HIV Infection and Dementia in Older Adults

Victor Valcour 1 and Robert Paul 2

1Hawaii AIDS Clinical Research Program and the Department of Geriatric Medicine, John A. Burns School of Medicine, University of Hawaii, Honolulu; and 2Department of Psychiatry and Human Behavior, Brown Medical School, Providence, Rhode Island

Human immunodeficiency virus (HIV) infection in older patients is becoming increasingly common as seropositive individuals live longer because of long-term antiretroviral treatment. Simultaneously, the development and expression of dementia among HIV-infected patients is evolving in the era of highly active antiretroviral therapy (HAART) and immune reconstitution. How long-term HAART interacts with chronic HIV infection and advanced age with regard to cognition is not fully understood. This article provides an overview of HIV cognitive impairment as it relates to aging and presents some emerging issues in the field. Particular emphasis is placed on describing the changing landscape of HIV-related cognitive impairment and discussing possible concerns regarding the long-term effects of antiretroviral treatment. A brief discussion of potential adjunctive therapies to reduce cognitive symptoms associated with HIV infection in older individuals is provided.

Historically, persons aged >50 years with HIV infection were referred to as “older,” a classification supported by the relatively bell-shaped demographic distribution of US HIV/AIDS cases designated by the Centers for Disease Control and Prevention (figure 1). Around 10% of HIV-infected individuals fall in this older age group, which is a percentage that is roughly equivalent to the percentage of the general population in their retirement ages. Widespread use of antiretroviral therapy (ART) is beginning to alter this somewhat arbitrary distinction. Because of long-term survival of HIV-infected persons, the upper tail of the epidemic is beginning to extend into the older age groups. Currently, >60,000 HIV-infected individuals are >50 years old. The number of HIV-infected individuals >65 years of age increased from ~1000 to >10,000 in the past decade [2]. The US Senate Special Committee on Aging predicts that 50% of nationally prevalent AIDS cases will fall into this older age group by the year 2015 [3].

Older HIV-infected patients are either aging with HIV infection or becoming newly infected at older ages. These distinctions may have clinical and prognostic implications. Currently, older HIV-infected individuals belong primarily to the first group, having been infected in their 30s or 40s and living with chronic HIV infection and prolonged ART. In the Hawaii Aging with HIV Cohort, the mean self-reported duration since the first HIV test result among individuals ≥50 years old (mean age, 54.6 years) is 11.8 years, compared with 7.2 years for individuals <40 years old, which is roughly equivalent to the mean duration reported by other groups [4]. Although the Hawaii Aging with HIV Cohort is enrolled entirely in Hawaii, it appears to be reasonably representative of the US HIV-infected population, because the demographic constitution is similar to that of the Multicenter AIDS Cohort Study and because most of the individuals were born and raised in the continental United States. Exposure to ART is increased among older individuals in the Hawaii Aging with HIV Cohort as well. A mean of 5.1 years compared with a mean of 2.6 years of nucleoside reverse-transcriptase inhibitor exposure was self-reported by older participants, compared with younger participants, respectively (P<.001). The long-term consequences of chronic infection and extended exposure to ART with respect to the brain are not known.

Although it is currently less common, patients who develop HIV infection in their older years represent a special issue for health care providers, because it continues to be an invisible problem. Diagnosis is often delayed, and risk behaviors may be increasing in the absence of needed factors to support safer sexual practices [5, 6]. Although most cases of HIV infection among the older population occur in men, women account for more new cases of infection in this group, and nearly 70% of cases in older female persons occur among minority populations [7]. The magnitude of the problem may be understated,
has been noted. An increased proportion of individuals diag-
changed, and an increased incidence of MCMD relative to HAD
became widespread. However, HAD prevalence has not
factor, a decrease in incidence was seen after the use of HAART
cause advanced immune compromise is a major HAD risk
viduals with AIDS developed either HAD or MCMD [9]. Be-
advocate objective assessments of function.
barriers to functional assessment. Consequently, some centers
tional capabilities due to other illnesses can produce further
performance. Confidentiality issues and confounding of func-
and may not have reasonable insight into expected levels of
retired or have decreased their work load for medical reasons
nition can be problematic among older patients who are often
activities or work. Determining functional decline due to cog-
ning of 1 acquired cognitive or motor abnormality. Both require
that cognitive difficulties reduce the ability to complete daily
ecessary in at least 2 cognitive domains, with an additional abnormality
in either motor function or motivation and/or emotional con-
trol. Representing milder impairment, MCMD requires at least
2 cognitive and/or behavioral symptoms and an objective find-
ing of 1 acquired cognitive or motor abnormality. Both require
that cognitive difficulties reduce the ability to complete daily
activities or work. Determining functional decline due to cog-
nition can be problematic among older patients who are often
retired or have decreased their work load for medical reasons
and may not have reasonable insight into expected levels of
performance. Confidentiality issues and confounding of func-
tional capabilities due to other illnesses can produce further
barriers to functional assessment. Consequently, some centers
advocate objective assessments of function.
Before the widespread use of HAART, up to 30% of indi-
viduals with AIDS developed either HAD or MCM [9]. Be-
cause advanced immune compromise is a major HAD risk
factor, a decrease in incidence was seen after the use of HAART
became widespread. However, HAD prevalence has not
changed, and an increased incidence of MCMD relative to HAD
has been noted. An increased proportion of individuals diag-
osed with dementia now have a CD4 cell count >200 cells/
3 [10]. Incomplete neuropsychological improvement follow-
ning HAART has been described [10, 11], and the rate of
 HIV encephalitis at autopsy may be increasing [12]. Taken
together, there is evidence to suggest that the brain remains
vulnerable in the era of HAART, and significant cognitive diff-
ficulties may persist within the limits of current treatment
approaches.
Both epidemiological data and focused research initiatives
identify an increased rate of HAD among older patients [8, 13,
14}. The Multicenter AIDS Cohort Study identified a relative
hazard ratio for dementia of 1.60 per decade of life at AIDS
onset [15]. Similarly, after controlling for duration of infection,
use of HAART, and CD4 T lymphocyte count, older patients
are 3 times more likely to meet structured HAD criteria in a
research setting [13]. Whether there is an additive or synergistic
relationship between aging and HIV on neuropsychological
testing performance is not fully known, because discrepant re-
ports exist [4, 16–18].
Identifying the specific mechanisms related to increased risk
for HAD is not straightforward. The presence of coexisting
diseases, particularly neurodegenerative disorders, among older
patients limits our ability to identify HIV-specific etiologies
[19]. It is not known whether HIV infection, per se, increases
the risk for other age-related neurodegenerative disorders, per-
haps decreasing the age of onset. Such a relationship would
not be surprising, considering that other conditions, when co-
existing (e.g., cerebral infarction and Alzheimer’s disease),
lower the threshold for clinical expression of dementia [20].
The term “dementia in HIV” may be more appropriate for
older patients, given existing challenges in confidently exclude
contributing factors.
Characteristics of dementia among HIV-infected patients:
past and present. Dementia due to HIV infection is consid-
ered to be a “subcortical” dementia, because the cognitive
symptoms are predominately characterized by difficulties in
cognitive functions purportedly subserved by white matter
pathways and specific gray matter nuclei that lie deep in the
subcortical regions of the brain. Patients with HAD often ex-
hibited slowed response times, marked slowness in psychomotor
speed, poor cognitive flexibility, and emotional lability or ap-
athy. The impact on cortical brain regions may be more com-
mon in the era of HAART, altering the clinical expression of
cognitive impairment. Such changes have been identified in
neuropsychological testing profiles and in neuroimaging by
positron emission tomography [21, 22]. Milder cognitive ab-
normalsities are more frequent, and HAD subtypes have been
introduced, reflecting chronic progressive, active, and nonpro-
gressive disease courses [23]. Markers of immune activation
in the CSF (e.g., β-2-microglobulin) that were classically described
with HAD may now have less specificity for active disease [24],

Figure 1. Estimated percent of persons living with HIV/AIDS in the
United States in 2003, by age group, based on Centers for Disease Control
and Prevention data [1].

Dementia in HIV-infected patients
Existing definitional criteria for dementia and the epidemi-
ology of dementia associated with HIV. The American Academy of Neurology designates 2 main categories of HIV-related
cognitive impairment, including HIV-associated dementia
(HAD) and minor cognitive motor disorder (MCMD). In general,
a diagnosis of HAD necessitates an acquired abnormality
in at least 2 cognitive domains, with an additional abnormality
in either motor function or motivation and/or emotional con-
trol. Representing milder impairment, MCMD requires at least
2 cognitive and/or behavioral symptoms and an objective find-
ing of 1 acquired cognitive or motor abnormality. Both require
that cognitive difficulties reduce the ability to complete daily
activities or work. Determining functional decline due to cog-
nition can be problematic among older patients who are often
retired or have decreased their work load for medical reasons
and may not have reasonable insight into expected levels of
performance. Confidentiality issues and confounding of func-
tional capabilities due to other illnesses can produce further
barriers to functional assessment. Consequently, some centers
advocate objective assessments of function.
and current CD4 T lymphocyte count is less useful [10]. Meanwhile, markers that were classically associated with Alzheimer’s disease may be emerging. Because disease severity is generally milder, some discussion has ensued advocating greater reliance on neuropsychological testing results to categorize asymptomatic, mild, moderate, and severe impairment rather than using diagnostic categorization. This contention is supported by the knowledge that milder degrees of impairment remain risks for HIV disease progression, poor medication adherence (particularly among older adults), and encephalitis [25–27].

In contrast to most other types of dementia, temporal fluctuation in cognitive deficits have been seen in contemporary cohorts of HIV-infected patients [23]. This fluctuation may represent a relapsing and/or remitting pattern of cognitive impairment and would not be surprising, because cognitive findings are believed to reflect inflammatory processes that may fluctuate over time and because vacillation occurs in a number of secondary factors, such as degree of viral suppression, medication adherence, treatment regimens, and drug toxicities. One study demonstrated a relationship between CSF oxidative stress and a progressive disease course [28], and another suggested that undetectable CSF β-2-microglobulin and undetectable CSF HIV RNA do not preclude active disease [24]. From a clinical perspective, it is important to note that cognitive abnormalities remain prevalent and, though less severe, remain risk factors for meaningful outcomes in the era of HAART.

EMERGING ISSUES AND CONTROVERSIES RELATING TO HIV INFECTION AND DEMENTIA IN OLDER PATIENTS

Immune reconstitution. Having a low CD4 lymphocyte count increased the risk for HAD in the pre-HAART era, likely through indirect means. After the advent of HAART, the mean CD4 cell count in patients diagnosed with HAD increased substantially [10, 22], rendering CD4 cell counts less clinically useful. Nadir CD4 cell count, the lowest CD4 cell count ever achieved, may have diagnostic utility in the short-term. Nadir CD4 cell count correlates to prevalent distal symmetric polyneuropathy among older (but not younger) individuals [29] and to neurocognitive impairment [30]. This marker may be particularly relevant to individuals who were infected before HAART was readily available or who sustain low CD4 cell counts before diagnosis of HIV infection—2 situations that are more common among older patients.

There is some speculation that age-related changes in immune function may negatively influence HIV disease outcome among older individuals. Age-related changes in immune function include decreased ability to respond to novel pathogens and decreased proliferation of T lymphocytes [31, 32]. Several investigators have posited that immunosenesence will result in accelerated HIV disease progression in older patients [31, 33].

On the other hand, the overall impact of these changes may be partly mitigated by enhanced adherence to ART [34].

Control of HIV viremia. HIV is thought to enter the CNS early in infection [35]. Mild cognitive abnormalities have been identified early in infection using sensitive neuropsychological measures (reviewed in [36]) and functional neuroimaging [37]. Nevertheless, great variability in the timing of clinically significant cognitive difficulties is seen. It is likely that the indirect effects of HIV, particularly inflammatory responses, are vitally important (reviewed in [38]). Controlling plasma viremia is the standard of care for individuals with low CD4 cell counts. One might surmise that this would control cognitive sequelae among successfully treated individuals. There are several important caveats, however, resulting in markedly dampened optimism, and clinical experience mandates continued vigilance.

First, there is evidence to suggest that CNS compartmentalization of the virus occurs. Phylogenetic analyses and HIV resistance profiles from the brains of dementia patients support this concept [39, 40]. Plasma HIV RNA levels are not necessarily reflective of brain parenchymal exposure and vulnerability. Because of proximity, CSF may serve as a better marker of brain vulnerability, although it is not necessarily reflective of degree of parenchymal infection. Some studies indicate that CSF viremia may reflect risk for cognitive impairment [41, 42].

The clinical implications are immediately evident. Although it is not possible to measure the degree of brain parenchymal infection, measurement of CSF HIV RNA can be done and may provide some clinical utility, particularly among patients who deteriorate during successful peripheral control of virus [43]. This may suggest treatment approaches, because some antiretrovirals are thought to have better activity in the CNS, whereas others are actively transported out [44]. It is not yet known whether ART regimens with profiles that suggest high levels of CNS penetration should be broadly recommended, because limited data exist. There is sufficient evidence from cross-sectional studies and case reports to suggest individualized decisions regarding ART choice and CSF HIV RNA monitoring among selected cases [43, 45, 46].

Eradicating HIV from PBMCs may be important as well. A leading hypothesis for HIV entry into the brain relates to trafficking of monocyes from the periphery into the CNS (i.e., the Trojan horse effect). Intracellular levels of HIV DNA in PBMCs relate to both HIV disease progression [47] and prevalent HAD [48], with the relationship to HAD remaining significant among individuals with undetectable plasma HIV RNA.

HAART neurotoxicity. The neurotoxicities of some antiretrovirals have been demonstrated [49, 50]. Newer antiretrovirals appear to have improved toxicity profiles; however, older patients have often survived extensive past exposure to more toxic antiretrovirals, and others continue the regimen because of resistance profiles. Although speculative, long-term
treatment in a more vulnerable host (e.g., older individuals) may expose cognitive consequences.

Particular concern can be raised for the metabolic changes related to HAART. Lipid abnormalities, glucose intolerance, and a condition akin to the metabolic syndrome are associated with HAART [51] and relate to cardiovascular sequelae [52]. Among the seronegative population, these risk factors relate to cerebrovascular disease and cognitive impairment. To date, this relationship has not been uniformly demonstrated in HIV-infected patients [53, 54]; however, cerebrovascular endothelial changes have been identified in patients with lipodystrophy [55], and diabetes has been linked to HAD [56]. These findings suggest continued vigilance is required.

**Aging and contributing causes to dementia.** Historically, there was little need to consider age-related neurodegenerative diseases as contributing causes to cognitive impairment in HIV infection, because infection existed almost exclusively among younger individuals. This supposition no longer exists, raising new issues regarding the diagnosis and treatment of HAD. Currently, there is little formal basis on which a clinician can confidently determine the etiology of cognitive impairment in an older HIV-infected patient. Relying on signs, symptoms, and neuropsychological profiles may be problematic in the face of newly identified changes in the presentation and course of HAD. If HIV infection lowers the threshold for the clinical presentation of other neurodegenerative disease (cerebral reserve hypothesis), then these challenges may even impact middle-aged patients.

Existing data suggest that an overlap in neuropathology is reasonable to consider. The pathology typically attributed to Alzheimer disease has now been reported in HIV-infected patients, including increased brain β-amyloid deposition [57], increased extracellular amyloid plaques [58], and decreased CSF β-amyloid levels [22]. Neprolysin, an enzyme responsible for amyloid degradation in the extracellular environment, is inhibited by Tat [59]. Similar to Alzheimer disease, the existence of an apolipoprotein ε4 allele correlates to HAD [60], possibly in an age-dependent fashion [61]. Parkinson disease may be another particularly vulnerable disease for older HIV-infected patients, given the importance of the basal ganglia and dopaminergic pathways in both diseases [62, 63].

**TREATMENT OPTIONS: PAST, PRESENT, AND FUTURE**

Currently, the mainstay of HAD treatment is the initiation of HAART and maintenance of undetectable plasma viremia. There is little basis on which to make recommendations for individuals who experience cognitive deterioration while on HAART with adequate plasma and CSF viral control [43]. Some controversy remains as to whether this does occur; however, there are limited data supporting the contention that progression can occur within the context of current treatment parameters [24, 64]. The existence of confounding factors and a paucity of molecular markers are notable research disadvantages for identifying treatment options for HAD. The hypothesis that “actively progressive HIV dementia” [28, p. 176] is associated with ongoing oxidative stress has received some attention. Two studies evaluating the efficacy of selegiline (enrollment complete) and minocycline (in development) are underway.

Selegiline is a dopamine agonist used in the treatment of Parkinson disease. The drug exhibits supportive trophic effects on damaged neurons as well as antioxidant qualities. In preliminary studies, HIV-seropositive individuals receiving selegiline for 10 weeks experienced improvement in memory and fine motor speed [65]; although early reports from the larger placebo-controlled study have been disappointing [66]. Minocycline is an antibiotic with anti-inflammatory effects and good brain penetration at tolerable doses. In a pigtail macaque model of simian immunodeficiency virus encephalitis with rapidly progressive disease, minocycline was associated with decreased inflammatory markers, intermediates of neuronal apoptosis, and simian immunodeficiency virus concentrations in brain aggregates [67]. These effects were observed at doses that would be considered tolerable in humans, suggesting that minocycline may be a useful adjunctive therapy.

Several other agents have been considered. A study evaluating the efficacy of memantine, a low-to-moderate affinity N-methyl-d-aspartate receptor antagonist, has been completed based on in vitro evidence that memantine blocks neuronal injury resulting from gp120 and Tat [68] and improves hippocampal function in a mouse model of HIV encephalitis [69]. Results of the clinical trial are not yet published. Use of the CNS stimulant modafanil resulted in improved performance in neuropsychological testing profiles in an open-label, 4-week evaluation [70]. A placebo-controlled study is under consideration. Additional adjunctive targets have been proposed [71], including neurotropic factors (e.g., brain-derived neurotropic factor, nerve growth factor, and insulin growth factor) and anti-inflammatory agents (e.g., IL-4, IL-10, and erythropoietin). A particularly interesting approach focuses on GSK-3β, an enzyme that is expressed in the brain and may play a role in cellular signaling. To our knowledge, evaluation of these theoretical targets remains preclinical.

Providing treatment approaches that are specific to older HIV-infected patients is problematic, given a paucity of research addressing this issue. An algorithmic approach for all ages has been proposed and has broad applicability to older patients [43]. It may be warranted to broaden the differential of alternative etiologies for impairment among older patients. It is reasonable to speculate that medications known to abate Alzheimer disease symptoms may have some efficacy in older patients when a combination of neurodegenerative etiologies may...
underlie the clinical syndrome. However, there are no clinical trials on which to base such recommendations. It is important to have a high level of suspicion for HIV infection in older individuals newly identified to have dementia and thought to be HIV-seronegative. This concern would be most warranted if the dementia has predominantly subcortical features, if concomitant constitutional symptoms exist, or if the patient is relatively young (perhaps in their 60s) for the typical age of onset of common neurodegenerative disorders.

SUMMARY

There is little question that the natural history of HIV infection is changing in the contemporary era, and advanced age will likely be an important moderator of clinical outcome associated with the disease. The observation that HIV, advanced age, and concomitant neurodegenerative disorders may interact in additive or synergistic ways raises many questions regarding best practice among this population. To date, no consensus has been established regarding optimal approaches, and no clinical trials have specifically addressed older HIV-infected patients. It is likely that HIV will represent the most common infectious etiology of dementia until a cure for HIV infection is identified. Clinicians are encouraged to consider HIV infection a primary contributor to cognitive impairment in older individuals thought to be HIV-seronegative and to integrate the possibility that age-related cognitive disorders may contribute to clinical findings in older HIV-infected patients.

Acknowledgments

Financial support. National Institute of Neurological Disorders and Stroke (grant 1U54NS43049 to V.V.); the National Institute of Allergy and Infectious Diseases (grant 5U01 AI34853 to V.V.); and the National Institute of Mental Health (grant K23MH065857 to R.P.).

Potential conflicts of interest. V.V. and R.P.: no conflicts.

References

Rouzioux C, Hubert JB, Burgard M, et al. Early levels of HIV-1 DNA.


