The Neurology of AIDS

Second edition

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7.2 HIV neurocognitive disorders

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Introduction

In this chapter, we will define the various neurocognitive disturbances associated with HIV infection, describe their characteristics, and discuss our current understanding of their epidemiology. We shall also review the current state of the literature on neuropathological and disease-related correlates of cognitive disturbances, risk factors that may contribute to cognitive complications, and the significance of cognitive disturbances in terms of social–occupational functioning, health, and early mortality, as well as effects of treatment.

Definitions

Historically, terms were used to describe neurocognitive complications in ways that were often imprecise, and sometimes contradictory. For example, neuropathological concepts such as encephalitis were applied to clinical phenomena; additionally, terms such as 'dementia' were sometimes applied very broadly, so as to encompass even the most minor forms of cognitive disturbance. Such practices have created obvious difficulties in scientific and clinical communication. More importantly, lack of agreed upon research definitions has hampered studies into the epidemiology, prognosis, and treatment of these conditions. For these reasons, we have chosen in this chapter to provide definitions of the terms that we employ. Such definitions should increase the readability of our chapter. Hopefully, they might also serve the broader purpose of sharpening our diagnostic terminology.

Neurocognitive, Neurobehavioral

If we view the brain as an apparatus for processing information, then it is useful to consider these information management activities in terms of several processes. Examples of such 'neurocognitive' processes or abilities include perceptual abilities, abstraction (conceptualization), executive functions, perceptual motor integration, learning, and remembering. Additionally, attention is usually regarded as a focusing and selecting process necessary for many of the other cognitive operations. Neurocognitive functioning can also be described in terms of its speed and efficiency, as well as its flexibility.

The term 'neurobehavioral' more broadly encompasses the neurocognitive processes delineated above, plus other brain-mediated behaviors such as mood and affect, temperament, adaptive (coping) abilities, and personality. Generally speaking, significant changes in neurocognitive functioning are the most specific indicators of underlying pathologic changes in the brain. Other neurobehavioral changes can occur for many non-neuropathological reasons, for example, mood changes can be brought on by the realization of the seriousness of one's illness, and distortions in ability to cope secondary to the pain, discomfort, and disability associated with AIDS can produce apparent disturbance in personality. For these reasons, we shall focus our attention in this chapter specifically on neurocognitive complications.

Neurocognitive assessment

Information on cognitive functioning derives both from patient history (self-report) and direct examination. It goes without saying that a careful history should always be the starting point, and persons with HIV infection, particularly AIDS, ought to be questioned closely on possible changes in attention/concentration, mental efficiency, ability to learn and recall, or reduced psychomotor performance.

Unfortunately, the value of self-reported information depends heavily on subjective factors that are not always easy for the clinician to evaluate. For instance, some patients tend to deny problems, while others tend to amplify them. Also, terms such as 'memory problems' or 'difficulty in concentrating' can have very different meaning to different patients. For these reasons, as well as others, self-reported cognitive difficulties often do not correlate well with objective findings from neuropsychological testing or neurological examination.

Some data from the University at California San Diego HIV Neurobehavioral Research Center (HNRC) illustrate this point (Fig. 1). In this case, seropositive patients were asked about a number of subjective complaints that were then grouped into the general categories of 'cognitive' (example: complaint of memory loss), affective (example: feeling depressed or anxious), and neuromotor (example: gait disturbance). These clusters of self-reported complaints were then correlated with more objective indicators, including results of neuropsychological examination, mood measures, medical status, and neurological examination. As can be seen, 'cognitive' self-reports were actually correlated better with mood measures than with neuropsychological and neurological measures (Fig. 2).

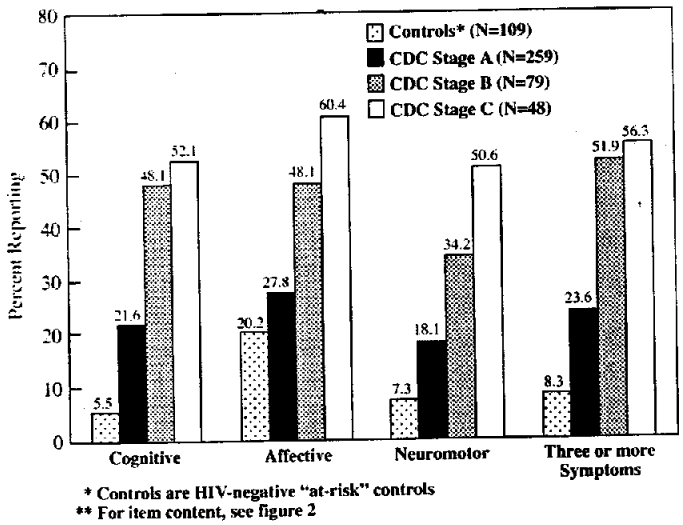


Fig. 1 Prevalence of cognitive, affective, and neuromotor symptoms at different stages of HIV disease. Controls are HIV-negative 'at risk' controls. For item content, see Fig. 2. (Adapted from Mehta *et al.* (1996).)

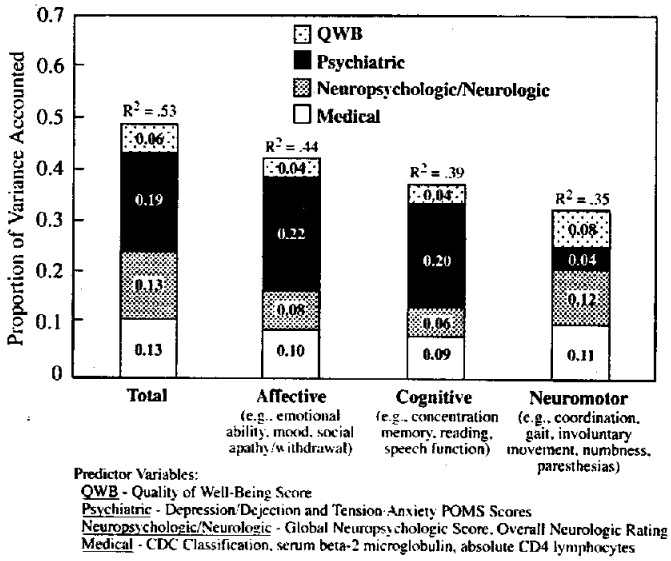


Fig. 2 Prediction of self-reported neurobehavioral symptoms. The predictor variables are as follows. QWB: Quality of Well-being Score; Psychiatric: Depression/Dejection and Tension/Anxiety POMS scores; Neuropsychological/Neurological: Global Neuropsychological Score, Overall Neurological Rating; Medical: CDC classification, serum beta-2 microglobulin, absolute CD4 lymphocytes. (From HNRC, unpublished data.)

For such reasons, it is essential that, before a diagnosis of a neurocognitive disorder is made, the patient be examined by procedures that have documented validity and reliability. Ideally, neuropsychological testing should be accomplished, but other procedures such as structured mental status examinations or cognitive screening procedures can also be used (for further discussion of this topic see Chapter 7.1).

Neuropsychological tests

Neuropsychological tests can be viewed as probes of different cognitive abilities such as learning, recall, or perceptual motor skills. It is important to remember that there is no perfect test that corresponds exactly to a putative cognitive ability. Furthermore, tests vary in terms of their sensitivity and specificity, as well as the degree to which they are affected by other general factors such as age, education, and cultural background. For this reason, it is important to assess cognitive ability domains utilizing more than one test of each domain.

It is also essential that a neuropsychological test abnormality not be equated to neurocognitive impairment. People can have difficulties with one or another neuropsychological test for many reasons, some of them nonneurological. Therefore, a clinical diagnosis cannot be based on a single test, nor a very small grouping of tests that might not properly cover all relevant ability areas.

Neuropsychological deficit

We use the term neuropsychological deficit to refer to a clear-cut abnormality in a cognitive ability area. For example, a person might have been administered three tests of learning (for example, a short story, a nonverbal test, and a list of words). Let us say that such an individual scored below generally accepted norms on all of these tests. It would then be possible to conclude that such an individual has a learning deficit. However, to term an individual neurocognitively 'impaired' requires that more than one ability area is deficient. In this example, if an individual had problems in learning only, and performed well in areas such as perceptual motor skills, executive functions, recall of information, and verbal skills, we would conclude that the person has a learning deficit and nothing more.

Neurocognitive impairment

The term 'neurocognitive (neuropsychological) impairment' is used when an individual has deficits in two or more cognitive areas, established by valid and reliable neuropsychological or mental status assessment.

Neurocognitive disorder

A neurocognitive disorder exists when neuropsychological impairment is accompanied by disturbance in day-to-day functioning. This disturbance can be in the area of occupation, social functioning, or other health-related functioning. Two levels of neurocognitive disorder are recognized:

- mild neurocognitive disorder (minor cognitive motor disorder). Mild neurocognitive disorder exists when a person has deficits in two or more cognitive areas that interfere at least mildly with day-to-day functioning.
- dementia (HIV-associated dementia, HIV-associated dementia complex). Dementia exists when neurocognitive impairment is so severe in nature that it interferes markedly with day-to-day functioning. Persons diagnosed with dementia typically are unable to work, and some may not be able to care for themselves. The term 'dementia' should be reserved for those who have significant cognitive impairment that interferes markedly with day-to-day life (Fig. 3).

HIV dementia

The essential features of HIV dementia are disabling cognitive impairment, usually accompanied by motor dysfunction and behavioral change. Cognitive impairment is characterized by mental slowness, forgetfulness, and poor concentration. Behavioral changes may include apathy, lethargy, and diminished spontaneity and emotional responses. Motor symptoms include loss of fine motor control, clumsiness, unsteady gait, and tremor.

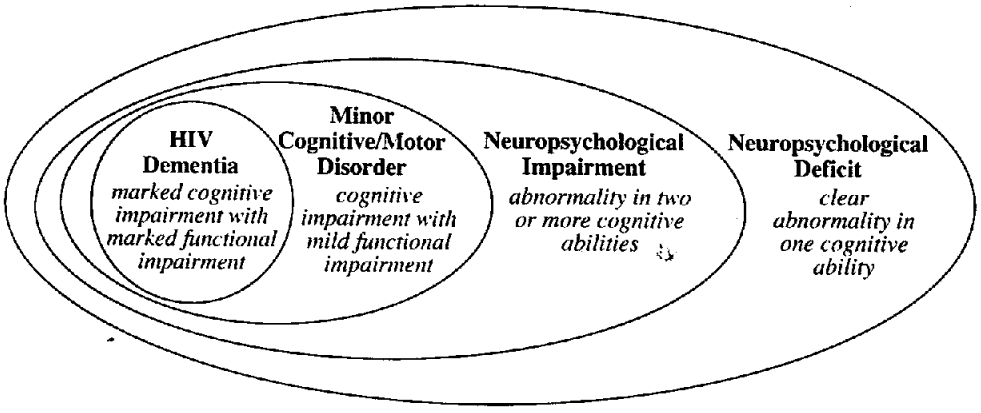


Fig. 3 Schematic representation of the relationship of neuropsychological deficits, impairment, minor cognitive/motor disorder, and dementia in HIV infection.

The terms 'AIDS dementia complex,' 'HIV dementia', 'HIV encephalopathy', and 'HIV-associated dementia complex' are synonymous. Minor degrees of cognitive and motor impairment that are not sufficient to diagnose as dementia are termed 'HIV-associated minor cognitive/motor disorder' (mild neurocognitive disorder).

The term 'HIV encephalitis' (HIVE) should be reserved for the pathological features of multinucleated giant cell encephalitis with HIV identified in the brain and should not be used to describe the clinical syndrome. Similarly, while HIV-associated dementia complex frequently develops concurrently with other HIV-associated neurological disorders such as myelopathy and neuropathy, it appears that these are all discrete disorders with different manifestations, courses, and pathogenetic mechanisms. Thus, the practice of lumping these disorders together as neuroAIDS can be misleading.

Diagnostic criteria for HIV dementia

A diagnostic scheme for HIV dementia that is valid and reliable must meet at least the following three requirements. It must include: (1) clearly defined, objectifiable inclusion criteria; (2) specific exclusion criteria; and (3) a specified threshold for making the diagnosis. Unfortunately, several commonly used schemes do not meet all of these requirements. For example, the Memorial Sloan Kettering (MSK) scheme contains gradations that range from minor cognitive disturbances to a profound incapacitating disorder. It also integrates neurological deficits related specifically to myelopathy, focusing on ambulation function. Thus, the scale does not adequately separate the cognitive and behavioral impairments of brain disease from the myelopathic impairments (Price and Brew 1988). A World Health Organization (WHO) scheme suffers from similar problems, permitting dementia to be diagnosed even when relatively mild, functionally insignificant cognitive disturbances are present (Maj 1990).

We believe that in order for the term HIV dementia to have utility, it should be reserved for patients who develop severe cognitive impairment that interferes markedly with day-to-day life. This is in keeping with the tradition of the American Psychiatric Association's *Diagnostic and statistical manual* (DSM; American Psychiatric Association 1980, 1994) and conforms to the proposal developed by the American Academy of Neurology (AAN) AIDS Task Force (Janssen *et al.* 1991). The AAN criteria are reproduced in Tables 1 and 2, and are compared to the research criteria proposed by Grant and Atkinson (1995), the latter representing an effort to refine the DSM approach.

Epidemiology of HIV dementia

HIV-associated neurological manifestations—dementia, myelopathy, and neuropathy—have become common neurological disorders in young Americans, with about 65 000 new cases annually in the USA (Janssen *et al.* 1992). Within the first year or two of clinical experience with AIDS it

Table 1 Simplified version of the 1991 American Academy of Neurology definitional criteria for HIV dementia (Janssen *et al.* 1991)

HIV-1-associated dementia complex

Probable (must have each of the following):

1. Acquired abnormality in two or more cognitive domains, present for at least 1 month, and cognitive dysfunction impairing work or activities of daily living, not solely attributable to systemic illness
2. Acquired abnormality in motor function or performance, verified by clinical examination and/or neuropsychological tests and/or decline in motivation, emotional control, or change in social behavior
3. Absence of clouding of consciousness for a period of time sufficient to establish (1)
4. No other etiology present (e.g. medical, psychiatric, substance abuse, CNS infection, or neoplasm).

Possible (must have one of the following):

1. (1), (2), and (3) above are present, but an alternative etiology is present and the cause of (1) above is not certain
2. (1), (2), and (3) above are present, but the etiology is not certain due to an incomplete evaluation

Table 2 Criteria for HIV dementia as defined by Grant and Atkinson (1995)

HIV-1-associated dementia (HAD)

1. Marked acquired impairment in cognitive functions, involving at least two ability domains (e.g. memory, attention): typically the impairment is in multiple domains, especially in learning of new information, slowed information processing, and defective attention/concentration. The cognitive impairment can be ascertained by history, mental status examination, or neuropsychological testing
2. The cognitive impairment produces marked interference with day-to-day functioning (work, home life, social activities)
3. The marked cognitive impairment has been present for at least 1 month
4. The pattern of cognitive impairment does not meet criteria for delirium (e.g. clouding of consciousness is not a prominent feature) or, if delirium is present, criteria for dementia need to have been met on a prior examination when delirium was not present
5. There is no evidence of another, pre-existing etiology that could explain the dementia (e.g. other CNS infection, CNS neoplasm, cerebrovascular disease, pre-existing neurological disease, or severe substance abuse compatible with CNS disorder)

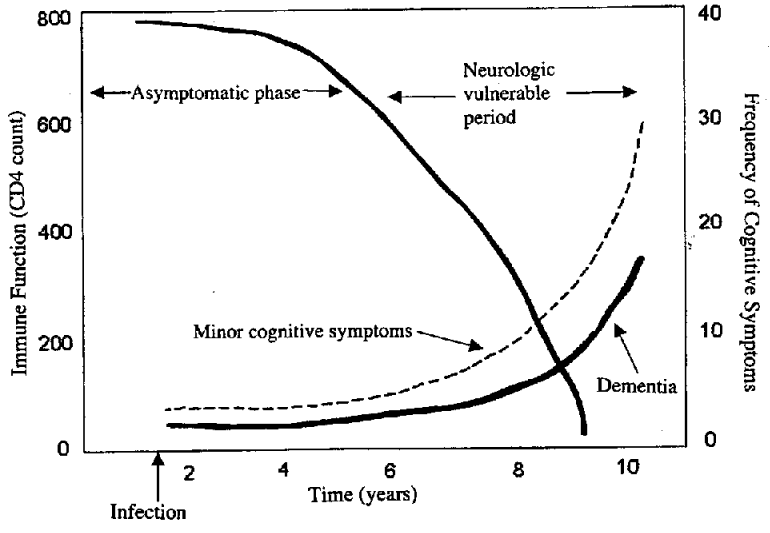


Fig. 4 Approximate frequencies of HIV-associated dementia complex and cognitive impairment and timing relative to systemic disease. Note 'vulnerable' period after AIDS (McArthur *et al.* 1997).

became apparent that many patients developed cognitive impairment (Levy *et al.* 1985; Snider *et al.* 1983). At first, this psychomotor slowing and mental dulling was mistakenly attributed to 'depression' or 'delirium' or attributed to opportunistic infections of the nervous system. Now it is recognized that mild neurocognitive disorder develops in about 20–30% of people with advanced AIDS and frank dementia in 10–20%, with an annual incidence after AIDS of approximately 7% (Fig. 4; McArthur *et al.* 1993). Typically, dementia develops insidiously over a few weeks or months in a patient with advanced immunodeficiency or frank AIDS, although some patients show some insidious cognitive decline before AIDS (Selnes *et al.* 1991*b*). Navia and colleagues (Navia and Price 1987) were among the first to recognize that dementia could be an initial manifestation of AIDS. They described 29 patients in whom HIV dementia developed before other AIDS-defining illnesses, six of whom were medically asymptomatic at the time of onset of dementia. Surveillance data from the Centers for Disease Control (CDC) indicate that HIV dementia comprises 3% of all first AIDS-defining illnesses in the USA (Centers for Disease Control and Prevention 1995). When HIV dementia develops with less advanced immunodeficiency, its progression is frequently less rapid than the course of dementia occurring in patients with advanced immunosuppression (Bouwman *et al.* 1996). This suggests that, although HIV dementia can occur before severe immune suppression, its progression is more rapid with advanced systemic disease, paralleling the immune defects and systemic effects of increasing HIV load and cytokine production (Price *et al.* 1988).

Prevalence and incidence of HIV dementia

Initial reports of the prevalence of dementia in AIDS varied from 7% to 66%, depending on the referral population studied and the selection criteria used. Navia *et al.* (1986) found two-thirds of an autopsy group to have been demented, while in contrast McArthur (1987) described dementia in only 16% from a neurological referral population consisting predominantly of individuals with symptomatic HIV infection. Portegies *et al.* (1993) diagnosed HIV dementia in 7.5% (40 of 536) of symptomatic HIV-infected individuals in Amsterdam referred for neurological evaluation between 1982 and 1992. An identical prevalence of HIV dementia was reported among individuals with AIDS in California from 1989 to 1991 (Reardon *et al.* 1992). Maj *et al.* (1994), reporting on data from Munich, Sao Paulo, Kinshasa, Nairobi, and Bangkok, noted a prevalence ranging from 4.4% to 6.5% (*Diagnostic and statistical manual of mental disorder* 3rd edn, revised (DSM-III-R) criteria) or 5.9–6.9% (International Classification of Diseases (ICD10) criteria) among symptomatic HIV-infected persons. Data from the Multicenter AIDS Cohort Study (MACS), a large prospective study of homosexual men in the United States, showed a cumulative prevalence of dementia of 15–20% after AIDS (McArthur *et al.* 1993). Prevalence figures of HIV dementia reflect not only the incidence, but also the survival rate; thus, the prevalence of a condition like HIV dementia with short survival will be lower than that of a condition like Kaposi's sarcoma that has longer survival. Table 3 gives estimates for prevalence figures for HIV dementia at different stages of HIV infection.

Although the prevalence of dementia has been reasonably defined, accurate estimates of the incidence of dementia have been lacking until recently. The surveillance figures from the CDC are useful, but generally only apply to dementia as the initial manifestation of AIDS because the CDC reporting system does not routinely capture secondary diagnoses occurring after AIDS. In 1990 in the USA in persons 20–59 years old, the incidence of HIV dementia was 1.9 per 100 000 population (Janssen *et al.* 1992). These CDC data have shown that HIV dementia is reported in about 7% of US patients with AIDS (probably reflecting underreporting), but is the initial AIDS-defining illness in only 2.8%. Day *et al.* (1992) found an annual incidence of dementia among symptomatic HIV-infected individuals of 14% and McArthur *et al.* (1993) found an annual incidence of 7.1 %.

The Edinburgh cohort of intravenous drug users followed since 1986 had an incidence of approximately 9% and is the only study with data on seroconversion showing a mean time from seroconversion to dementia of about 9 years (Pretsell *et al.* 1996). These data are comparable to the 7% incidence (after AIDS) and the 15% cumulative prevalence figures from the MACS (McArthur *et al.* 1993).

There have been reports of a dramatic decline in the frequency of HIV dementia related to the earlier and more widespread use of antiretrovirals after 1987 (Portegies *et al.* 1989; Chiesi *et al.* 1990). These studies are reviewed and put into perspective by Catalan and Thornton (1993). For example, Portegies *et al.* (1989) diagnosed dementia in only 2% of patients who had received zidovudine compared to 36% who had never received antiretrovirals and demonstrated a dramatic drop in the incidence (period prevalence) of dementia.

The epidemiology of HIV-associated neurological disease in the industrialized world has changed significantly in the era of highly active antiretroviral therapy (HAART). These changes have occurred concurrently with changes in the treatment patterns for HIV infection over the past 10 years. In the Multicenter AIDS Cohort Study (MACS), a longitudinal cohort of gay/bisexual men from Baltimore, Pittsburgh, Chicago, and Los Angeles studied from 1990 to 1992, monotherapy and no therapy were the predominant forms of treatment. From 1993 to 1995, multidrug therapy without protease inhibitors (that is, dual therapy) and monotherapy were the predominant forms of treatment. From 1996 to the present, HAART has become the predominant form of treatment. Using data from the MACS (Sacktor *et al.* 2001) the past decade was subdivided into each of these three smaller time periods to compare the mean incidence of HIV dementia. Since the introduction of HAART in 1996, the incidence of HIV dementia has declined significantly by about 50% compared to the early 1990s (Fig. 5). The HNRC experience also bears out that incidence of neurocognitive impairment was significantly less since the beginning of the era of HAART (1996 and later) than previously (Fig. 6). We also examined the CD4 count of HIV dementia cases in these three time periods. From 1990 to 1992, the majority of HIV dementia cases occurred with advanced immunosuppression with a CD4 count < 200. In contrast, from 1996 to 1998, more cases of HIV dementia were presenting with CD4 counts > 200 (Fig. 7).

These results are similar to those found by others. In a European study of homosexual men, Brodt *et al.* (1997) found a decreased rate of HIV-associated central nervous system (CNS) disease from 1992 to 1996. In the

Table 3 Estimated prevalence of HIV dementia

Stage	Prevalence (%)
Medically asymptomatic	< 1
Initial AIDS condition	3
Symptomatic HIV disease	5–10
Advanced HIV disease	10–20

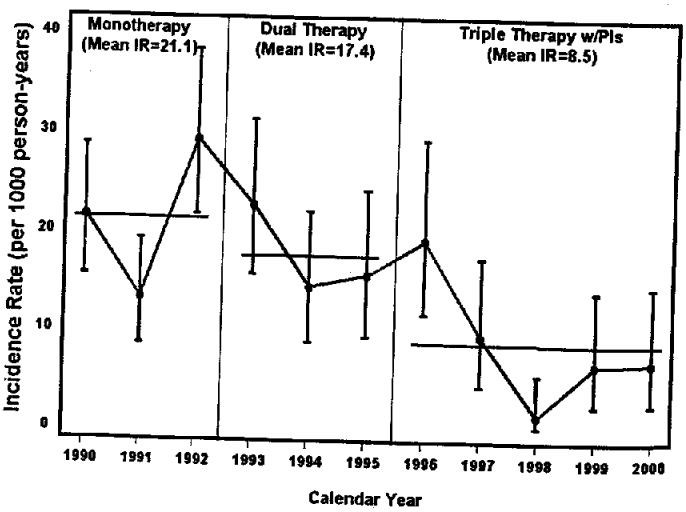


Fig. 5 Incidence of dementia during three epochs of antiretroviral treatment. IR, Incidence rate; PIs, protease inhibitors.

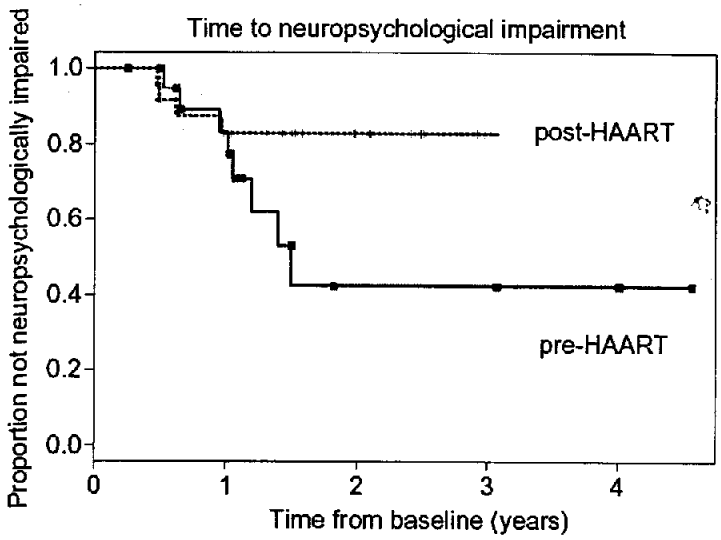


Fig. 6 Kaplan–Meier survival estimate for distribution of time to neurocognitive impairment (in years) on or before 31 December 1995 (pre-HAART) versus on or after 1 January 1996 (post-HAART). Tick marks on curves represent censored observations. HAART, Highly active antiretroviral therapy (Deutsch *et al.* 2001).

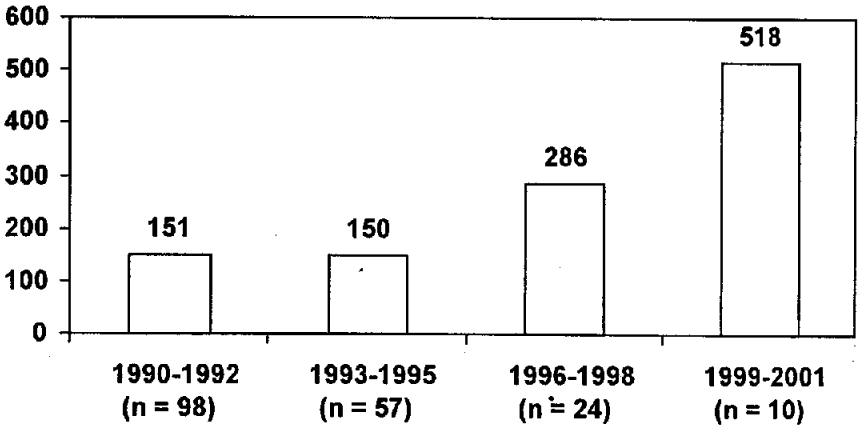


Fig. 7 Dementia cases have less immunosuppression with modern antiretroviral treatments.

Multicenter European EuroSIDA study of 17 nations with 7300 individuals, the incidence of HIV dementia had also decreased by about 50% (Mocroft *et al.* 2000). The median CD4 count at diagnosis of HIV dementia had also increased slightly in the EuroSIDA study. In the Australian National AIDS Registry, 1992–1997, Dore *et al.* (1999) also reported a decreasing number of HIV dementia cases over this time period. However, HIV dementia constituted a greater proportion of AIDS-defining illnesses, relative to other conditions. They also found that the median CD4 count for HIV dementia appeared to be increasing.

Similar results were seen in a university clinic with predominantly intravenous drug users. At the Johns Hopkins HIV clinic in Baltimore, Maryland, the incidence rate for HIV dementia had significantly decreased, comparing the rates from 1994 and 1998 (Fig. 8; Moore and Chaisson 1999).

Data on the changes in the prevalence of HIV dementia are much less extensive. In the Johns Hopkins HIV clinic, the prevalence of HIV dementia in approximately 1300 patients has remained stable from 1994 to 2000, and may be showing a slight trend towards an increase (Fig. 9). In contrast, in a university clinic in Essen, Germany evaluating 563 patients, there was a small decrease in the prevalence of HIV dementia, comparing the prevalence in 1995 and 1996, to that of 1997 and 1998 (Maschke *et al.* 2000). Further studies are needed to evaluate changes in the prevalence of HIV dementia in the era of HAART.

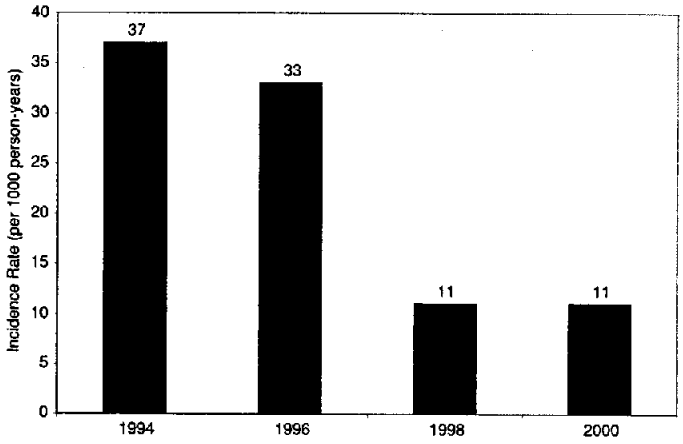


Fig. 8 Decline in HIV dementia incidence since HAART initiation.

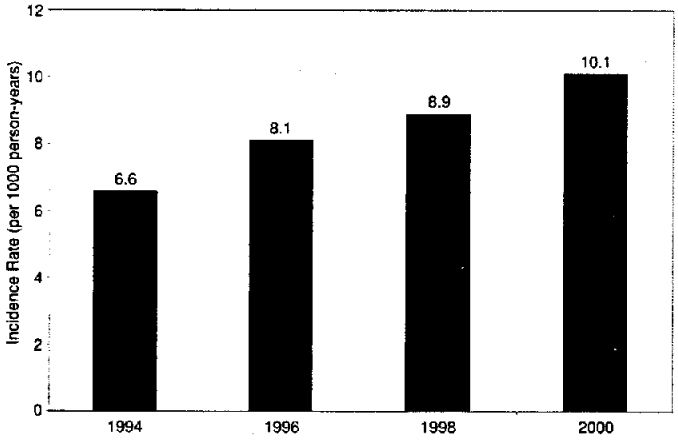


Fig. 9 HIV dementia prevalence may be rising as those on HAART survive longer.

Risk factors for HIV dementia

Several groups of investigators prior to the HAART era searched for markers or determinants of dementia risk. In a study based on a San Francisco cohort, Wang *et al.* (1995) found that HIV dementia was associated with increasing age, a diagnosis of AIDS, and injection drug use. Earlier MACS data, based on a prospective follow-up of 492 homosexual men who developed AIDS-defining illnesses during the period 1984 through 1991, produced an estimate of risk factors for the development of HIV-associated dementia. Using a proportional hazards model, the following variables were found to be significant predictors: lower hemoglobin and body mass index 1–6 months before AIDS, more constitutional symptoms 7–12 months before AIDS, and older age at AIDS. These data suggest that dementia develops in parallel with progressive systemic disease (McArthur *et al.* 1993). Demographic characteristics, specific AIDS-defining illness, AZT use before AIDS, and CD4-positive lymphocyte count before AIDS were not significant predictors of dementia.

Prior to HAART, baseline levels of plasma HIV RNA and CD4 counts were predictive of a subsequent hazard of developing HIV dementia (Childs *et al.* 1999). Using MACS data adjusted for age and education, individuals with baseline plasma HIV RNA > 30 000 copies/ml had a relative hazard of developing dementia 9.1 times that of those with < 500 copies/ml. Individuals with a CD4 count < 200 had a 3.4-fold greater hazard of developing dementia relative to those with a CD4 count > 500.

Risk factors for HIV dementia were also examined in the Dana Consortium for Therapy of HIV Dementia and Related Disorders (Stern *et al.* 2001). The Dana Consortium recruited from 1994 to 1996 included HIV-seropositive subjects at high risk for HIV dementia defined by having subjective complaints of memory or concentration problems, and either a CD4 count below 200 or cognitive impairment on neuropsychological testing and a CD4 count below 300. Factors associated with the development of HIV dementia included deficits on tests of psychomotor speed and executive dysfunction, a diagnosis of HIV-associated minor cognitive/motor disorder, a history of HIV-related medical symptoms, extrapyramidal signs on a neurological examination, depression, functional difficulties, low hemoglobin, and high serum beta-2 microglobulin levels.

There has been some evidence that cerebrospinal fluid (CSF) HIV RNA concentration may be a more specific marker for HIV neurocognitive impairment than plasma values. For example, Ellis and colleagues noted that the presence of neurocognitive disorders in AIDS correlates better with viral load (Ellis *et al.* 1997) and chemokine concentrations (Letendre *et al.* 1999) in the CSF than in plasma. Additionally, elevated HIV RNA levels in CSF predict increased subsequent risk for the development of neurocognitive disorders (Ellis *et al.* 2002). Finally, reduction in CSF viral load is more closely associated with neurocognitive improvement following combination antiretroviral treatment, than is change in plasma HIV RNA (Letendre *et al.* 1998). These observations suggest that high CSF virion and chemokine concentrations, particularly in advanced HIV disease, may reflect a greater burden of productive infection and immune activation in brain parenchyma.

Neuropsychological features of HIV-associated dementia

Several groups of investigators have probed the neuropsychological profile of HIV dementia. The earliest, most prominent impairments include motor and psychomotor dysfunction, memory impairment, and frontal/executive dysfunction (Grant *et al.*1987; Heaton *et al.*1995; Tross *et al.* 1988; Selnes and Miller 1994).

Motor dysfunction may go undetected because it is overshadowed by the cognitive and behavioral aspects of HIV dementia or is unrecognized as reflecting an evolving dementia process. In one consecutive series, 50% of patients with dementia had gait disturbance as one of their presenting symptoms (Harrison and McArthur 1995). Arendt *et al.* (1990, 1994*a*) have focused on more sophisticated measures to assess motor dysfunction and have shown significant delay in reaction time and motor control. The same group has also investigated gait disturbance and has shown that postural reflexes are impaired in individuals with HIV dementia (Arendt *et al.* 1994*b*). It is uncertain whether these changes reflect basal ganglion dysfunction or subtle myelopathy.

Interestingly, in a macaque simian immunodeficiency virus (SIV) model, impairment of motor skill tasks was the most reliable indicator of CNS infection and deficits were identified more frequently in motor skills than visual recognition memory or recent memory. Although the monkeys showed motor skill deficits, there was no particular regional involvement or association with pathological abnormalities and the monkeys exhibited normal behavior (Murray *et al.* 1992).

From the earliest descriptions of the neurocognitive disorders associated with HIV infection, primary disturbances seemed to be attributable to dysfunction in the striatum and frontostriatal connections. This finding fits with the neuropsychological concept of subcortical dementia, with the principal features of reduced attentional set-shifting, slowness of information processing, reduced fluency, impaired acquisition of motor skills, difficulty on tests involving 'egocentric spatial processing' (Martin 1994), and impaired free recall with relatively preserved recognition recall (Fig. 10). These neuropsychological features fit with the pattern of subcortical dementia as encountered in extrapyramidal diseases, including Huntington's disease and Parkinson's disease, progressive supranuclear palsy, and normal pressure hydrocephalus.

Work with quantitative magnetic resonance imaging (MRI) scans to correlate neuropsychological impairment or clinical neurological disease with

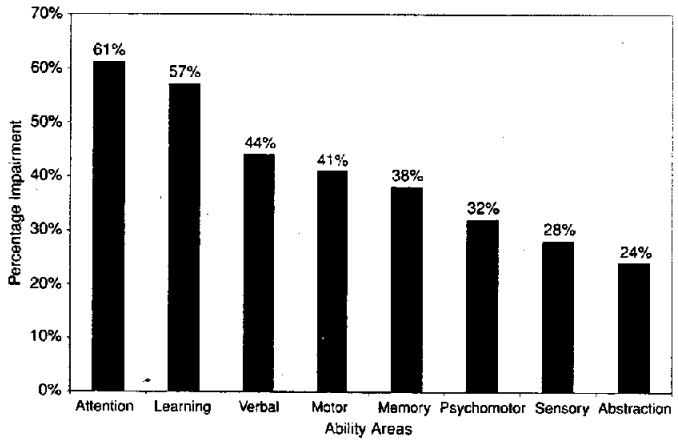


Fig. 10 Prevalence of deficits within each ability area for HIV-positive subjects rated as being neuropsychologically impaired, indicating a 'subcortical' pattern. (Modified from Heaton *et al.* (1995).)

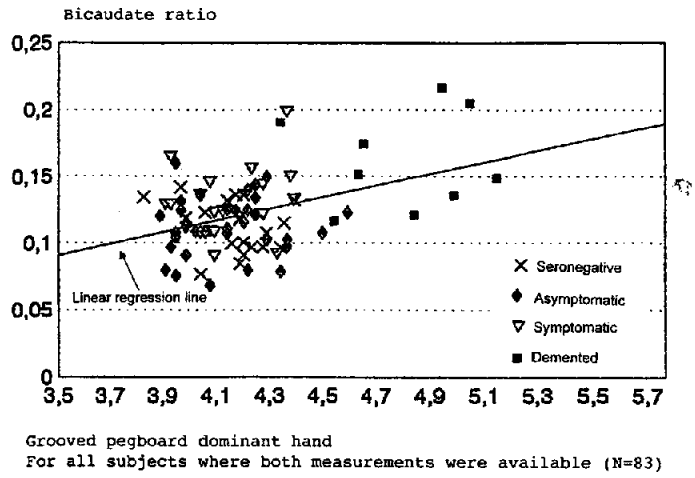


Fig. 11 Scatterplot of Grooved Pegboard dominant hand (logarithmic scale) and bicaudate ratio (Hestad *et al.* 1993).

regional volume loss shows a significant correlation between measures of basal ganglia volume and neuropsychological performance (Hestad *et al.* 1993; Aylward *et al.* 1995). Hestad *et al.* (1993) found significant correlation between caudate region atrophy as measured by enlargement of the bicaudate ratio (BCR) and impaired performance on several measures of neurocognitive performance, including Grooved Pegboard, Verbal Fluency, and the Trail Making Test. This suggests that subcortical damage, and particularly caudate region atrophy, underlies the subcortical pattern of neuropsychological impairment (Fig. 11). A number of pathological studies have shown that the predominance of pathology is seen within the frontostriatal areas (Kure *et al.* 1991; Budka *et al.* 1991). Cortical regions are not spared, however, and investigators have clearly shown in AIDS both neocortical volume loss as well as neocortical neuronal loss (Aylward *et al.* 1995) with dendritic pruning and synaptic simplification (Wiley and Achim 1994). It seems plausible that HIV dementia begins as a subcortical process, which then evolves and progresses to involve cortical areas.

Neurocognitive impairment and mild neurocognitive disorder (minor cognitive–motor disorder)

We have noted that the term 'neurocognitive impairment' may be used to describe the circumstance of a person who performs below expectations for his or her age, education, and cultural background in two or more cognitive ability areas. While the detection of such neurocognitive impairment may be important in research, and may at times be predictive of future consequences, the presence of neurocognitive impairment is not equivalent to the diagnosis of a neurocognitive disorder. To meet criteria for mild neurocognitive disorder, there must be neurocognitive impairment of sufficient degree to affect day-to-day functioning at least to a mild degree. The disorder needs to be present at least 1 month; and there are certain exclusion criteria. Two criterion sets in use at this time are presented in Tables 4 and 5. One was developed by the AAN AIDS Task Force (Janssen *et al.* 1991) and the other by Grant and Atkinson (1995). The criterion sets overlap considerably; the Grant and Atkinson set attempts to provide more precise criteria that may enhance reliability across diagnostic settings.

The relationship between neurocognitive impairment and mild neurocognitive disorder is uncertain. For example, the likelihood of transition from impairment to disorder is not known. An analogous situation exists with the diagnosis of diabetes. Abnormal values on a fasting oral glucose tolerance test (GTT) indicate some impairment in glucose handling; such impairment, however, is not tantamount to the diagnosis of diabetes, which requires meeting other criteria. As with the abnormal GTT, neuropsychological impairment in an HIV-infected person could indicate 'real' HIV-related CNS disturbance, but such disturbance might never progress to a clinically relevant stage.

Table 4 Simplified version of 1991 American Academy of Neurology definitional criteria for minor cognitive/motor disorder (Janssen *et al.* 1991)

HIV-1-associated minor cognitive/motor disorder

Probable (must have each of the following):

1. Acquired cognitive/motor/behavioral abnormalities, verified by both a reliable history and by neurological neuropsychological tests
2. Mild impairment of work or activities of daily living
3. Does not meet criteria for HIV dementia or HIV myelopathy
4. No other etiology present

Possible (must have one of the following):

1. (1), (2), and (3) above are present, but an alternative etiology is present and the cause of (1) is not certain
2. (1), (2), and (3) above are present, but the etiology of (1) cannot be determined due to incomplete evaluation

Table 5 Criteria for mild neurocognitive disorder as defined by Grant and Atkinson (1995)

HIV-1-associated mild neurocognitive disorder (MND)

1. Acquired impairment in cognitive functioning, involving at least two ability domains, documented by performance of at least 1.0 standard deviation below the mean for age–education–appropriate norms on standardized neuropsychological tests. The neuropsychological assessment must survey at least the following abilities: verbal/language; attention/speeded processing; abstraction/executive; memory (learning, recall); complex perceptual–motor performance; motor skills
2. The cognitive impairment produces at least mild interference in daily functioning (at least one of the following):
   (a) self-report of reduced mental acuity, inefficiency in work, homemaking, or social functioning
   (b) observation by knowledgeable others that the individual has undergone at least mild decline in mental acuity, with resultant inefficiency in work, homemaking, or social functioning
3. The cognitive impairment has been present for at least 1 month
4. The cognitive impairment does not meet criteria for delirium or dementia
5. There is no evidence of another pre-existing cause for the MND*

* If the individual with suspected MND also satisfies criteria for a major depressive episode or substance dependence, the diagnosis of MND should be deferred to a subsequent examination conducted at a time when the major depression has remitted or at least 1 month has elapsed following termination of dependent-substance use.

Epidemiology of HIV-associated minor cognitive, motor disorder (MCMD)

The incidence and prevalence of MCMD are poorly understood. This is primarily because these diagnostic criteria are relatively new and insufficient epidemiological research has been completed.

At the HNRC an attempt has been made to operationalize the MCMD diagnosis. Figure 12, based on experience with approximately 975 seropositive persons at CDC stages A, B, and C, and approximately 200 at-risk seronegative controls, indicates the point prevalence of neurocognitive impairment, MCMD, and dementia in this series. It will be noted that impairment was only detected in approximately 15% of seronegative controls, 27% of persons in CDC stage A, 25% in person in CDC stage B, and 18% in C. The rate of MCMD was low in the medically asymptomatic phase of infection (5%) but increased to 18% during the symptomatic

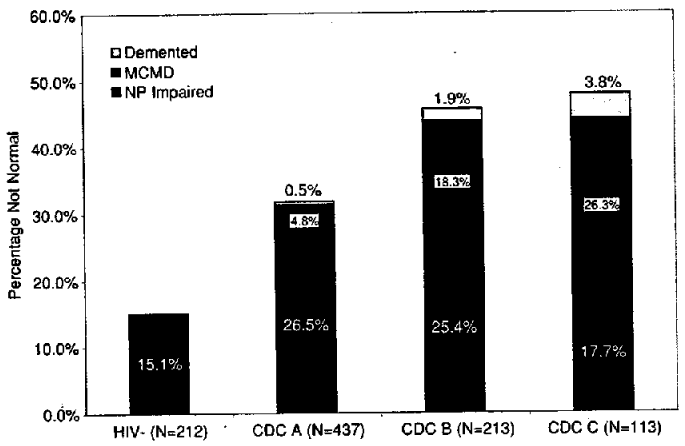


Fig. 12 Percentage of subjects with neurocognitive disorders. NP, Neuropsychologically. (From HNRC, unpublished data.)

phases of the disease. HIV dementia was detected in 0.5% of medically asymptomatic individuals, in 1.9% of CDC B individuals, and 3.8% of those with AIDS-defining illness (Fig. 12).

Neuropsychological studies in asymptomatic HIV infection

Many groups of investigators (both in the USA and abroad) have used neuropsychological test batteries in asymptomatic HIV-seropositive individuals to probe for 'early' HIV-associated cognitive deficits. Some general statements may be made. First, while some studies have detected a higher frequency of cross-sectional neuropsychological test abnormalities than in seronegative controls, few have shown that these cognitive impairments are progressive, or are predictive of the later development of MCMD or clinical dementia. The clinical significance of new cognitive symptoms or test impairment in asymptomatic HIV infection is uncertain because the reported neuropsychological abnormalities do not necessarily affect everyday function, may not progress, and, in some individuals, may improve on retesting. In some studies, the abnormalities may reflect the effects of low levels of education, age, premorbid neurological disease, and alcohol and drug use, rather than the consequences of HIV infection. Interpreting data across the different studies is difficult for several reasons, which have been carefully reviewed by Ingraham *et al.* (1990). Different definitions of 'medically asymptomatic' HIV infection are used across studies. For example, it may be anticipated that a medically asymptomatic cohort with a mean CD4 count of 500 has less advanced HIV infection than an asymptomatic cohort with a mean CD4 count of 250. Some of the studies have included individuals with very low or very high educational levels that might skew the results in one direction or another. Relatively few studies have examined the effect of language and ethnicity in detail. The largest, the WHO Neuropsychiatric Study, found global neuropsychological impairment to be increased among asymptomatic seropositive subjects compared to controls in two of six centers (Maj *et al.* 1994). Newman, Harrison, and colleagues (Newman *et al.* 1995) showed an inverse relationship between the size of the study and the likelihood of detecting a difference in neuropsychological performance between asymptomatic seropositives and seronegatives; however, their review did not have the benefit of recent larger studies. The frequency of reported neuropsychological impairment varies widely among different studies. At least one critical factor in this variability is how each study defines 'impairment.' Some have defined outlier status on the basis of standardized scores (e.g. the MACS), while others have included clinical ratings of neuropsychological test batteries (e.g. HNRC). The degree of severity of impairment required to define 'abnormality' clearly influences the reported frequency of neuropsychological impairment. Finally, some studies were organized to screen individuals for a drug trial, in which case there might be a bias on the part of the investigators toward detecting impairment or on the part of the subjects toward impaired performance.

In an extensive literature review, White *et al.* (1995) summarized the findings from neuropsychological studies of asymptomatic HIV-1-infected individuals published between 1987 and 1994. The median rate of neuropsychological impairment was 35% in asymptomatic seropositives (range 0–50%) and 12% (range 0–42%) in seronegative controls. White *et al.* concluded that a major factor in whether impairment was detected by a study had to do with the extensiveness or comprehensiveness of the neuropsychological assessments. Thus, studies with 'large' batteries of tests were more likely to report impairment. White *et al.* interpreted this as suggestive 'that a modest increase in the risk of neuropsychological impairment is probably associated with HIV-1 infection, even in medically asymptomatic subjects'. Therefore, despite considerable research on this topic, a simple omnibus conclusion regarding the absolute risk and significance of mild neurocognitive impairment in asymptomatic HIV-infected individuals is impossible to make at this time. There is evidence that some medically asymptomatic seropositives manifest neuropsychological abnormalities, and a proportion of these individuals may experience 'real life' consequences, such as greater likelihood of being unemployed and reduced life quality, and might even have shorter survival. As Martin (1994) has stated, 'we should always take (cognitive) complaints seriously ... Cognitive complaints should be carefully evaluated with appropriate measures and not summarily dismissed because of the absence of other HIV-related symptoms or a CD4 count that exceeds some predetermined number'.

An important biological question is whether neurological dysfunction: (1) is slowly progressive during HIV infection (Alzheimer's disease model); (2) only develops after some critical level of CNS damage is reached (Parkinson's disease model: parkinsonian symptoms develop only after 80% or more of substantia nigra neurons are lost); (3) is a relapsing–remitting disorder early, with progression in only a subset of cases later on (MS model); or (4) whether HIV mild neurocognitive disorder represents a process separate from the more fulminant HIV dementia (alcohol brain disease model—many alcoholics manifest neurocognitive disorder; Wernicke–Korsakoff syndrome occurs in only a few later-stage alcoholics, and its pathogenesis involves mechanisms that are different from those producing the more common variety of neurocognitive disorder). More sophisticated studies examining neuropsychological, performance, function, and markers of systemic immune function and HIV replication will be needed to address these questions. It appears that, rather than a true state of viral latency existing during the asymptomatic stage of HIV infection, there is a state of continuous viral replication with gradually accumulating viral burden, pulses of viral replication, and progressive CD4 lymphocyte depletion.

Preliminary data from Dal Pan *et al.* (1993) using various measures of peripheral blood viral load did not show any association between deterioration in neuropsychological performance and higher levels of viral load. However, these studies were performed before the availability of potentially more reliable and sensitive polymerase chain reaction (PCR)-based technology. Results from Podraza *et al.* (1994) suggest that 'CD4 levels do not predict the presence or degree of neuropsychological disturbance in the early stages of HIV infection'. They identified poorer neuropsychological performance on measures of psychomotor speed and higher rates of impairment even in asymptomatic individuals with high CD4 counts compared to seronegative subjects. They also identified an association between duration of infection and subtle abnormalities in neuropsychological performance (Bornstein *et al.* 1994). Data from the HNRC series generally confirm these impressions. For example, in an examination of approximately 400 seropositive individuals, Heaton *et al.* (1995) found no significant association between CD4 number and degree of neurocognitive impairment. The same study also confirmed an association between higher CSF (but not serum) β_2-microglobulin (a marker of immune activation) and neuropsychological performance.

Several studies evaluating the relationship between neurocognitive performance and CSF viral load have demonstrated a significant relationship

between CSF HIV RNA levels and the severity of HIV dementia (McArthur *et al.* 1997; Ellis *et al.* 1997). This association suggests that increasing levels of viral replication in the CNS contribute to the development of neurological disease.

However, a recent study in the Northeastern AIDS Dementia Cohort (NEAD Cohort) evaluated the relationship among plasma and CSF HIV RNA levels, immune activation markers, and neurological status in a cohort of individuals with advanced HIV infection who were predominantly on HAART (McArthur *et al.* 2002). In this study, there were no differences in plasma or CSF HIV RNA levels or immune activation markers among individuals with normal neurocognitive performance, MCMD, or HIV dementia, even after adjustments for baseline CD4 count and antiretroviral therapy. These results suggest that, with widespread HAART usage, HIV RNA and immune activation markers may fail to discriminate milder degrees of HIV-associated neurocognitive impairment in advanced HIV infection, and that the degree of CNS HIV infection and immune activation may be substantially attenuated in patients on HAART compared to patients in the pre-HAART era.

In addition to studies of viral dynamics and host immune response, another window on mechanisms underlying neurocognitive disturbance will emerge when carefully conducted ante-mortem/post-mortem observations are completed. Until recently, progress on understanding the neuropathological substrate of MCMD and dementia has been slow. For example, earlier work indicated that HIVE, traditionally defined as myelin pallor, presence of multinucleated giant cells, microglial nodules, etc., was only present in about 50% of cases with an ante-mortem diagnosis of dementia (Glass *et al.* 1993). However, more recent work utilizing more precise ante-mortem neurocognitive characterization suggests that the presence of HIV-associated neurocognitive impairment, even in its milder forms, is actually a very good predictor of HIVE at autopsy. In the Cherner *et al.* (2002) study 18 of 19 subjects with neurocognitive impairments before death were found to have HIVE post-mortem, for a positive predictive value of 95%. Not all persons with autopsy diagnosis of HIVE had neurocognitive abnormality in life, however, indicating either that HIVE in some cases develops as a late agonal event, or that less severe changes associated neuropathologically with HIVE may be present before clinical manifestations become evident.

When measures of HIV burden in the brain are added to diagnostic criteria for HIV encephalitis (Masliah *et al.* 1992), there is an improved association between clinical diagnosis and dementia and detection of HIVE at neuropathology (Wiley and Achim 1994). Furthermore, post-mortem MRI morphometry (which quantitates regional anatomic changes) showed good correspondence between regional burden of HIV and atrophy of cortical and subcortical substructures (Heindel *et al.* 1994). HNRC data indicate a good correspondence between both brain HIV burden and loss of synaptodendritic complexity and ante-mortem neurocognitive performance (Masliah *et al.* 1997; Everall *et al.* 1999). An interesting point in the study (Masliah *et al.* 1997) was its demonstration for the first time that diagnosis of minor cognitive motor disorder was associated with significant loss of dendritic complexity, providing evidence that mild neurocognitive disorder has a neuropathological basis.

Functional impact of neuropsychological impairment/MCMD

A WHO report on the neuropsychiatric aspects of HIV-1 infection concluded that 'There is no evidence for an increase of clinically significant (i.e. functionally limiting) neuropsychiatric abnormalities in CDC Groups II or III HIV seropositive (i.e. asymptomatic) individuals as compared to HIV-1 seronegative controls' (World Health Organization 1988). The WHO Neuropsychiatric AIDS Study found that the frequency of neurological abnormalities and impaired functioning for everyday activities was higher in symptomatic, but not asymptomatic seropositive subjects, compared to controls (Maj *et al.* 1994). Information from the HNRC, reflecting more recent research on the topic, indicates that this conclusion might have been premature. For example, Heaton *et al.* (1994) reviewed the employment status of 289 seropositive individuals. Taking all cases into account, the rate of unemployment in neurocognitively normal seropositives was 9.7%; that among neurocognitively impaired individuals was 26.9%. Although only 37 of the cases in Heaton *et al.*'s study suffered from major AIDS-defining complications, the authors reanalyzed their data excluding any individuals with constitutional symptoms. Among such asymptomatic seropositives, the rate of unemployment among neurocognitively normal persons was 7.9% and that among the neurocognitively impaired was 17.5%, a statistically significant twofold increase (Fig. 13). The same study considered self-report of efficiency of work functioning among those seropositive individuals who were employed. Taking only those who were medically asymptomatic, Heaton *et al.* noted that 30% of asymptomatic employed individuals with neurocognitive impairment reported a subjective decrease in work functioning; only 4% of neurocognitively normal individuals reported such a decrease (Fig. 14).

Table 6 Likelihood of having HIV encephalitis (HIVE) according to neurobehavioral diagnosis (Cherner *et al.* 2002)

	Number (%) of cases where HIVE is		
Diagnosis*	**Present**	**Absent**	***N***
HAD	4 (100)	0	4
MCMD	10 (100)	0	10
NPI	4 (80)	1 (20)	5
Normal	9 (45)	11 (55)	20
Total	27	12	39

* HAD, HIV-associated dementia; MCMD, minor neurocognitive disorder; NPI, asymptomatic neuropsychological impairment.

The above HNRC data were confirmed in a study from the Columbia University HIV group. Albert *et al.* (1995) noted an eightfold increase in work disability among HIV seropositives with impaired neuropsychological performance. The Dana Consortium on Therapy for HIV Dementia and Related Cognitive Disorders (1996) in a cohort of individuals with advanced HIV infection categorized MCMD using an algorithm based on the AAN criteria. They found that functional performance was significantly worse among those with MCMD than among HIV-positive individuals without neuropsychological impairment.

Unemployment is, of course, only a very coarse indicator of functional impact from neurocognitive impairment. For example, a person may remain employed, but may be working at a less demanding and less remunerative occupation. To our knowledge, comprehensive studies of

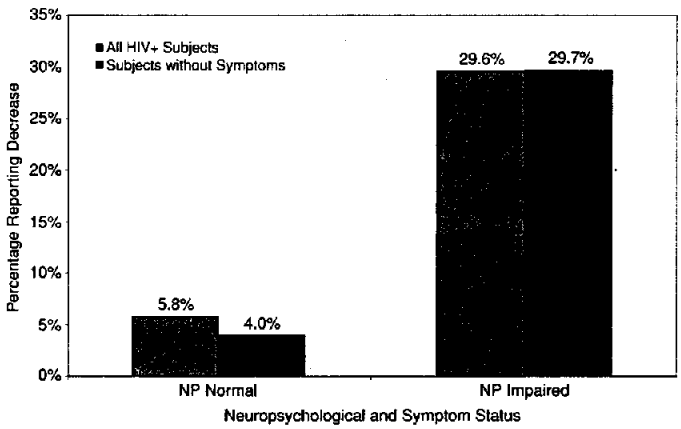


Fig. 13 Unemployment rates for neuropsychologically (NP) normal and (NP) impaired HIV-positive subjects with and without clinical symptoms. (185 subjects were NP normal and 104 were NP impaired; excluding subjects with clinical symptoms, 152 were NP normal and 80 were NP impaired; Heaton *et al.* 1991).

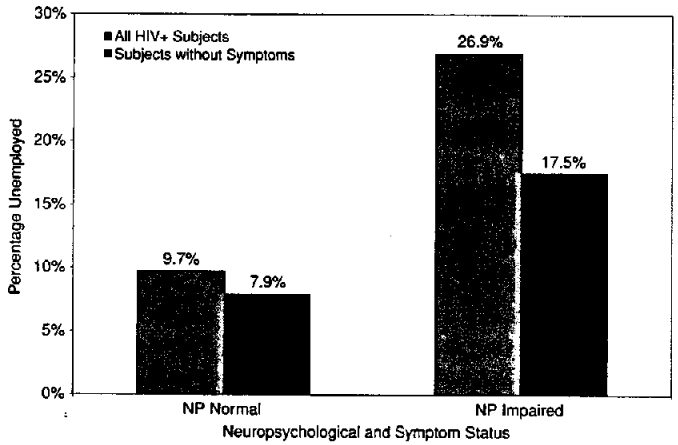
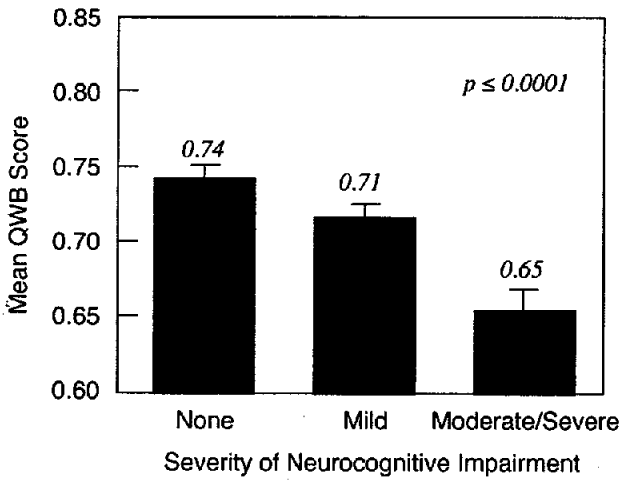


Fig. 14 Percentage of employed HIV-positive subjects with and without clinical symptoms reporting a subjective decrease in vocational functioning (87 subjects were neuropsychologically (NP) normal and 44 were NP impaired; excluding subjects with clinical symptoms, 76 were NP normal and 37 were NP impaired; Heaton *et al.* 1991).



Note: Means are based on baseline visits of 312, 186, and 75 HIV+ subjects respectively. The error bars shown are standard errors of the means.

Fig. 15 Quality of Well-Being (QWB) score as a function of cognitive impairment severity. Note. Means (left to right) are based on baseline visits of 312, 186, and 75 HIV+ subjects, respectively. (From HNRC, unpublished data courtesy of Dr. Robert Kaplan).

actual types of employment and the economic impacts of cognitive impairment have not yet been completed. Results from an initial study at the HNRC examining the relationship between HIV-related neurocognitive impairment and performance on standardized measures of vocational functioning (Heaton *et al.* 1996*a*) suggest that the decrease seen in the impaired group's ability to perform work-related tasks may translate into hundreds, if not thousands, of jobs that these subjects are no longer able to perform adequately. Additionally, as the data on self-reported work performance from Heaton *et al.* (1994) suggest, there is a place for more fine-grained analysis of the actual efficiency of the individual in the workplace. More recent work indicates that HIV cognitive disturbances are related to poorer performance on laboratory-based tasks of activities of daily living, such as medication management and home finances (Heaton *et al.*, in press) as well as on computer-based assessments of driving ability (Marcotte *et al.* 1999).

More generally, there is a lack of research on quality of life implications in regard to neurocognitive disorders associated with HIV. One exception is some recently reported data on health-related quality of life, measured by the quality of well-being (QWB) scale, and neurocognitive impairment. As can be seen from Fig. 15, there is a steady loss of quality-adjusted life-years in relation to increasing degree of neurocognitive impairment.

Additionally, neurocognitive impairment is associated with increased likelihood of mortality. This increased hazard of death applies not only to those who become frankly demented; for instance, Mayeux *et al.* (1993) reported earlier death in those who were neuropsychologically impaired but not demented. Recently, the HNRC group noted that diagnosis of MCMD was associated with higher mortality risk. Also, when adjustments were made for disease indicators, those who were neurocognitively impaired but did not meet criteria for MCMD also had significantly reduced life expectancy (Ellis *et al.* 1996).

In summary, although information on 'real life' implications of HIV-associated neurocognitive impairment remains fragmentary, those data that have been reported indicate that such impairments may be associated with reduced work efficiency, greater likelihood of unemployment, some reduction of health-related life quality, and earlier mortality.

Neurocognitive status over time

The natural course of neurocognitive disorders associated with HIV infection remains poorly understood. While it is generally agreed that those who develop definite dementia are likely to deteriorate further neurocognitively over a period of months, resulting in earlier mortality, the time courses of neuropsychological impairment and MCMD are not well understood.

The results of longitudinal neuropsychological investigations from several large cohort studies, including the MACS, indicate no deterioration in neuropsychological performance in medically asymptomatic seropositive individuals over a period of up to 36 months (Table 7; Selnes *et al.* 1990, 1992; Gastaut *et al.* 1990; Saykin *et al.* 1991; Helmstaedter *et al.* 1992; Robertson *et al.* 1992; Whitt *et al.* 1993; Karlsen *et al.* 1993).

In a longitudinal study over 7 years performed within the MACS (Selnes *et al.* 1995) changes in cognitive function were examined before and after development of clinical AIDS or a CD4 count less than 200/mm³. The study population included participants either with clinical AIDS ($N = 52$) or who had at least one measurement of CD4 count less than 200/mm³ ($N = 57$) and who had at least four separate neuropsychological evaluations—two or more before and two or more after the diagnosis of AIDS. A group of subjects who developed HIV dementia or other CNS diseases ($N = 29$) was also included for comparison. The neuropsychological test battery included measures of attention, memory, constructional abilities, and psychomotor speed. Before AIDS, the CNS disease group showed significant decline only on measures of psychomotor speed. For all other measures, there was no evidence of decline in performance before AIDS in the other groups. The group with clinical AIDS showed significant decline on psychomotor speed after the development of AIDS, but no decline on other cognitive measures.

Table 7 Longitudinal neuropsychological studies in asymptomatic HIV infection

Study (year)	Cohort	Follow-up (months)	Cases/ controls
Selnes *et al.* (1990)	Homosexuals	18	238/170
Saykin *et al.* (1991)	Homosexuals	18	21/21
Gastaut *et al.*(1990)	Homosexuals	6–18	50/8
Selnes *et al.*(1992)	Injecting drug users	12	37/69
Helmstaedter *et al.*(1992)	Hemophiliacs	20	62/–
Whitt *et al.* (1993)	Hemophiliacs	24	25/25
Robertson *et al.*(1992)	Homosexuals	24	118/0
Karlsen *et al.*(1993)	Homosexuals	24	36/–
Selnes *et al.*(1992)	Injecting drug users	37	19/40

The group with CD4 count less than 200 did not show significant decline on any of the cognitive measures after the development of AIDS (defined by CD4 count less than 200). Sensory neuropathy was associated with a significant decline in performance on measures of psychomotor speed. Antiretroviral therapy was not associated with any measurable changes in neuropsychological performance.

In the same cohort, Sacktor *et al.* (1996) showed that transient changes in neuropsychological function were relatively frequent. For example, using a measure of cognitive decline based on an individual's performance on Trail Making and Symbol Digit tests, a transient (or 'nonsustained') decline of 2 or more standard deviations was seen in 62% of HIV-seropositive individuals. Using a more conservative criterion for decline that required that the individual performance decline be sustained for two or more visits, only 15% of the group showed sustained decline. Those who had identifiable sustained decline had a fivefold higher risk of developing dementia, threefold higher risk of developing AIDS, and twofold higher risk of death.

Some studies have concluded that neurocognitive worsening does occur. Newman, Harrison, and colleagues' (1995) review identified four longitudinal studies that noted neurocognitive decline during follow-up periods of several years. A detailed analysis based on 2 years of comprehensive neuropsychological assessment of the HNRC series indicates that the likelihood of neuropsychological worsening is associated both with degree of neurocognitive impairment and HIV disease status. From Table 8 it will be seen that the likelihood of neuropsychological deterioration increases with stage of disease from 26% after 2 years in CDC stage A to 67% in CDC stage C.

In the HNRC series, the 1 year incidence of progression to MCMD was 2% in neurocognitively normal HIV$^+$ participants ($N = 169$) and 11% in those who were neurocognitively impaired ($N = 66$; Fig. 16). In addition, of those who reached criteria for a diagnosis of minor cognitive motor disorder 3% deteriorated to HAD. The data in Fig. 16 also indicate that substantial numbers of 'mildly impaired' persons may actually improve. This underscores the importance of longitudinal follow-up before making an assumption that neurocognitive impairment is permanent.

Why some people improve over time remains an open question. While the most obvious answer may be 'practice effect' and other sources of error in neuropsychological measurement, another possibility is that the mildest form of brain disorder associated with HIV might actually have a fluctuating course, somewhat akin to what is found in demyelinating disorders. It is clear now that, even during the lengthy asymptomatic phase of HIV infection, bursts of viral replication occur and there is no true viral latency. These 'viral bursts' might be accompanied by further brain seeding influencing neuropsychological performance. This would help explain an interesting finding by Sacktor *et al.* (1996) presented above. These authors noted a significant association between 'sustained' neurocognitive decline and the likelihood of developing dementia in the future. However,

Table 8 Percentage of subjects who evidenced neuropsychological decline (based upon clinical ratings; HNRC unpublished data, courtesy Dr Robert K. Heaton)*

	Percentage (number in total sample for each cell) evidencing neuropsychological decline	
Patients' status	**1 year**	**2 years**
HIV negative	3.6 (83)	10.1 (69)
CDC A†	16.8 (161)	25.7 (105)
CDC B†	21.0 (62)	53.5 (43)
CDC C†	34.5 (29)	66.7 (9)

* The analysis includes only those subjects that remained within the same CDC classification during the indicated time period.

† CDC A, Asymptomatic HIV infection; CDC B, symptomatic HIV infection, not A or C; CDC C, AIDS indicator conditions. Based on US centers for Disease Control (CDC) 1993 Classification system (ref CDC, 1992).

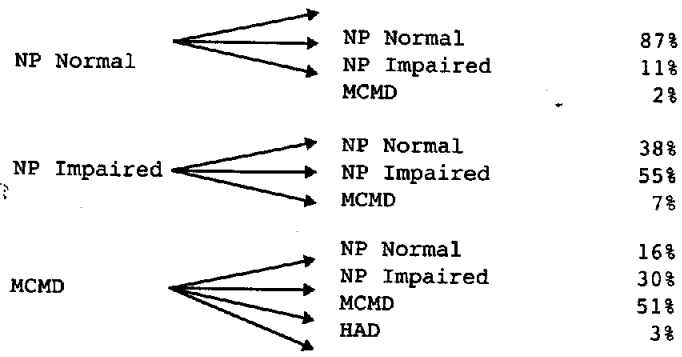


Fig. 16 One-year transitions in neurocognitive status, based on initial classification of neuropsychologically (NP) normal, NP impaired, or MCMD. (From HNRC, unpublished data.)

there was also a significant, though not as powerful, association between 'nonsustained' neurocognitive worsening and subsequent diagnosis of dementia. It seems possible that nonsustained decline is indicative of a relapsing-remitting process in the CNS that only in some cases becomes progressive.

In the HNRC series a follow-up of up to 8 years of a group of 130 HIV$^+$ persons judged to be neuropsychologically normal at the beginning of the study, 12% evidenced a relapsing remitting neurocognitive pattern. Of importance, despite relatively mild impairment (when present), those with such fluctuating courses had much higher mortality than persons who remained neurocognitively normal (Fig. 17). Thus, even non-sustained cognitive impairment may suggest presence of an underlying process predictive of higher mortality.

Possible risk factors for neurocognitive impairment

Substance use

Abuse of alcohol and other substances can be associated with neurocognitive impairment (Grant 1987; Grant *et al.* 1978; Reed and Grant 1990; Carlin and O'Malley 1996; Rourke and Loberg 1996). At the same time, the risk of becoming HIV-infected and the abuse of substances are heavily intertwined. Injection drug use may account for up to a quarter of cases of HIV transmission; additionally a subset of those who are not injection drug users may be heavy users of alcohol, cocaine, and other substances. Intoxication with these substances or the need to purchase them can create circumstances that increase likelihood of risky sexual behavior linked to HIV transmission. Given these facts, it is reasonable to ask whether the neurocognitive impairment seen in some seropositive individuals is explained by alcohol or other substance abuse. The considerations in evaluating neurocognitive results in HIV$^+$ substance abusers have been reviewed by Stern (1994). He noted that, in addition to chemical class of substance, one needs to consider abstinence status (i.e. currently using, short-term abstainer, long-term abstainer), pharmacological therapy (e.g. methadone), and general factors associated with substance abuse. The latter include likelihood of educational disadvantage, minority group membership, and possibility of illnesses and injuries (e.g. head injuries) that may be associated with the drug-abusing lifestyle.

Despite these considerations, it is interesting that there is little concrete information at this time to indicate that history of substance use either accounts for, or interacts with HIV serostatus to result in neurocognitive impairment. For example, detailed analysis from the HNRC 500 series, which focused on a group of men who were not injection drug users but some of whom had substantial alcohol and drug histories, did not reveal any independent contribution of substances to neurocognitive impairment (Heaton *et al.* 1995). White *et al.* (1995) compared the results of seven studies based primarily on intravenous drug users (IVDUs), with those of 34 studies that utilized sexual transmission risk groups. White *et al.* con-

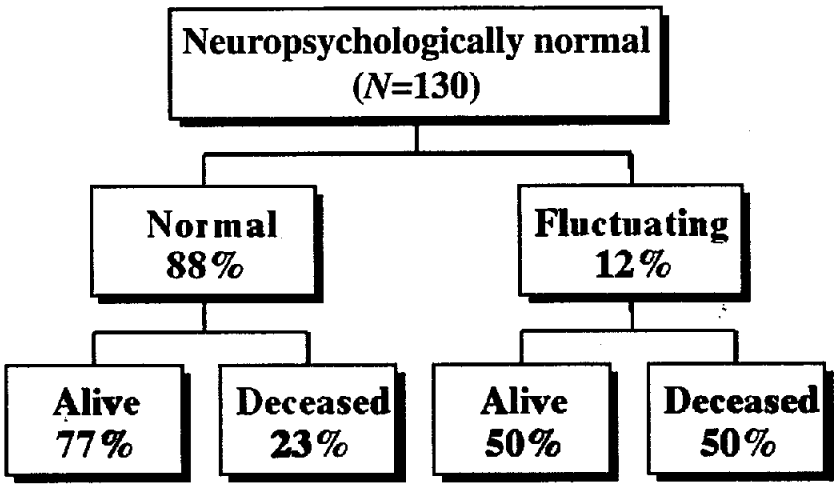


Fig. 17 Two to eight year mortality in persons with normal versus fluctuating neuropsychological status.

cluded that the likelihood of detecting impairment was no higher in the IVDU groups than in the sexual transmission group. The review of Stern (1994) reached a similar conclusion, though in this case the author noted one study that suggested there might be an interaction between prior history of head injury and serostatus in detecting neuropsychological test abnormality.

In a study of 102 HIV seropositive intravenous drug users (AIDS-free HIVA seropositive individuals participating in an ongoing cohort study in Baltimore), age and education were the most important predictors of neuropsychological test performance. The frequency of reported use of marijuana, heroin, cocaine, barbiturates, and alcohol was not statistically associated with performance on the tests. This suggests that chronic substance abuse may not, in fact, be a major confounder in interpretation of the neuropsychological performance of chronic substance abusers (Concha *et al.* 1992). This conclusion is in contrast to an Italian study that suggested that cognitive function was affected by chronic and current use of toxic substances (Grassi *et al.* 1995). The effect appeared to be reversible when drug use was discontinued.

Some of the most recent work has focused on the problem of methamphetamine abuse in HIV-infected persons. Besides the fact that abuse of this drug is common and may co-occur with other risk behaviors (e.g. unprotected anal intercourse in men who have sex with men), there is good evidence that methamphetamine is neurotoxic (Davidson *et al.* 2001). Furthermore some of the mechanisms of injury (excitotoxicity, apoptosis) and neural circuitry targets (e.g. basal ganglion and frontostriatal connections) may share commonalities with putative mechanisms and targets of HIV injury (e.g. see Langford *et al*, submitted). Data from HNRC indicate that there may be additive neurocognitive insult in HIV$^+$ persons who have histories of methamphetamine dependence. Thus, Rippeth *et al.* (2004) report an almost 50% increase in rate of neuropsychological impairments of various degrees in HIV$^+$ methamphetamine users versus those with only one risk factor (Fig. 18).

The effects of risk behavior group

White's comprehensive review compared sexual contact, intravenous drug use, and blood transfusion. Although the number of studies and sample size of individual studies from transfusion recipients were relatively small, there is no evidence at this point to conclude that there are any differences among risk behavior groups. In one study comparing two cohorts, one the MACS (homosexual men) and the other the AIDS Link to Intravenous Experience (ALIVE) cohort (IVDUs), Concha *et al.* (1997) found that risk behavior did not significantly affect neuropsychological performance.

Disease progression

HIV disease progression tends to be associated with increased likelihood of developing neurocognitive impairment. Table 8, summarizing experience from the HNRC cohort, shows that the likelihood of cognitive deterioration is highest among those with AIDS-defining conditions. Marder *et al.* (1995) reported that neurological signs (specifically extrapyramidal and release signs) were more likely to develop over time in HIV seropositive individuals with moderately reduced CD4 counts (baseline CD4 count = 407) than seronegatives. These neurological signs appeared to be markers for cog-

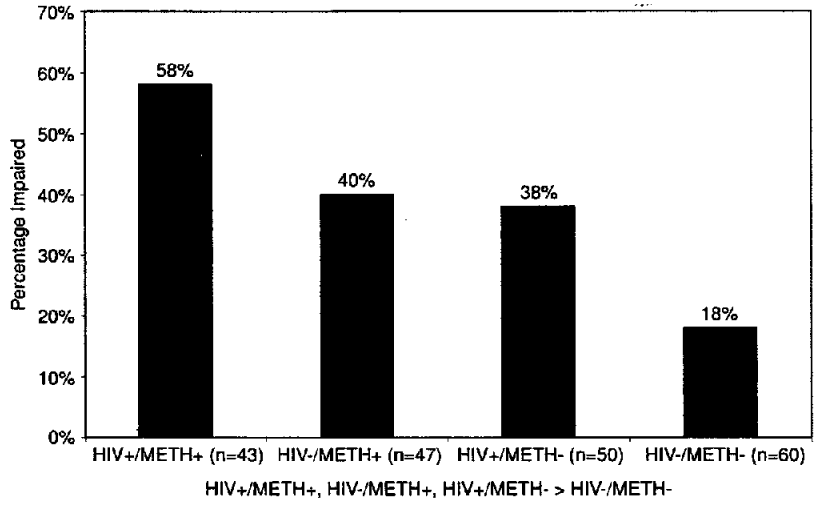


Fig. 18 Global neuropsychological impairment in relation to HIV and methamphetamine (METH) risk status (Rippeth *et al.* 2004).

nitive impairment. In the Selnes series, subjects who developed clinical AIDS evidenced a mild decline in fine motor skills, which might have been related to the development of subclinical or clinical sensory neuropathy or to cerebral involvement (Selnes *et al.* 1990). There were no significant changes in other cognitive domains. Results of a prospective study of patients with AIDS-related complex (ARC) followed for 6 months to 2 years are consistent with the findings from the Selnes study (Dunbar *et al.* 1992). The performance of 15 ARC (equivalent to CDC stage B) patients who progressed to AIDS was compared to that of a group of ARC patients who did not develop AIDS. There was a trend toward greater impairment among the progressers; however, there were few statistically significant differences between the two groups, and the area in which both progressers (to AIDS) and non-progressers showed some degree of impairment was primarily motor function. Another study examined longitudinal changes in cognition in a group of methadone-maintained patients and found significant decline in psychomotor speed over a 4-year period of follow-up (Silberstein *et al.* 1993). Only 12 patients had symptomatic HIV disease, however, limiting the interpretation of this study.

Age and education

Age and education exert significant independent effects on the results of neuropsychological testing and cognitive screening examinations, such as the Mini-Mental State Examination (MMSE). The magnitude of these effects depends on the demands of the task in question. Tests that require little cognitive input (such as simple motor tasks) are sensitive to age effects, but not to education, tasks that require access to information or skills acquired in the past (e.g. tests of semantic memory) are highly sensitive to education, but less so to aging, and many tasks show significant influences from both (e.g. episodic memory tests, tests of novel problem-solving, complex perceptual motor performance). The likelihood that some particular test will be influenced by age or education has been reviewed in detail by Heaton *et al.* (1986, 1996*b*).

Because of the very substantial effect of age and education on many neuropsychological test measures, it is critical that interpretation of these data takes age and education into account. From the standpoint of research designs, it is evident that experimental and control groups need to be closely matched on age and education; furthermore, test selection must take into account floor and ceiling effects. Thus, 'easy' tests such as serial 7s or the MMSE will not detect differences between controls and seropositive individuals who have MCMD if the groups are composed primarily of college graduates; on the other hand, administration of a relatively 'hard' test such as Paced Auditory Serial Addition to groups of adults with ninth grade education may not detect changes that are actually present in the seropositive group because even controls will perform relatively poorly. This means that, particularly for testing that may be used for clinical diagnosis, the neuropsychological battery used must contain tests for which norms have been developed based on age and education. Large databases have been reported by Heaton *et al.* (1991), Selnes *et al.* (1991*a*), and Concha *et al.* (1995).

In evaluating the results of testing in seropositive individuals, the effects of age and education need to be considered from two distinct vantage points. First, one must be assured that whatever test abnormalities are noted do not simply reflect the application of inappropriate norms to the population in question. Second, one must consider whether age and/or education are interacting with serostatus to reveal a cognitive impairment.

The results from Satz (1993) illustrate this point. This author reanalyzed MACS data reported earlier by Miller *et al.* (1990). In Miller *et al.*'s study, it was noted that asymptomatic seropositive men performed identically to seronegative controls on the MACS test battery. The rate of impairment in both groups was comparable, approximately 15%. However, when Satz split the sample into those with less than 12 years of education and those who were better educated, the rate of impairment among the worst educated asymptomatics rose to 38%, a rate rather similar to that reported by Grant *et al.* (1987) and Heaton *et al.* (1995). Satz suggested that the differences in findings between better and less educated samples might reflect the operation of 'cerebral reserve', i.e. less education might be reflective of worse 'cerebral endowment', allowing a disease process to reveal impairment earlier. While such an explanation is plausible, the fact that Satz did not observe a statistically significant interaction between serostatus and age makes this explanation less likely. An alternative possibility is that well-educated seropositives, even those with subtle CNS disturbance, found the tests too easy to reveal their impairment.

However, as HIV seropositive individuals are living longer as a result of HAART, recent data are suggesting an increase in cognitive dysfunction among older HIV seropositive individuals. In one series, 87% of older AIDS patients were found to have abnormal neurocognitive testing results when compared to seronegative controls (Hinkin *et al.* 2001). In another series, older HIV seropositive adults were found to have a significantly higher number of minor cognitive/motor disorder symptoms when compared to younger individuals (Goodkin *et al.* 2001). A longitudinal cohort to evaluate aging and HIV-associated neurocognitive function has recently begun at the University of Hawaii. Preliminary data from this new cohort suggest that older HIV seropositive individuals (defined as age 50 or greater) have an increased frequency of HIV dementia compared to younger HIV seropositive individuals (defined as age 20–39), and a pattern of increasing degree of dementia severity was seen in the older cohort compared to the younger cohort (Valcour *et al.* 2002).

Further studies are required to determine whether aging increases a person's vulnerability to an HIV-associated neurocognitive disorder.

Fatigue and constitutional symptoms

Since many HIV-positive persons will experience fatigue and various constitutional symptoms, especially as their disease progresses, it may be reasonable to ask whether increasing rates of neuropsychological impairment reflect lack of motivation due to malaise or fatigue. Heaton *et al.* (1995) attempted to address this issue in a subset of the HNRC 500 series. Subjects were divided into CDC groups, and then subdivided according to the presence or absence of several symptoms commonly associated with HIV. As Table 9 reveals, there was no systematic association between presence of constitutional symptoms and neuropsychological impairment within groups of subjects stratified by CDC classification.

Though one study cannot be considered as conclusive, given the fact that the HNRC 500 participants were examined with 8 hours of neuropsychological tests, the lack of an association suggests that constitutional factors do not play a major role in detecting impairment. In a separate study, Hasenauer *et al.* (1996) examined performance on the Grooved Pegboard and also found no significant fatigue effects.

Mood

Another theoretical confound in neuropsychological assessment of HIV-positive individuals may be the presence of mood disturbances, especially major depression. Rates of major depression are elevated in HIV^+ persons (as they are also in seronegative individuals who are at risk for HIV infection; Atkinson *et al.* 1988). A few reports have suggested that there is correlation between neuropsychological findings and mood (Kocsis *et al.* 1989; Temoshok *et al.* 1989). However, the preponderance of studies has not established such an association (Atkinson *et al.* 1988; Heinrichs 1987; Poutiainen *et al.* 1988; Fitzgibbon *et al.* 1989; Grunberger *et al.* 1989; Kovner *et al.* 1989; Hinkin *et al.* 1992; Grant *et al.* 1993).

Data from the HNRC 500 series indicated that persons who had neuropsychological impairment were slightly more likely to experience major depression than unimpaired subjects (14.1% versus 6.0%, $p = 0.009$; Heaton *et al.* 1995). There were no significant associations with measures of anxiety in this study. However, when subjects with major depression and anxiety were excluded from the HNRC analysis, the rates of neuropsychological impairment in those individuals with no mood disorder were about the same as for the whole sample, indicating that mood disturbance did not explain the disproportionate rise in impairment among seropositives. From the various studies reported, it seems reasonable to conclude that both mood disturbance and neurocognitive impairment occur more frequently in seropositive individuals; however, these disorders appear to evolve independently.

Summary

Neuropsychological and neuropsychiatric involvement are common in HIV infection, manifest either as minor cognitive/motor disorder or frank dementia. Current estimates are that 10–20% of individuals with AIDS will develop frank dementia and perhaps another 20–30% will develop lesser degrees of cognitive or motor dysfunction. Neurocognitive impairment is detected in some medically asymptomatic HIV-infected persons; however, only a minority have cognitive and functional impairment sufficient to make the diagnosis of MCMD. Neuropsychological abnormalities in HIV neurocognitive disorders reflect predominantly subcortical involvement, at least initially, with prominent psychomotor slowing, memory loss (i.e. learning difficulty), and difficulties with speeded information processing, mental flexibility, and motor control. The development of sensitive and reliable neuropsychological test batteries now means that evolving neurocognitive impairment can be detected at a relatively early stage in individuals at risk for HIV dementia. Neurocognitive impairments detected in this manner predict presence of HIVE at autopsy, and may be related to injury of the synaptodendritic apparatus engendered by HIV products, host immune responses, or both. Detection of HIV neurocognitive impairments may permit more timely initiation of neurologically directed therapies before irreversible neuronal damage and death have occurred. Although the incidence of HIV dementia has stabilized in recent years, probably as a result of more widespread antiretroviral use, the concern exists that, as survival with profound immunodeficiency is extended, so the number of individuals worldwide with HIV dementia will increase, posing enormous burdens on neurological services, other providers, and caregivers.

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