The Neurology of AIDS

Second edition

Edited by
Howard E. Gendelman
Igor Grant
Ian Paul Everall
Stuart A. Lipton
and Susan Swindells

OXFORD
UNIVERSITY PRESS
2005

7.2 HIV neurocognitive disorders

Igor Grant, Ned Sacktor, and Justin McArthur

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).

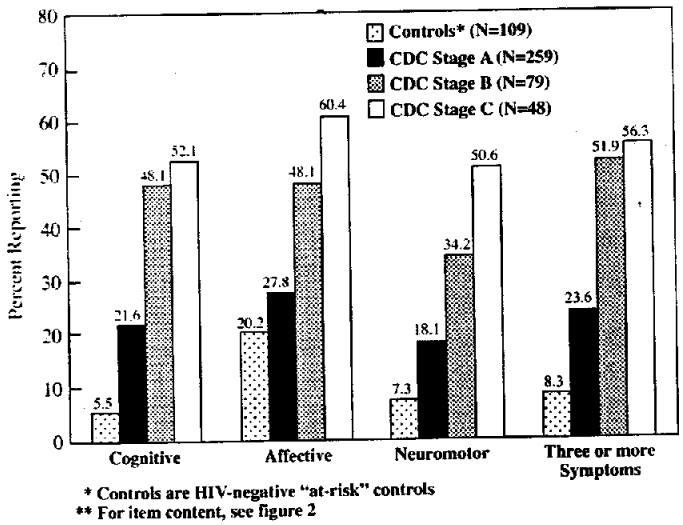

Fig. 1 Prevalence of cognitive, affective, and neuromotor symptoms at different stages of HIV disease. Controls are HIV-negative 'at risk' controls. For item content, see Fig. 2. (Adapted from Mehta *et al.* (1996).)

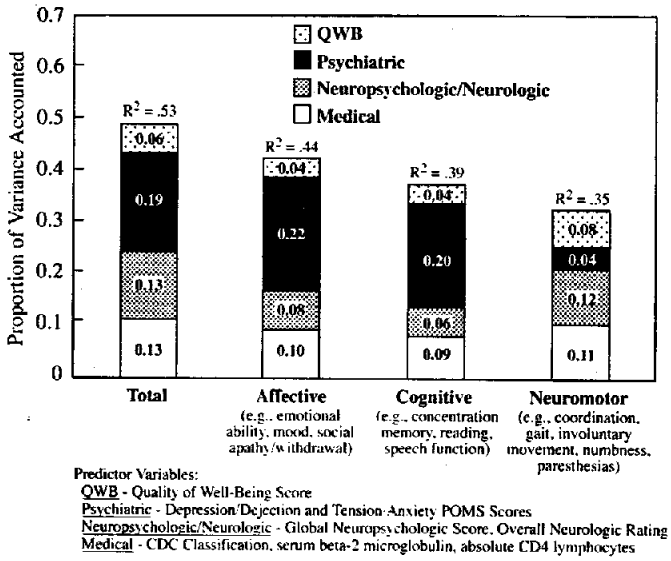

Fig. 2 Prediction of self-reported neurobehavioral symptoms. The predictor variables are as follows. QWB: Quality of Well-being Score; Psychiatric: Depression/Dejection and Tension/Anxiety POMS scores; Neuropsychological/Neurological: Global Neuropsychological Score, Overall Neurological Rating; Medical: 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.

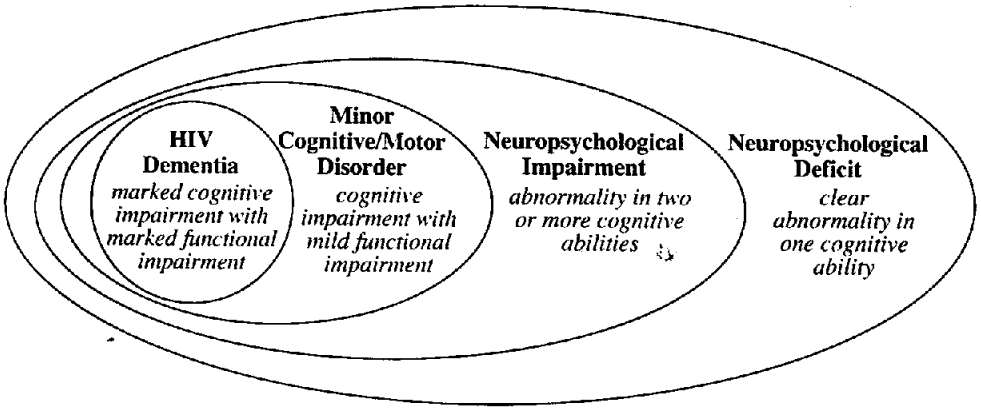

Fig. 3 Schematic representation of the relationship of neuropsychological deficits, impairment, minor cognitive/motor disorder, and dementia in HIV infection.

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)

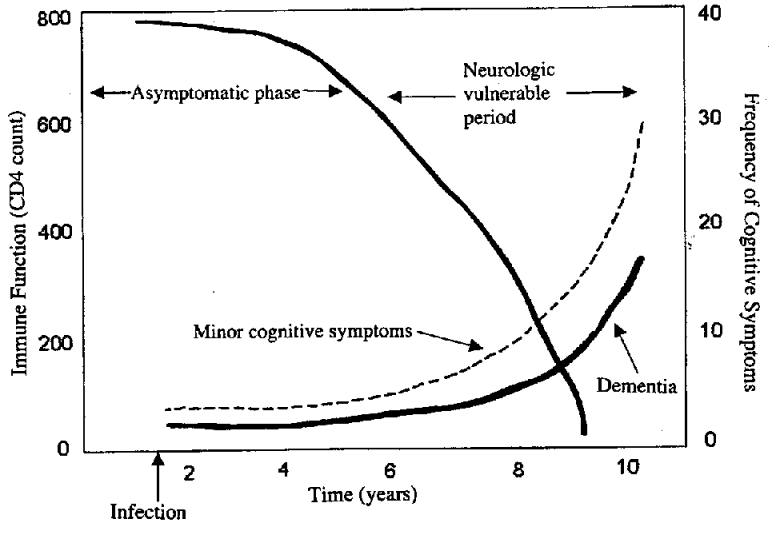

Fig. 4 Approximate frequencies of HIV-associated dementia complex and cognitive impairment and timing relative to systemic disease. Note 'vulnerable' period after AIDS (McArthur *et al.* 1997).

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

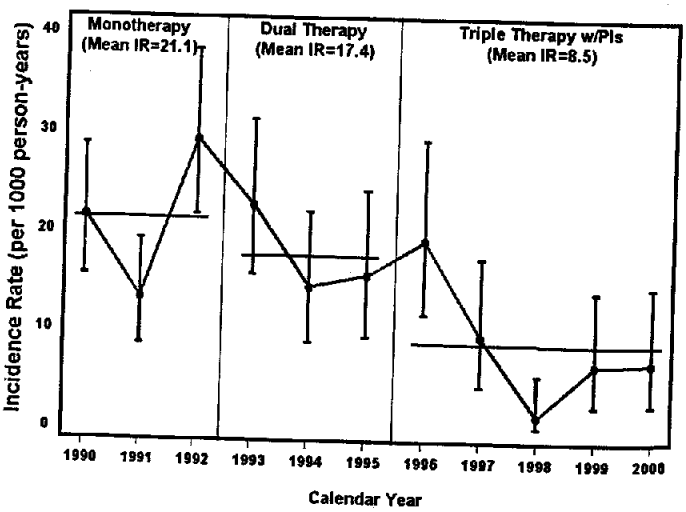

Fig. 5 Incidence of dementia during three epochs of antiretroviral treatment. IR, Incidence rate; PIs, protease inhibitors.

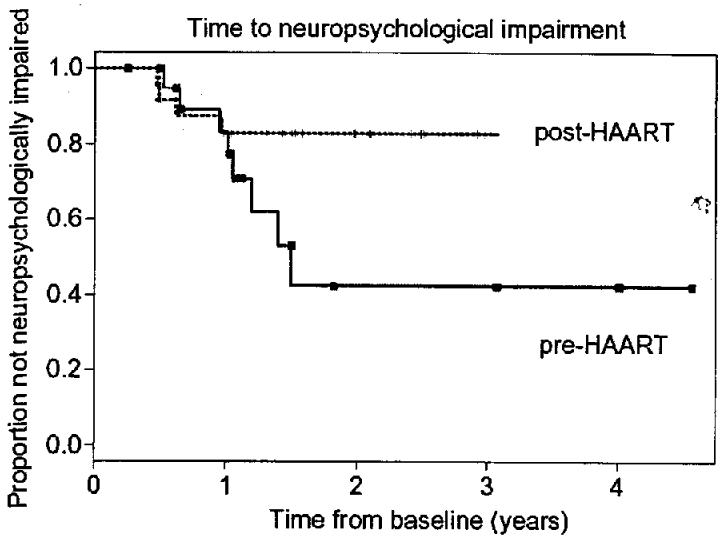

Fig. 6 Kaplan–Meier survival estimate for distribution of time to neurocognitive impairment (in years) on or before 31 December 1995 (pre-HAART) versus on or after 1 January 1996 (post-HAART). Tick marks on curves represent censored observations. HAART, Highly active antiretroviral therapy (Deutsch *et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

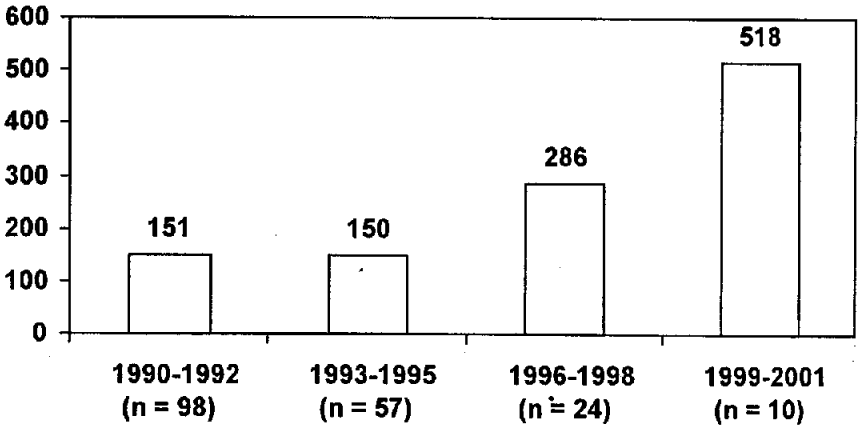

Fig. 7 Dementia cases have less immunosuppression with modern antiretroviral treatments.

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.

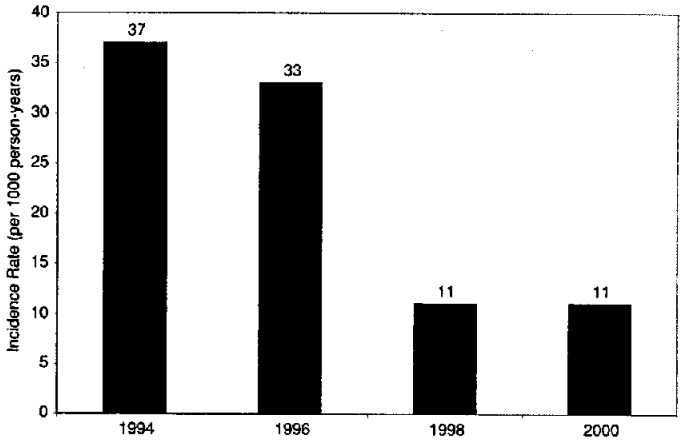

Fig. 8 Decline in HIV dementia incidence since HAART initiation.

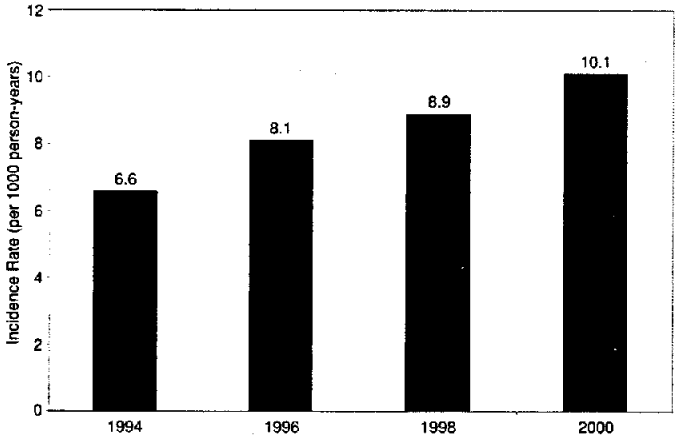

Fig. 9 HIV dementia prevalence may be rising as those on HAART survive longer.

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

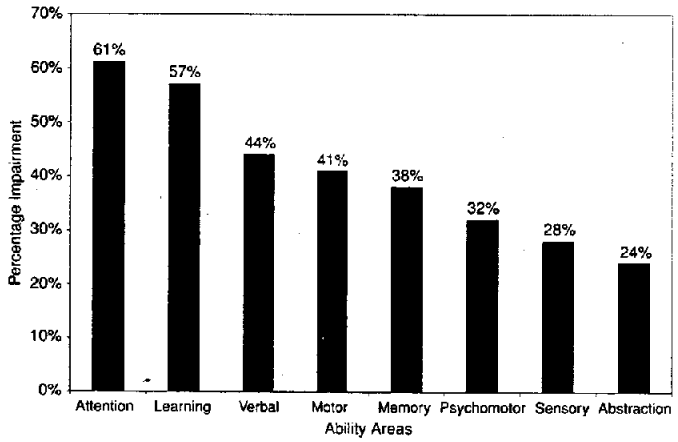

Fig. 10 Prevalence of deficits within each ability area for HIV-positive subjects rated as being neuropsychologically impaired, indicating a 'subcortical' pattern. (Modified from Heaton *et al.* (1995).)