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Human immunodeficiency virus–associated dementia: An evolving disease

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This article reviews the changing epidemiology of HIV-associated dementia, current concepts of the different patterns of dementia under the influence of highly active antiretroviral therapy, and reviews therapeutic aspects. *Journal of NeuroVirology* (2003) **9,** 205–221.

Keywords: brain; cerebrospinal fluid; cognitive impairment; dementia; HIV-1

Introduction

Since the initial descriptions of cases of a previously rare disease, *Pneumocystis carinii* pneumonia, among homosexual men in Los Angeles in 1981, acquired immunodeficiency syndrome (AIDS) has expanded to become a global pandemic, threatening not only the health of millions, but eroding the socioeconomic stability of many countries, particularly in sub-Saharan Africa. In the past two decades, almost 22 million people worldwide have died of AIDS, and 1 in every 200 Americans is infected with human immunodeficiency virus type 1 (HIV-1). (UNAIDS, 2000). Our concept of the biology of HIV infection has changed radically from a model of virological latency to one of continuous active HIV replication throughout infection (Ho *et al*, 1995). The introduction of highly active antiretroviral therapy (HAART) regimes in the mid-1990s has resulted in a 50% decline in AIDS death rate, decreased maternal-infant transmission rates, reductions in incidence rates of opportunistic infections, and a 40% to 50% decrease in the incidence of HIV-associated dementia (Brodt *et al*, 1997; Sacktor *et al*, 2001a). Nonetheless, AIDS-associated neurological diseases including HIV-associated dementia (HIV-D) and sensory neuropathies (HIV-SN) continue to be major causes of morbidity and mortality. This suggests that HAART does not provide complete protection against neurological damage in HIV/AIDS (Bouwman *et al*, 1998). The blood-brain barrier prevents the central nervous system (CNS) penetration of antiretroviral agents, and the brain may serve as a sanctuary for HIV, with persistent HIV replication within perivascular macrophages, the principal target in the CNS. These cells may allow reseeding of the periphery, making the CNS both a sanctuary *and* a reservoir. This review will summarize clinically relevant aspects of the 'changing face' of HIV-D, and identify critical questions for further research. A second review article in this issue (Albright *et al*, p. 222–227) will survey the current concepts of pathology and pathogenesis.

Epidemiology of HIV infection and AIDS

The World Health Organization (WHO) estimates that worldwide there have been 22 million deaths from AIDS and that the number of infected people reached 60 million in 2000 (Joint United Nations Program on HIV/AIDS, 2001). Sixteen thousand new infections occur each day and the HIV/AIDS epidemic is growing most rapidly in China, India, Eastern Europe, and sub-Saharan Africa. The results of clinical trials of combination potent antiretrovirals, and the subsequent widespread introduction of HAART have produced a new era of optimism for HIV-infected people, and their providers (Shapiro *et al*, 1999). A 60% fall in death rates was seen in the USA from 1996 to 1998, attributable to the use of combination antiretrovirals (Palella *et al*, 1998). However, for the majority

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of HIV-infected persons worldwide, these expensive treatments remain out of reach and only financial support from developed countries can enable the distribution of antiretroviral treatment.

Neurological manifestations of HIV infection

Overview of HIV neurological manifestations

Most neurological illnesses occur during the later stages of HIV disease, developing concurrent with immunodeficiency (Johnson *et al*, 1988). HIV affects the nervous system in two ways: *directly*, producing distinct neurological syndromes, or *indirectly*, by causing immunodeficiency with resultant susceptibility to opportunistic infections and neoplasms. The common reactivated or opportunistic processes are listed in Table 1. Effective treatments have been developed for several of these processes, and primary prophylaxis is particularly useful for cerebral toxoplasmosis (Johnson *et al*, 1988). Incidence rates began to fall in the early 1990s (Brodt *et al*, 1997) and have fallen further since the introduction of HAART because of immune restoration in HAART-treated patients (Sacktor *et al*, 2001a). Other reviews comprehensively cover the diagnosis and management of these opportunistic disorders (Marra, 1999).

HIV-D constitutes about 5% of new AIDS-defining illnesses in the USA. Although the *incidence* has fallen under the influence of HAART, the cumulative *prevalence* has actually risen with the improved survival in AIDS (Figure 1). HIV-associated sensory neuropathies have shown rising rates of both incidence and prevalence rates, and currently comprise the commonest neurological conditions.

Biology of HIV infection relevant for CNS disease

The brain may serve as a sanctuary for unchecked HIV replication, both because the blood-brain barrier may prevent CNS penetration of antiretrovirals, and also because perivascular macrophages, one of the principal targets within the CNS, may serve as long-lived sequestered sites for HIV. Within the brain, the majority of virus is unintegrated, and it is unknown whether it can give rise to infectious particles (Pang *et al*, 1990; Shaw *et al*, 1985). Follicular dendritic cells may serve as another potential reservoir, and have been demonstrated to sequester infectious virions for up to 9 months (Burton *et al*, 2002). After acute infection with HIV, the immune system is stimulated to control the virus and a lower level of HIV viremia is established following the initial peak viremia. The level of this viral "set-point" appears to be an important predictor of both systemic and neurological disease progression (Childs *et al*, 1999). Interestingly, this is not the case for some simian immunodeficiency virus (SIV) models of encephalitis (Zink *et al*, 1999). HIV-specific immune responses, both humoral and cellular (cytotoxic T cells), develop to a variable degree. The major direct effect of HIV infection on the immune system is the profound and progressive loss of CD4 lymphocytes. This leads to impaired cellular immunity, and the development of reactivated latent infections or infections with organisms that are normally not pathogenic ("opportunistic"). In addition, the loss of the regulatory CD4 subset appears to lead to a dysregulation of macrophages, with the overproduction of a variety of proinflammatory cytokines and chemokines (Griffin, 1997).

HIV can enter the nervous system early after infection, but productive infection is rarely detectable before immunosuppression has developed. Based upon phylogenetic analyses of HIV gp160, the route of CNS infection appears to primarily involve infected monocytes (Liu *et al*, 2000). As HIV/AIDS progresses, the proportion of circulating activated monocytes increases (Gartner *et al*, 2000; Pulliam *et al*, 1997), leading to more trafficking of these cells into the CNS. The peripheral activation of circulating monocytes is probably a critical step that permits their ingress into the brain (Gartner *et al*, 2000). The brains of asymptomatic HIV-seropositive individuals contain no, or very little, HIV DNA (Bell *et al*, 1993; Donaldson *et al*, 1994), and even when DNA is

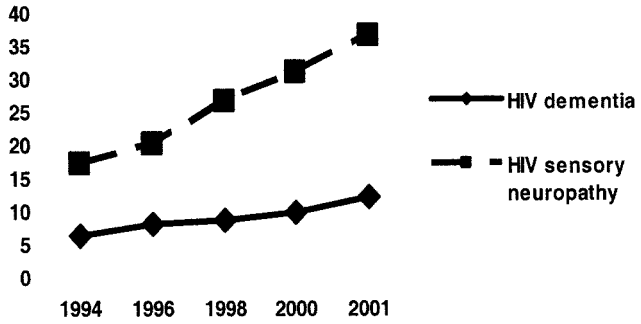

Figure 1 Rising *prevalence* of HIV-associated neurological disorders in JHU HIV Clinic (despite HAART effect on HIV-D incidence rates).

Table 1 Neurological complications of HIV-1 infection

HIV-1–associated
HIV-1 encephalopathy
HIV-associated cognitive-motor disorder
HIV-1 meningitis
Vacuolar myelopathy
Peripheral neuropathies
Distal sensory polyneuropathy
Antiretroviral toxic neuropathy
Ascending neuromuscular syndrome
Mononeuritis multiplex
Inflammatory demyelinating polyneuropathies
HIV-associated polymyositis
Opportunistic infections
Cerebral toxoplasmosis
Tuberculosis
Cryptococcal meningitis
Cytomegalovirus retinitis/encephalitis/polyradiculitis
Progressive multifocal leukoencaphalopathy
Other viral/fungal/bacterial/protozoal CNS infections
Neoplasms
Primary CNS lymphoma
Metastatic systemic lymphoma
Metastatic Kaposi sarcoma

present, there is little evidence of expression of HIV structural proteins (Kibayashi *et al*, 1996; Sinclair *et al*, 1992, 1994; Sinclair and Scaravilli, 1992). We believe that reseeding of the CNS by activated monocytes, with the establishment of productive CNS infection, only occurs later in HIV disease, after the development of immunosuppression (Gartner and Liu, 2002). Macrophage activation within the CNS and peripheral nervous system (PNS) is likely to be a critical factor for the development of both HIV-D and sensory neuropathies, as is discussed below (Gartner, 2000; Keswani *et al*, 2002; Tyor *et al*, 1995). The consequences of exposure to drugs of abuse in combination with CNS HIV infection may be synergistic with regard to pathogenesis. For example, the finding that HIV-seropositive injection drug users (IDUs) show more severe neuronal loss and atrophic neurons in the substantia nigra, compared non-IDU's (Reyes *et al*, 1991) adds to the concern that dopaminergic dysfunction is prominent in HIV/AIDS. This is reviewed more extensively in *in vitro* studies by Nath *et al* (2000) in which the viral proteins Tat and gp120 had synergistic neurotoxicity with cocaine or methamphetamine.

Most investigators believe that neurons are rarely, if ever, the site of productive HIV infection, and that perivascular macrophages are the primary target. However, astrocytes may serve as important targets for restricted HIV infection (Takahashi *et al*, 1996), which, although nonproductive, could nonetheless affect astrocytic and neuronal function. The loss of homeostasis caused by the astrocytosis that is induced during HIV brain infection may indeed be a critical event in HIV-D. The dopamine system may also be damaged in HIV/AIDS, and the clinical manifestations of dopaminergic dysfunction can be prominent, and are summarized later.

Antiretroviral therapy and CNS disease

In the past few years, several therapeutic advances have led to concrete improvements both in the medical care and for the prognosis of HIV-infected individuals. The first is an understanding of the direct relationship between viral replication and immunological and clinical progression, which reinforces the need to suppress viral replication to control the infection. The second is the wider availability of multiple, potent antiretroviral regimens that can provide effective suppression of HIV. The third major change is the ability to monitor the response to therapy through the convenient and reliable measurement of plasma HIV RNA levels, which, with CD4 counts, has become a routine part of clinical care. In addition, resistance to antiretrovirals can now be relatively easily measured with genotypic, phenotypic assays, or assays that provide a 'virtual phenotype' (Deeks and Abrams, 1997). Incomplete adherence, underdosing, and pharmacokinetic interactions with other medications can result in the development of drug resistant strains of HIV-1 (Condra and Emini, 1997). Strict adherence to HAART regimens is critical to achieve virological suppression because of the ability of actively replicating HIV to rapidly develop drug resistance. In the widely quoted Patterson study (Paterson *et al*, 1999), 81% of subjects with >95% adherence had complete viral suppression compared to only 6% with <70% adherence. Cross-resistance to an entire class of drugs can develop even with transient nonadherence. There is growing information about the significant effect of cognitive impairment on HAART adherence. Deficits in working memory impact on medication adherence, and can be reversed by verbal prompting devices (Andrade *et al*, 2001). A number of factors can influence adherence with complicated medication regimes, including substance abuse, depression, high pill burden or frequent dosing, and "forgetting" (Bangsberg *et al*, 2001; Lucas *et al*, 2002; Singh *et al*, 1996). Measures to improve adherence to HAART are crucial to the health of the individual as well as the population at large because poor adherence may increase the likelihood of the transfer of resistant strains of HIV.

The role of compartment-specific resistance mutations has been explored to a very limited extent, and has produced somewhat conflicting results depending on whether DNA or RNA is used for the assays. For example, Wong *et al* (1997) showed a discordance in resistance patterns among quasispecies isolated from brain, spleen, and lymph node autopsy tissue (using viral DNA). Brain-derived reverse transcriptase sequences appear to be biogenetically distinct from spleen and lymph node derived sequences. The number of resistance mutations correlated both with the length of antiretroviral treatment and the degree of cerebrospinal fluid (CSF) penetration of the specific nucleoside agent. In contradistinction, comparing viral RNA from both brain and systemic tissues, we found that patterns of the major reverse transcriptase mutations appeared to be concordant in most subjects (McClernon *et al*, 2001). It is possible that differences between these studies are explained by blood contamination. In paired plasma and CSF, significant differences are found in the positions and frequencies of wild-type and drug-selected variants in about one third of subjects (Cunningham *et al*, 2000). The inference drawn from these studies is that there might be independent development of drug resistance in the CNS in some patients, but in most settings the major resistance mutations are concordant between plasma and CSF.

The 16 antiretroviral agents now approved for use in the USA all act either to inhibit reverse transcriptase, or protease. Further details can be found in a recent review (Sepkowitz, 2001). New agents in development may block fusion steps, chemokine receptors, or the integration of HIV-1. Guidelines for the use of antiretroviral therapy (ART) have been developed by expert panels, and include the broad recommendation that all symptomatic patients, and asymptomatic patients with immunodeficiency (CD4

$<350/\mu$l) or plasma HIV RNA levels >55,000 copies/ml be treated with combination ART regimens (Yeni *et al*, 2002) (and at http://www.hivatis.org). With HAART, dramatic reductions in plasma HIV levels can be seen within weeks, producing a sustained (or "durable") virological suppression. Immunological response occurs over a few months, and can be dramatic, with normalization of CD4 counts. Initially, the rise in CD4 counts is due to a redistribution or expansion of predominantly existing memory T lymphocytes from the lymphoid tissue. These only respond to specific antigens, so that the overall immune response remains constricted with a "limited repertoire." Later, naive T-cells are produced from the bone marrow and thymus and the repertoire of T-cell responses can potentially increase (Powderly *et al*, 1998; Roederer, 1998). Prolonged therapy may produce continuing immune improvement, with the restoration of specific immune responses to pathogens (Autran *et al*, 1997). Prophylactic therapies can be safely discontinued in individuals whose CD4 count has been restored by HAART to above 200/mm^3 (Furrer *et al*, 1999). However, reconstitution of the immune system can result in aberrant inflammatory responses to opportunistic infections and apparent "flares" in the activity of opportunistic infections (Race *et al*, 1998). It is uncertain whether this phenomenon will become relevant for neurological diseases.

Both nucleoside-sparing and protease-sparing regimens have been developed to attempt to minimize some of the toxicities associated with long-term use of these agents. Structured treatment interruption (STI) has been proposed as a strategy to reduce the cumulative toxicities of HAART, and to allow for stimulation of HIV-specific immune responses (Dybul *et al*, 2001). However, STI requires complicated timing of medication switches, and a recent study of STI showed prompt rise in plasma and CSF HIV RNA levels, falls in CD4 counts, and increases in viral replicative capacity (Deeks *et al*, 2001). Of particular concern, CSF HIV RNA levels were noted to rebound very rapidly after STI even though there was no apparent clinical correlate (Price *et al*, 2001b) (R Price, personal communication, 2002).

Potent antiretroviral treatments have resulted in significant improvements in survival, for example the mortality among people with CD4 counts <100/mm^3 has dropped from 35:100 person-years (PY) in 1993 to 10:100 PY in 1997 (Palella *et al*, 1998). HAART is actually one of the most cost-effective treatments for maintaining both quality and length of life, comparable to the use of antihypertensives for stroke prevention (Bartlett and Gallant, 2001). It is beyond the scope of this review to discuss the long-term effects of potent antiretroviral regimens; however, it is now clear that these combinations can produce significant metabolic effects, including hypertriglyceridemia, fat remodeling or lipodystrophy, pancreatitis, lactic acidosis, and mitochondrial toxicity. Peripheral neuropathies have become one of the common treatment-limiting side effects (Moore *et al*, 2000).

Epidemiology of HIV-associated dementia and myelopathy

The HIV epidemic is now affecting women and IDUs with increasing proportions, yet the majority of previous neurological studies have been in cohorts of homosexual men. The HIV-associated CNS syndromes—dementia and myelopathy—are novel, debilitating conditions that generally do not develop until advanced HIV infection. Typically, patients will have had other AIDS-defining illnesses before the onset of these neurological syndromes. HIV-D was added as an AIDS indicator illnesses in 1987, and termed *HIV-1 encephalopathy* (or HIV-E). Occasionally HIV-D develops before profound immunosuppression, but in general, it is rare among *healthy* HIV-1–infected persons. For example, the prevalence of HIV-D was only 0.4% during the asymptomatic phase of infection (Miller *et al*, 1990), but rises to 16% among patients with symptomatic HIV infection (McArthur, 1987). Before HAART, the cumulative risk of developing HIV-D during the lifetime of an HIV-seropositive person was estimated to be 15% to 20% (McArthur *et al*, 1993). The exact risk of developing HIV-D in the HAART era is not yet known. Data from the JHU HIV Clinic indicate a rising prevalence of HIV-D (Figure 1); the prevalence of HIV-D rose from 6.6:100 person-years in 1994 to 10.1 in 2000. Published risk factors include high plasma HIV RNA levels, low CD4+ counts (Childs *et al*, 1999) anemia, low body mass index, older age, lower hemoglobin levels and more constitutional symptoms before AIDS (McArthur *et al*, 1993), injection drug use (Janssen *et al*, 1992), and female sex (Chiesi *et al*, 1996). Older age is also an important risk factor, as recent data from the Hawaii Aging with HIV cohort suggests that older HIV-positive individuals (age $\geq$50 years) are nearly twice as likely to meet criteria for HIV-D than younger HIV-positive individuals (Valcour *et al*, 2002). At the other end of the age spectrum, neurological complications among HIV-seropositive children have become much less frequent in developed countries. More subtle forms of cognitive impairment termed minor cognitive/motor disorder (MCMD) exist in at least 30% of symptomatic HIV-seropositive adults (Janssen *et al*, 1989; Sacktor *et al*, 2002). The functional impact of MCMD has been demonstrated to impact on several important areas, including medication adherence (Albert *et al*, 1999; Andrade *et al*, 2001) and driving ability (Marcotte *et al*, 1999). In addition, the presence of MCMD indicates a worse prognosis for AIDS (Mayeux *et al*, 1993; Sacktor *et al*, 1996). MCMD appears to have a very high positive predictive value (95%) for the subsequent detection of HIV-E at autopsy (Cherner *et al*, 2002).

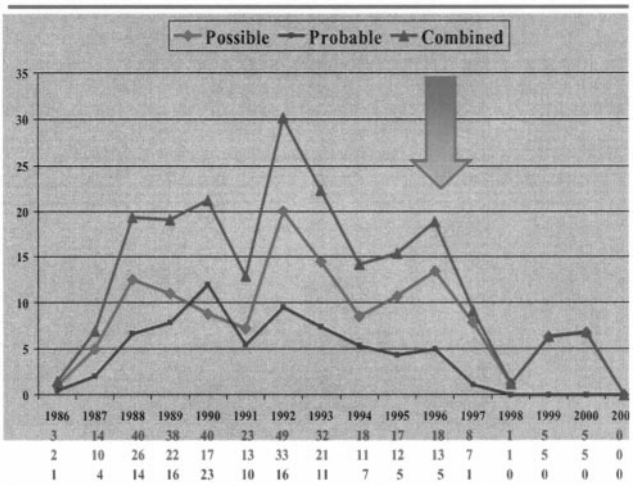

Figure 2 Declining incidence of HIV dementia in the Multicenter AIDS Cohort Study: This reflects the increasing use of HAART (*large arrow*) in this population of homosexual men and probably represents a best-case scenario in that other population groups, particularly, injection drug users, may be unable to achieve such good virological control, and may therefore continue to be at risk for HIV-D.

The incidence rates of HIV-D in a cohort of 2,734 HIV-seropositive homosexual men decreased significantly by 53% from 21.3 per 1000 person-years from 1990 to 1992, to 10.0 per 1000 person-years from 1996 to 1998, reflecting the impact of HAART (Figure 2) (Sacktor *et al*, 2001a). Perhaps surprisingly, MCMD has apparently not reduced in frequency with HAART. We, and others, have shown that HIV-D and minor cognitive-motor disorder remain very prevalent among HIV-seropositive individuals with CD4 <200. For example, both the Northeastern AIDS Dementia Cohort (NEAD) and the AIDS Clinical Trails Group (ACTG)-based ALLRT cohorts report an approximate *current* prevalence of cognitive impairment of 30%. Contemporary cohorts of individuals with advanced HIV/AIDS have highlighted the high prevalence and incidence of MCMD. For example, in collaboration with investigators at Columbia University, University of Rochester, and Northwestern University, we compared the prevalence of MCMD in cohorts studied before and after the introduction of HAART. There was no significant decline in the prevalence of MCMD, which remained about 37% even in the post-HAART cohort (Sacktor *et al*, 2002). This suggests that HAART has not eliminated HIV-associated cognitive impairment in individuals with advanced HIV infection. The cumulative incidence of dementia in the NEAD cohort was 25% at 1 year and 38% at 2 years. The cumulative incidences of dementia in the Dana (pre-HAART) and NEAD (majority using HAART) cohorts were virtually superimposable. The presence of MCMD was highly predictive for subsequent dementia in the NEAD cohort, even after controlling for education, premorbid IQ, and depression (odds ration 2.19, $P < .01$). Transitions from a neurologically normal state to MCMD or HIV-D are not necessarily unidirectional. Thus within the NEAD cohort, transitions were noted in *both* directions. For HIV-positive subjects at Johns Hopkins within the NEAD cohort, 44% of HIV-D subjects had progressed from a nondemented status to HIV-D over a 6-month period. In addition, 37.5% of HIV-D subjects improved to nondemented status over a 6-month period (McDermott M., unpublished observations).

Another issue is the reliability of clinical classifications, both for clinical practice and for research work that utilizes clinically characterized specimens or tissues. Much work has been done in the Alzheimer's disease field to standardize assessments. Within the NEAD cohort, using computerized algorithms that are perhaps more objective than clinical rating scales and consensus conferences, the degree of agreement for staging the severity of neurological impairments with MCMD and HIV-D has been excellent (Marder *et al*, 2002).

Genetic influences on HIV-dementia

Major histocompatibility (MHC) class II genes have also been shown to influence the course and severity of multiple sclerosis (Weinshenker *et al*, 1998). Both viral and host genetic differences have been proposed as determinants for HIV-D. Specific envelope sequences were identified from autopsy tissue, and found more frequently in demented individuals (Power *et al*, 1993). Others have shown that specific sequence differences confer different biological properties, for example, an increased ability to produce neuronal toxicity *in vitro* (Power *et al*, 1998), or to stimulate the production of proinflammatory cytokines (Khanna *et al*, 2000). Although research is continuing in this area, the focus has begun to swing to consider that differences in host genetics are greater influences on the risk for, and subsequent course of, HIV-D. HLA haplotypes have been studied in the MACS, but the influence on the risk for dementia was relatively low (McArthur *et al*, 1999a) (Table 2). The relationship with class I alleles was relatively weak, however, two—B51 and A24—were apparently protective. For class II alleles, a heightened risk for HIV-D was identified for DQA1-0300, DQB1-0500, and DRB1-09199. By contrast to this relatively weak effect, polymorphisms in tumor necrosis factor (TNF)-α (codon 308) were detected four times more frequently in HIV-D subjects than nondemented subjects (Quasney *et al*, 2001). This is the same polymorphism that has been associated with a higher risk of death from cerebral malaria (McGuire *et al*, 1994). ApoE4 has also been proposed as a genetic risk factor (Corder *et al*, 1998), as well as CCR5 (Gonzalez *et al*, 2001). In a large and well-controlled study, specific polymorphisms in monocyte chemoattractant protein (MCP)-1 were found to increase the risk for HIV-D almost fivefold (Gonzalez *et al*, 2002).

Table 2 HLA alleles and haplotypes associated with dementia

HLA phenotype	*Dementia +* *Control −*	*Dementia +* *Control +*	*Dementia −* *Control −*	*Dementia −* *Control +*	*Relative odds*	P *value*
Class I						
B51	5	2	50	13	0.39	.07
A24	4	2	48	16	0.25	.013
Class II						
DQA1*0500	15	17	58	28	0.54	.05
DQB1*0500	31	13	59	15	2.07	.02
DRB1*0100	27	7	76	8	3.38	.003
DRB1*0100 and DQA1*0100	21	4	86	7	3.00	.012
DRB1*0100/DQB1*0500	27	7	76	8	3.38	.003
DRB1*0700/DQB1*0200	20	5	83	10	2.0	.07

At this point, none of these host genetic markers has definitively been proven to be useful as a predictive marker. However, it seems highly plausible that differences in the genetic control of the host's immune system influence an individual's risk for HIV-D, as is the case for systemic lupus erythematosus (Tsao, 2002), multiple sclerosis (Weinshenker *et al*, 1997), and Alzheimer's disease (Price *et al*, 1998).

Clinical features of HIV-associated dementia and myelopathy

The typical presentation of HIV-D includes cognitive, behavioral, and motor dysfunction, and has been characterized as a *subcortical* dementia. The typical presentation of HIV-D have been described (see Navia *et al*, 1986), and we will emphasize some of the atypical and changing features. The initial symptoms of HIV-D can be subtle and overlooked, or misdiagnosed as depression. In the early stages, memory loss, mental slowing, reading and comprehension difficulties, and apathy are frequent complaints (Figure 3). The typical cognitive deficits of HIV-D are characterized primarily by (1) memory loss that is selective for impaired retrieval; (2) impaired ability to manipulate acquired knowledge; (3) personality changes that are characterized by apathy, inertia, and irritability; and (4) general slowing of all thought processes. However, considerable individual variability in presentation has been reported (Navia *et al*, 1986). Children can also be affected by a progressive encephalopathy, microcephaly, developmental delay, then progressive loss of developmental milestones. Other conditions that may mimic HIV-D include progressive multifocal leukoencephalopathy (PML), cytomegalovirus (CMV) encephalitis, cryptococcal meningitis, primary CNS lymphoma, and major affective disorders. Gait disturbance, with nonspecific stumbling and tripping, is a common early manifestation, and impairment of fine manual dexterity is also very frequent. Examination findings include impaired rapid movements of eyes and limbs, diffuse hyperreflexia, release signs, and sometimes parkinsonism (Mirsattari *et al*, 1998). Tremor or myoclonus are uncommon, but have been reported (Maher *et al*, 1997). New onset mania, or a heightened sensitivity to neuroleptic agents, can also be seen in some patients (Hriso *et al*, 1991). These need to be distinguished from the frequent CNS toxicities of the non-nucleoside reverse transcriptase inhibitor efavirenz, which can include agitation, disturbed sleep, and even catatonia (Sabato *et al*, 2002). The prominence of motor slowing and impaired movements adds to the concern that dopaminergic dysfunction is prominent in HIV/AIDS (Nath *et al*, 2000) 'Pure' cerebellar syndromes, which may reflect atypical forms of HIV-E (Tagliati *et al*, 1998), and a relapsing-remitting illness, not unlike multiple sclerosis, have been described, albeit rarely (Berger *et al*, 1989). The University of California San Diego group have recently reported a series of patients with a severe form of leukoencephalopathy (Langford *et al*, 2002). The syndrome developed in patients failing HAART, and the neuropathological features included intense perivascular infiltration by HIV gp41–immunoreactive monocytes/macrophages and lymphocytes, widespread myelin loss, axonal injury, microgliosis, and astrogliosis. It is uncertain whether this is in fact a new pathological entity, or simply a more severe version of the HIV leukoencephalopathy that was described in one third of demented subjects (Glass *et al*, 1993).

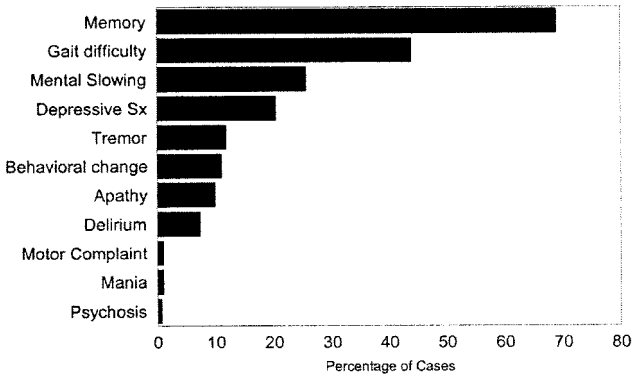

Figure 3 Frequency of symptoms in HIV dementia among 300 subjects personally examined at the JHU HIV Neurology Program.

The vacuolar myelopathy associated with HIV-1 is a slowly progressive myelopathy characterized by prominent vacuolar changes in the ascending and descending tracts. It affects 5% to 10% of patients with AIDS, but has been identified pathologically in almost 50% at autopsy during the pre-HAART epoch (Dal Pan *et al*, 1994). Occasionally, the myelopathy develops before, or without dementia, but usually the two progress in parallel. It manifests as a progressive spastic paraparesis, with sensory ataxia. The sensory neuropathies are reviewed in Keswani *et al* (2002).

Progression of HIV-associated dementia

HIV-D progresses at a variable rate (Bouwman *et al*, 1998), with a mean survival of under 1 year in untreated patients. As the dementia advances, more widespread deficits develop, including a global dementia, often accompanied by vacuolar myelopathy and sensory neuropathies. Prominent psychomotor slowing, a history of injection drug use, and low CD4 counts appear to predict more rapid neurological progression, at least in untreated cases (Bouwman *et al*, 1998). Autopsies showed an increased abundance of the macrophage activation marker, HAM56, in those with rapid progression (Glass *et al*, 1995). Correlations have also been demonstrated between the rapidity of neurological progression, increased expression of inducible nitric oxide synthase (iNOS) mRNA (Adamson *et al*, 1999), and astrocyte apoptosis (Thompson *et al*, 2001). These studies were all performed prior to the introduction of HAART, but taken together, suggest that CNS inflammation influences the rate of neurological deterioration in HIV-D.

Interpretation of CSF HIV RNA assays in HIV-D
The quantification of plasma HIV RNA has become a critical tool for monitoring levels of replicating HIV. Studies using reverse transcriptase–polymerase chain reaction (RT-PCR), branched DNA techniques, or enzymatic amplification assays have demonstrated that HIV RNA quantification is a powerful predictor of decreases in CD4+ lymphocyte count, progression to AIDS, and death (Hogervorst *et al*, 1995; Mellors *et al*, 1997; Schooley, 1995). Plasma viral load strongly predicts the prognosis of HIV/AIDS (Mellors *et al*, 1997), and the combined measurement of plasma HIV RNA and CD4+ lymphocytes provides an even more accurate forecast (Mellors *et al*, 1996). A higher plasma HIV RNA set-point is predictive of HIV-D (Childs *et al*, 1999).

In contrast to plasma surrogate markers, the utility and predictive value of CSF analysis is less clear. Certainly CSF abnormalities are common in HIV-D, with elevated CSF levels of HIV RNA and immune activation markers occurring in most demented individuals. CSF levels of HIV RNA correlate with the severity of neurological deficits (Brew *et al*, 1997; Ellis *et al*, 1997; McArthur *et al*, 1997), at least in the pre-HAART era. CSF HIV RNA levels may be predictive of subsequent neurological deterioration and transition into HIV-D (Ellis *et al*, 2002). The correlation between CSF HIV RNA levels and neurological status in HAART-treated individuals appears to be much weaker now than in the pre-HAART era. Although De Luca *et al* (2002) did demonstrate a significant correlation in HAART-treated patients, the much larger NEAD cohort, which also had high rates of HAART usage, showed no such relationship (Figure 4) (McArthur *et al*, 2002). We infer from this that HAART can effectively suppress both HIV levels and immune activation markers among individuals with advanced HIV disease, and that the introduction of HAART may actually have attenuated the severity of neurological disease.

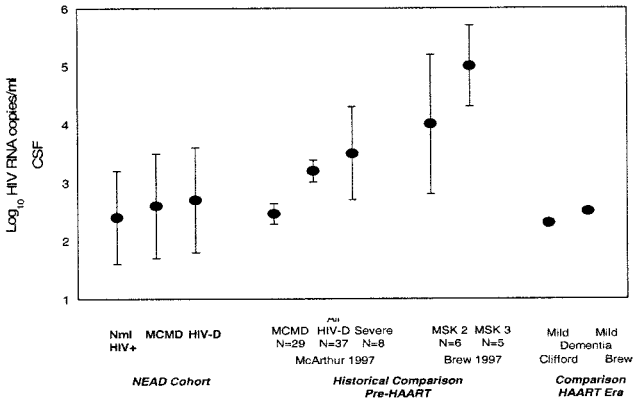

Figure 4 Comparison of CSF HIV RNA values in contemporary NEAD cohort (>70% HAART) treated with earlier untreated cohorts.

Several studies have conclusively shown that either dual therapy or HAART can suppress CSF HIV RNA levels rapidly, particularly in antiretroviral-naive individuals. For example, the majority of patients treated with two nucleoside reverse transcriptase inhibitors (NRTIs) for 3 months had undetectable CSF HIV RNA (Foudraine *et al*, 1998). Declines in CSF HIV RNA with HAART appear to correlate with the successful reversal of neurological deficits (Ellis *et al*, 2000; Marra *et al*, 1999). Despite these overall cohort effects, on an individual basis, CSF virological failures remain common, especially in community-based settings (McArthur *et al*, 1999b). Several groups have examined the dynamics of HIV replication after the initiation or interruption of highly active antiretroviral therapy. Ellis *et al* (2000) and Price *et al* (2001a) both suggested that CSF and plasma HIV replication dynamics are relatively independent in advanced HIV disease, with a compartmental discrepancy in HIV-D. To date, the determinants of virological failure in the CSF have not been fully defined, and the clinical significance of CSF virological persistence remains uncertain. The concern is that that it may indicate persistence of CNS HIV replication and Ellis' recent observations suggest

Table 3 Anti-HIV drugs

Drug	*Date approved*	*CSF:plasma*
Nucleos/tide RT inhibitors		
Retrovir (zidovudine, AZT)	3/1987	0.3–1.35
Zerit (stavudine, d4T)	6/1994	0.16–0.97
Ziagen (abacavir)	12/1998	0.3–0.42
Videx (didanosine, ddl)	10/1991	0.16–0.19
Epivir (lamivudine, 3TC)	11/1995	0.11
Hivid (zalcitabine. ddC)	6/1992	0.09–0.37
Viread (tenofovir)	10/2001	Unknown
Non-nucleoside RT inhibitors		
Viramune (nevirapine)	6/1996	0.28–0.45
Rescriptor delavirdine)	7/1997	0.02
Sustiva (efavirenz)	11/1998	0.01
Protease inhibitors		
Crixivan (Indinavir)	3/1996	0.02–0.06
Fortovase (saquinavir)	12/1995	<0.05
Viracept (nelfinavir)	4/1997	<0.05
Norvir (ritonavir)	3/1996	<0.05
Kaletra (lopinavir + ritonavir)	11/2000	<0.05
Agenerase (amprenavir)	3/1999	<0.05

a high rate of subsequent neurological deterioration in those with high CSF HIV RNA levels (Tyler and McArthur, 2002).

Table 3 indicates the CSF:plasma ratio for available agents. In general, for the higher the ratio, the higher the CSF penetration. However, the CSF levels of a drug are not necessarily directly related to its parenchymal penetration. There is inadequate human data on the actual parenchymal penetration of antiretrovirals. Another unanswered issue is whether specific HAART regimens can provide superior CNS virological suppression than other regimens. We believe that the principal effect of HAART may occur outside the CNS, perhaps by reducing the proportion of circulating activated monocytes, the cells presumed to carry HIV into the brain (Pardridge, 2002). On a theoretical basis, some of the nucleoside analogues might be anticipated to penetrate the brain parenchyma more effectively than others (Groothuis and Levy, 1997). On theoretical grounds, both the NRTIs and the protease inhibitors (PIs) should have restricted access to the brain parenchyma, because the blood-brain barrier either limits their entry, or active efflux mechanisms exist. For example, the PIs should be eliminated from the brain through through the actions of P-glycoprotein, which is expressed at the blood-brain barrier (Groothuis and Levy, 1997; Pardridge, 2002). For the NRTIs, organic acid transport systems may mediate the penetration into the brain and CSF, although their clinical importance is undefined (Schaner *et al*, 1999; Thomas and Segal, 1997). Inhibitors of P-glycoprotein (e.g., verapamil, or nifedipine) and of organic acid transporters (uricosuric compounds such as the poorly tolerated probenecid, or benzbromarone) have been proposed for the treatment of established HIV-E. To date, neither the selective inhibition of these efflux systems nor the monitoring of antiretroviral levels in CSF has entered clinical practice. In a recently reported study of 50 subjects, more prominentviral load reductions from baseline CSF (1.14 $\log_{10}$ copies/ml) were observed in those receiving 'CNS-penetrating' HAART regimens than those with theoretically less penetrant drug regimens(a reduction of only 0.05 $\log_{10}$ copies/ml). This suggests that CSF virological suppression is correlated with predicted CNS antiretroviral drug penetrance. However, neurocognitive improvement with HAART appears to be independent of this variable and it remains to be determined whether specific HAART regimens are more efficacious for treatment of established HIV-D (Sacktor *et al*, 2001b).

Utility of CSF immune activation markers and resistance patterns in HIV-D

Various CSF markers of immune activation such as neopterin (Brew *et al*, 1990), β2-microglobulin (Brew *et al*, 1989), and quinolinic acid (Heyes *et al*, 1991) also correlate with the severity of HIV-D, and also decline with HAART treatment. In the pre-HAART era, CSF immune activation markers including β2-microglobulin, neopterin, and eicosanoids were significantly elevated in HIV-D (Brew *et al*, 1990; Griffin *et al*, 1991, 1994). Levels or activity of matrix metalloproteinase (MMP)-2, MMP-7, and MMP-9 were all increased in CSF from patients with HIV-D (Conant *et al*, 1999). Studies of SIV encephalitis suggest that the ratio of MCP-1 in blood and CSF may predict, or at least predate, the development of encephalitis (Zink *et al*, 2001). In the NEAD cohort, where HAART was used in >70% subjects, there was no correlation between neurological status and CSF levels of TNF-α, MCP-1, or macrophage colony-stimulating factor (M-CSF), suggesting that immune activation markers are less frequently elevated in contemporary HAART-using cohorts, compared to studies from 5 to 10 years ago.

The role of measuring viral resistance patterns in either plasma or CSF remains to be established, and has not yet entered clinical practice for treatment of HIV-D. The detection of resistance mutations generally requires an HIV RNA level of >400 copies/ml, so for CSF, where levels are often lower, resistance testing is frequently not feasible. Some studies have shown that there can be discordance between plasma and CSF resistance patterns (R Ellis, personal communication, 2002) (P Cinque, personal communication, 2002) (Wendell *et al*, 2001). Further studies are needed to determine the clinical relevance of these observations.

Radiological markers for HIV-D

Magnetic resonance imaging in HIV-D typically demonstrates both cortical and central atrophy, and characteristic confluent signal abnormalities within the deep white matter. These changes represent an increased brain water content, and are reversible with

HAART (Filippi *et al*, 1998). Perfusion studies have indicated that there is an increased degree of permeability of the blood-brain-barrier in HIV-D (Berger and Avison, 2001; Chang *et al*, 2002).

Proton magnetic resonance spectroscopy (MRS) (Price *et al*, 1999) is a noninvasive tool with high reproducibility that measures the concentrations of specific brain metabolites that reflect CNS function. In HIV-D, MRS shows increases in choline and myoinositol (reflecting inflammation and astrocytosis) and reductions in *N*-acetyl aspartate (indicating neuronal injury) (Figure 5). Brain metabolite levels correlate strongly with various clinical and biochemical indices of neurological progression in HIV-seropositive individuals such as severity of HIV-D, overall functional level, CD4 cell count, plasma viral load, and CSF viral load (Chang *et al*, 1999). Cerebral metabolite levels can normalize after 9 months of treatment with HAART, although the changes appear to lag behind improvements in CD4 count and CSF HIV RNA levels (Chang *et al*, 2001). A large study of MRS, performed in the context of a clinical trial of the *N*-methyl-D-aspartate (NMDA) antagonist memantine, has demonstrated the feasibility of using MRS data acquired at multiple academic centers (B Navia, submitted to *Annals of Neurology*). Furthermore, there may be different patterns of MRS abnormalities. A so-called 'basal ganglia' pattern with elevated *myo*-inositol in the basal ganglia is potentially indicative of inflammation, and a 'neuronal' pattern with reduced *N*-acetylaspartate levels in subcortical and cortical regions, corresponding to diffuse neuronal injury, can be seen (Yiannoutsos, 2002).

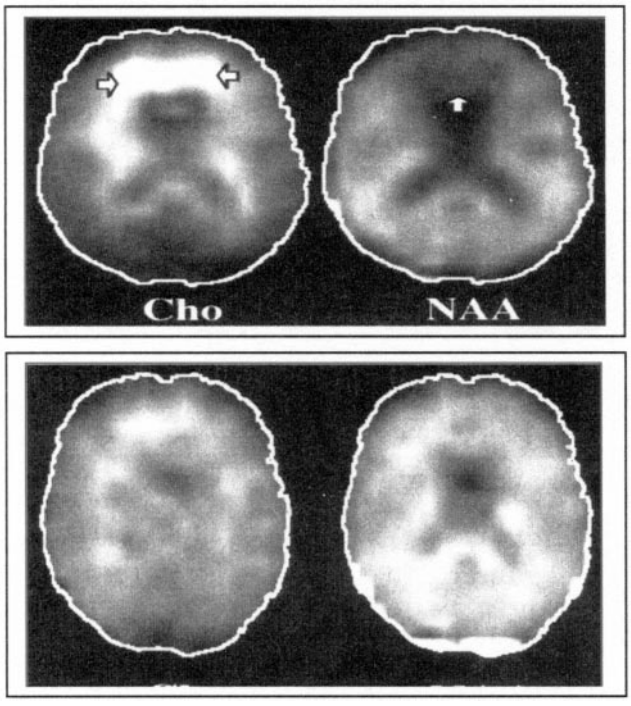

Figure 5 Magnetic spectroscopic imaging in HIV-D. Top panel indicates increased choline (CHO) and reduced NAA in frontal lobes (*arrow*), compared to control subject in bottom panel (Barker *et al*, 1995).

MRS has thus been shown to be sensitive to changes in brain cellular metabolism in patients with HIV-D and may be useful as a marker of regional brain injury (Chong *et al*, 1993, 1994; Confort-Gouny *et al*, 1992; Jarvik *et al*, 1993; Menon *et al*, 1990, 1992). However, most of these studies were performed before the introduction of HAART and it is likely that MRS abnormalities may be attenuated by HAART, as we have observed for CSF HIV RNA (Pomper and Sacktor, unpublished observations).

Treatment of HIV-associated dementia

Neuropsychological batteries have been used to track improvements in neurological and neuropsychological deficits of HIV-D and MCMD, and have been included as the *primary* outcome measure in all of the placebo-controlled trials of antiretroviral therapy, and also for trials of adjunctive agents (Sacktor and McArthur, 1997; Schifitto *et al*, 2001; Sidtis *et al*, 1993). Although specific neuropsychological instruments that measure psychomotor speed may indeed be sensitive to HIV-D, the relationship of changes in neuropsychological performance to improvements *in function* has not yet been demonstrated Price and Sidtis, 1990; Schifitto *et al*, 2001). A substantial proportion of individuals with HIV-D or MCMD actually show partial reversal of neuropsychological deficits. For example, Cohen and colleagues (2001) reported that women taking HAART for 18 months had significant improvements in psychomotor and executive functions, although those not taking HAART declined. Tozzi *et al* (1999) also found sustained improvements in neurocognitive performance after 6 months of HAART therapy, as did Ferrando's group (Ferrando *et al*, 1998). Potent antiretroviral regimens, usually consisting of three or more antiretrovirals are considered "standard of care," and there is no longer any role for monotherapy or dual therapy for the treatment of HIV-D. For example, in 1313 adults with advanced HIV/AIDS (CD4 counts <50cells/mm^3), four regimens were tested: AZT, alternating monthly with ddl; AZT + ddC; AZT + ddl; or AZT + ddl + nevirapine, and a four-item quantitative neurological performance battery score administered. Triple therapy and the AZT/ddl combination preserved or improved neurological performance compared to the alternating dual therapy ZDV/ddl and ZDV/ddC regimens ($P < .001$), paralleling their impact on survival (Price *et al*, 1999). More recent studies with protease-containing regimens have also confirmed the effects of HAART in reversing the neurocognitive deficits of HIV-D, showing improvements in motor and psychomotor speed (Ferrando *et al*, 1998; Sacktor *et al*, 2000b).

Only one placebo-controlled trial of HAART in HIV-D has been conducted; a trial of high-dose

zidovudine monotherapy in the late 1980s (Sidtis *et al*, 1993). Significant improvements on neurocognitive performance were observed. In the era of HAART, there have been no placebo-controlled trials for HIV-D. However, instructive results were derived from an "add-on" study of high-dose abacavir to background HAART therapy (Brew *et al*, 2000). One hundred and five HIV-1 infected subjects with mild-to-moderate HIV-D were randomized to receive abacavir (600 mg twice daily) or matched placebo added to a stable HAART regimen. The primary outcome measure was the change over 12 weeks in a composite score derived from the mean of eight neuropsychological tests. The median change from baseline was comparable between the two groups (+0.76 SD units for the abacavir group and +0.63 for placebo) (Figure 6). Those receiving abacavir had greater decreases in CSF HIV-1 RNA. The unanticipated results from this study were (a) that the augmentation of HAART with one drug provided no additional improvement in neuropsychological performance; and (b) that neuropsychological improvements continued, even after 8 or more weeks of HAART. These findings suggest that a reversal of neurological deficits may be slow. Interestingly, 83% of the subjects enrolled into this study had *normal* CSF levels of CSF β2-microglobulin at baseline, suggesting that active CNS inflammation in this group was not present.

Some individuals fail to respond to HAART. These occurrences may correspond to an irreversible stage of pathology with prominent neuronal loss and "burnt-out" inflammation. The measurement of CSF HIV RNA levels, combined with markers of CNS inflammation and apoptosis, may provide critical information regarding the persistence of CNS infection and damage. The identification of predictive factors of treatment response will be of great importance to better understand the course of HIV-D, and for its pathogenetic mechanisms. Determinants of treatment response are still unclear, but would obviously be useful in selecting individuals with established dementia perhaps for more aggressive regimens. A recent observational study of 28 patients who were followed longitudinally after HAART initiation suggests that a history of injection drug use, incomplete plasma virological suppression, and the type of antiretroviral regimen predicted a lack of neurological response Dougherty *et al*, 2002). Levels of CSF β2-microglobulin were twofold higher in those who showed neurological response with HAART, suggesting that higher initial levels of CNS inflammation correlate with reversible neurological deficits. Differences in neurological response to therapy were not dependent on the initial severity of dementia, self-reported medication adherence, CD4 counts, or baseline plasma HIV RNA levels Dougherty *et al*, 2002).

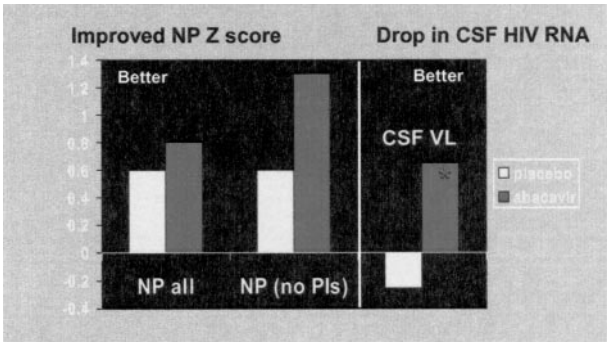

Figure 6 Abacavir add-on trial for HIV-D. NP improvement was observed both for those receiving abacavir add-on, and for those of stable HAART. CSF HIV RNA levels dropped for abacavir add-on recipients, but neuropsychological performance improved in both groups. Courtesy of Dr B Brew.

The role of genetic differences in determining treatment response is of great interest, especially with the observations from psychiatry of genetic differences in response to antidepressants (Hahn and Blakely 2002). As one example of genetic susceptibility in HIV/AIDS, HLAB57-positivity correlates (The Dana Consortium on the Therapy of HIV Dementia and Related Cognitive Disorders, 1998) with a heightened risk of abacavir sensitivity (Mallal *et al*, 2002). Polymorphisms in the *mdr* gene have been shown to correlate with higher plasma levels of protease inhibitors (Fellay *et al*, 2002). The relationship between antiretroviral drug concentrations in plasma and CSF and polymorphisms in the *mdr* gene controlling the expression of P-glycoprotein at the blood-brain barrier are being explored, and may have therapeutic importance.

Adjuvant therapies for HIV-D

Given that immune activation is likely to play a pivotal role in sustaining or magnifying the CNS damage induced by HIV-1, attention has focused on *adjunctive* therapies targeted at attenuating the CNS effects of inflammatory products. These have included the NMDA antagonist memantine, the calcium channel blocker nifidepine, the platelet-activating factor antagonist lexipafant, the TNF-α antagonists pentoxifylline and CPI1189, and an experimental antioxidant, thioctic acid. The results of most trials (shown in Table 4) have been disappointing, with either no or only modest effects on neuropsychological function. One agent, however, the monoamine oxidase (MAO)-B inhibitor selegiline, has been shown to improve memory in two separate placebo-controlled studies Sacktor *et al*, 2000a; The Dana Consortium on the Therapy of HIV Dementia and Related Cognitive Disorders, 1998). Although its mechanism of action is speculative, and may involve an antioxidant effect, a larger phase II trial is underway in the USA, with results expected in 2004.

Changing features of HIV-D in the era of HAART

Although the prevalence of HIV-D in contemporary cohorts is actually increasing, the severity of neurological disease appears to be milder since the introduction of HAART. For example, in our own

Table 4 Placebo-controlled trials of adjunctive agents for HIV dementia

Agent	*Action*	*Conclusions*
Nimodipine (Navia *et al*, 1998)	Calcium channel	NP trend
Peptide T (Heseltine *et al*, 1998)	Uncertain—possibly chemokine receptor blockade	No effect
OPC14117 (The Dana Consortium on Therapy of HIV Dementia and Related Cognitive Disorders, 1997)	Antioxidant	NP trend
Thioctic acid vs selegiline (The Dana Consortium on the Therapy of HIV Dementia and Related Cognitive Disorders, 1998)	Antioxidant, neuroprotectant	Selegiline + effect on NP performance
Lexipafant (Schifitto *et al*, 1999)	PAF antagonist	+ NP effect
Memantine (Navia, in press)	NMDA antagonist	+ NP effect (but only after completion of double-blind phase)
CPI-1189 (Clifford *et al*, 2002a)	TNFα antagonist	Minimal effect on NP performance

referral cohort, the percentage of newly diagnosed moderate or severe dementia (MSK 2 or 3) has fallen very dramatically: from about 6.6% in 1989 to 1.0% in 2000. Prior to the introduction of HAART, the course of HIV-D was usually progressive over 6 to 9 months, leading in a stereotypic manner to severe neurological deficits and death (McArthur, 1987; Navia *et al*, 1986). Since the introduction of HAART in 1996, however, the course of HIV-D appears to be much more variable. Most HAART-treated individuals with HIV-D remain neurologically stable, or may show some partial reversal of neurological deficits, for years after starting HAART.

We hypothesize that HIV-D in the era of HAART may now have three distinct subtypes: (1) a 'subacute progressive' dementia in untreated patients with a clinical syndrome of severe, progressive dementia similar to that seen in the pre-HAART era; (2) a 'chronic active' dementia in patients on HAART with poor adherence or with viral resistance who are at risk for neurological progression; and (3) a 'chronic inactive' dementia in patients on HAART with good drug adherence and effective virological suppression who have had some recovery from neuronal injury and remain neurologically stable (Figure 7).

The development of surrogate markers to identify these three HIV-D subtypes would be of great importance in understanding the clinical course and pathogenetic mechanisms of HIV-D and in planning future treatments. Currently available clinical and laboratory markers of HIV-D may be less useful, in the era of HAART. Neuroimaging markers, in concert with clinical and laboratory markers, may be necessary to identify patients with HIV-D who are at risk for progression.

Several independent contemporary studies have shown that the levels of CSF HIV RNA appear to be significantly lower in *untreated* subjects with HIV-D than those seen in pre-HAART studies (Clifford *et al*, 2002b; McArthur *et al*, 2002). This might suggest that under the pressure of HAART, HIV envelope may have evolved towards a less virulent type (J Wong,

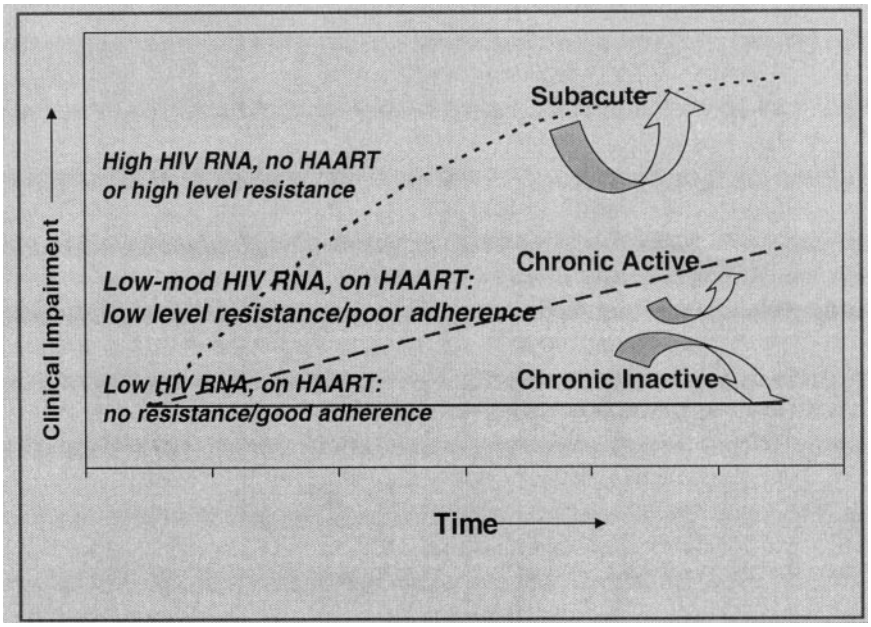

Figure 7 Model of different patterns of HIV dementia in era of HAART.

personal communication, 2002). These observations suggest that both the phenotype and the biological markers of HIV-D have undergone an evolution, and perhaps the virus has become attenuated under the influence of HAART.

Summary

We are entering a new era in the AIDS epidemic. HIV/AIDS has become a chronic *manageable* disease, at least for those in the developed world. There has been tremendous progress in the development of potent antiretroviral therapies, with impressive and encouraging effects on the prognosis of HIV infection, and a positive impact on the incidence rates of neurological diseases. Patients with HIV infection can anticipate much improved survival, but this requires the regular use of multiple expensive medications, which may have cumulative toxicities on metabolism and peripheral nerves. Even in the USA, significant problems with medical access and adherence may continue to limit the availability and success of treatment. Consideration of the CNS compartment separate from the rest of the body has become even more important with these new therapies because of the issues of CNS penetration of antiretrovirals, and sequestration of HIV. The diagnosis and therapy of many of the CNS opportunistic processes has improved, and incidence rates in Europe and the USA are dropping. As we encounter more and more "long-term survivors," new opportunistic processes may be identified, or novel complications of therapy recognized. In addition, as HIV-positive long-term survivors enter their 5th and 6th decade of life, neuropathological comorbidity from age-associated processes (e.g., vascular or neurodegenerative disease) needs to be considered in evaluating cognitive impairment in the older HIV-positive individual. The differentiation between HIV-induced cognitive impairment and other potential etiologies of cognitive impairment among older HIV-positive individuals remains as an important area of future study. The changing face of HIV-D, in the context of the evolving pandemic, poses new challenges for framing research questions. Table 5 below summarizes some of the treatment-related issues that will need to be considered in future research.

Table 5 Critical research studies needed in HIV-associated dementia in the era of HAART

- Certainty of clinical categorization? Many patients may have long-term, stable cognitive impairment
- Clinical specimens ~ consider not only patterns of HAART exposure, but severity and course of HIV-D
- Autopsy specimens ~ need to consider when HAART was discontinued prior to death
- Role of gender differences in neurological disease manifestations and progression
- Consider adjunctive therapies
- Consider the influence of alcohol and drugs of abuse on neurological disease and pathogenesis
- Genetic polymorphisms ~ both as determinants of risk and treatment response

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