

HIV-associated Dementia

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Epidemiology of HIV Dementia

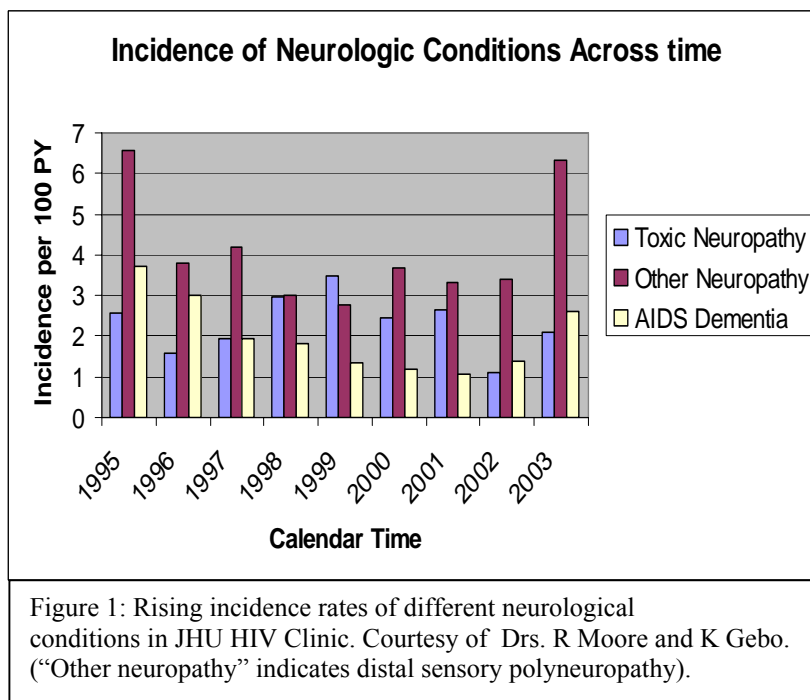
The World Health Organization (WHO) estimates that worldwide there are 40 million people living with HIV/AIDS in 2003, and there were 3 million AIDS deaths in 2003. This total does not include the 20 million people around the world who have already died of AIDS. There were 5 million people newly infected with HIV in 2003. The vast majority, 26.6 million people, almost 70% of HIV cases globally are in Sub-Saharan Africa. The second major pocket of HIV infection is in South and Southeast Asia, with 6.1 million people infected. Areas with rapid increases in infection rates recently include Sub-Saharan Africa, China, and Eastern Europe(2). However, the incidence of dementia in these regions where HIV is most prevalent remains unknown. It is possible that the combination of different viral clades and host genetic factors may influence the presence of dementia.

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(3). A 60% fall in death rates was seen in the USA from 1996 to 1998, attributable to the use of combination antiretrovirals(4). The mean time to death from the time of diagnosis for HIV-D in the pre-HAART era was 6 months(5), but in the post-HAART era this mean time to death has lengthened to 44 months(6). However, for the majority 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.

The Global Fund to Fight AIDS, Tuberculosis and Malaria was created to dramatically increase resources to fight three of the world's most devastating diseases, and to direct those resources to areas of greatest need. It is a partnership between governments, civil society, the private sector and affected communities, and represents an innovative approach to international health financing. The fund for HIV has set the goal of treating 3 million by 2005 ('3x5 plan'), but remains underfunded and unlikely to reach its target.

Incidence rates began to fall in the early 1990s(7) and have fallen further since the introduction of HAART because of immune restoration in HAART-treated patients. HIV-D constitutes about 5% of new AIDS-defining illnesses in the USA. Although the incidence had fallen under the influence of HAART, we have recently seen **increases** in the incidence rates of both HIV-D and sensory neuropathies, and the cumulative prevalence has been rising steadily since the introduction of HAART with the improved survival (Figure 1). Even in the pre-HAART era, in adults, only 3% of AIDS cases

presented initially with dementia as their first AIDS defining illness; more typically, dementia develops



after constitutional symptoms, immune deficiency and systemic opportunistic processes. (8-10) However, cognitive impairment eventually developed in about 30% of people with AIDS and frank dementia in about 15%. (11, 12) In the HAART era, cognitive impairment is still frequent, affecting 20-30% of HIV+ individuals (2), even though the temporal progression of HIV-D appears to have been altered by HAART, with most patients now showing an attenuated form of dementia, which with treatment is slowly progressive or static.

Risk factors: Early in the pandemic, it was clear that “sicker” patients often developed HIVD. Hence studies showed that anemia, low weight, and constitutional symptoms, were predictors of the subsequent development of HIV-D (Table 1). (11, 13). Higher plasma HIV RNA set-points before treatment and lower CD4 counts are also predictive, both of dementia and sensory neuropathy (14), suggesting that there is a link between systemic disease progression and the development of neurological disease. Recently, the attention has focused on host genetic factors. ApoE4 gene correlates with severity of dementia likely by making neurons more vulnerable to oxidative stress(15, 16), MCP-1 mutations and mutations in its receptor CCR2 (64-I allele) (17)correlate with presence of dementia likely by influencing macrophage infiltration (18)and TNF receptor mutations also correlate with presence of dementia likely by influencing neuronal vulnerability to TNF induced toxicity(19).

Table 1: Risk factors for HIV dementia	
1.	Unsuppressed plasma or CSF HIV RNA
2.	CD4 <200
3.	Extremes of age
4.	History of drug abuse
5.	Anemia
6.	Low body weight
7.	Genetic factors
	ApoE4
	MCP-1, CCR-2
	TNF receptor polymorphisms

Terminology

The terms AIDS dementia complex, HIV dementia, HIV encephalopathy, and *HIV-associated dementia complex*, are synonymous. Minor degrees of cognitive, motor, and functional impairment which are not sufficient to diagnose dementia are termed "*HIV-associated minor cognitive/motor disorder*." Because some patients with this minor impairment do not progress to frank dementia, it is reasonable to maintain this as a separate term. The term "*HIV encephalitis*" should be reserved for the pathological features of multinucleated giant cell encephalitis with HIV identified in the brain and not used to describe the clinical syndrome (20). Similarly, while HIV-associated dementia complex can develop concurrently with other HIV-associated neurologic disorders such as myelopathy and neuropathy, it appears that these are all discrete disorders with different manifestations, courses, and pathogenetic mechanisms.

Subtypes of HIV dementia:

In the era of HAART, the course of HIV dementia appears to have changed, hence recently new terms have been introduced. HIV-D may now have four distinct subtypes: (1) a ‘*subacute progressive*’ dementia in untreated patients with a clinical syndrome of severe, progressive dementia

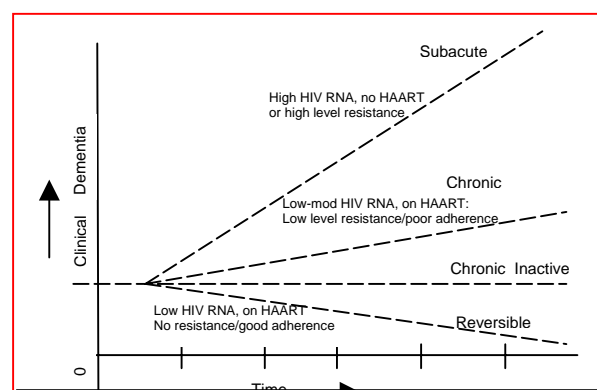


Figure 2: Course of HIVD in the HAART era (Sacktor and McArthur JN 2005)

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; (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; and (4) a ‘*reversible*’ dementia also in patients on HAART with good drug adherence and effective virological suppression (Figure 2).

Other rare subtypes being recognized include:

HIV demyelinating leukoencephalopathy in AIDS patients failing HAART and is characterized by massive infiltration of HIV infected monocytes/macrophages into the brain and extensive white matter destruction(21).

Acute encephalopathy associated with “immune reconstitution inflammatory syndrome” (IRIS) in which patients with high viral loads and low CD4 counts when treated with HAART develop an acute infiltration of CD8 cells in the brain(22).

HIV vacuolar leukoencephalopathy in which the histopathology is similar to HIV vacuolar myelopathy (23)

Fulminant HIV dementia in which the symptoms progress over days and result in death within 2 months from onset of neurological symptoms(24). The latter two subtypes were described prior to the use of ART.

Clinical Features of HIV Dementia

In adults, the clinical manifestations of HIVD suggest early and predominant subcortical involvement. (5)

1. Cognitive: Typical symptoms of HIV-D include increasing forgetfulness, difficulty with concentration, apathy, inertia, waning interest in work and hobbies resulting in social withdrawal and loss of libido. Patients complain of losing track of conversations and the plots of books and films and of taking longer to complete more complex daily tasks. Impaired short term memory causes difficulty with remembering appointments, medications, and telephone numbers. Neuropsychological testing shows a) memory loss selective for impaired retrieval, b) impaired manipulation of acquired knowledge, and c) a general slowing of psychomotor speed and thought processes (Figure 3). Often these patients have good insight into the cognitive impairment and aphasias and apraxias are absent and attention and calculation are not affected, thus differentiating them from patients with cortical dementias. However, occasionally, generalized seizures may occur (25).

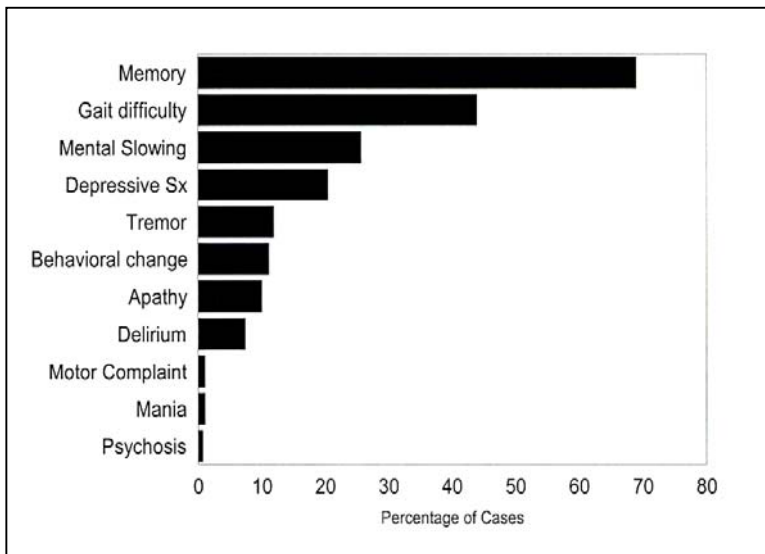


Figure 3. Frequency of symptoms in HIV dementia among 300 subjects personally examined by Justin McArthur at JHU HIV Neurology program

The most sensitive test combinations for detecting neuropsychological impairment in HIV

infected patients are the Hopkins Verbal Learning Test-Revised (HVLT-R; Total Recall) and the Grooved Pegboard Test nondominant hand (PND) pair and the HVLT-R and WAIS-III Digit Symbol (DS) subtest pair (sensitivity = 78% and 75%, respectively). Both test combinations (HVLT-R/PND, HVLT-R/DS) were more accurate than the HIV Dementia Scale (HDS) in classifying HIV+ participants as neuropsychologically (NP) impaired or unimpaired(26). The HIV Dementia Scale is a modification of the Minimental Status Exam. (27). It has the advantage of being extremely simple and rapid, and can be easily used by non-neurologists (see Figure 2).

With advancing dementia, new learning and memory deteriorate, there is a further slowing of mental processing, and abulia with reduced output of spontaneous speech (see Table 2). The terminal phases of the syndrome are characterized by a global impairment with severe psychomotor retardation and mutism

This reinforces the need for neuropsychological testing of individuals at highest risk of developing HIVD (Figure 4). However, the influence of premorbid conditions, including previous head trauma, learning disability, as well as the effects of systemic illness and substance abuse need to be considered carefully when interpreting results from neuropsychological testing. Age and education are particularly critical variables (28)

Table 2. Late Features of HIV Dementia
Global cognitive impairment
Mutism/abulia
Hyperreflexia, hypertonia
Diffuse release signs
Severe psychomotor retardation
Reduced insight/denial
Hallucinations
Spastic weakness: myelopathy, neuropathy
Sensitivity to neuroleptic agents
Seizures

2. Motor Motor complaints include poor handwriting, insecure balance, and a tendency to drop things easily. Gait difficulty is a relatively early symptom. Often they may develop a postural tremor, and occasionally, dystonia or choreoathetoid movements (29). Rarely, a subcortical myoclonus may manifest (30). These patients are inquisitively sensitive to extrapyramidal side effects of neuroleptic drugs (31). These symptoms are all suggestive of basal ganglia dysfunction. Neurological examination is often normal in the early stages of HIVD, although there may be impairments of rapid eye and limb movements and diffuse hyperreflexia. As HIVD progresses, increased tone develops, particularly in the lower extremities, and is usually associated with clonus, frontal release signs, and hyperactive reflexes. Some of these signs may reflect the effects of an accompanying HIV-related myelopathy (32). In some patients myelopathy is the predominant neurological problem, with severe paraparesis with only mild cognitive involvement. The clinical features include the progressive development of a spastic paraparesis, with variable sensory ataxia and bladder involvement. No sensory level is evident, and the arms are usually spared. Sensory neuropathy may develop concurrently. *Focal* neurological signs usually point to CNS opportunistic processes rather than HIVD.

Figure 4 HIV Dementia Scale Version 2.0 (Power et al., 1995)

Score Max

MEMORY - REGISTRATION

Give four words to recall (dog, hat, green, peach) - 1 second to say each. Then ask the patient all 4 after you have said them.

() 6

PSYCHOMOTOR SPEED

Ask patient to write the alphabet in upper case letters horizontally across and record time in seconds. 0-21 sec = 6; 21.1 - 24 sec= 5; 24.1 - 27 sec= 4; 27.1 - 30 sec= 3; 30.1 - 33 sec= 2; 33.1 - 36 sec= 1; >36 sec= 0

() 4

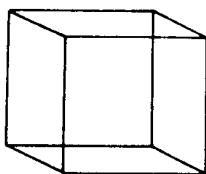
MEMORY - RECALL

Ask for 4 words from Registration above. Give 1 point for each correct. For words not recalled, prompt with a cue (see instructions).

() 2

CONSTRUCTIONAL

Copy 3D cube below - record time in seconds.<25 sec = 2; 25 - 35 sec= 1; >35 sec =0



____ / 12 Total. In general a score of <6/12 indicates a significant abnormality

3. Behavioral Friends and partners report change in personality with apathy and social withdrawal and blunting of emotional responsiveness. Considerable variability in presentation has been reported, and in 5% agitation or mania may be the initial manifestation. (5). The early symptoms are often subtle and may be overlooked or confused with psychiatric complaints, the effects of substance abuse, or delirium (see Table 2). Many of these patients are sensitive to the effects of sedatives, which may provoke delirium (33).

A functional scale developed by Dr. Richard Price is useful in monitoring the progression of HIV dementia (Table 3).

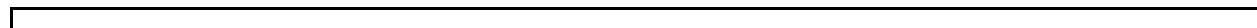
Table 3 Clinical Staging of HIV dementia: The "Memorial Sloan Kettering" scale	
Stage	Clinical description
Stage 0 (normal)	Normal mental and motor function
Stage 0.5 (equivocal/subclinical)	Absent, minimal, or equivocal symptoms without impairment of work or capacity to perform ADL. Mild signs (snout response, slowed ocular or extremity movements) may be present. Gait and strength are normal.
Stage 1 (mild)	Able to perform all but the more demanding aspects of work or ADL but with unequivocal evidence (signs or symptoms that may include performance on neuropsychological testing) of functional intellectual or motor impairment. Can walk without assistance.
Stage 2 (moderate)	Able to perform basic activities of self-care but cannot work or maintain the more demanding aspects of daily life. Ambulatory, but may require a single prop.
Stage 3 (severe)	Major intellectual incapacity (cannot follow news or personal events, cannot sustain complex conversation, considerable slowing of all outputs) or motor disability (cannot walk unassisted, requiring walker or personal support, usually with slowing and clumsiness of arms as well).
Stage 4 (end stage)	Nearly vegetative. Intellectual and social comprehension and output are at a rudimentary level. Nearly or absolutely mute. Paraparetic or paraplegic with urinary and fecal incontinence.

Differential Diagnosis In patients who present with mild cognitive impairment several possibilities need to be considered (see Table 4).

Table 4. Differential Diagnosis of Mild HIV Dementia
Anxiety
Depression
Alcohol
Recreational drugs
Medication side effects
Metabolic encephalopathy
Vitamin B ₁₂ deficiency
Drug interactions with protease inhibitors

In patients who present with dementia and motor abnormalities, several opportunistic infections need to be considered in the differential diagnosis. Differentiation from infections such as CMV encephalitis, cerebral toxoplasmosis, neurosyphilis, and cryptococcal or tuberculous meningitis is critical. Table 5 lists features that may be helpful in establishing the diagnosis of HIV dementia. Table 6 indicates the clinical features which distinguish HIV dementia from other CNS processes. A CNS opportunistic infection easily mistaken for HIV dementia is CMV encephalitis. Since the introduction of HAART, incidence rates of CMV disease have dropped considerably. Features distinguishing CMV encephalitis from HIV dementia include: co-existing CMV infection (retinitis, colitis, etc); hyponatremia reflecting CMV adrenalitis; and periventricular abnormalities on MRI consistent with a periventriculitis. Clinical features in children include microcephaly, progressive motor dysfunction and developmental delay, leading to loss of milestones, with death occurring within the first few years of life. (34, 35)

Table 5. Clinical Features Useful for Diagnosis of HIV-1 related Dementia
HIV-1 seropositivity
History of progressive cognitive/behavioral decline with apathy, memory loss, slowed mental processing
Neurological exam: diffuse CNS signs including slowed rapid eye/limb movements, hyperreflexia, hypertonia, and release signs
Neuropsychological assessment: impairment in at least two areas including frontal lobe, motor speed, and non-verbal memory
CSF analysis: exclusion of neurosyphilis and cryptococcal meningitis
Imaging studies: diffuse cerebral atrophy with ill-defined white matter hyperintensities on MRI, exclusion of opportunistic processes
Absence of major psychiatric disorder or intoxication
Absence of metabolic derangement, eg, hypoxia, sepsis
Absence of active CNS opportunistic processes



Disorder	HIV Dementia	CMV Encephalitis	PML
Features	memory, mental slowing, gait	delirium, seizures, brainstem signs	focal neuro signs
Course	several months	days-weeks	weeks-months
MRI	diffuse atrophy/ deep WM diffuse hyperintensity	normal or periventriculitis	subcortical WM lesions
CSF	non-specific: immune activation	PCR+ 90%	PCR+ 60%

AAN Criteria (1991)

HIV-1-associated dementia complex (ADC)

Criteria for 1 and 2 must be met:

1. Scores 1 SD below age- and education-adjusted norms on two of eight neuropsychological tests or 2 SDs below the norms on one of eight tests
2. Requires assistance or has difficulty (due to either physical or cognitive deficit) in one of the following IADL:
 - Using the telephone
 - Handling money
 - Taking medication
 - Performing light housekeeping
 - Doing laundry
 - Preparing meals
 - Shopping for groceries
 - Getting to places out of walking distance

and

Must meet either 1 or 2 of the following:

1. Any impairment in the following: lower extremity strength, coordination, finger tapping, alternating hand movements, leg agility, or performance on grooved pegboard 2 SDs below mean (dominant hand)
2. Self-reported frequent depression that interferes with function, loss of interest in usual activities or emotional lability, or irritability

HIV-1-associated minor cognitive/motor disorder

Does not meet criteria for HIV-1-associated cognitive/motor disorder and meets 1 and 2 of the following:

1. Deficit in at least two of the following:
 - Mental slowing: digit symbol at least 1 SD below age- and education-adjusted norms
 - Memory: Rey Auditory Verbal learning test (total) at least 1 SD below norms
 - Motor dysfunction: any impairment in finger tapping or pronation/supination
 - Incoordination: mild impairment in gait or clumsiness
 - Emotional lability or apathy/withdrawal

and

2. Deficit in at least one of the role function measures attributed in part to cognitive function:
 - Need for frequent rests
 - Cut down on amount of time in activities
 - Accomplish less than desired
 - Cannot perform activities as carefully as one would like
 - Limited in work or activities
 - Difficulty performing activities
 - Requires special assistance to perform activities

Survival with HIV dementia: Without treatment, HIVD is typically rapidly progressive, with a mean survival of about 6 months, less than half the average survival of non-demented AIDS patients (6, 36, 37). Occasionally, patients may remain mildly demented and cognitively stable until death. This variability is in part dependent upon the severity of immunodeficiency at the onset of dementia. Those with CD4 counts <100 progress more rapidly. Survival of patients has improved since the introduction of HAART.

Laboratory Findings

CSF.

Indication: The majority of patients with HIVD have minor CSF abnormalities identical to those found in neurologically normal HIV seropositives.

Lumbar puncture is important to exclude OI's in the patient with suspected HIVD who has fever or other atypical features(38). In a typical case, however, screening of peripheral blood for cryptococcal antigen, vitamin B₁₂, and RPR is adequate.

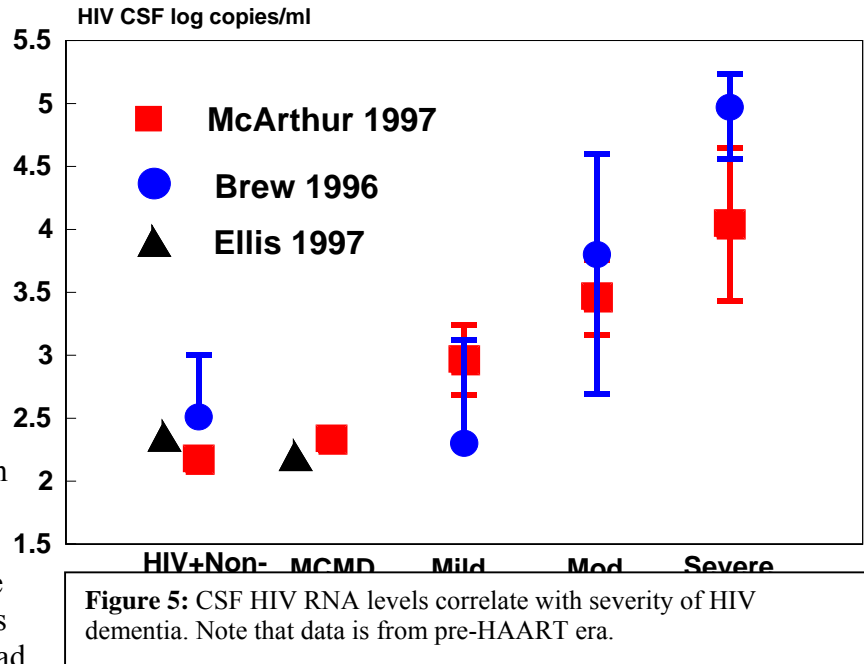
Findings: The CSF is usually acellular, or shows a mild lymphocytic pleocytosis. HIV-1-producing T cells appear in CSF and that their percentage and number correlate with cell-free viral load in CSF, even though the CSF total white cell count remains the best predictor for CSF viral load.

In HIV-1 infection, CSF white cell counts seem to contain a large number of uninfected cells. (39). Elevated total protein is found in about 65% of cases and increased total immunoglobulin (IgG) fraction in up to 80%. (40). Oligoclonal bands are found in up to 35%, but myelin basic protein is usually not elevated.

CSF viral load: In an individual patient, the absolute levels of CSF HIV RNA are not diagnostic of HIV-D. However, CSF HIV RNA levels correlate with the severity of dementia (Figure 5), and it is useful to measure CSF levels if dementia develops despite systemic virological suppression (41-44). The scenario of progressive HIVD with high CSF HIV RNA when plasma HIV RNA is suppressed is termed “CNS escape.” It is seen more frequently now that patients receive HAART for longer periods of time. Even with successful suppression of plasma HIV, there might be viral sequestration within the central nervous system, with “escape” of HIV replication.

Surrogate markers for HIVD in CSF: Several cytokine, chemokine, macrophage activation markers have been shown to be dysregulated in patients with HIV infection and particularly in patients with HIV-D. Examples of some of the recently published markers are shown in the table 7. However, none of these markers have penetrated clinical practice and none have been used as endpoints to monitor the effects of drug therapy in clinical trials. Most studies have been conducted with small numbers, eg sample sizes <20. Furthermore, it is more likely that a panel of markers (or the ratio of CSF:plasma, e.g., (45) may be more useful than a single marker in monitoring the effects of therapy.

There are currently several large ongoing studies in which CSF (or plasma) is being collected and neuropsychological testing is being performed. These cohorts include: the JHU Oxidative stress cohort (MH71150-01A1, P.I. N. Sacktor starting in January 2005); the NEAD-2 cohort (PI: Justin McArthur (NS049465); A5001 ALLRT (Neurology PI: Ron Ellis), the MACS (Neuro PI, N. Sacktor); and CHARTER (PI: Igor Grant) and the National Neuro-AIDS Tissue



Consortium. It is likely that these studies will lead to the development of better surrogate markers for HIVD.

Table 7: Recently identified markers for HIVD

Marker	Role	Reference
CSF		
Fractalkine	Associative	(46)
sFas	Associative	(47)
protein carbonyl	Associated with mild dementia	(48)
sphingolipid products	Associated with mild dementia	(49)
urokinase-type plasminogen activator	Associative	(50)
Blood		
4348 kD protein in cultured blood monocytes	Associative	(51)
MCP-1 polymorphisms	Predictive	(18)
Associative marker = correlates cross-sectionally; Predictive marker = longitudinal prediction (52)		

Prior to the use of ARTs, the immune activation marker, $\beta 2$ microglobulin, was useful in diagnosis, particularly in mild dementia in the absence of opportunistic infections (OI's), and a value >3.8 mg/dl has a positive predictive value of 88% (53-55). Quinolinic acid levels are also increased in patients with HIV dementia but is a non-specific finding (56, 57).

2. *Imaging studies.* Imaging studies are critical in the evaluation of suspected HIVD to exclude opportunistic processes. Table 8 contrasts the different radiological patterns.

Table 8. Radiological Pattern of HIV-related CNS Disease				
Disorder	Number	Pattern	Enhancement	Location
HIV encephalitis	diffuse	ill-defined	0	deep white
Toxoplasmosis	1 - many	ring mass	++	basal ganglia
1° lymphoma	1 - several	solid mass	+++	periventricular
PML	1 - several	no mass effect	0	subcortical white
Cryptococcus	1 - many	"lacunar"	0	basal ganglia
CMV encephalitis	1 - several	confluent	++	periventricular

The most commonly reported abnormality on CT scan of the brain is cerebral atrophy(58, 59) (Figure 7). Up to 50% of patients with mild neurologic deficits exhibit atrophy and/or white matter abnormalities on MRI (Figure 6) (60). Early atrophy is principally subcortical(61). The white matter changes may be extensive and confluent, patchy, or even punctate (Figure 6). The larger confluent abnormalities appear to be correlated neuropathologically with perivascular macrophages and extravasation of serum protein(62), suggestive of blood brain barrier compromise secondary to cerebral inflammation and with viral load(63). Any BBB breakdown, if present, must be subtle however, since these white matter abnormalities are generally considered to be non-enhancing (but see below).

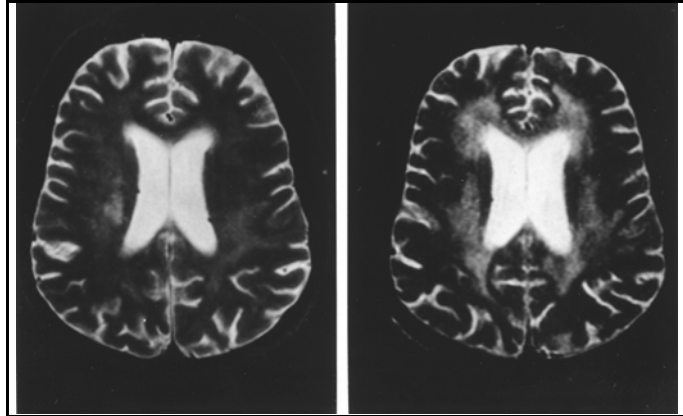
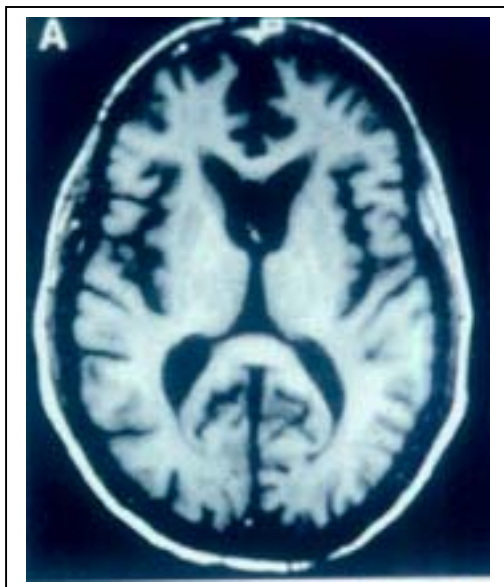


Figure 6. Progressive changes in the white matter on T-2 weighted MRI scans in a patient with HIVD taken 6 months apart

Atrophy and white matter abnormalities are generally not considered diagnostic, since they are also seen in 10-20% of neurologically normal seropositive patients (60). Furthermore, with the possible exception of the degree of caudate atrophy, these changes are poorly correlated with dementia severity (64), although there is some evidence that white matter changes in HIVD patients may be reversed by HAART, and that these changes may be associated with neurologic improvement (65). Profound cortical as well as subcortical atrophy, together with extensive confluent white matter abnormalities are common features of advanced dementia. In summary, routine radiologic studies serve principally to exclude other neurological disorders in seropositive patients, but have limited utility in the unequivocal diagnosis of HIV dementia.



Quantitative MRI at 1.5 T reveals no significant white matter enhancement, and a small but significant enhancement in sub-cortical gray matter consistent with BBB breakdown, which is correlated with dementia severity (66). Similar studies at 3 T find increased contrast enhancement in frontal white matter, suggesting that the earlier lower field study may have been limited by scanner sensitivity [L.

Figure 7. Cerebral atrophy in patient with HIVD: Note atrophy in the frontal and temporal cortex and basal ganglia. There is relative sparing of the posterior regions of the brain.

Chang, personal communication]. Among other advanced MRI techniques, diffusion tensor imaging (DTI) which probes microstructural changes in white matter, has demonstrated loss of fiber anisotropy in normal appearing white matter in neurologically normal seropositive subjects (67), while magnetization transfer contrast (MTC) imaging reveals

a significant reduction in the MT ratio in white matter lesions, possibly reflecting gliosis .

Metabolic imaging studies suggest early changes in subcortical gray and frontal white matter may precede the onset of motor-cognitive decline. Thus positron emission tomography (PET) reveals striatal hypermetabolism in patients prior to and early in the development of mild

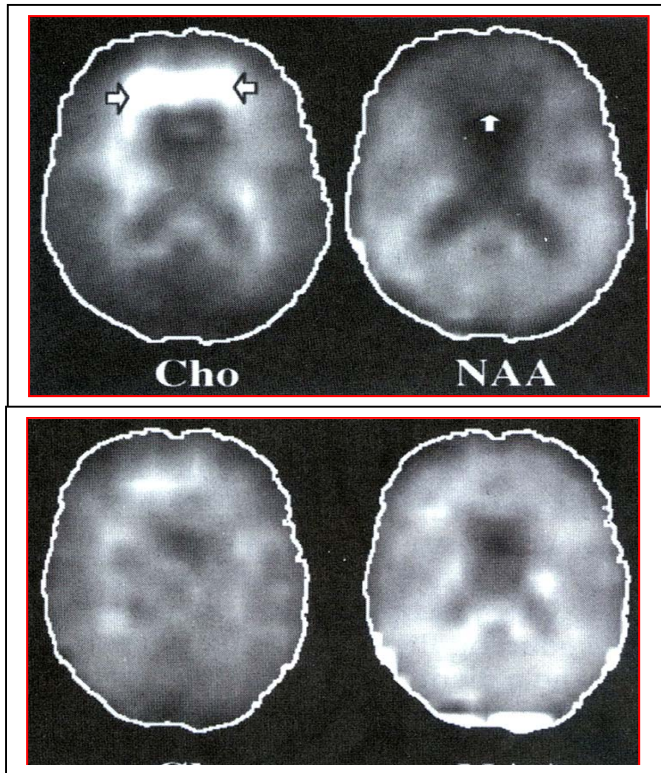


Figure 8: magnetic spectroscopic imaging in HIV-D. Top panel indicates increased choline (CHO) and reduced NAA in frontal lobes (arrow), compared to control subject in bottom panel. (reproduced from (1))

cognitive/motor impairment, with subsequent basal ganglia hypometabolism in the setting of more advanced disease(68-70). PET imaging reveals a decrease in dopaminergic transporters in the putamen compared to caudate which is similar to that seen in Parkinson’s disease(71). Magnetic resonance spectroscopy (MRS) reveals increased frontal white matter myoinositol, a marker of microglial activation, and decreased basal ganglia N-acetyl aspartate, a neuronal marker, in patients with mild cognitive motor decline as well as those with more advanced disease (72) (Figure 8). These metabolic changes suggest that neuronal stress and/or drop-out in the basal ganglia, either in parallel with, or as a result of activation of CNS inflammatory pathways, underlie the development of dementia (73).

Source of CSF HIV RNA. One of the main questions in interpreting CSF HIV RNA levels is whether the CSF reflects brain tissue levels. Potential sources of CSF HIV RNA include meninges, choroid plexus,

parenchyma, and trafficking lymphocytes. Presumably, the parenchymal levels are the most relevant for the study of neurological disease. From the studies to date, we do not have a clear answer to this. CSF HIV RNA might derive from different sources at different stages of HIV infection. Price and Staprans discuss this in an editorial, and use the phrases “transitory” infection (trafficking cells) and “autonomous” infection (parenchymal infection of macrophages and microglia) (74). The Johns Hopkins group has shown that different brain regions have similar levels of HIV RNA, but there is only a weak correspondence between brain and CSF HIV levels (9, 75) Wiley et al. showed that CSF levels and parenchymal levels did not correlate when CSF levels were low (less than 10^5 copies/ml), but did correlate when CSF levels exceeded 10^6 copies/ml (76).

Pathogenesis of HIV dementia

Mechanism of viral entry across the blood brain barrier: While it is possible for HIV infected lymphocytes, free viral particles and some HIV proteins to cross the intact blood brain barrier (BBB), the BBB may also be disrupted in HIV infection. This occurs as a consequence of CNS

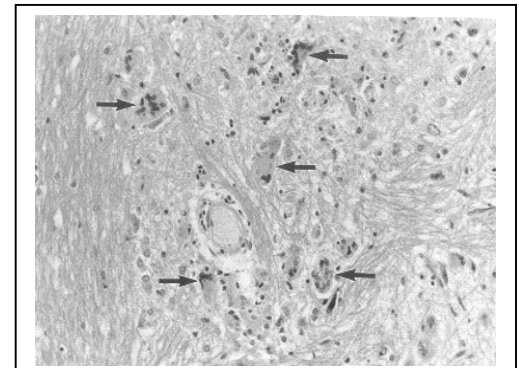
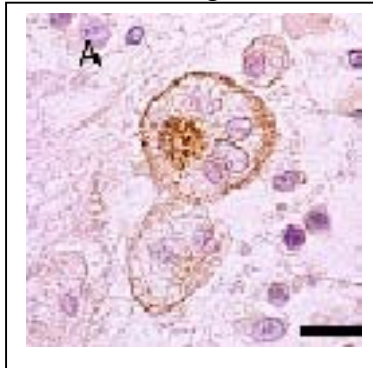
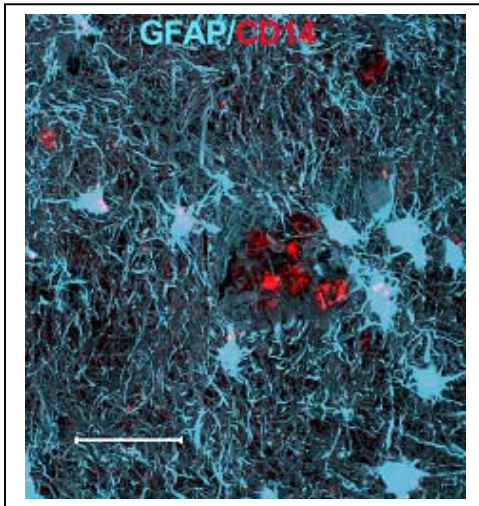
endothelial cell dysfunction and/or because of changes in proteins of the basal lamina (see table). A compromised BBB also allows entry of free viral particles and infected monocytes into the brain. These cells may enter through tight junctions or more likely, by pushing their way through the capillary endothelial cells (77). In addition, elevated levels of metalloproteinases within the CNS (78) can weaken the basal lamina so that migrating leukocytes will more easily make their way through (79, 80). Activated astrocytes produce MCP-1 which is the most potent chemokine for monocytes which aids the influx of monocytes into the brain (45, 81).

Cell types Infected: Two cell types, monocyte-derived cells (microglia and macrophages) and astrocytes, clearly have been shown to be infected by HIV (82-88). However, these cells differ from each other in several biological aspects and the manner in which they express HIV products (see table 9).

Table 9: Characteristics of microglial and astrocytic infection

	Microglia	Astrocytes
Predominant viral strains	monocytotropic	lymphotropic
Morphological changes	Vacuolation, multinucleated giant cell formation, cytopathic infection	No morphological changes, non-cytopathic infection
Viral replication	productive	Restricted, latent, inducible by cytokines, over production of regulatory proteins Nef and Rev
Viral receptors	CD4, CCR5, CCR3	Mannose receptor

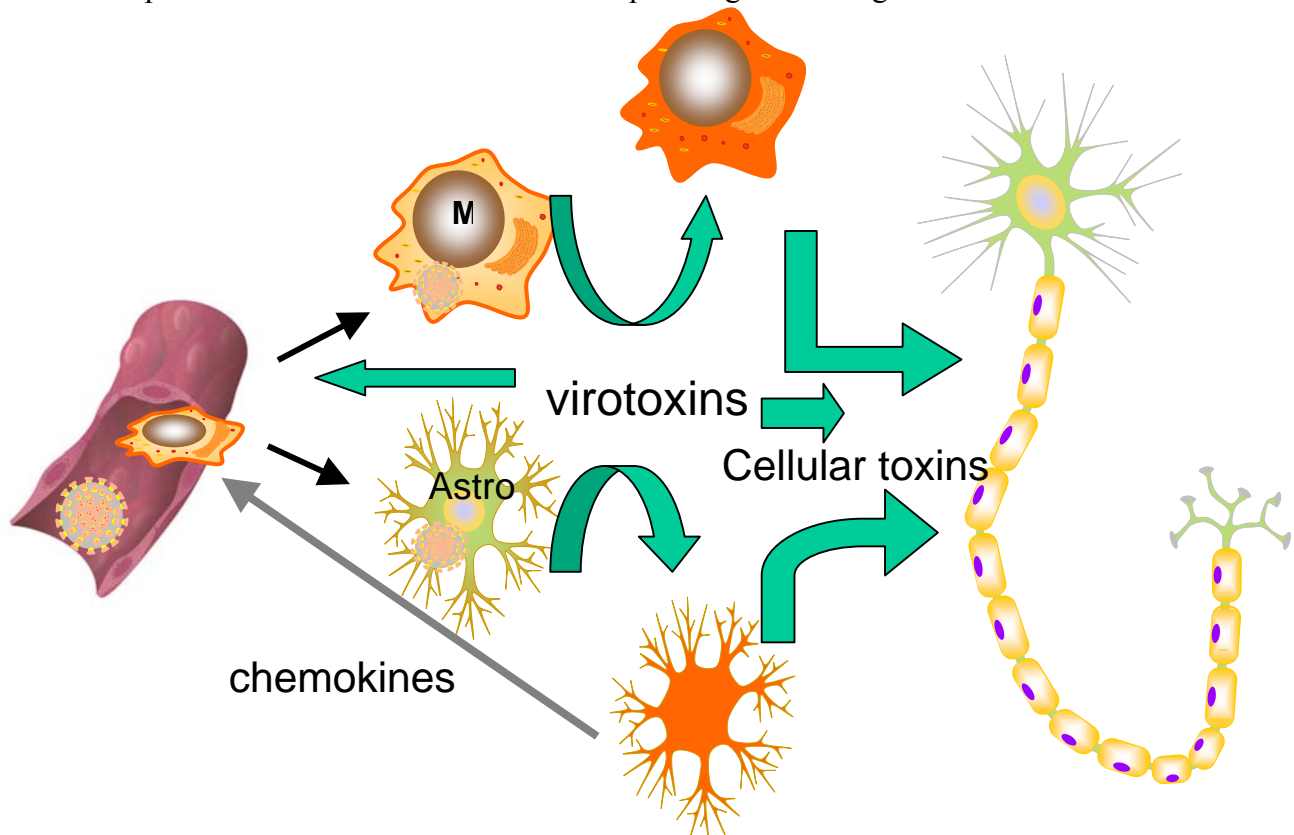
Viral evolution in the CNS: HIV strains may evolve within the central nervous system (89) (Cheng-Mayer et al., 1989; Chesebro et al., 1992; Chiodi et al., 1989). How these strains may contribute to the pathogenesis of HIV dementia and drug resistance is currently under intense investigation.



. Histopathological findings in HIVE: (A) A confocal image showing prominent astrocytosis (blue) and infiltrating macrophages (red) (kindly provided by Carlos Pardo, Johns Hopkins University). (B) MNGC immunostaining for gp120 (brown). (C) Multiple MNGC in the perivascular regions (arrows)

Pathology and Neuronal cell loss: The pathological hallmark of HIV-1 infection of the brain is the presence of multinucleated giant cells in the brain which are formed by a syncytia of HIV-1 infected macrophages(90). Prominent dendritic pruning (91), loss of synaptic density(92) and neuronal cell loss (93, 94) may occur within infection of the neurons suggesting that neuronal dysfunction maybe indirectly mediated. Neuropathological changes are most prominent in the basal ganglia (94) and the hippocampus. Neuronal losses of 50-90% were observed in interneurons of the hippocampus (91) as well as the pyramidal and non-pyramidal cells in the hippocampus (95, 96). Neuronal cell loss has also been shown in the substantia nigra (97) and globus pallidus (98). Cortical pathology is characterized by loss of large neurons in the orbitofrontal cortex (99, 100). Temporal and parietal cortices were found to have a 20% reduction in cortical width (101). The occipital cortex seems to be relatively spared. Despite these profound neuronal changes, neurons are only rarely infected. This suggests that products released from HIV infected cells must be directly or indirectly responsible for causing neurotoxicity. These products can be broadly classified into two groups. Those encoded by the viral genome have been termed virotoxins and those encoded by the host genome have been called cellular toxins (102) (see table---). It is likely that the viral products can activate glial cells setting up a chain of events leading to neuronal dysfunction at distant regions.

Important differences between the neuropathological finding in children and adults is the



vascular mineralization and calcification in the basal ganglia and the absence of white matter pallor in children.

Hit and run phenomenon and synergistic neurotoxicity: Prolonged continuous exposure to the viral proteins may not be necessary to induce neurotoxicity. Rather, a transient exposure may be sufficient to trigger a cascade of events that eventually result in neuronal damage (103, 104). These viral proteins, once available in the extracellular environment may cause neurotoxicity either by direct action on the neuronal cells or may activate glial cells to cause the release of neurotoxic substances (Figure 3). Their ability to activate glial cells allows the viral proteins to amplify their neurotoxic potential and cause damage at distant sites. Further, the viral proteins may synergise with one another or with other neurotoxic substances such as glutamate to cause neurotoxicity (105). In doing so, subthreshold levels of virotoxins and cellular toxins could combine together to cause neurotoxicity. Summarized below is an exhaustive review of the effects of viral proteins on brain cells.

Table 8

Structural proteins	Neurons		Astrocytes		Macrophages/microglia		Endothelial cells		Progenitors
	<u>Up regulation/activation</u>	<u>Down regulation</u>	<u>Up regulation/activation</u>	<u>Down regulation</u>	<u>Up regulation/activation</u>		<u>Up regulation/activation</u>	<u>Down regulation</u>	<u>Down regulation</u>
Gp120	Ca uptake via L-type Ca channels	BDNF	iNOS	β-adrenergic function	TNFα		Cytotoxicity/apoptosis		proliferation
	CXCR4	Neuron specific enolase	Tyrosine kinase		IL-1β		ICAM-1		ERK
	Apoptotic pathways	MAP kinase	Na/H exchange	Glutamate influx	PGE-2		Mu opioid receptor		
	Oxidative stress	Dopamine transport	Release of arachidonic acid	GFAP	Oxidative stress		PKC		
	sphigomyelinase		ROS release	glutamate transporter EAAT2	p53				
	p53		cyclic GMP phosphodiesterase		Ntox				
	JNK and ERK		ICAM-1		Release of arachidonic acid				
	CXCL10		CXCL10		TGFβ-1				
	mixed lineage kinase 3		Endothelin-1		large-conductance apamin-sensitive potassium channels				
	PKC		CD23		Endothelin-1				
	Glutathione peroxidase				No effect on quinolinic acid production				

	corticotropin-releasing hormone, vasopressin in hypothalamus								
	Glycine site of NMDA receptor								
	Nor-adrenaline release								
Gp41		glutathione	Glutamate release	amyloid precursor protein release	IL β -1		No effect on T cell or monocyte adhesion		
			complement factor C3		No effect on quinolinic acid production				
			iNOS						
			IL-10						
Tat	Polyamine sensitive site and Zn allosteric site of NMDA receptor	neprilysin	MCP-1, RANTES	Glutamate uptake	TNF α	cAMP	Oxidative stress	claudin-1, claudin-5, and ZO-2	*Proliferation of neuronal cells
	Phosphorylation of NMDA receptor	LRP ligands	iNOS		CCR5		MCP-1, IL-6, IL-8	No effect on occludin and ZO-1	*histone H3/H4-acetylation
	Ca release from IP-3 pools	Dopamine release	IL-6, IL-8, IP-10		IL-1 β , IL-6		E-selectin		Cytotoxicity of glial precursors
	Ca uptake via VOCC	Neuronal organization	MMP-1 and -2		chemotaxis		T-cell adhesion		
	Oxidative stress		Id-1		Platelet activating factor		NF-kB, AP-1, PKC		
	Apoptotic cascade		GFAP		Quinolinic acid		FAK		
	Endonuclease G		Ant-apoptotic pathways				iNOS and e-NOS		

	Par-4		XCL1					
	Acetyl choline release		VCAM-1, ICAM-1					
	Neurotoxicity in CA3 neurons of hippocampus		PKC, NF-kB					
	long-term potentiation		PrP					
	GSK-3 β							
	MAP kinase		MAP-kinase					
Nef	neurotoxicity		astrocytosis		MMP-9			
			IP-10		Quinolinic acid			
			MAP-kinase, JNK, PKC					
Vpr	Apoptotic pathways		necrosis					
	Forms ion channels							

VOCC= voltage operated calcium channels; ICAM=Intercellular adhesion molecule-1; JNK= c-Jun N-terminal kinase; ERK= p42 extracellular-regulated kinase; PKC=protein kinase C; LRP= low-density lipoprotein receptor-related protein receptor; PrP=Prion related protein; Focal adhesion kinase; ZO= zonula occludens

For complete set of transcripts modulated by gp120 by microarray analysis and subtractive hybridization see Galey et al 2003 and Su et al., 2004

* Tat effects represent effects in neuroblastoma cells or PC12 cell line

Treatment of HIV dementia

1. *Antiretroviral therapy: CNS penetration.* There have been several important advances in the past few years which have led to concrete improvements in the care and prognosis of HIV-infected individuals. The first is an understanding of the direct relationship between viral replication and immunologic disease progression, which reinforces the need to suppress viral replication at the earliest point to control the infection. This has led to the so-called “Hit Early, Hit Hard” philosophy arising out of the 1996 reports showing that HAART could suppress viral replication in patients who began therapy early in the course of their HIV disease. The second is the wider availability of multiple, potent antiretroviral regimens that can be combined in various ways to provide effective suppression of HIV. The third major change is the ability to monitor the response to therapy through regular 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 or phenotypic assays. In patients who fail to achieve HIV suppression with antiretroviral therapy it is often uncertain whether this reflects development of resistance, incomplete adherence, or inadequate delivery of antiretroviral agents to the target site. This is potentially of even greater importance for the treatment of CNS infection given the relatively limited penetration of most of the available antiretroviral agents.

Today, a typical antiretroviral regimen consists of at least three agents: one to two protease inhibitors or a non-nucleoside reverse transcriptase inhibitor combined with two nucleoside analogs. The goal of therapy is to reduce measurable plasma viral burden to "below the level of detection". In patients with HIV dementia the goal should be to maximize the number of CSF penetrating ARTs that the patient is on and to achieve virological control in CSF as well. Viral load testing has made it possible to individualize therapy and to more accurately determine the best time to initiate or change therapy, long before declining CD4+ counts would have given evidence of active viral replication. The published pharmacokinetic data for CSF penetration for available agents is shown in Table 9 below.

CSF-penetrating ARTs are defined as those drugs with CSF concentrations (as determined by the median concentration from human studies) that exceeds the level needed to inhibit replication of HIV (as determined by the median 50% inhibitory concentration in the ViroLogic PhenoSense assay(106)). Specifically, these are stavudine (D4T), zidovudine (ZDV), abacavir (ABV), efavirenz (EFV), nevirapine (NVP), and indinavir (IDV). (107). At this point it is not entirely clear what the optimum regime is for treating HIV-D. Recent data suggests that neurological improvement is better with the use of regimens that contain several drugs which potentially enter the CSF (108).

Table 9: Antiretroviral Drugs - Generic and Trade Names, Characteristics

Generic Name	Abbreviation	Trade Name	Manufacturer	Usual Dosage	Common Side Effects (Comments)
Nucleoside RT inhibitors					
zidovudine	AZT, ZDV	Retrovir	Glaxo Wellcome	300 mg BID	Bone marrow suppression, GI upset, headache, myopathy
didanosine	ddI	Videx	Bristol Myers	200 mg BID	Peripheral neuropathy,

			Squibb	(125 mg BID if <60 kg) or 300-400 mg qd	pancreatitis, diarrhea (take on empty stomach)
zalcitabine	ddC	HIVID	Roche	0.75 mg TID	Peripheral neuropathy, pancreatitis, oral ulcers
stavudine	d4T	Zerit	Bristol Myers Squibb	40 mg BID (30 mg BID if <60 kg)	Peripheral neuropathy
lamivudine	3TC	Epivir	Glaxo Wellcome	150 mg BID	Anemia, GI upset
abacavir	ABC	Ziagen	Glaxo Wellcome	300 mg bid	GI upset, hypersensitivity reaction
adefovir	ADV	Preveon	Gilead	60-120 mg QD	GI upset, elevated transaminases, nephrotoxicity (must take with L-carnitine 500 mg/day)
Non-nucleoside RT inhibitors					
nevirapine	NVP	Viramune	Roxane/Boehringer Ingelheim	200 mg qd X 14 Days then 200 mg BID	Rash
delavirdine	DLV	Rescriptor	Upjohn	400 mg TID	Rash
efavirenz	EFV	Sustiva	DuPont Merck	600 mg QD	Dizziness, nightmares, 'disconnectedness', rash
Protease inhibitors					
saquinavir	SQV	Invirase Fortovase	Roche	600 mg TID 1200 mg TID	(Take with a fatty meal, or up to 2 hours after meal)
indinavir	IDV	Crixivan	Merck	800 mg q 8 hr	Kidney stones, hyperbilirubinemia (take on an empty stomach)
ritonavir	RTV	Norvir	Abbott	600 mg BID	GI upset, circumoral paresthesias, diarrhea, fatigue
nelfinavir	NFV	Viracept	Agouron	750 mg TID or 1250 mg BID	Diarrhea (take with food)
amprenavir	141W94	Agenerase	Glaxo Wellcome	1200 mg BID	Rash, headache, GI upset

Drugs in shaded boxes have the best CSF penetration

Antiretroviral therapy: effect on HIV levels in the CSF. There is relatively little information about the effects of antiretroviral therapy on CSF constituents of HIV levels. In patients with HIVD, measurement of response to therapy has traditionally relied upon changes in neuropsychological tests. As new therapies are considered and tested, so are alternative methods to measure neurological response being developed. CSF HIV RNA levels have not yet been validated as a measure of treatment effect, but changes appear to bear a relationship to neurological function. Improvements in neuropsychological performance correlates with declines in CSF HIV RNA levels. Those who did not show CSF HIV RNA decreases did **not** have neuropsychological improvement. (9, 107).

The CSF penetrance of the protease inhibitors is poor, however, emerging studies have reported successful suppression of HIV in CSF with long term use of protease inhibitors. Collier et al reported that nine of ten patients on chronic indinavir therapy had CSF HIV RNA less than 200 copies/ml with a range of CSF indinavir levels from 51 to 449 nM, above the IC95. In

another 9 individuals with CSF HIV levels determined before initiation of indinavir, and then after 8 weeks of therapy, significant reductions were observed. Findings from another study that included pharmacokinetic modelling indicate that indinavir is actively transported out of the CSF (P 0.001 compared with a passive transport-only model) (109). In a similar study, (110) a strong correlation was found between plasma and CSF HIV RNA levels ($r = 0.870$; $p .001$). in a treatment trial with ritonavir and saquinavir. The plasma:CSF HIV RNA ratio was high before or early in treatment (median, 38; interquartile range [IQR], 13,97), but low (median, 0.29; IQR, 0.17, 7.5) in those failing therapy (group C, $p .001$). Low levels of saquinavir (2 ng/ml) and ritonavir (25 ng/ml) in the CSF were observed, with a CSF:plasma drug concentration ratio of or = 0.005 (0.5%) in all study subjects evaluated ($n = 11$) The authors concluded that the low drug levels and inverted ratio of HIV RNA in the CSF compared with plasma early in plasma virologic breakthrough suggests CSF virologic failure may contribute to failure of plasma virologic response. Nelfinavir levels in the CSF were undetectable (111).

In a pilot study, we examined plasma and CSF HIV RNA in 35 patients at variable times after the initiation of HAART. CSF HIV RNA levels were suppressed to undetectable levels in only 50% after 6 months of therapy. Self-reported adherence was a significant factor in the success of therapy, with “poor” adherence associated with virological suppression in only 25%. Significantly better virological suppression was observed in a carefully monitored study using abacavir in combination with other ART’s. (112). The drug also has good CSF penetration (113). Interruption of HAART has been shown to have a rebound effect on CSF viral load and pleocytosis(114)

Kinetics of virological suppression. Two studies examined the kinetics of changes in CSF HIV RNA levels after the initiation of HAART. In one study of two patients, five CSF samples were obtained over one week. (44). The half lives of plasma HIV RNA were 0.94 and 1/0 days, falling by approximately one log over 4 days. The half life in the CSF compartment was 5 days, falling by one log over 20 days. A second kinetics study also showed that CSF suppression might lag plasma response. Staprans et al, evaluated 8 subjects with 3-5 LP’s after initiation of HAART. Neurologically normal subjects showed rapid reductions in CSF HIV RNA levels that paralleled declines in plasma. By contrast, two demented subjects had markedly slower declines in HIV levels in CSF than plasma. A slower decay in the CSF correlates with lower initial blood CD4 T lymphocyte counts (115).

Drug Interactions

Drug interactions involving antiretroviral agents have become increasingly important with the introduction of combination therapy involving protease inhibitors and non-nucleoside reverse transcriptase inhibitors (NNRTIs) (Table 3; <http://aidsinfo.nih.gov/drugs>). In fact, one of the most widely used protease inhibitor combinations uses this interaction to boost levels of lopinavir in combination with low dose ritonavir. All protease inhibitors are substrates and inhibitors of the hepatic cytochrome p450 enzyme system. Ritonavir is the most powerful inhibitor, saquinavir the weakest, and indinavir and nelfinavir are intermediate. Examples of drug interactions arising from inhibition of cytochrome p450 include the increases in rifampin and rifabutin levels with ritonavir, and to a lesser degree, with the other protease inhibitors. Some protease inhibitors are also inducers of cytochrome p450. Examples of this type of

interaction include the lowering of ethinyl estradiol, triptans, Viagra and zidovudine levels by nelfinavir and ritonavir.

Dual protease inhibitor regimens make use of drug interactions to increase drug levels and/or prolong half-lives. Ritonavir increases saquinavir levels by more than ten-fold, allowing saquinavir to be given at a reduced dose twice daily. Nelfinavir also increases saquinavir levels, but the effect is less dramatic and does not allow dose reduction. Ritonavir also increases drug levels of nelfinavir and indinavir.

The NNRTIs are also metabolized through the CYP3A pathway, leading to significant drug interactions with protease inhibitors. Nevirapine induces cytochrome p450 enzymes, leading to reductions in protease inhibitor levels. In contrast, delavirdine inhibits cytochrome p450 and increases protease inhibitor levels. With both drugs, the effect is greatest with saquinavir, intermediate with indinavir, and negligible with ritonavir. There are conflicting data on drug interactions between nevirapine and nelfinavir. Efavirenz is both a modest inhibitor and a modest inducer of the cytochrome P450 system. While it decreases indinavir levels and reduces saquinavir levels by 61%, it increases the AUC of nelfinavir by 20%. Of importance to neurologists are the anticonvulsants. Drugs such as phenytoin, carbamazepine and phenobarbital should be used with caution and if used drug levels and viral loads should be closely monitored. Alternative anticonvulsants such as topiramate and gabapentin may be considered.

Interactions with recreational drugs (reviewed in(116)): All protease inhibitors (PIs) and nonnucleoside reverse transcriptase inhibitors are substrates and potent inhibitors or inducers of the cytochrome P450 system. Many classes of recreational drugs, including benzodiazepines, amphetamines, and opioids, are also metabolized by the liver and can potentially interact with antiretrovirals. Controlled interaction studies are often not available, but clinically significant interactions have been observed in a number of case reports. Overdoses secondary to interactions between the "rave" drugs methylenedioxymethamphetamine (MDMA) or gamma-hydroxybutyrate (GHB) and PIs have been reported. PIs, particularly ritonavir, may also inhibit metabolism of amphetamines, ketamine, lysergic acid diethylamide (LSD), and phencyclidine (PCP). Case series and pharmacokinetic studies suggest that nevirapine and efavirenz induce methadone metabolism, which may lead to symptoms of opiate withdrawal. A similar interaction may exist between methadone and the PIs ritonavir and nelfinavir, although the data are less consistent. Opiate metabolism can be inhibited or induced by concomitant PIs, and patients should be monitored for signs of toxicity and/or loss of analgesia. PIs should not be coadministered with midazolam and triazolam, since prolonged sedation may occur.

Table 10. Drugs That Should Be Avoided With Protease Inhibitors

Drug Category	Indinavir	Ritonavir *	Saquinavir	Nelfinavir	Alternatives
Analgesics	(none)	meperidine piroxicam propoxyphene	(none)	(none)	ASA oxycodon acetaminophen
Anti-Mycobacterial	rifampin	rifabutin **	Rifampin rifabutin	rifampin	For rifabutin(as alternative for MAI treatment): clarithromycin, ethambutol (treatment, not prophylaxis), or azithromycin
Antihistamine	astemizole terfenadine	astemizole terfenadine	Astemizole terfenadine	astemizole terfenadine	loratadine
GI	cisapride	cisapride	Cisapride	cisapride	limited experience
Antidepressant	(none)	bupropion	(none)	(none)	fluoxetine

					desipramine
Neuroleptic	(none)	clozapine pimozide	(none)	(none)	limited experience
Psychotropic	midazolam triazolam	clorazepate diazepam estazolam flurazepam midazolam triazolam zolpidem	(none)	midazolam triazolam	temazepam lorazepam
Ergot Alkaloid	dihydroergo tamine ergotamine (various forms)	dihydroergotami ne ergotamine (various forms)	Dihydroergota mine ergotamine (various forms)	dihydroergotam ine , ergotamine*** (various forms)	limited experience
Miscellaneous	Grapefruit juice reduces indinavir levels by 26%	Desipramine increased 145%: reduce dose Theophylline levels decreased: dose increase	Grapefruit juice increases saquinavir levels **		

The contraindicated drugs listed are based on theoretical considerations. Thus, drugs with low therapeutic indices yet with suspected major metabolic contribution from cytochrome P450 3A, CYP2D6, or unknown pathways are included in this table. Actual interactions may or may not occur in patients.

** Reduce rifabutin dose to one quarter of the standard dose.

** This is likely a class effect. * Reduce rifabutin dose to one quarter of the standard dose (150

* mg qod).

CNS penetration of ART: Groothuis and Levy have summarized some of the issues in relating plasma CSF and brain concentrations of antiretroviral agents(117). They stress that drug concentrations in the different compartments may be quite different, and that using CSF concentrations to estimate brain extracellular fluid levels may overestimate the latter. The estimation of brain tissue levels of drug needs to take into account not only the plasma concentration, but also the degree of protein binding and lipophilicity. Additional factors which will end to lower tissue levels include diffusion in brain tissue, and a lack of correction for drug which is within the intravascular space. (118). The CSF: plasma ratios for available antiretrovirals are very variable, reflecting individual drug differences in lipid solubility molecular size and the state of ionization. In fact, the relevance of this ratio to actual brain concentrations is uncertain, and relatively few data are available. As an example, the CSF: plasma ratios for several antiretroviral drugs are based on a few patients samples, and usually do not include patients with HIVD, where the blood-brain-barrier may be more permeable. (119)

Enhancement of ART delivery to brain: Important factors that prevent ART entry into brain include the active efflux of protease inhibitors by p-glycoprotein on brain endothelial cells(120). For the NRTI's, organic acid transport systems may mediate the penetration into the brain and

CSF, although their clinical importance is undefined (121, 122). Inhibitors of p-glycoprotein (eg, 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 encephalitis. To date, the selective inhibition of these efflux systems has not entered clinical practice.

The effects of combination ART on dementia: A substantial proportion of individuals with HIV-D or MCMD actually show partial reversal of neuropsychological deficits. For example, Cohen and colleagues(123) 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(124) also found sustained improvements in neurocognitive performance after 6 months of HAART therapy, as did Ferrando's group(125). 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. 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(126).

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., unpublished study). Abacavir had been shown to have good CSF penetration and was active in macrophages, HIV's principal target cell within the brain. (Brew, et al, 1998) Ninety-nine individuals with HIVD were randomized to add abacavir, 600 mg BID, or placebo, onto stable background ART. The patients were heavily pretreated with ART, and in fact only 10% had wild type virus at entry. Perhaps surprisingly, very few subjects showed neurological deterioration during the 12 weeks of the study: Only 2 in the placebo group, and none on abacavir. Overall, both groups showed improvements in neuropsychological performance on standardized tests, with a trend favoring abacavir. The more severely impaired group on abacavir showed a greater improvement than placebo recipients. The CSF virological response favored abacavir with a 0.64 log drop during the study, while the placebo group showed a rise of 0.25 log. Improvement in neuropsychological performance was also seen in both treatment groups. Abacavir did reduce CSF viral load to great extent than background ART. There are multiple important implications from this study including: a) single changes in ART are not likely to be very effective; b) the progression of dementia may be different in an era when combination therapies are used; and c) other types of outcome measures, in addition to neuropsychological testing may be needed to detect changes.

Difficulties with antiretroviral therapy of HIVD

1. Drug resistance: The role of resistance testing may become important in selection of ART combinations for demented patients, most of whom are heavily pre-treated and are likely to have multiple resistance mutations (as in the abacavir trial where 90% of subjects had resistance mutations at baseline). There is no direct utility from examining resistance patterns in CSF because there is generally concordance between the CSF and plasma with respect to genotypic resistance mutations.
2. Drug adherence: Adherence is important in maintaining virological suppression, particularly

in patients with cognitive impairment. New techniques for improving adherence including directly observed therapy, pill counts, intensive education, and electronic monitors, and being applied to this problem.

3. Lack of suitable animal model: One of the difficulties in designing effective therapies for HIV dementia is the lack of usable animal model of CNS disease to test new therapies. Neither the FIV or SIV models have been widely used to test therapies to block the pathological or behavioral changes of encephalitis. SCID mice (which have severe immunodeficiency) inoculated intracerebrally with HIV-infected monocytes show promise as a “test bed” for new dementia therapies (127). Despite some limitations, this model may permit screening of both new antiretroviral agents as well as the adjunctive therapies which may block the pathophysiological events leading to neural injury.
4. Lack of effect on virus post integration: Once the virus gets integrated, the available ARTs have no effect on the cellular reservoirs. Protease inhibitors may still prevent new viral particles from being formed, but the production of early viral proteins may continue. Some these early proteins such as Tat have neurotoxic properties, thus there is a need for development of antiretroviral strategies that act earlier in the life cycle of the integrated virus.

Neuroprotective agents for HIV Dementia

Since the neurons themselves are not infected with HIV but rather succumb to soluble mediators released from other HIV infected cells or activated glial cells, there is an excellent opportunity to try and develop reagents that may block these pathways(128). Extensive research into the neuropathogenesis of HIV dementia has suggested that normal defense mechanisms against microbial agents such as oxidative burst by macrophages and cytokine production are greatly activated in patients with HIV infection. However, these defense mechanisms are not effective in getting rid of the virus. These substances in turn have neurotoxic properties(129). Hence controlling their production may be of therapeutic benefit in patients with HIV infection. Interestingly, HIV has adapted itself to the host in ways such that products from these very anti-microbial defense mechanisms, such as free radicals and TNF can actually lead to enhanced viral replication (130, 131). This sets up a detrimental positive feedback loop, interruption of which may be neuroprotective.

Due to the absence of good surrogate markers of HIV dementia, definitive studies require large numbers of patients that can be accomplished only by multicenter studies. These studies are also expensive thus limiting the number of agents that can be tested. Due to the changing pattern of antiretroviral therapy, the neuroprotective agents have to be used in conjunction with the best antiretroviral regimen that makes the studies challenging to analyze. Further, the batteries of neuropsychological testing, methods of analysis and reporting strategies also vary between the studies, making them difficult to compare. Several early phase 2 studies with small sample sizes have been conducted where the primary end point was safety and tolerability while efficacy was a secondary outcome measure. Even though most of these drugs were shown to be safe, only two late phase 2 studies have been conducted, one with peptide T and another with memantine while yet another one with selegiline is underway. In these three studies efficacy was the primary endpoint. To date not a single phase 3 trial has been conducted with these agents in patients with HIV dementia. Although no clear therapeutic efficacy in neuropsychological performance has been noted with any of the agents tested so far, and the early phase 2 studies

were not powered to do so, careful analysis of these studies did show that some of the individual neuropsychological tests either showed statistically significant or a trend for improvement with the tested drug (Table). In general, none of the drugs had any significant effect on CD4 cell counts or surrogate markers such as beta-2 microglobulin or neopterin in blood or CSF where studied. None of these drugs have yet penetrated clinical practice in HIVD.

Table: Placebo controlled trials of neuroprotective therapy in HIV dementia

Agent	Action	Patients* #enrolled/ #completed	Dosage	Concomitant antiretroviral therapy	Duration of study	Conclusions
Nimodipine	L-type calcium channel antagonist	P=11/7 D (high dose)=13/10 D(low dose)=14/11	60mg, 5 times/day 30 mg, 5 times/day	NRTI	16 weeks	Trend for improvement in NP at highest dose only
Peptide T	Possibly chemokine receptor blockade	P=109/77 D=106/66	2mg, 3 times/day intranasally	NRTI	6 months	No effect
OPC-14117	Anti-oxidant	P=15/9 D=15/7	240mg/day	NRTI	12 weeks	Trend for improvement in memory and time gait test
Selegiline	Anti-oxidant, neuroprotectant	P=9 Selegiline=9 Thioctate=9 Both=9	Selegiline- 2.5mg, 3 times a week Thioctate- 1200mg/d	NRTI	10 weeks	Improvement in verbal learning. Trend for improvement in recall and psychomotor speed
Selegiline Transdermal system	Anti-oxidant neuroprotectant	P=5/4 D=9/8	1.0mg/cm X 15cm ² patch	NRTI	10 weeks	Positive effect on NP
Lexipafant	PAF antagonist	P=14/13 D=16/14	500mg/day	HAART	10 weeks	Trend for improvement in verbal learning and timed gait
Memantine (Navia B, submitted)	NMDA antagonist	140	40mg/day by week four	HAART	16 weeks	Trend for NP improvement (only 4 wk after completion of double-blind phase). Significant improvement in MRS
CPI-1189	TNF antagonist	P=21/16 D(high dose)=22/20 D(low dose)=22/20	100 mg/day; 50 mg/day	HAART	10 weeks	No effect on neurocognition. Improvement in peg board test at highest dose

*P= placebo, D=drug.; NP=neuropsychological tests

Table: Experimental approaches

Class of a compounds	Available for clinical use
Estrogens/flavinoids	

Selenium	
Neurotrophic agents	BDNF
Glutathione mimics	N-acetyl-cysteine
Anti-TNF agents	Thalidomide, pentoxifylline, Rolipram, Perfenidone
Anti-glutaminergic agents	Ramecimide, Riluzole, Limotrogine, Pentamidine
GSK inhibitors	Lithium, Valproate
MMP inhibitors	

Symptomatic treatment. Patients with HIV dementia are extremely susceptible to the adverse effects of psychoactive drugs, so hypnotics and anxiolytics should be avoided (31, 132)

- a) Neuroleptics: Atypical antipsychotics are the drugs of choice due to its selective action on D3 and D4 receptors(133). However, olanzapine is metabolized primarily by CYP1A2 and glucuronosyl transferases, both of which are induced by the HIV protease inhibitor ritonavir. Hence higher dosages of olanzapine may be needed if administered with other liver enzyme inducing agents(134). Small doses of neuroleptics, such as haloperidol (Haldol) 0.5 mg may be needed in the agitated or combative patient.
- b) Antidepressants: If marked inertia is present, selective SSRI's such as fluoxetine (Prozac) can be tried in doses 25 to 50% of the usual dose, or Ritalin. Tricyclic antidepressants may precipitate delirium because of their anticholinergic effect, and if used, serum levels should be monitored frequently.
- c) Anticonvulsants: As discussed above, levitaretam, gabapentin or topiramate are the preferred anticonvulsants due to their lack of drug-drug interactions. Valproate should be particularly avoided because *in vitro* studies suggest that it can induce viral replication, and because of its effects on cytochrome p450 (135).
- d) Headaches: Intractable vascular headaches may develop in some patients. Initial treatment should include migraine prophylaxis (136). Triptans should be used cautiously because of interactions with protease inhibitors. Non-responders may require treatment with opiates.
- e) Parkinsonism: Dopamine agonists may be used for patients that manifest Parkinsonism. However, the response is usually poor.
- f) Sleep disturbances: A variety of sleep abnormalities may occur in patients with HIV infection due to a number of causes which may include painful peripheral neuropathies that responds to adequate control of pain(137), sleep apnea from lipodystrophy due to use of protease inhibitors(138). Insomnia may also be caused by efaverinz (139, 140)
- g) Medico legal issues: In patients with progressive dementia, medico-legal issues should be discussed at any early stage before the dementia becomes too severe. These include, establishing a power of attorney, completion of a living will, and arrangement for the dispersal of assets.
- h) Driving: HIV+ NP-impaired individuals are at increased risk for on-road driving impairments, hence where available, simulator testing may help identify driving-impaired individuals(141)

References:

1. McArthur JC. HIV dementia: an evolving disease. *J Neuroimmunol* 2004;157(1-2):3-10.
2. Sacktor N. The epidemiology of human immunodeficiency virus-associated neurological disease in the era of highly active antiretroviral therapy. *J Neurovirol* 2002;8 Suppl 2:115-121.
3. Shapiro MF, Morton SC, McCaffrey DF, Senterfitt JW, Fleishman JA, Perlman JF, et al. Variations in the care of HIV-infected adults in the United States: results from the HIV Cost and Services Utilization Study. *Jama* 1999;281(24):2305-2315.
4. Palella FJ, Jr., Delaney KM, Moorman AC, Loveless MO, Fuhrer J, Satten GA, et al. Declining morbidity and mortality among patients with advanced human immunodeficiency virus infection. HIV Outpatient Study Investigators. *N Engl J Med* 1998;338(13):853-860.
5. Navia BA, Jordan BD, Price RW. The AIDS dementia complex: I. Clinical features. *Annals of Neurology* 1986a;19:517-524.
6. Dore GJ, McDonald A, Li Y, Kaldor JM, Brew BJ. Marked improvement in survival following AIDS dementia complex in the era of highly active antiretroviral therapy. *Aids* 2003;17(10):1539-1545.
7. Brodt HR, Kamps BS, Gute P, Knupp B, Staszewski S, Helm EB. Changing incidence of AIDS-defining illnesses in the era of antiretroviral combination therapy. *Aids* 1997;11(14):1731-1738.
8. Janssen ES, Wanyanwi OC, Selik RM, Stehr-Green JK. Epidemiology of human immunodeficiency encephalopathy in the United States. *Neurology* 1992;42:1472-1476.
9. McArthur JC, McClernon DR, Cronin MF, Nance-Sproson EE, Saah AJ, St. Clair M, et al. Relationship between human immunodeficiency virus associated dementia and viral load in cerebrospinal fluid and brain. *Ann Neurol* 1997;42:689-698.
10. Navia BA, Price RW. The acquired immunodeficiency syndrome dementia complex as the presenting or sole manifestation of human immunodeficiency virus infection. *Arch Neurol* 1987;44(1):65-69.
11. McArthur JC, Hoover DR, Bacellar H, Miller EN, Cohen BA, Becker JT, et al. Dementia in AIDS patients: incidence and risk factors. Multicenter AIDS Cohort Study. *Neurology* 1993;43(11):2245-2252.
12. Moore RD, Chaisson RE. Natural history of HIV infection in the era of combination antiretroviral therapy. *Aids* 1999;13(14):1933-1942.
13. Royal W, 3rd, Updike M, Selnes OA, Proctor TV, Nance-Sproson L, Solomon L, et al. HIV-1 infection and nervous system abnormalities among a cohort of intravenous drug users. *Neurology* 1991;41(12):1905-1910.
14. Childs EA, Lyles RH, Selnes OA, Chen B, Miller EN, Cohen BA, et al. Plasma viral load and CD4 lymphocytes predict HIV-associated dementia and sensory neuropathy. *Neurology* 1999;52(3):607-613.
15. Cutler RG, Haughey NJ, Tammara A, McArthur JC, Nath A, Reid R, et al. Dysregulation of sphingolipid and sterol metabolism by ApoE4 in HIV dementia. *Neurology* 2004;63(4):626-630.
16. Corder EH, Robertson K, Lannfelt L, Bogdanovic N, Eggertsen G, Wilkins J, et al. HIV-infected subjects with the E4 allele for APOE have excess dementia and peripheral neuropathy [see comments]. *Nat Med* 1998;4(10):1182-1184.
17. Singh KK, Ellis RJ, Marquie-Beck J, Letendre S, Heaton RK, Grant I, et al. CCR2 polymorphisms affect neuropsychological impairment in HIV-1-infected adults. *J Neuroimmunol* 2004;157(1-2):185-192.

18. Gonzalez E, Rovin BH, Sen L, Cooke G, Dhanda R, Mummidi S, et al. HIV-1 infection and AIDS dementia are influenced by a mutant MCP-1 allele linked to increased monocyte infiltration of tissues and MCP-1 levels. *Proc Natl Acad Sci U S A* 2002;99(21):13795-13800.
19. Quasney MW, Zhang Q, Sargent S, Mynatt M, Glass J, McArthur J. Increased frequency of the tumor necrosis factor-alpha-308 A allele in adults with human immunodeficiency virus dementia. *Ann Neurol* 2001;50(2):157-162.
20. Budka H. The definition of HIV-specific neuropathology. *Acta Pathol Jpn* 1991;41(3):182-191.
21. Langford TD, Letendre SL, Larrea GJ, Masliah E. Changing patterns in the neuropathogenesis of HIV during the HAART era. *Brain Pathol* 2003;13(2):195-210.
22. Miller RF, Isaacson PG, Hall-Craggs M, Lucas S, Gray F, Scaravilli F, et al. Cerebral CD8+ lymphocytosis in HIV-1 infected patients with immune restoration induced by HAART. *Acta Neuropathol (Berl)* 2004;108(1):17-23.
23. Schmidbauer M, Budka H, Okeda R, Cristina S, Lechi A, Trabattoni GR. Multifocal vacuolar leucoencephalopathy: a distinct HIV-associated lesion of the brain. *Neuropathol Appl Neurobiol* 1990;16(5):437-443.
24. Bassiri A, Holden J, Wong M. A case of fulminant human immunodeficiency virus dementia. *Clin Infect Dis* 1995;21(5):1313-1314.
25. Pascual-Sedano B, Iranzo A, Marti-Fabregas J, Domingo P, Escartin A, Fuster M, et al. Prospective study of new-onset seizures in patients with human immunodeficiency virus infection: etiologic and clinical aspects. *Arch Neurol* 1999;56(5):609-612.
26. Carey CL, Woods SP, Rippeth JD, Gonzalez R, Moore DJ, Marcotte TD, et al. Initial validation of a screening battery for the detection of HIV-associated cognitive impairment. *Clin Neuropsychol* 2004;18(2):234-248.
27. Power C, Selnes OA, Grim JA, McArthur JC. HIV Dementia Scale: a rapid screening test. *J Acquir Immune Defic Syndr Hum Retrovirol* 1995;8(3):273-278.
28. Valcour V, Shikuma C, Shiramizu B, Watters M, Poff P, Selnes O, et al. Higher frequency of dementia in older HIV-1 individuals: the Hawaii Aging with HIV-1 Cohort. *Neurology* 2004;63(5):822-827.
29. Nath A, Jankovic J, Pettigrew LC. Movement disorders and AIDS. *Neurology* 1987;37:37-41.
30. Maher J, Choudhri S, Halliday W, Power C, Nath A. AIDS dementia complex with generalized myoclonus. *Mov Disord* 1997;12(4):593-597.
31. Mirsattari SM, Power C, Nath A. Parkinsonism with HIV infection. *Mov Disord* 1998;13(4):684-689.
32. Fuchs D, Murr C, Reibnegger G, Wachter H. HIV myelopathy. *Neurology* 1994;44(3 Pt 1):578-579.
33. Fernandez F, Levy JK, Mansell PW. Management of delirium in terminally ill AIDS patients. *Int J Psychiatry Med* 1989;19(2):165-172.
34. Mintz M. Neurological and developmental problems in pediatric HIV infection. *J Nutr* 1996;126(10 Suppl):2663S-2673S.
35. Lobato MN, Caldwell MB, Ng P, Oxtoby MJ. Encephalopathy in children with perinatally acquired human immunodeficiency virus infection. *Pediatric Spectrum of Disease Clinical Consortium. J Pediatr* 1995;126(5 Pt 1):710-715.
36. Bouwman FH, Skolasky RL, Hes D, Selnes OA, Glass JD, Nance-Sproson TE, et al.

- Variable progression of HIV-associated dementia. *Neurology* 1998;50(6):1814-1820.
37. Mayeux R, Stern Y, Tang MX, Todak G, Marder K, Sano M, et al. Mortality risks in gay men with human immunodeficiency virus infection and cognitive impairment. *Neurology* 1993;43(1):176-182.
 38. Hollander H, McGuire D, Burack JH. Diagnostic lumbar puncture in HIV-infected patients: analysis of 138 cases. *Am J Med* 1994;96(3):223-228.
 39. Neuenburg JK, Sinclair E, Nilsson A, Kreis C, Bacchetti P, Price RW, et al. HIV-Producing T Cells in Cerebrospinal Fluid. *J Acquir Immune Defic Syndr* 2004;37(2):1237-1244.
 40. Elovaara I, Iivanainen M, Valle SL, Suni J, Tervo T, Lahdevirta J. CSF protein and cellular profiles in various stages of HIV infection related to neurological manifestations. *J Neurol Sci* 1987;78(3):331-342.
 41. Goswami KK, Miller RF, Harrison MJ, Hamel DJ, Daniels RS, Tedder RS. Expression of HIV-1 in the cerebrospinal fluid detected by the polymerase chain reaction and its correlation with central nervous system disease. *Aids* 1991;5(7):797-803.
 42. Conrad AJ, Schmid P, Syndulko K, Singer EJ, Nagra RM, Russell JJ, et al. Quantifying HIV-1 RNA using the polymerase chain reaction on cerebrospinal fluid and serum of seropositive individuals with and without neurologic abnormalities. *J Acquir Immune Defic Syndr Hum Retrovirol* 1995;10(4):425-435.
 43. Brew BJ, Pemberton L, Cunningham P, Law MG. Levels of human immunodeficiency virus type 1 RNA in cerebrospinal fluid correlate with AIDS dementia stage. *J Infect Dis* 1997;175(4):963-966.
 44. Ellis RJ, Hsia K, Spector SA, group atHnrc. Cerebrospinal fluid human immunodeficiency virus type 1 RNA levels are elevated in neurocognitively impaired individuals with acquired immunodeficiency syndrome. *Annals of Neurology* 1997;42:679-688.
 45. Zink MC, Coleman GD, Mankowski JL, Adams RJ, Tarwater PM, Fox K, et al. Increased macrophage chemoattractant protein-1 in cerebrospinal fluid precedes and predicts simian immunodeficiency virus encephalitis. *J Infect Dis* 2001;184(8):1015-1021.
 46. Cotter R, Williams C, Ryan L, Erichsen D, Lopez A, Peng H, et al. Fractalkine (CX3CL1) and brain inflammation: Implications for HIV-1-associated dementia. *J Neurovirol* 2002;8(6):585-598.
 47. Towfighi A, Skolasky RL, St Hillaire C, Conant K, McArthur JC. CSF soluble Fas correlates with the severity of HIV-associated dementia. *Neurology* 2004;62(4):654-656.
 48. Turchan J, Pocernich CB, Gairola C, Chauhan A, Schifitto G, Butterfield DA, et al. Oxidative stress in HIV demented patients and protection ex vivo with novel antioxidants. *Neurology* 2003;60(2):307-314.
 49. Haughey NJ, Cutler RG, Tamara A, McArthur JC, Vargas DL, Pardo CA, et al. Perturbation of sphingolipid metabolism and ceramide production in HIV-dementia. *Ann Neurol* 2004;55(2):257-267.
 50. Cinque P, Nebuloni M, Santovito ML, Price RW, Gisslen M, Hagberg L, et al. The urokinase receptor is overexpressed in the AIDS dementia complex and other neurological manifestations. *Ann Neurol* 2004;55(5):687-694.
 51. Luo X, Carlson KA, Wojna V, Mayo R, Biskup TM, Stoner J, et al. Macrophage proteomic fingerprinting predicts HIV-1-associated cognitive impairment. *Neurology* 2003;60(12):1931-1937.
 52. McArthur JC, McDermott MP, McClernon D, St Hillaire C, Conant K, Marder K, et al.

- Attenuated central nervous system infection in advanced HIV/AIDS with combination antiretroviral therapy. *Arch Neurol* 2004;61(11):1687-1696.
53. Buffet R, Agut H, Chieze F, Katlama C, Bolgert F, Devillechabrolle A, et al. Virological markers in the cerebrospinal fluid from HIV-1-infected individuals. *Aids* 1991;5(12):1419-1424.
 54. McArthur JC, Nance-Sproson TE, Griffin DE, Hoover D, Selnes OA, Miller EN, et al. The diagnostic utility of elevation in cerebrospinal fluid beta 2- microglobulin in HIV-1 dementia. Multicenter AIDS Cohort Study. *Neurology* 1992;42(9):1707-1712.
 55. Brew BJ, Dunbar N, Pemberton L, Kaldor J. Predictive markers of AIDS dementia complex: CD4 cell count and cerebrospinal fluid concentrations of beta 2-microglobulin and neopterin. *J Infect Dis* 1996;174(2):294-298.
 56. Heyes MP, Brew B, Martin A, Markey SP, Price RW, Bhalla RB, et al. Cerebrospinal fluid quinolinic acid concentrations are increased in acquired immune deficiency syndrome. *Advances in Experimental Medicine and Biology* 1991a;294:687-690.
 57. Heyes MP, Ellis RJ, Ryan L, Childers ME, Grant I, Wolfson T, et al. Elevated cerebrospinal fluid quinolinic acid levels are associated with region-specific cerebral volume loss in HIV infection. *Brain* 2001;124(Pt 5):1033-1042.
 58. Levy RM, Bredesen DE, Rosenblum ML. Neurological manifestations of the acquired immunodeficiency syndrome (AIDS): experience at UCSF and review of the literature. *J Neurosurg* 1985;62(4):475-495.
 59. Bursztyjn EM, Lee BC, Bauman J. CT of acquired immunodeficiency syndrome. *AJNR Am J Neuroradiol* 1984;5(6):711-714.
 60. Post MJ, Berger JR, Duncan R, Quencer RM, Pall L, Winfield D. Asymptomatic and neurologically symptomatic HIV-seropositive subjects: results of long-term MR imaging and clinical follow-up. *Radiology* 1993;188(3):727-733.
 61. Stout JC, Ellis RJ, Jernigan TL, Archibald SL, Abramson I, Wolfson T, et al. Progressive cerebral volume loss in human immunodeficiency virus infection: a longitudinal volumetric magnetic resonance imaging study. HIV Neurobehavioral Research Center Group. *Arch Neurol* 1998;55(2):161-168.
 62. Power C, Kong PA, Crawford TO, Wesselingh S, Glass JD, McArthur JC, et al. Cerebral white matter changes in AIDS dementia: alterations of the blood-brain barrier. *Ann Neurol* 1993;34(3):339-350.
 63. Filippi CG, Ulug AM, Ryan E, Ferrando SJ, van Gorp W. Diffusion tensor imaging of patients with HIV and normal-appearing white matter on MR images of the brain. *AJNR Am J Neuroradiol* 2001;22(2):277-283.
 64. Paul R, Cohen R, Navia B, Tashima K. Relationships between cognition and structural neuroimaging findings in adults with human immunodeficiency virus type-1. *Neurosci Biobehav Rev* 2002;26(3):353-359.
 65. Thurnher MM, Schindler EG, Thurnher SA, Pernerstorfer-Schon H, Kleibl-Popov C, Rieger A. Highly active antiretroviral therapy for patients with AIDS dementia complex: effect on MR imaging findings and clinical course. *AJNR Am J Neuroradiol* 2000;21(4):670-678.
 66. Berger JR, Arendt G. HIV dementia: the role of the basal ganglia and dopaminergic systems. *J Psychopharmacol* 2000;14(3):214-221.
 67. Pomara N, Crandall DT, Choi SJ, Johnson G, Lim KO. White matter abnormalities in HIV-1 infection: a diffusion tensor imaging study. *Psychiatry Res* 2001;106(1):15-24.
 68. von Giesen HJ, Antke C, Hefter H, Wenserski F, Seitz RJ, Arendt G. Potential time

- course of human immunodeficiency virus type 1-associated minor motor deficits: electrophysiologic and positron emission tomography findings. *Arch Neurol* 2000;57(11):1601-1607.
69. Rottenberg DA, Moeller JR, Strother SC, Sidtis JJ, Navia BA, Dhawan V, et al. The metabolic pathology of the AIDS dementia complex. *Ann Neurol* 1987;22(6):700-706.
70. Rottenberg DA, Sidtis JJ, Strother SC, Schaper KA, Anderson JR, Nelson MJ, et al. Abnormal cerebral glucose metabolism in HIV-1 seropositive subjects with and without dementia. *J Nucl Med* 1996;37(7):1133-1141.
71. Wang GJ, Chang L, Volkow ND, Telang F, Logan J, Ernst T, et al. Decreased brain dopaminergic transporters in HIV-associated dementia patients. *Brain* 2004;127(Pt 11):2452-2458.
72. Laubenberger J, Haussinger D, Bayer S, Thielemann S, Schneider B, Mundinger A, et al. HIV-related metabolic abnormalities in the brain: depiction with proton MR spectroscopy with short echo times. *Radiology* 1996;199(3):805-810.
73. Avison MJ, Nath A, Greene-Avison R, Schmitt FA, Bales RA, Ethisham A, et al. Inflammatory changes and breakdown of microvascular integrity in early human immunodeficiency virus dementia. *J Neurovirol* 2004;10(4):223-232.
74. Price RW, Staprans S. Measuring the "viral load" in cerebrospinal fluid in human immunodeficiency virus infection: window into brain infection? [editorial; comment]. *Ann Neurol* 1997;42(5):675-678.
75. Johnson RT, Glass JD, McArthur JC, Chesebro BW. Quantitation of human immunodeficiency virus in brains of demented and nondemented patients with acquired immunodeficiency syndrom. *Annals of Neurology* 1996;39:392-395.
76. Wiley CA, Soontornniyomkij V, Radhakrishnan L, Masliah E, Mellors J, Hermann SA, et al. Distribution of brain HIV load in AIDS. *Brain Pathol* 1998;8(2):277-284.
77. Zink C, Carter DL, Flaherty MT, Mankowski JL, Clements JM. *The SIV/Macaque Model: Unraveling the Mysteries of HIV Encephalitis*. NY, NY: Chapman & Hall, 1998.
78. Conant K, McArthur JC, Griffin DE, Sjulson L, Wahl LM, Irani DN. Cerebrospinal fluid levels of MMP-2, 7, and 9 are elevated in association with human immunodeficiency virus dementia. *Ann Neurol* 1999;46(3):391-398.
79. Anthony DC, Miller KM, Fearn S, Townsend MJ, Opdenakker G, Wells GM, et al. Matrix metalloproteinase expression in an experimentally-induced DTH model of multiple sclerosis in the rat CNS. *J Neuroimmunol* 1998;87(1-2):62-72.
80. Rosenberg GA. Matrix metalloproteinases in brain injury. *J Neurotrauma* 1995;12(5):833-842.
81. Conant K, Garzino-Demo A, Nath A, McArthur JC, Halliday W, Power C, et al. Induction of monocyte chemoattractant protein-1 in HIV-1 Tat-stimulated astrocytes and elevation in AIDS dementia. *Proceedings of the National Academy of Sciences* 1998;95:3117-3121.
82. Gabuzda DH, Ho DD, de la Monte SM, Hirsch MS, Rota TR, Sobel RA. Immunohistochemical identification of HTLV-III antigen in brains of patients with AIDS. *Ann Neurol* 1986;20(3):289-295.
83. Kleinschmidt A, Neumann M, Moller C, Erfle V, Brack-Werner R. Restricted expression of HIV1 in human astrocytes: molecular basis for viral persistence in the CNS. *Res Virol* 1994;145(3-4):147-153.
84. Koenig S, Gendelman HE, Oreste JM, et al. Detection of AIDS virus in macrophages in

- brain tissue from AIDS patients with encephalopathy. *Science* 1992;233:1089-1093.
85. Ranki A, Nyberg M, Ovod V, Haltia M, Elovaara I, Raininko R, et al. Abundant expression of HIV Nef and Rev proteins in brain astrocytes in vivo is associated with dementia. *Aids* 1995;9(9):1001-1008.
 86. Sharer LR, Saito Y, Epstein LG, Blumberg BM. Detection of HIV-1 DNA in pediatric AIDS brain tissue by two-step ISPCR. *Adv Neuroimmunol* 1994;4(3):283-285.
 87. Tornatore C, Chandra R, Berger JR, Major EO. HIV-1 infection of subcortical astrocytes in the pediatric central nervous system. *Neurology* 1994;44(3 Pt 1):481-487.
 88. Takahashi K, Wesselingh SL, Griffin DE, McArthur JC, Johnson RT, Glass JD. Localization of HIV-1 in human brain using polymerase chain reaction/in situ hybridization and immunocytochemistry. *Ann Neurol* 1996;39(6):705-711.
 89. Cheng-Mayer C, Levy JA. Distinct biological and serological properties of human immunodeficiency viruses from the brain. *Ann Neurol* 1988;23(Suppl):S58-61.
 90. Navia BA, Cho ES, Petito CK, Price RW. The AIDS dementia complex: II Neuropathology. *Annals of Neurology* 1986b;19:525-535.
 91. Masliah E, Ge N, Morey M, DeTeresa R, Terry RD, Wiley CA. Cortical dendritic pathology in human deficiency virus encephalitis. *Lab Invest* 1992;66:285-291.
 92. Everall IP, Heaton RK, Marcotte TD, Ellis RJ, McCutchan JA, Atkinson JH, et al. Cortical synaptic density is reduced in mild to moderate human immunodeficiency virus neurocognitive disorder. HNRC Group. HIV Neurobehavioral Research Center. *Brain Pathol* 1999;9(2):209-217.
 93. Masliah E, Ge N, Achim CL, Hansen LA, Wiley CA. Selective neuronal vulnerability in HIV encephalitis. *J Neuropathol Exp Neurol* 1992;51(6):585-593.
 94. Everall I, Barnes H, Spargo E, Lantos P. Assessment of neuronal density in the putamen in human immunodeficiency virus (HIV) infection. Application of stereology and spatial analysis of quadrats. *J Neurovirology* 1995;1(1):126-129.
 95. Fox L, Alford M, Achim C, Mallory M, Masliah E. Neurodegeneration of somatostatin-immunoreactive neurons in HIV encephalitis. *J Neuropathol Exp Neurol* 1997;56(4):360-368.
 96. Spargo E, Everall IP, Lantos PL. Neuronal loss in the hippocampus in Huntington's disease: a comparison with HIV infection. *J Neurol Neurosurg Psychiatry* 1993;56(5):487-491.
 97. Reyes MG, Faraldi F, Seng CS, Flowers C, Fariello R. Nigral degeneration in acquired immune deficiency syndrome (AIDS). *Acta Neuropathol* 1991;82(1):39-44.
 98. Factor SA, Podskalny GD, Barron KD. Persistent neuroleptic-induced rigidity and dystonia in AIDS dementia complex: a clinico-pathological case report. *J Neurol Sci* 1994;127(1):114-120.
 99. Gray F, Haug H, Chimelli L, Geny C, Gaston A, Scaravilli F, et al. Prominent cortical atrophy with neuronal loss as correlate of human immunodeficiency virus encephalopathy. *Acta Neuropathol* 1991;82(3):229-233.
 100. Ketzler S, Weis S, Haug H, Budka H. Loss of neurons in the frontal cortex in AIDS brains. *Acta Neuropathol* 1990;80(1):92-94.
 101. Wiley C, Masliah E, Morey M, et al. Neocortical damage during HIV infection. *Annals of Neurology* 1991;29:651-657.
 102. Nath A, Geiger JD. Neurobiological Aspects of HIV infections: neurotoxic mechanisms. *Prog Neurobiol* 1998;54:19-33.
 103. Jones M, Olafson K, Del Bigio MR, Peeling J, Nath A. Intraventricular injection of

- human immunodeficiency virus type 1 (HIV-1) Tat protein causes inflammation, gliosis, apoptosis, and ventricular enlargement. *J Neuropathol Exp Neurol* 1998;57:563-570.
104. Nath A, Conant K, Chen P, Scott C, Major EO. Transient exposure to HIV-1 Tat protein results in cytokine production in macrophages and astrocytes : A hit and run phenomenon. *J Biol Chem* 1999;274:17098-17102.
105. Nath A, Haughey N, Jones M, Anderson C, Bell J, Geiger J. Synergistic increases in neurotoxicity by the HIV-1 proteins Tat and gp120 neuroprotection by memantine. *Ann Neurol* 2000;47:in press.
106. Petropoulos CJ, Parkin NT, Limoli KL, Lie YS, Wrin T, Huang W, et al. A novel phenotypic drug susceptibility assay for human immunodeficiency virus type 1. *Antimicrob Agents Chemother* 2000;44(4):920-928.
107. Letendre SL, McCutchan JA, Childers ME, Woods SP, Lazzaretto D, Heaton RK, et al. Enhancing antiretroviral therapy for human immunodeficiency virus cognitive disorders. *Ann Neurol* 2004;56(3):416-423.
108. Cysique LA, Maruff P, Brew BJ. Antiretroviral therapy in HIV infection: are neurologically active drugs important? *Arch Neurol* 2004;61(11):1699-1704.
109. Martin C, Sonnerborg A, Svensson JO, Stahle L. Indinavir-based treatment of HIV-1 infected patients: efficacy in the central nervous system. *Aids* 1999;13(10):1227-1232.
110. Kravcik S, Gallicano K, Roth V, Cassol S, Hawley-Foss N, Badley A, et al. Cerebrospinal fluid HIV RNA and drug levels with combination ritonavir and saquinavir. *J Acquir Immune Defic Syndr* 1999;21(5):371-375.
111. Aweeka F, Jayewardene A, Staprans S, Bellibas SE, Kearney B, Lizak P, et al. Failure to detect nelfinavir in the cerebrospinal fluid of HIV-1-- infected patients with and without AIDS dementia complex. *J Acquir Immune Defic Syndr Hum Retrovirol* 1999;20(1):39-43.
112. Lanier ER, Sturge G, McClernon D, Brown S, Halman M, Sacktor N, et al. HIV-1 reverse transcriptase sequence in plasma and cerebrospinal fluid of patients with AIDS dementia complex treated with Abacavir. *Aids* 2001;15(6):747-751.
113. McDowell JA, Chittick GE, Ravitch JR, Polk RE, Kerkering TM, Stein DS. Pharmacokinetics of [(14)C]Abacavir, a Human Immunodeficiency Virus Type 1 (HIV-1) Reverse Transcriptase Inhibitor, Administered in a Single Oral Dose to HIV-1-Infected Adults: a Mass Balance Study. *Antimicrob Agents Chemother* 1999;43(12):2855-2861.
114. Price RW, Deeks SG. Antiretroviral drug treatment interruption in human immunodeficiency virus-infected adults: Clinical and pathogenetic implications for the central nervous system. *J Neurovirol* 2004;10 Suppl 1:44-51.
115. Staprans S, Marlowe N, Glidden D, Novakovic-Agopian T, Grant RM, Heyes M, et al. Time course of cerebrospinal fluid responses to antiretroviral therapy: evidence for variable compartmentalization of infection. *Aids* 1999;13(9):1051-1061.
116. Antoniou T, Tseng AL. Interactions between recreational drugs and antiretroviral agents. *Ann Pharmacother* 2002;36(10):1598-1613.
117. Groothuis DR, Levy RM. The entry of antiviral and antiretroviral drugs into the central nervous system [see comments]. *J Neurovirol* 1997;3:387-400.
118. Blasberg RG, Groothuis DR. Chemotherapy of brain tumors: physiological and pharmacokinetic considerations. *Semin Oncol* 1986;13(1):70-82.
119. Hurwitz AA, Berman JW, Lyman WD. The role of the blood-brain barrier in HIV infection of the central nervous system. *Adv Neuroimmunol* 1994;4(3):249-256.

120. Kim RB, Fromm MF, Wandel C, Leake B, Wood AJ, Roden DM, et al. The drug transporter P-glycoprotein limits oral absorption and brain entry of HIV-1 protease inhibitors. *J Clin Invest* 1998;101(2):289-294.
121. Schaner ME, Gerstin KM, Wang J, Giacomini KM. Mechanisms of transport of nucleosides and nucleoside analogues in choroid plexus. *Adv Drug Deliv Rev* 1999;39(1-3):51-62.
122. Thomas SA, Segal MB. The passage of azidodeoxythymidine into and within the central nervous system: does it follow the parent compound, thymidine? *J Pharmacol Exp Ther* 1997;281(3):1211-1218.
123. Cohen RA, Boland R, Paul R, Tashima KT, Schoenbaum EE, Celentano DD, et al. Neurocognitive performance enhanced by highly active antiretroviral therapy in HIV-infected women. *Aids* 2001;15(3):341-345.
124. Tozzi V, Balestra P, Murri R, Galgani S, Bellagamba R, Narciso P, et al. Neurocognitive impairment influences quality of life in HIV-infected patients receiving HAART. *Int J STD AIDS* 2004;15(4):254-259.
125. Ferrando S, van Gorp W, McElhiney M, Goggin K, Sewell M, Rabkin J. Highly active antiretroviral treatment in HIV infection: benefits for neuropsychological function. *Aids* 1998;12(8):F65-70.
126. Ferrando SJ, Rabkin JG, van Gorp W, Lin SH, McElhiney M. Longitudinal improvement in psychomotor processing speed is associated with potent combination antiretroviral therapy in HIV-1 infection. *J Neuropsychiatry Clin Neurosci* 2003;15(2):208-214.
127. Persidsky Y, Gendelman HE. Development of laboratory and animal model systems for HIV-1 encephalitis and its associated dementia. *J Leukoc Biol* 1997;62(1):100-106.
128. Gelbard HA. Neuroprotective strategies for HIV-1-associated neurologic disease. *Ann N Y Acad Sci* 1999;890:312-313.
129. Gendelman HE, Persidsky Y, Ghorpade A, Limoges J, Stins M, Fiala M, et al. The neuropathogenesis of the AIDS dementia complex. *Aids* 1997;11(Suppl A):S35-45.
130. Wilt SG, Milward E, Zhou JM, Nagasato K, Patton H, Rusten R, et al. In vitro evidence for a dual role of tumor necrosis factor-alpha in human immunodeficiency virus type 1 encephalopathy [see comments]. *Ann Neurol* 1995;37(3):381-394.
131. Richard MJ, Guiraud P, Didier C, Seve M, Flores SC, Favier A. Human immunodeficiency virus type 1 Tat protein impairs selenogluthathione peroxidase expression and activity by a mechanism independent of cellular selenium uptake: consequences on cellular resistance to UV-A radiation. *Arch Biochem Biophys* 2001;386(2):213-220.
132. Hriso E, Kuhn T, Masdeu JC, Grundman M. Extrapyramidal symptoms due to dopamine-blocking agents in patients with AIDS encephalopathy. *Am J Psychiatry* 1991;148(11):1558-1561.
133. Bagchi A, Sambamoorthi U, McSpiritt E, Yanos P, Walkup J, Crystal S. Use of antipsychotic medications among HIV-infected individuals with schizophrenia. *Schizophr Res* 2004;71(2-3):435-444.
134. Penzak SR, Hon YY, Lawhorn WD, Shirley KL, Spratlin V, Jann MW. Influence of ritonavir on olanzapine pharmacokinetics in healthy volunteers. *J Clin Psychopharmacol* 2002;22(4):366-370.
135. Romanelli F, Jennings HR, Nath A, Ryan M, Berger J. Therapeutic dilemma: the use of anticonvulsants in HIV-positive individuals. *Neurology* 2000;54(7):1404-1407.

136. Mirsattari SM, Power C, Nath A. Primary headaches with HIV infection. *Headache* 1999;39:3-10.
137. Hahn K, Arendt G, Braun JS, von Giesen HJ, Husstedt IW, Maschke M, et al. A placebo-controlled trial of gabapentin for painful HIV-associated sensory neuropathies. *J Neurol* 2004;251(10):1260-1266.
138. Schulz R, Lohmeyer J, Seeger W. Obstructive sleep apnea due to HIV-associated lipodystrophy. *Clin Infect Dis* 2003;37(10):1398-1399.
139. Nunez M, Gonzalez de Requena D, Gallego L, Jimenez-Nacher I, Gonzalez-Lahoz J, Soriano V. Higher efavirenz plasma levels correlate with development of insomnia. *J Acquir Immune Defic Syndr* 2001;28(4):399-400.
140. Gallego L, Barreiro P, del Rio R, Gonzalez de Requena D, Rodriguez-Albarino A, Gonzalez-Lahoz J, et al. Analyzing sleep abnormalities in HIV-infected patients treated with Efavirenz. *Clin Infect Dis* 2004;38(3):430-432.
141. Marcotte TD, Wolfson T, Rosenthal TJ, Heaton RK, Gonzalez R, Ellis RJ, et al. A multimodal assessment of driving performance in HIV infection. *Neurology* 2004;63(8):1417-1422.