

# Dementia and Neurocognitive Disorders Due to HIV-1 Infection

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## ABSTRACT

Human immunodeficiency virus-type 1 (HIV-1) infection is the most common preventable and treatable cause of neurocognitive impairment in individuals under age 50 years. Although the incidence of HIV-associated dementia has decreased over the past few years due to combination antiretroviral therapy (cART), the prevalence of less severe HIV-associated neurocognitive impairment continues to increase. HIV-associated neurocognitive impairment is a significant burden to persons living with HIV infection, caregivers, and the health care system. Neurocognitive changes associated with HIV are typically subcortical, consisting of the triad of cognitive, behavior, and motor dysfunction. HIV-associated dementia and HIV-associated neurocognitive impairment are clinical diagnostic syndromes with neuropsychological performance testing, neuroimaging, and cerebral spinal fluid studies providing additional information. With the advent of more effective cART, the incidence of fatal opportunistic complications has dramatically diminished. Accordingly, the present review focuses on primary HIV-induced disease of the central nervous system, rather than its opportunistic complications.

**KEYWORDS:** HIV-associated dementia, AIDS, HIV neurocognitive impairment

## EPIDEMIOLOGY

In the United States, human immunodeficiency virus (HIV) infection affects nearly 1 million people. Worldwide, the prevalence is ~40 million. The number of HIV-infected individuals over age 50 years is rapidly growing, and incident cases are accelerating fastest among women, intravenous drug users, and ethnic minorities.<sup>1</sup>

Early in the epidemic, dementia associated with HIV was a common sequela of advanced disease with more than 50% of all HIV-infected patients having dementia prior to death. A balance existed for HIV-associated dementia between a high rate of incidence and rapid loss of prevalent cases due to AIDS-related mortality. The introduction of monotherapy (single agents such as zidovudine) led to a reduction in dementia and overall

mortality, but recovery of prevalent cases was incomplete, resulting in an overall increase in the proportions of individuals with HIV neurocognitive impairment—either with minor cognitive motor disorders (MCMD) or neuropsychologically impaired.<sup>2</sup> More recently, combination antiretroviral therapy (cART) has continued to augment these trends, resulting in further declines in prevalent dementia, while at the same time increasing the overall proportion of individuals with HIV-associated neurocognitive impairment. The end result has been an alteration of the face of HIV. What was once an almost uniformly fatal illness is now a chronic disease requiring long-term medical management (Fig. 1).<sup>3</sup>

HIV affects the brain at an early stage of infection. The brain serves as an important reservoir for this virus. Symptoms can result directly from infection

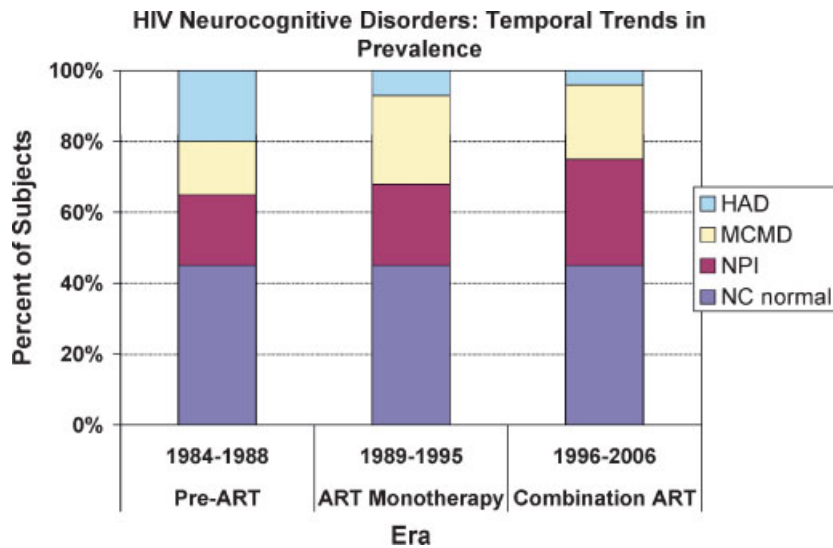
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**Figure 1** Schematic representation of changes in prevalence of different forms of HIV-related cognitive impairment in successive eras of antiretroviral therapy. MCMD, minor cognitive motor disorder; HAD, HIV-associated dementia; NPI, neuropsychologically impaired; NC normal, neurocognitively normal.

producing distinct neurological symptoms or indirectly by increased susceptibility to opportunistic infections and HIV-related malignancies.

**NEUROPATHOGENESIS**

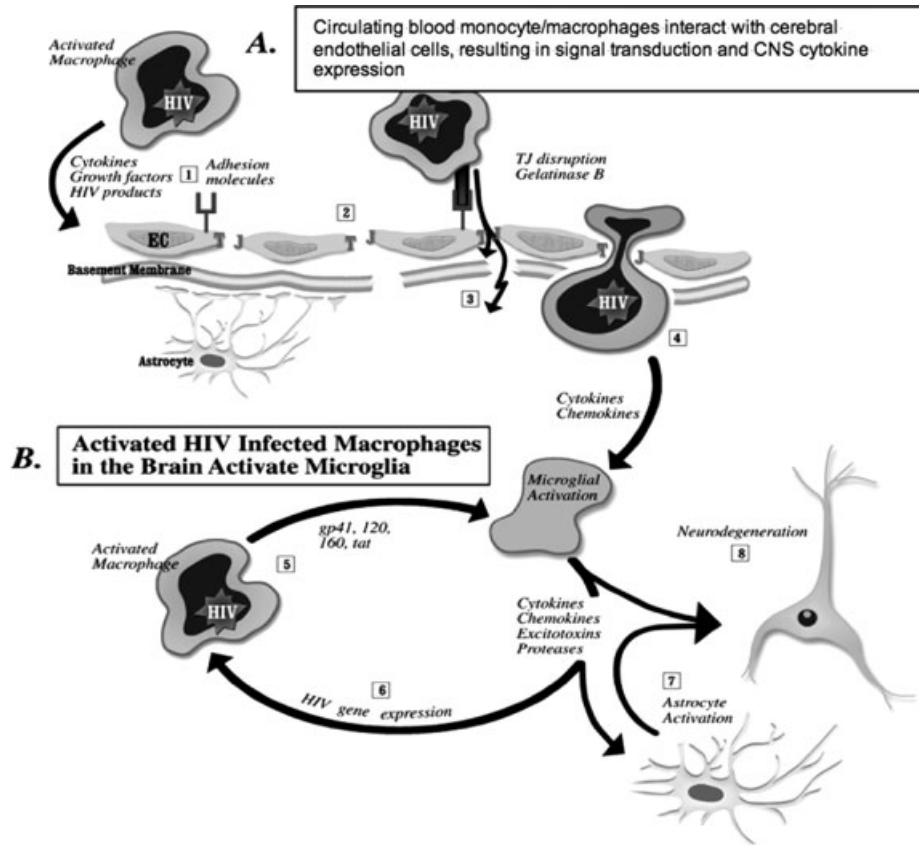
HIV is a retrovirus, meaning that its genomic form, HIV RNA, must be reverse transcribed by a virally encoded enzyme to complete its life cycle. Lentiviruses, a subcategory of retroviruses of which HIV is a member, exert their pathogenic effects through chemokines, chemical mediators that regulate the complex interactions between cells and that are required for normal functioning. The lentiviruses, as a group, have a predilection to both invade (neurotropism) and cause disease (neurovirulence) in the central nervous system (CNS). HIV infection of the host cell is mediated by the CD4-receptor and the CXCR4 and CCR5 coreceptors.<sup>4</sup> The CCR5 coreceptor is the main coreceptor for macrophage-tropic HIV-1, whereas CXCR4 is the main coreceptor for T cells. Entry into the CNS is via a “Trojan horse” mechanism, likely involving infected macrophage-monocyte cells crossing the blood-brain barrier (BBB). Microglial cells and macrophages support continued productive infection in the brain, whereas neurons and oligodendrocytes are rarely infected (Fig. 2).<sup>5</sup>

Two views have been postulated concerning the effect of HIV within the CNS.<sup>6</sup> One is that the CNS suffers from repeated transitory exposures with virus repeatedly transported into the CNS via monocytes. A dynamic equilibrium exists such that virus also returns to the body. On the other hand, the CNS may also serve as a relatively autonomous reservoir of infection producing virus locally and perhaps evolving independently from other loci of infection in the body. Most

likely, both types of infection exist with one subtype dominating over the other in different stages of the infection.

Neuropathologic evaluation of brain tissue is characterized by several features that individually are nonspecific (white matter pallor, microglial nodules, multinucleated giant cells, and gliosis), but when occurring as a constellation in the setting of known HIV infection, produce a characteristic neuropathologic signature. The pathological findings are typically mild, even in cases where dementia is severe. Although elevated viral loads in the brain appear to be important in the development of advanced HIV-associated dementia, there is little correlation between severity and viral load.<sup>7</sup> Neuronal loss can be demonstrated but correlates only modestly with cognitive status. Instead, severe damage to dendrites and synapses is readily evident.<sup>4</sup> The scarcity of infected cells and the imprecise correlation between the severity of pathology and the degree of dementia indicates that host factors are likely to play a role in neuropathogenesis. Hence, a combination of pathogenic mechanisms, such as the individual viral strain and host cell responses to HIV infection, are likely to explain much of the variability of this disease.

The highest concentrations of virus are found in the basal ganglia (especially the globus pallidus), subcortical regions, and the frontal cortices as demonstrated by immunohistology, quantitative polymerase chain reaction, and virus isolation.<sup>8</sup> The reason for this regional localization remains unclear. It may relate to the route of viral entry through the cerebrospinal fluid (CSF) and its proximity to these regions; it may relate to patterns of monocyte trafficking within the brain parenchyma; or it may be due to relative selective differences in vulnerability of certain brain regions.



**Figure 2** A “Trojan horse” mechanism likely exists with infected macrophages crossing the BBB. These macrophages lead to microglial and astrocyte activation with neurodegeneration occurring by secondary mechanisms. Neurons and oligodendroglia are not directly infected. (Modified with permission from Langford D, Masliah E. Crosstalk between components of the blood brain barrier and cells of the CNS in microglial activation in AIDS. *Brain Pathol* 2001;11:306–312.)

## DIAGNOSIS

### Clinical Features and Course

Disabling dementia due to HIV is recognized when a patient’s cognitive abilities decline over a period of weeks or months and a characteristic triad of cognitive, behavioral, and motor dysfunction occurs. In early stages, the general neurological examination is often normal with the exception of mild difficulties in concentration and sustained attention. Affected patients may complain of difficulties in performing everyday chores because they are easily distracted and lose their train of thought for sequential mental or motor tasks. These symptoms are constantly present and frequently intrude on activities of daily living, with common everyday tasks taking longer and becoming more laborious. Motor symptoms are often mild and may consist of a slowing of repetitive movements or balance problems. Absence of focal cortical signs such as apraxias, agnosias, or aphasias assists in distinguishing the condition from Alzheimer’s disease and other dementing conditions. Patients with HIV-associated dementia have difficulty learning new information, such as word lists, but they do not show the rapid forgetting that is commonly seen in Alzheimer’s disease.

Advanced stages of HIV-associated dementia are now rarely seen. In these more severe cases both cognitive and motor dysfunction are more distinct. Patients have severe impairment in activities of daily living such that complex tasks often take longer or cannot be adequately completed. Speech output may also be delayed. Both thought and emotional content are usually impoverished with behavioral changes leading to a loss of spontaneity and initiative. Motor abnormalities may be demonstrated by slowed fine rapid movements, clumsiness, gait unsteadiness, and loss of balance. The neurological examination often shows frontal release signs, spasticity, and hyperreflexia, particularly in the legs.

Because HIV-associated dementia is now relatively uncommon, increasing efforts have focused on identifying milder cases of HIV-associated neurocognitive impairment, either MCMD or neuropsychological impairment. Conventional bedside cognitive testing using instruments such as the Mini-Mental State Examination (MMSE) or the HIV Dementia Scale is adequate for assessing patients with severe dementia but is not reliable for revealing impairment in most patients with HIV-associated neurocognitive impairment. Among individuals with a college education the MMSE is not

sufficiently sensitive, and among those with lesser degrees of education it yields many false-negatives. Comprehensive neuropsychological testing with application of appropriate normative corrections is much more sensitive and specific, as discussed below.

The diagnoses of HIV-associated dementia and HIV-associated neurocognitive impairment are made by clinical criteria after considering other potential causes. Comorbidities such as substance use disorders, major depression, and hepatitis C infection are very common and do not necessarily obviate a diagnosis of HIV-associated neurocognitive impairment. No single laboratory test establishes the diagnosis, but ancillary studies are useful for supporting or refuting it. Useful ancillary studies include neuropsychological testing and neuroimaging studies such as brain magnetic resonance imaging (MRI) and CSF analysis.

### Role of Neuropsychological Testing

When available, neuropsychological testing is very helpful in supporting the clinical diagnosis and evaluating the potential contributions of comorbidities. Useful screening neuropsychological tests are those that examine psychomotor speed, such as the Trailmaking Tests, Grooved Pegboard, and Digit-Symbol. Also useful are tests of verbal and nonverbal learning (e.g., the Hopkins Verbal Learning Test) and sustained attention (Paced Auditory Serial Addition Test).<sup>9</sup> Such tests should only be administered by an experienced examiner, but appropriately trained individuals are increasingly available as large-scale clinical trials incorporate these instruments.<sup>10</sup>

Interpretation of neuropsychological performance is by comparison to normative data with appropriate normative corrections for age, education, and sometimes other demographic variables. Neuropsychological test results provide an objective outcome that can be used to measure changes in performance over time, including worsening due to the progression of disease or improvements related to starting new cART (see below). Neuropsychological test results can assist in the determination of whether the patterns of impairment are most consistent with HIV-associated dementia or other conditions such as a learning disability, depression, or previous brain insult. Premorbid conditions, including previous head trauma, learning disability, as well as the effects of systemic illness and substance abuse, may affect neuropsychological test performance and interpretation in HIV patients.

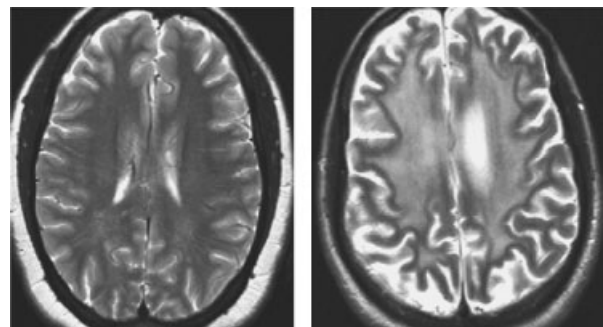
### Neuroimaging

Neuroimaging has increasingly become an important component in the evaluation of HIV-associated neurocognitive impairment and HIV-associated dementia.

Both structural and functional imaging methodologies have been used to characterize these disorders. MRI can provide support for the diagnosis of HIV-associated dementia and also help to eliminate alternative etiologies. Functional/metabolic imaging remains a research tool, although possibilities for clinical application may soon occur.

Anatomical MRI scans of HIV-associated dementia patients typically show cerebral atrophy with corresponding ventricular enlargement. Increases in ventricular size correlate loosely with the degree of cognitive impairment, but simple visual inspection does not provide a useful metric for these changes. More useful findings (Fig. 3) are demonstrated on T2-weighted images (in particular fluid level-attenuated inversion recovery). On these images, patchy confluent areas of high signal intensity are often seen within the white matter with sparing of subcortical U fibers.

The clinical diagnosis and monitoring of HIV-associated neurocognitive impairment is made difficult and laborious by various comorbidities, effects of concomitant medications, and other factors. There is great interest in developing a surrogate marker of overall brain health and disease in HIV to streamline diagnosis and monitoring. Recently, magnetic resonance spectroscopy (MRS) has been utilized. Reductions in N-acetyl aspartate, a marker of mature neurons and their axonal processes, often accompany increases in choline and myoinositol, reflecting increased cell turnover and inflammation.<sup>11</sup> Unfortunately, MRS measurements are typically used only in clinical studies with limited ability to precisely define small regions of interest that are often affected by HIV. More recently, functional neuroimaging using blood oxygen level-dependent (BOLD) functional



**Figure 3** MRI findings in a patient with HIV-associated dementia (right) in comparison to normal (left) at approximately the same level. T2-weighted images show diffuse, symmetrical, confluent hyperintensities throughout the hemispheric white matter with prominent atrophy (widened sulcal markings). There is no enhancement with gadolinium contrast (not shown) and there is no mass effect. This appearance is typical in HIV-associated dementia but is neither sensitive (i.e., some HIV-associated dementia patients may not show this finding) nor pathognomonic (i.e., other disease processes may yield a very similar MRI picture).



magnetic resonance imaging has been used to evaluate HIV-related brain dysfunction. BOLD maps associated with a simple cognitive task have shown decreased activation in areas commonly associated with attention to increased activation in adjacent and contralateral brain regions. These results may reflect reduced efficiency in typical attention networks and recruitment of additional neural areas.<sup>11</sup> The novel technique of arterial spin labeling can provide baseline measurements of resting cerebral blood flow in HIV patients with varying degrees of cognitive impairment. A significant decrease in resting perfusion was observed with increasing degree of cognitive impairment for this completely noninvasive method.<sup>12</sup>

### Cerebral Spinal Fluid

Analysis of CSF in HIV infection is another modality that can assist in the diagnosis of HIV-associated dementia. Like neuroimaging, CSF analysis can rule out certain confounding etiologies.<sup>13</sup> CSF analysis can be critical for the diagnosis of cryptococcal meningitis (direct visualization and antigen detection), cytomegalovirus, and other CNS infections. The presence of HIV-1 in the CSF alone is not reliable for the diagnosis of HIV-associated neurocognitive impairment. Although CNS infection is associated with cognitive impairment, the virus is often present in the CSF of neurologically normal HIV patients as well. In the era before cART was available, among patients with more advanced disease (blood CD4<sup>+</sup> lymphocytes below 200/ $\mu$ L), higher CSF viral loads correlated with worse neuropsychological test performance and tended to be independent of plasma levels.<sup>14</sup> However, among patients with less advanced disease (CD4<sup>+</sup> cells above 200/ $\mu$ L), CSF HIV RNA levels did not correlate with neuropsychological test impairment but were more closely related to plasma levels and to the degree of pleocytosis. Since the introduction of cART, CSF HIV RNA has become a less reliable marker as most patients attain full suppression (e.g., undetectable CSF viral loads).

### Treatment

cART (also known as highly active antiretroviral therapy) refers to the use of multiple (three or more) antiretroviral drugs from different classes that attack various stages in the viral life cycle. The rationale for combining drugs from different classes, rather than using single agents or just one class, is based on the understanding that HIV replication is both copious ( $\sim 10^9$  copies per day) and error-prone. Errors introduced during each replication cycle permit the virus to quickly become resistant to single agents or drug classes. Therefore, the purpose of cART is to exert

selection pressure on multiple viral genes, reducing the likelihood that mutations will arise in the right combinations to render the virus resistant to all of the drugs in a regimen.

The direct effect of cART is to reduce viral replication below the level of detection of currently available assays for retroviral RNA. This in turn reduces the CD4 lymphocyte destruction that is a major pathogenic feature of HIV disease. As a result, significant restoration of immune function frequently occurs and disease progression is slowed or arrested. Although the actual survival benefit of cART has yet to be seen as it has been available for just 10 years, it is believed that cART-treated individuals, although still infected by HIV, might nevertheless be able to live full lives. Unfortunately, for several reasons, including most prominently drug resistance and secondarily difficulties in maintaining adherence to the complicated medication regimens, only about half of patients achieve full success with cART.<sup>15</sup> The remainder may show only partial or no benefit.

There is considerable evidence that cART is at least partially effective in restoring cognitive function in HIV. Although symptomatic HIV disease remains a nonspecific general indication for antiretroviral therapy (ART) among individuals with HIV infection, consensus treatment guidelines specific for HIV-associated neurocognitive impairment patients have yet to be formulated. Thus, current recommendations for starting or changing cART are based on plasma viral load and HIV systemic disease indicators, regardless of the presence or absence of HIV-associated neurocognitive impairment. If local brain infection underlies HIV-associated neurocognitive impairment, then it is logical to assume that targeting ART to the CNS might benefit HIV-associated neurocognitive impairment. However, for reasons described below, only a limited number of current antiretrovirals have adequate CNS penetration.

The CNS is very delicate and evolutionarily built to protect itself against exogenous, potentially toxic molecules. The BBB owes its existence to the tight junctions of the endothelial cells of the brain capillaries. Several factors affect the penetration of a drug across the BBB into the CNS. Although the tight junctions of capillary endothelium in the brain prevent the diffusion of many polar (water-soluble) molecules, more lipophilic drugs readily diffuse across the BBB. Drugs that are highly protein bound have lower unbound concentrations, and hence less drug is available to cross the barrier.<sup>16</sup> Once the drug enters the brain it may be returned to the blood by efflux transporters. To date, three classes of transporters have been implicated in the efflux of drugs from the brain: the multidrug resistance protein, P-glycoprotein, and multispecific organic anion transporter.<sup>17</sup>

These transporters may minimize the effective CNS penetration of drugs.<sup>18</sup>

Despite extensive research, substantial controversy remains about whether antiretroviral drug penetration into the CNS is clinically important and whether monitoring viral load in CSF is useful in treating HIV-associated neurocognitive impairment. Letendre et al demonstrated that among HIV-associated neurocognitively impaired individuals initiating a new cART regimen, those receiving more highly CNS-penetrating antiretroviral regimens were more likely to successfully suppress CSF viral load.<sup>17</sup> Those individuals who achieved CSF suppression (viral load < 50 c/mL) had better neurocognitive outcomes. These findings suggest that neurocognitive outcomes of ART may be enhanced by the planned application of a drug selection and clinical monitoring strategy that optimizes the treatment of CNS infection. However, the formulation of widely accepted recommendations for a CNS-targeted ART strategy would require a level of clinical evidence that has not yet been developed. Formal clinical trials for adequately evaluating HIV-associated neurocognitive impairment treatment strategies have been difficult to implement due to evolving standards, and there is concern that choices made solely based on CNS penetration might limit therapeutic options.

## CONCLUSIONS

The remarkable pace at which effective new drugs and strategies for combining them in ART regimens have been developed has transformed the landscape of primary HIV CNS disease in Western countries. Disabling dementia, once an untreatable condition, has become an eminently treatable neurological condition with a substantial component of reversible neuronal injury becoming evident. However, there remains a significant burden of lesser degrees of cognitive impairment that persist in individuals who now may live for many years with effective cART. Two therapeutic frontiers in this area are the development of improved strategies for optimizing the penetration of antiretroviral therapy into CNS tissues, thereby maximizing viral suppression there, and the development of adjuvant therapies designed to enhance intrinsic mechanisms of CNS repair and protect neurons from further injury. Strategies to improve CNS antiretroviral drug penetration include selecting agents with optimal chemical properties to penetrate the BBB and monitoring drug levels as well as viral load in CSF to ensure the best possible virological response. Areas of adjuvant therapy development include agents that protect against excitotoxic injury, such as the uncompetitive N-methyl-D-aspartate receptor antagonist memantine and drugs that affect cytokine signaling within the CNS.

## ACKNOWLEDGMENTS

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