Perspective on HIV Infection and Aging: Emerging Research on the Horizon

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A greater prevalence of human immunodeficiency virus (HIV)–infected individuals aged >50 years is projected. This epidemiologic trend will continue to increase as a result not only of greater survival rates among HIV-infected patients who receive treatment, but also of delayed recognition of older individuals with occult HIV disease. Historically, it was thought that, despite viral responses to highly active antiretroviral therapy (HAART) among older individuals that approximate those of younger individuals, older persons infected with HIV could not mount as vigorous an immune response as do younger HIV-infected individuals. However, recent evidence suggests that older HIV-infected individuals may do just as well, because they may be more compliant with their antiretroviral regimens. Limited data are available on the safety and tolerability of HAART in this population. Emerging evidence suggests that metabolic, neuropsychiatric, and cardiovascular morbidities could be exacerbated by use of antiretrovirals or by HIV infection itself. Additional research is needed to optimize the care of older HIV-infected patients.

THE HIDDEN EPIDEMIC

Since the epidemic of HIV infection began, the HIV-infected population has evolved to include a growing proportion of older HIV-infected individuals. HIV-infected patients aged >50 years now represent 10%–13% of the HIV-infected population in the United States [1]. Some US states report a relatively elevated prevalence of HIV infection among older individuals. For instance, a higher-than-average prevalence of individuals aged >50 years has been reported among individuals with AIDS in Florida (13%) and Hawaii (20%) [2–4]. Older persons tend not to be perceived by their physicians as having any risk factors for HIV infection and, consequently, are less likely to be tested for HIV than are younger adults. Misdiagnosis is common, and older patients tend to receive diagnoses later in the course of HIV infection [5–8]. El-Sadr et al. [9] investigated the prevalence of undiagnosed HIV infection among elderly patients by testing for HIV antibodies in serum samples obtained from patients aged ≥60 years without a history of HIV infection who had died in their institution. Thirteen (5%) of 257 serum samples obtained from patients aged 60–79 years contained HIV antibodies, although none of the deaths of the 13 HIV-infected patients were directly attributable to HIV infection. It is anticipated that the prevalence of older individuals with HIV infection will continue to increase as a result of a combination of new cases related to high-risk activity and higher survival rates associated with advances in antiretroviral therapies.

THE INFLUENCE OF AGE ON IMMUNE FUNCTION: HOW DO OLDER PATIENTS SURVIVE WITH HIV/AIDS, COMPARED WITH YOUNGER HIV-INFECTED INDIVIDUALS?

The present state of research with regard to age, immunity, and HIV infection seems to suggest a parallel between age-related immune down-regulation and HIV-related immune dysfunction. Aging has been associated with a decreased production of IL-2 and IL-2 receptors [10–13]. Lower responsiveness to IL-2 has been implicated as a mechanism for compromised T cell function, leading, in turn, to a shift from a naive to a memory T cell phenotype [14]. When an older individual becomes chronically infected with HIV, the depletion of naive CD4 T cells becomes more pronounced, compared with what happens in younger HIV-infected individuals. Investigators have surmised that this might lead to a delayed immune response [15]. Other researchers have indicated that the poorer CD4 cell response in elderly persons may also be related to thymus involution with age and decreased thymus productivity.
Table 1. Results of the Cox proportional hazard regression analysis of predictors of survival in HIV-infected patients, according to age group and HAART status.

<table>
<thead>
<tr>
<th>Variable</th>
<th>Hazard ratio (95% CI)</th>
<th>SE</th>
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<tbody>
<tr>
<td><strong>Younger group</strong></td>
<td></td>
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<tr>
<td>No receipt of HAART (yes vs. no)</td>
<td>1.0</td>
<td>...</td>
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<tr>
<td>Receipt of HAART (yes vs. no)</td>
<td>0.415 (0.248–0.695)</td>
<td>0.109</td>
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<tr>
<td><strong>Older group</strong></td>
<td></td>
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<tr>
<td>No receipt of HAART (yes vs. no)</td>
<td>2.364 (1.422–3.929)</td>
<td>0.613</td>
</tr>
<tr>
<td>Receipt of HAART (yes vs. no)</td>
<td>0.669 (0.372–1.201)</td>
<td>0.200</td>
</tr>
<tr>
<td>Sex (male vs. female)</td>
<td>1.111 (0.694–1.844)</td>
<td>0.287</td>
</tr>
<tr>
<td>MSM (yes vs. no)</td>
<td>1.038 (0.674–1.597)</td>
<td>0.228</td>
</tr>
<tr>
<td>CD4 cell count at time of enrollment (1 cell/mm³)</td>
<td>0.996 (0.995–0.997)</td>
<td>0.006</td>
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<tr>
<td>Year of enrollment (centered on 1996)</td>
<td>1.155 (1.046–1.276)</td>
<td>0.058</td>
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</tbody>
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**NOTE.** After controlling for sex, homosexual behavior, CD4 cell count at enrollment, and the year of enrollment (centered on 1996), older patients had 2.36 times the hazard of dying than did younger untreated patients. Younger patients treated with HAART had a hazard ratio of 0.415, which represents a 58.5% decrease in the hazard ratio for death, compared with younger untreated patients. Exposure to HAART decreased the hazard of death to 0.669 relative to the younger untreated group, but this was not significant. Note that the estimated hazard ratio for the older treated group is <1.0, as opposed to the older untreated group. Adapted from [34]. MSM, men who have sex with men; older group, patients aged ≥50 years; younger group, patients aged <50 years.

[16]. Older HIV-infected individuals may not be able to achieve as brisk an increase in the CD4 lymphocyte count as younger HIV-infected individuals.

In the pre-HAART era, several studies demonstrated that, after HIV seroconversion, patients aged ≥50 years tended to have a more rapid progression towards AIDS, and poorer survival after the diagnosis of AIDS was established [17–27]. In the HAART era, subsequent studies also suggested that older patients infected with HIV had a delayed immune recovery [28–30]. Viard et al. [31] reported data on the influence of age on immune recovery for 1956 patients in the EuroSida study. By multivariate analysis, they found that there was an inverse relationship between age and maximum CD4 cell response (P = .023).

However, more recent studies of older HIV-infected individuals and their response to HAART seem to refute all these findings. Tumbarello et al. [32] compared responses to HAART in younger and older HIV-infected patients and did not observe age-related differences in viral suppression, immune recovery, or clinical outcome, despite the presence of comorbid conditions in the older age groups. In a case-control study of 101 older HIV-infected patients (mean age, 57 years) who were matched with 202 younger HIV-infected patients, Fair Wellons et al. [33] concluded that, although HIV-infected patients aged ≥50 years had increases in the CD4 cell count that were similar to those in younger HIV-infected patients, a greater proportion of older patients attained an undetectable HIV RNA level, compared with the younger group (11% vs 26%; P = .01). Greater compliance with treatment by older HIV-infected patients may explain these findings, because older patients were more likely to be adherent to their antiretroviral regimen than were younger patients, who were more likely to interrupt treatment.

The mortality data, however, are the most compelling. In a retrospective cohort study, Perez et al. [34] compared mortality rates for 253 HIV-infected individuals aged ≥50 years and for 535 younger HIV-infected patients. Although information on compliance with therapy and the presence of comorbid conditions was not provided, older HIV-infected individuals who were not receiving HIV antiretrovirals had twice the hazard rate for death than did younger, untreated HIV-infected individuals (table 1). These findings suggest that deference of therapy or failure to diagnose HIV infection in older individuals may have a more adverse impact on their survival, compared with younger HIV-infected individuals (figures 1 and 2). After initiation of HAART, older patients had a 2-fold reduction in the hazard rate for death and a 72% reduction in mortality, after adjustment for confounders. After 3 months, there were no statistically or clinically significant differences in the survival rate between the treated younger and older HIV-infected groups.

**TOLERABILITY AND SAFETY OF HAART IN THE POPULATION OF OLDER HIV-INFECTED PERSONS**

There have relatively been few studies examining the tolerability and safety of antiretrovirals in older HIV-infected patients. Older age is associated with age-related decrease in renal function. A study investigating the elimination of zidovudine in elderly patients found that it was substantially reduced, resulting in toxic serum drug levels [35]. Older age is also associated
with decreases in hepatic function. This could lead, in turn, to higher serum levels of HIV drugs metabolized in the liver and to decreased tolerability in older HIV-infected patients [36]. Knobel et al. [37] compared the response to HAART consisting of a protease inhibitor (PI), which is predominantly metabolized by the liver, plus 2 nucleoside reverse-transcriptase inhibitors (NRTIs) in HIV-infected patients aged <40 years and in patients aged ≥60 years. Although there were no statistically significant differences between the 2 groups with regard to virologic and immunologic outcomes, only 10 (36%) of 38 older patients continued to receive a regimen that contained a PI for 24 months; the remainder had therapy switched to a nonnucleoside reverse-transcriptase inhibitor (NNRTI). Adverse events were significantly more common during receipt of the PI-containing regimen, with an incidence of 64% among persons aged ≥60, compared with an incidence of 35% in the younger age group \(P = .001\). Drug-related toxicity and lower tolerability in the older age group were hypothesized to be due to age-related decreases in albumin levels and hepatic function in this study.

Older age and the presence of comorbidities need to be taken into account when it comes to the safety and tolerability of HIV antiretrovirals. Various medical conditions, including cardiac, renal, hepatic, oncologic, neurologic, and psychiatric illnesses, tend to be more frequently diagnosed in older patients. This entails the prescribing of medications other than those for HIV infection and leads to concern of drug-drug interactions in older HIV-infected patients who are concurrently receiving HAART. In a retrospective study, Shah et al. [38] investigated comorbid conditions and the receipt of non-HIV medications in 165 HIV-infected individuals who were receiving antiretrovirals, who were ≥55 years old, and who attended 3 New

![Figure 1](image.png)

**Figure 1.** Cumulative mortality rate for HIV-infected patients who were not exposed to HAART, according to age group (patients aged ≥50 years [older patients] and patients aged <50 years [younger patients]). Survival estimates were conditioned on the date of initiation of HAART. Patients who received HAART some time after enrollment had a delayed entry time, and their data did not contribute to the risk sets until the time that HAART was started. Patients who received HAART before enrollment were left truncated on the basis of the time that had elapsed between beginning HAART and enrollment. Adapted from [34]. Cum Surv, cumulative survival.
York City HIV clinics. A total of 89% had comorbid conditions, and 81% were taking non-HIV medications. Comorbid conditions and use of concurrent medications for treatment of conditions other than HIV infection along with HAART did not result in a greater incidence of toxicity or treatment-limiting adverse effects in that study.

PHARMACOLOGY OF ANTIRETROVIRALS IN OLDER HIV-INFECTED PATIENTS

Most clinical studies investigating new antiretrovirals routinely exclude HIV-infected patients with advanced age and/or concurrent comorbid condition, or the studies do not compared data on older patients with data on younger patients [39]. Prior pharmacokinetic data suggest that aging affects hepatic metabolism. A study from Finland investigated the effect of aging on the drug metabolism of antipyrine in 266 subjects. Liver biopsy concentrations of cytochrome P450 and plasma antipyrine (phenazone) clearance rates were compared in 3 groups of subjects (subjects aged 20–29 years, 40–69 years, and >70 years). The study demonstrated a reduced rate of drug metabolism of up to 30% after 70 years of age ($P<.001$). This study, among others, suggests that drugs predominantly metabolized in the liver are dependent on hepatic function, which decreases with increasing age [36]. One could infer from this pharmacological study that, when older HIV-infected patients are treated with doses of antiretrovirals routinely recommended for younger adults, potential greater toxicity might result. To date, there have been no pharmacokinetic studies of antiretroviral drugs in older HIV-infected patients. Both NNRTIs and PIs are metabolized by cytochrome p450 in the liver, and HIV-infected elderly patients may have significantly higher drug exposure when treated with commonly used NNRTIs and PIs. If true, this would render the elderly population more vulnerable to short- and long-term drug toxicities.

Little prospective research on the toxicity of HAART has been focused on the geriatric population. Adler et al. [40] hy-
pothesized that elderly patients are especially at risk of experiencing more severe toxicity as a result of age-related declines in renal function and in hepatic function and decreases in albumin levels, which may result in pharmacokinetic parameters that are significantly altered than those observed in younger, healthier individuals. Clearance of drugs is reduced in association with old age, congestive heart failure, cirrhosis, or conditions that diminish cardiac output and hepatic blood flow. Exposure to higher concentrations of drugs may result in greater drug intolerance and/or organ toxicity, which may also contribute to additional changes in the metabolic pathways of these organs. In addition, the risk for toxicity is exacerbated by the multitude of medical problems and resulting polypharmacy, which renders the HIV-infected geriatric population particularly vulnerable to unforeseen toxicity associated with HAART. Prospective studies are needed to evaluate the appropriateness of current dosing of HAART in the elderly HIV-infected population. If pharmacokinetic parameters are significantly different in the elderly population, additional studies need to be performed to either make age-dependent modifications in dosing recommendations or to develop other strategic approaches for this unique population.

**MENOPAUSE AND THE USE OF HORMONAL REPLACEMENT THERAPY IN OLDER WOMEN INFECTED WITH HIV**

Limited data are available about menopause and the use of hormonal replacement therapy in older HIV-infected women. Clark et al. [41] evaluated the prevalence of perimenopausal symptoms (with use of a validated climacteric scale), along with the use of hormone replacement therapy, through a survey administered to older HIV-infected women (mean age at menopause, 47 years). Hormonal replacement therapy was used only by 11% of the postmenopausal women [42]. In another cohort of older HIV-infected women ($n = 84$), Clark et al. [43] studied characteristics predictive of death in a multivariate analysis. A CD4 cell count of <200 cells/mm$^3$, diagnosis of an opportunistic infection, not taking antiretrovirals, and not taking hormonal replacement therapy were all found to be predictors of increased mortality. Both studies suggest that relatively few older HIV-infected women are receiving hormonal replacement therapy, despite data suggesting that it might be associated with decreased mortality in that population.

**LOSS OF BONE MINERAL DENSITY: IMPLICATIONS FOR OLDER HIV-INFECTED PATIENTS**

The literature about the prevalence of osteopenia or osteoporosis in older HIV-infected individuals remains sparse. Most of the published studies of bone mineral loss have not specifically evaluated HIV-infected patients aged >50 years. HIV-infected patients exposed to a regimen that contains a PI were initially reported to have had a higher prevalence of reduced bone mineral density [44]. Additional work, however, demonstrated that HIV-infected patients, regardless of whether they were exposed to various combinations of HIV antiretrovirals or whether they were treatment naive, had a higher-than-expected prevalence of reduced bone mineral density, compared with a control group of HIV-uninfected patients. A cross-sectional study divided 142 subjects into the following subgroups: HIV-infected patients who were antiretroviral naive, HIV-infected patients who had been receiving HAART that did not contain a protease inhibitor for >1 year, HIV-infected patients who had been receiving HAART that contained a protease inhibitor for >1 year, and healthy subjects without HIV infection. Osteopenia and osteoporosis were diagnosed more frequently among HIV-infected patients than among HIV-uninfected control subjects ($P < .0001$). However, there were no differences in bone density among treatment-naive HIV-infected patients and patients in either of the treatment groups [45].

To elucidate potential sex-specific differences, investigators compared bone density by dual-energy x-ray absorptiometry (DEXA) in 84 HIV-positive women who were receiving HAART and in healthy, HIV-negative female control subjects who were similar in age, body mass index, and race. The mean age was 41 years, and no specific information was extracted with regard to older HIV-infected women. Bone density at the lumbar spine and hip was significantly reduced in HIV-positive subjects, compared with controls subjects, and osteopenia was seen in 64% and 30% of subjects, respectively ($P = .004$). Exposure to a PI, NRTI, or NNRTI did not affect DEXA scan results, indicating a lack of causality between exposure to antiretrovirals and loss of bone mineral density [46]. These data imply that HIV (which triggers cytokine activation) and not exposure to antiretrovirals may be the cause of decreased bone density in HIV-infected individuals.

Additional studies that evaluate osteopenia and osteoporosis in the older HIV-infected population are needed. An elevated alkaline phosphatase level or a low testosterone level in an HIV-infected patient should lead the physician to consider testing for osteoporosis; otherwise, recommendations regarding diagnosis and treatment of osteopenia and osteoporosis in older HIV-positive patients do not differ from recommendations for older HIV-negative individuals. Evaluation of nutritional status and exclusion of other potential secondary causes of osteoporosis are advisable. Administration of vitamin D and calcium and weight-bearing exercise should be optimized to preserve bone mass. For overt osteoporosis, hormone replacement, bisphosphonates, calcitonin, or raloxifene therapy should be considered. Although all of these therapies have been shown to slow bone loss, only treatment with bisphosphonates has reduced the risk of vertebral and nonvertebral fractures [47].
These therapies, however, have not been tested specifically in HIV-infected patients. As yet, there are no data regarding older HIV-infected patients [48].

NEUROCOGNITIVE RESEARCH ON HIV INFECTION AND AGING

Several studies have reported a decreased incidence of opportunistic infections of the CNS, as well as a decreased incidence of HIV-related dementia. Since 1996 and the advent of HAART, the incidence of HIV dementia has lowered by 50% [49, 50]. Yet, despite a decreased incidence of opportunistic infections associated with HAART and treatment of opportunistic infections, sequelae of HIV encephalitis continues to be detected in 25% of autopsy cases [51]. HAART benefits might be partial as a result of limited penetration of some of the antiretrovirals across the blood-brain barrier, allowing HIV to replicate in the brain microglia. HIV does not appear to contribute directly to the pathogenesis of HIV dementia. What seems more plausible is that the neuronal damage is indirectly caused by cytokines in an activated microglial environment. As cytokines are released in response to HIV, apoptosis, neuronal dropout, and decreased arborization of dendrites are triggered by release of toxic by-products (e.g., nitric oxide, superoxide anions, and platelet activating factor), and neuronal damage ensues [52]. An activated microglial environment is also seen in dementias other than HIV-associated dementias, such as Alzheimer disease and Parkinson disease [53]. Because younger individuals with AIDS are susceptible to dementia, this suggests a correlation between HIV-related dementia and the neurocognitive disorders associated with aging. Selective neuronal death, localized in the hippocampus, has been well described in subjects with Alzheimer disease, but this also occurs to a significant degree in patients with HIV-associated dementia [54]. Amyloid plaques and increased rates of apolipoprotein E4 expression have been found in the brains of older HIV-infected patients with dementia [55, 56].

The multicenter trial of the AIDS Clinical Trials Group (ACTG 5090) is investigating selegiline, which is used for the treatment of Parkinson disease, as a treatment adjunct for cognitive impairment associated with HIV infection. Despite the well-known association between older age and increasing incidence of dementia, few studies have investigated the complex interactions between HIV infection, aging, and neuropsychiatric diseases. Greater rates of HIV-associated dementia as the first AIDS-defining diagnosis are associated with older age in HIV-infected patients [57, 58]. Data are also beginning to emerge with regard to the confounding effect of concurrent alcohol or drug abuse in this population. This is evolving into an area for future research [59].

HIV INFECTION, AGING, AND INCREASED RISK OF CARDIOVASCULAR DISEASE

HAART has drastically lengthened the duration of survival for HIV-infected individuals and has led to shifting patterns of morbidities and mortality [60, 61]. However, better survival durations have led to an increased prevalence of HIV-related disorders of insulin metabolism, diabetes mellitus, lipodystrophy, and dyslipidemia [62–66]. Premature cardiovascular and cerebrovascular disease have also been described, but there is still considerable debate as to whether this increased risk stems from metabolic toxicities resulting from use of HIV antiretrovirals, from endothelial disruption due to HIV itself, or both [67–73]. Chronic infection with HIV triggers the release of various cytokines and may create a proinflammatory state in which cholesterol metabolism is altered [74]. In turn, this proatherogenic milieu may lead to elevations of levels of very low–density lipoprotein and triglycerides. Some of these lipid changes, which have been observed in HIV-infected patients, may be unrelated to the effects of antiretrovirals [75–77], although PIs and NNRTIs have also been associated with lipid disorders [78].

In a large retrospective study, Bozette et al. [79] studied the risk of cardiovascular and cerebrovascular disease among 36,766 HIV-infected patients who were receiving antiretrovirals and who were observed at Veterans Affairs Medical Centers between January 1993 and June 2001. Ten percent of this cohort was aged ≥55 years. In this retrospective study, there was no increase in cardiovascular or cerebrovascular mortality directly attributable to antiretrovirals. More recently, however, a prospective observational cohort study of 23,468 HIV-infected patients conducted from 1999 to 2002 refuted these earlier findings by reporting the incidence of myocardial infarction associated with exposure to HAART. Although the absolute risk remained low, longer exposure to combination antiretroviral therapy (which included either a PI or a NNRTI) was independently associated with a 26% relative increase in the rate of myocardial infarction per year of exposure. In both univariate and multivariate analyses, older age was consistently associated with an increased risk [80]. Taken together, the metabolic toxicities of HAART and the proatherogenic state induced by chronic HIV-infection may render older HIV-infected patients particularly vulnerable to accelerated atherosclerosis and may result in an increased risk of cardiovascular disease.

FUTURE DIRECTION

Increasingly more individuals are living and growing older while infected with HIV. Age should be taken into consideration to optimize the care of older HIV-infected patients. This was
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