Depression Inventory. *Psychological Assessment*, 5, 173-181.
- Wechsler, D. (1981). *Wechsler Adult Intelligence Scale-Revised*. New York: Psychological Corporation.
- White, D. A., Heaton, R. K., Monsch, A. U., & the HNRC Group. (1995). Neuropsychological studies of asymptomatic human immunodeficiency virus-type-1 infected individuals. *Journal of the International Neuropsychological Society*, 1, 304-315.
- Wilkie, F. L., Eisdorfer, C., Morgan, R., Loewenstein, D. A., & Szapocznik, J. (1990). Cognition in early human immunodeficiency virus infection. *Archives of Neurology*, 47, 433-440.
- Wilkins, J. W., Robertson, K. R., Snyder, C. R., et al. (1991). Implications of self-reported cognitive and motor dysfunction in HIV-positive patients. *American Journal of Psychiatry*, 148, 641-643.