REVIEW

The ageing of HIV: implications for geriatric medicine

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Abstract

The prevalence of human immunodeficiency virus (HIV) in the over 50 age group is increasing as a consequence of younger adults ageing with HIV, in addition to new diagnoses in later life. We conducted searches in MEDLINE for English language studies published between January 1984 and January 2010 using search terms ‘HIV’, ‘AIDS’, ‘HIV testing’ and ‘HIV complications’ and selected articles relevant to adults aged 50 years and over. The prevalence, natural history and complications of HIV infection and treatment in older adults are reviewed.

In 2007 the Centers for Disease Control and Prevention in the United States reported that 16.8% of new diagnoses of HIV that year were in individuals aged over 50 years. Older adults are vulnerable to late or missed diagnosis, and poorer treatment outcomes, due to the misconception that they are not at risk. A heightened awareness of HIV as a possible diagnosis in older adults is becoming increasingly important. As the HIV population ages, the emergence of disease and treatment complications such as cardiovascular disease, osteoporosis and dementia are evident. Management of older adults with HIV and multiple co-morbidities presents challenges to infectious diseases physicians and geriatricians alike. Inclusion of older adults in future HIV clinical trials will help design healthcare models to provide for this growing population.

Keywords: HIV, AIDS, older adults, HIV testing, elderly

Introduction

The association between specific risk behaviours and human immunodeficiency virus (HIV) infection has led to the assumption that HIV is a disease of youth. However, epidemiological evidence now confirms that a significant number of people with HIV are living beyond the age of 50 years. In the era of highly active antiretroviral therapy (HAART), life expectancy for individuals diagnosed with HIV has dramatically increased [1]. The CASCADE collaboration followed 16,534 individuals for a median of 6.3 years. The excess mortality rate (per 1,000 person-years) decreased from 40.8 before the introduction of HAART to 6.1 in 2004–2006 [1].

In addition to this ‘ageing cohort’ effect, primary infection in older adults contributes to the prevalence of the disease in the older age group. The Centers for Disease Control (CDC) and Prevention in the United States reported an estimated 7,172 newly diagnosed cases in individuals aged over 50 years during 2007, representing greater than 16.8% of total diagnoses that year [2]. Of these, over 800 cases were aged over 65 years (Table 1). Importantly, this report also estimates that there were 5,800 newly infected individuals over the age of 50 years in 2006 representing 10% of new infections in that year (Table 2) [2]. Differentiating between new diagnoses and new infections gives clear indication that risk behaviour continues as an individual ages. We are embarking on an era of HIV as a chronic disease, where people age with it, rather than die from it shortly after diagnosis. Ageing individuals experience HIV infection as a complex chronic disease, often with multiple co-morbidities [3]. A greater understanding and awareness of the disease complex, including co-morbidities and complications of disease, and treatments is essential to provide for this ageing cohort within our health system.
The ageing of HIV

HIV was originally described in 1981 with an unusual clustering of Pneumocystis carinii pneumonia and Kaposi's sarcoma in a group of gay men. A cytopathic retrovirus was identified in 1983 and 2 years later serologic testing for HIV-1 was developed. Initial treatment for HIV became available in 1987, but management of HIV was revolutionized with the advent of combination HAART in 1996. When devising effective drug regimens, the purpose is to inhibit viral replication at various points during the viral life cycle and also more recently at entry points into the host cell. Triple antiretroviral therapy using combinations of nucleoside reverse transcriptase inhibitors (NRTIs), non-nucleoside reverse transcriptase inhibitors (NNRTIs) and protease inhibitors (PIs) now form the cornerstone of initial HIV treatment regimens. Drug choice is influenced by side-effect profile and potential drug–drug interactions with medications required for other chronic disease management.

As HIV infection is transmitted through sexual intercourse, exposure to contaminated blood and by perinatal transmission, it is often presumed that older individuals are at lower risk of contracting the virus. However, emerging social practices such as divorce and impotence treatments provide opportunities for additional relationships. This now means older adults may have increasing numbers of sexual partners and consequentially, greater risk exposure. The CDC statistics for 2007 reported 32% of new diagnoses of HIV were contracted through heterosexual contact. Male to male sexual contact and injecting drug users, traditionally felt to be higher risk groups, represented 52.6 and 11.5% of new diagnoses, respectively [2]. The CDC has recommended HIV testing, as routine, for all persons aged 13 to 64 years in all healthcare settings. There is no clear indication as yet whether patients over 65 years should be similarly screened routinely, despite increased incidence of both new disease diagnosis and new infections in this age group.

The goal of the recommendations is to promote earlier entry into care to reduce unnecessary mortality and facilitate prevention by behaviour modification that accompanies knowledge of serostatus [4]. This concept would appear particularly relevant in the older age group who, based on age alone, are at risk of late or missed diagnosis. Additionally, HIV cohort studies and clinical trials have focused on younger HIV-infected adults. The time has come where information available for younger age groups will need to be re-examined in the context of an ageing HIV demographic.

### Disease factors associated with HIV in the older adult

In the pre-HAART era, older adults had a more severe disease course with shorter survival times and rapidly declining CD4+ counts compared to younger counterparts [5, 6]. They also had shorter acquired immune deficiency syndrome (AIDS)-free intervals, more opportunistic infections and earlier development of associated malignancies. Although survival for all HIV-infected patients has dramatically improved in the HAART era [1], time from acquisition of HIV infection to AIDS or death remains shorter in older adults [7]. Age-related changes in immune function and immune response to pathogens with age likely play a significant role in this finding. Additionally, age and HIV have similar effects on the immune system with a decline in both B-cell and T-cell functions thus mimicking an accelerated immune decline. Clinical evidence of B-cell dysfunction is evident in both ageing and HIV with increased risk of serious infections [8]. The thymus involutes with both age [9] and HIV infection [10] resulting in hyporesponsive T cells. While antiretroviral therapy has been shown to allow recovery of thymic tissue [11], age-related thymic involution and depletion of naïve CD4+ T cells in older patients mean that CD4+ count increases with HAART are less evident than in younger counterparts [12].

An additional role of immune surveillance is elimination of malignant and pre-malignant cells from the circulation. It is acknowledged, with and without HAART, that those who are HIV-infected are more prone to a range of AIDS-defining and non-AIDS-defining malignancies [13]. However, while HAART dramatically reduces AIDS-defining illness and malignancies, it does not eliminate their incidence entirely.

### Table 1. Estimated numbers of HIV/AIDS cases by age at diagnosis in 2007 in 34 states and 5 US dependent areas with confidential name-based HIV infection reporting [2]

<table>
<thead>
<tr>
<th>Age (years)</th>
<th>Estimated number of HIV/AIDS cases in 2007</th>
</tr>
</thead>
<tbody>
<tr>
<td>Under 13</td>
<td>159</td>
</tr>
<tr>
<td>13–14</td>
<td>40</td>
</tr>
<tr>
<td>15–19</td>
<td>1,703</td>
</tr>
<tr>
<td>20–24</td>
<td>4,907</td>
</tr>
<tr>
<td>25–29</td>
<td>5,771</td>
</tr>
<tr>
<td>30–34</td>
<td>5,089</td>
</tr>
<tr>
<td>35–39</td>
<td>6,088</td>
</tr>
<tr>
<td>40–44</td>
<td>6,554</td>
</tr>
<tr>
<td>45–49</td>
<td>5,172</td>
</tr>
<tr>
<td>50–54</td>
<td>3,489</td>
</tr>
<tr>
<td>55–59</td>
<td>1,938</td>
</tr>
<tr>
<td>60–64</td>
<td>942</td>
</tr>
<tr>
<td>65 or older</td>
<td>803</td>
</tr>
</tbody>
</table>

### Table 2. Estimated number and rates (per 100,00 population) of new HIV infections in adults and adolescents 2006.

<table>
<thead>
<tr>
<th>Age at HIV infection (years)</th>
<th>Number of infections</th>
<th>% of total infections</th>
<th>Rate of infection</th>
</tr>
</thead>
<tbody>
<tr>
<td>13–29</td>
<td>19,200</td>
<td>34</td>
<td>26.8</td>
</tr>
<tr>
<td>30–39</td>
<td>17,400</td>
<td>31</td>
<td>42.6</td>
</tr>
<tr>
<td>40–49</td>
<td>13,900</td>
<td>25</td>
<td>30.7</td>
</tr>
<tr>
<td>≥50</td>
<td>5,800</td>
<td>10</td>
<td>6.5</td>
</tr>
</tbody>
</table>
Despite poor CD4+ recovery, older patients have been observed to achieve superior virologic responses with HAART compared to younger patients, a phenomenon evident in the French Hospital Database [14].

Please see Appendix 1 in the Supplementary data available at Age and Ageing online regarding CD4+ recovery.

Similarly, a retrospective case–control study by Wellons et al. showed a greater proportion of older individuals achieved virologic suppression on HAART with fewer treatment interruptions [15]. A proposed reason is better treatment adherence among older patients [16]. Despite these studies, a significant knowledge gap remains regarding older patients on HAART, as ‘older age’ is an excluding factor in major clinical trials.

Age-related changes which influence drug metabolism in older adults

Renal function declines with age and HIV infection, affecting drug clearance, the risk of drug toxicities and mortality associated with cardiovascular events. The incidence of kidney disease among HIV-infected individuals increases with age and type of HAART [17]. Additionally, liver volume, blood flow, drug metabolism and hepatoregenerative capacity all decrease with age. Risk behaviours leading to HIV infection in many patients also expose them to concomitant hepatitis B (HBV) or hepatitis C (HCV) infection. Both NNRTIs and PIs are metabolised by cytochrome p450 in the liver, potentially exposing older HIV-infected adults to significantly higher drug concentrations when treated with drugs from these subclasses.

Most clinical studies investigating new antiretroviral drugs routinely exclude patients with advanced age and/or multiple co-morbidities. However, it would seem logical to deduce that, when older individuals are treated with doses of antiretrovirals only studied in, and recommended for younger populations, potential greater toxicity might result. In addition, potential toxicity is exacerbated by a spectrum of co-morbid medical conditions and resultant polypharmacy, rendering the older HIV-infected population particularly vulnerable to HAART-associated toxicity. There is a lack of prospective literature examining current HAART dosing regimens in older adults. Therefore, it is difficult to estimate to what degree age-related factors contribute to greater drug toxicity in older adults. If pharmacokinetic parameters are found to differ significantly in older populations, additional studies examining age-dependent dosing modifications are warranted.

Age and co-morbidities

Cardiovascular disease

Age is a well-established independent risk factor for cardiovascular disease in the general population. Age has also been independently associated with increased risk of myocardial infarction (MI) in HIV-infected patients, due to premature atherosclerosis, as a consequence of antiretroviral-related metabolic toxicity and/or endothelial dysfunction [18]. The increased survival conferred by HAART has been accompanied by an increase in non-AIDS mortality, including cardiovascular disease [19].

Cardiovascular risk calculators used in non-HIV populations have been demonstrated to underestimate cardiovascular risk in HIV-infected cohorts [20]. More recently, coronary artery calcium (CAC) has been used as a surrogate marker to describe how biological age may differ to chronological age [21]. Adapting such CAC measurements to an HIV-infected population and using it in conjunction with standardised calculators of cardiovascular risk may improve risk prediction for this group [22]. Please see Appendix 2 in the Supplementary data available at Age and Ageing online for details of a study of CAC in an HIV-infected population.

During the pre-HAART era, HIV infection was associated with decreases in total cholesterol, high-density lipoprotein cholesterol and low-density lipoprotein cholesterol (LDL) levels, followed by increases in triglyceride levels as infection progresses to AIDS [25]. However, HAART increases LDL levels to pre-seroconversion levels [26]. The Data Collection on Adverse Effects of Anti-HIV Drugs study is an ongoing prospective, multi-cohort study evaluating long-term effects of HAART. This group has shown that PI-based HAART regimens increase MI risk partly due to increases in total cholesterol, triglycerides and LDL levels [27]. In 2008, this group also observed an increased risk of MI in patients with recent but not cumulative exposure to abacavir and didanosine of the NRTI drug class [28]. Although the mechanism through which these drugs render an individual at increased cardiac risk remains unknown, the authors postulate an association with vascular inflammation as the effect is soon reversed with drug cessation [28]. Drugs from the NNRTI drug class have also been associated with development of dyslipidemia [29], but the extent to which two of the more commonly used NNRTIS, efavirenz and nevirapine, are associated with MI remains unclear. Please see Appendix 3 in the Supplementary data available at Age and Ageing online for additional study of cardiac risk in all three major drug classes.

In an earlier analysis, by the same group, of 23,468 patients receiving combination HAART, the incidence of MI increased with increasing exposure to therapy (adjusted RR per year of exposure: 1.26; 95% CI: 1.12–1.41; P < 0.001). However, risk was also associated with several established cardiovascular risk factors, including older age (RR per 5-year increase in age: 1.38; 95% CI: 1.26–1.50; P < 0.001) [31].

Screening and management of dyslipidemia is a critical issue in the ageing HIV population as the combination of the pro-atherogenic state induced by chronic HIV infection and metabolic toxicities of medications renders older HIV-infected patients particularly vulnerable to an increased risk of cardiovascular disease. Therefore, devising class-sparing
HAART regimens may play a more significant role in the management of ageing HIV-infected individuals with multiple cardiac risk factors.

Bone loss
Osteopaenia and osteoporosis have traditionally been viewed as a disease spectrum, predominantly affecting postmenopausal women. However as the HIV-infected population ages, osteopaenia and osteoporosis are becoming more common metabolic complications in both men and women. A meta-analysis of studies published between 1966 and 2005 investigating the prevalence of reduced bone mineral density (BMD) in HIV-infected patients found that 67% of patients had reduced BMD, with 15% of those having osteoporosis [32]. HIV infection itself may cause chronic T-cell activation and increased production of pro-inflammatory cytokines enhancing osteoclast activity. Additional factors such as poor nutrition, sarcopaenia, steroid use, hypogonadism and opiate use may decrease BMD in HIV-infected individuals [33]. Smoking, a well-established risk factor for osteoporosis, has a higher prevalence among HIV-infected individuals compared to the general population [34].

The contribution of HAART to reduced BMD remains controversial with conflicting evidence in the published literature. Reports differ as to whether bone loss is a consequence of HIV infection or treatment. Dolan et al. found that exposure to a PI, NRTI or NNRTI did not affect Dual Energy X-Ray Densitometry (DEXA) scan results, suggesting a lack of causality between antiretroviral exposure and reduced BMD [35]. However, the meta-analysis by Brown et al. found that HAART-exposed individuals had a higher prevalence of reduced BMD and osteoporosis compared to controls [32]. Continuous HAART has also been shown to reduce BMD relative to intermittent HAART, suggesting drug therapy has adverse skeletal effects [36].

Alendronate alone, and in combination with vitamin D and calcium, has been shown to significantly increase BMD in HIV-infected men and women with osteopaenia and osteoporosis, compared to vitamin D and calcium alone [33, 37]. Despite this being in keeping with guidelines for older non-HIV-infected adults, one must exert caution in interpreting results, as most published studies of bone mineral loss have not specifically evaluated older HIV-infected patients. Additional studies examining reduced BMD in older HIV-infected individuals are needed. As this population ages, prevention of osteoporotic-linked fractures is likely to become a significant therapeutic goal.

CNS/dementia syndromes
Cognitive impairment is now a well-recognised manifestation of chronic HIV infection. Please see Appendix 4 in the Supplementary data available at Age and Ageing online for the original classification of HIV-associated neurocognitive disorder by the American Academy of Neurology in 1991.

In 2007 the classification of HIV-associated neurocognitive disorders (HAND) was updated to include three subclasses: asymptomatic neurocognitive impairment, mild neurocognitive disorder and HIV-associated dementia (HAD), in increasing level of debility [39]. Before the widespread use of HAART, up to 30% of individuals with AIDS developed HAD or mild cognitive motor disorder [40]. HAART has dramatically changed the course of neurologic manifestations of HIV; however, neuropsychological impairments persist [41].

It has been shown that HIV enters the central nervous system (CNS) via infected macrophages triggering inflammatory changes including the release of cytokines, neurotoxins and toxic viral proteins. This in turn interferes with protein turnover and synaptic function, impairing learning and memory formation [42]. Deficiencies of neurotransmitters glutamate [43] and dopamine [44] have also been implicated in the pathogenesis of HAND and may represent treatment targets for the future. Additionally, the differing propensity for HAART regimens to penetrate the CNS is an emerging area with growing evidence to support better cognitive improvements with drug regimens known to have greater CNS penetration [45].

The ageing brain is vulnerable to the neurocognitive effects of HIV. A cross-sectional analysis of 202 HIV-positive individuals in the Hawaii Aging with HIV Cohort found that HAD was more frequent in older HIV-infected adults [46]. Using functional magnetic resonance imaging to study brain metabolic demands, Ances et al. observed that increasing age and HIV infection caused significant decreases in baseline cerebral blood flow [47].

Historically, there was little need to consider age-related neurodegenerative diseases contributing to cognitive impairment in HIV infection, because infection existed almost exclusively among younger individuals. However, as the HIV-infected population ages, there is increasing recognition of an overlap between HAD and Alzheimer’s disease (AD). The pathology typically attributed to AD has been reported in HIV-infected patients, including increased brain β-amyloid deposition and increased extracellular amyloid plaques [48]. Deriving treatment approaches specific to older HIV-infected patients with cognitive impairment is problematic, given the paucity of research in this area. It is reasonable to speculate that medications known to be efficacious in slowing progression of AD may have some efficacy in older patients with a combination of neurodegenerative syndromes. However, there are no clinical trials on which to base such recommendations. Valproate, serotonin reuptake inhibitors and lithium have all shown favourable trends in treating HAND but trials to date have been small [49].

In the absence of a complete understanding of the underlying aetiologies associated with neurodegenerative decline in ageing HIV-infected individuals, clinicians should...
consider HIV infection as a possible contributor to cognitive impairment in older individuals thought to be seronegative. Similarly, clinicians should consider the possibility that age-related cognitive disorders may contribute to clinical findings in older HIV-infected patients.

Discussion and future directions

Earlier experience of HIV infection had led us to believe that HIV is a disease of younger adults with specific at-risk behaviours. However, we must see past these preset conceptions and recognise that HIV affects all domains of the age spectrum. We are living and learning in the era of HAART with a population of HIV-infected adults ageing with their disease. Additionally, we are diagnosing HIV in older adults later in life. We have seen evidence that older HIV-infected adults are at greater risk of late diagnosis and subsequently delayed treatment, often due to lack of clinical consideration of the diagnosis. Studies have shown that there is an inferior immunologic response to HAART among older individuals but a superior virologic response, possibly due to better adherence. Clinicians treating older adults must be more aware of the possibility of HIV infection in any adult.

HIV and ageing render individuals susceptible to similar disease processes and co-morbidities. Perhaps, taking a simplistic view, HIV accelerates the ageing process through either disease factors or as a consequence of treatment. Indeed, the common medical complications of infection and treatment seen in HIV-infected individuals, such as cardiovascular disease, dementia and osteoporosis, are not dissimilar to those seen in geriatric clinics on a routine basis. The presence or risk of co-morbidities in older persons has important bearing on antiretroviral selection, as avoidance of metabolic and other toxicities is a key issue. To date, there is insufficient research specifically examining the pharmacokinetics of HAART in older adults.

Regular screening and health maintenance are very important in older HIV-infected patients. In addition to baseline evaluations of cardiovascular risk, monitoring of fasting lipid and glucose levels, renal function and markers of metabolic bone disease should be undertaken within routine follow-up. The distinction between HAD and AD may always remain unclear but comprehensive neuropsychological evaluation and further clinical trials of established dementia treatments in HIV-infected individual with cognitive decline are required. Additionally, patients presenting to a geriatric service for evaluation of a dementia process, who have risk factors for HIV, should undergo HIV testing. Physicians and other healthcare providers have a responsibility to educate older adults about HIV risk and prevention. This includes taking a comprehensive sexual and drug history with possible HIV testing as part of routine care for older adults.

Finally, chronic HIV infection in a patient with multiple co-morbidities is a challenge to caregivers and healthcare providers. As new trainees in geriatric medicine become more aware of the manifestations of AIDS in the elderly, opportunities for joint infectious diseases and geriatric medicine collaboration will be possible, leading to a better understanding of manifestations unique to this population.

Key points

- The age profile of adults with HIV is changing.
- Patients with HIV are now ageing with the disease in addition to older adults receiving their diagnosis later in life.
- Co-morbidities such as cardiovascular disease, osteoporosis and dementia are common in ageing patients with HIV.
- Inclusion of older adults with HIV in therapeutic trials is necessary.
- A greater awareness, among geriatric physicians, of HIV as a possible diagnosis is important.

Conflicts of interest

None.

Supplementary data

Supplementary data are available at Age and Ageing online.

References

(The very long list of references supporting this review has meant that only the most important are listed here and are represented by bold text throughout the review. The full list of references is available at Age and Ageing online.)

6. Kalavijan RC, Landay A, Pollard RB et al. Age-related immune dysfunction in health and in human immunodeficiency virus (HIV) disease: association of age and HIV infection with naïve CD8+ cell depletion, reduced expression of CD28 on CD8+


