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REVIEW

Accelerated aging and human immunodeficiency virus infection: Emerging challenges of growing older in the era of successful antiretroviral therapy

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Abstract HIV-infected patients are living longer as a result of potent antiretroviral therapy. Immuno-inflammatory phenomena implicated in the normal aging process, including immune senescence, depreciation of the adaptive immune system, and heightened systemic inflammation are also pathophysiologic sequelae of HIV infection, suggesting HIV infection can potentiate the biological mechanisms of aging. Aging HIV-infected patients manifest many comorbidities at earlier ages, and sometimes with more aggressive phenotypes compared to seronegative counterparts. In this review, we describe relevant biologic changes shared by normal aging and HIV infection and explore the growing spectrum of clinical manifestations associated with the accelerated aging phenotype in HIV-infected individuals.

Keywords HIV · Aging · Immune senescence · Chronic inflammation · Cardiovascular · Frailty

Introduction

With improvements in antiretroviral therapy (ART), the number of life years lost due to HIV infection has been estimated to be as low as 0.4 to 1.4 years in some patients (van Sighem et al. 2010), but most studies continue to report gaps in life expectancy of up to 13 years despite ART (Lohse et al. 2007; ART-CC 2008; May et al. 2011). There is a consensus that ART is most beneficial if treatment is initiated at high CD4+ T-cell (CD4) counts. Increased survival of HIV-infected individuals and a rising incidence of new HIV infections in older persons (CDC 2008; Myers 2009) have changed the demographics of the infected population. At the end of 2008, almost half of patients living with HIV infection in the USA were ≥45 years old (CDC 2011a, b), and approximately a quarter of new AIDS diagnoses in 2009 occurred in persons aged ≥50 years (CDC 2011a, b).

The modern ART era has also witnessed a shift in the leading causes of mortality among HIV-infected persons from AIDS-related opportunistic infections and malignancies to non-AIDS malignancies, chronic liver diseases, and cardiovascular diseases (ART-CC-2010). Other conditions associated with aging such as chronic renal disease, bone fractures, frailty, neurocognitive impairment, and other non-AIDS disorders are increasingly important causes of morbidity (Deeks 2011; Hooshyar et al. 2007; Triant et al. 2007). While traditional risk factors, adverse effects of ART, and comorbidities clearly contribute to development of non-AIDS disorders, HIV infection itself has been implicated as well. Consistent with this, key features of the immuno-inflammatory pathology associated with normal aging are independently induced by HIV.

In this article, we review the immuno-inflammatory changes that occur with normal aging and HIV infection and highlight the clinical consequences of these processes overlapping in aging HIV-infected patients. Some of the major non-AIDS disorders in aging HIV-infected patients are discussed and opinions offered on ways in which evolving trends should shape HIV research priorities.

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Immuno-inflammatory pathology during normal aging

Aging is a natural process that culminates in physiologic decline and an increased risk of morbidity and mortality (Corsonello et al. 2010; Gruver et al. 2007). At the cellular level, accumulated stressors associated with aging result in immune senescence, a progressive multifactorial dysfunction in innate and acquired immunity that compromises immune surveillance and response to infection (Naesens 2011).

Although changes occur in the innate immune system (Avelino-Silva et al. 2011), the most overt immunologic manifestations of aging involve the adaptive immune system, particularly T-cell function. With aging, the hematopoietic compartment decreases in size, and bone marrow stromal cells secrete less interleukin (IL)-7, a factor vital to lymphocyte development (Gruver et al. 2007). In addition, the thymus undergoes involution and diminished thymopoiesis, possibly due to a shift toward a thymosuppressive cytokine milieu (Gruver et al. 2007). Peripherally, the aging immune system demonstrates a decreased naive: memory CD4 ratio, and there is enrichment of CD28− CD57+ CD8+ effector T cells; these are senescent cells with shorter telomeres and limited proliferative capacity but are capable of inducing a strong inflammatory response (Kalayjian et al. 2003). Shortening of telomeres has been implicated in the pathophysiology of age-associated diseases, possibly by causing dysfunction in inflammation and tissue repair (Naesens 2011; Rodier et al. 2009). Qualitative and quantitative changes may occur in T regulatory cells (Tregs), which play a key role in controlling host immune responses (Tsaknaridis et al. 2003). Finally, the naive B cell repertoire decreases with aging, and qualitative B cell dysfunction occurs, as evidenced by lower antibody responses to immunization and increased risk of some infections (Effros et al. 2008; Titanji et al. 2005).

Aging also promotes a pro-inflammatory milieu characterized by elevated levels of C-reactive protein (CRP), IL-6, and tumor necrosis factor (TNF)-α, a state sometimes referred to as "inflamm-aging" (Franceschi et al. 2007). Inflamm-aging has been implicated in the development of cardiovascular disease and neurodegenerative disorders and may serve as the proximate mediator of functional decline (Corsonello et al. 2010; Franceschi et al. 2007) and frailty (Bortz 2002). In addition, aging is associated with self-reinforcing cycles of nuclear and mitochondrial DNA (mtDNA) damage associated with mitochondria-generated reactive oxygen species (Paradies et al. 2011; Alexeyev et al. 2004).

HIV-induced immuno-inflammatory changes

Some of the changes to the adaptive immune system in HIV infection are strikingly similar to those that occur with normal aging. For example, HIV results in T cell replicative senescence with enrichment of CD28− CD57+ CD8 T cells (Kalayjian et al. 2003). A disproportionate loss of naive T cells (through naive cell recruitment into the memory pool and by direct HIV-mediated cell loss) leads to an inverted naive: memory T cell ratio (Di Mascio et al. 2006). In addition, HIV-associated thymic dysfunction impairs naive T cell production and limits regeneration of the naive T cell pool (Kalayjian et al. 2003). Finally, lymphatic collagen deposition occurs during HIV infection with progressive dysfunction of lymph node architecture leading to impaired T cell homeostasis and T cell/dendritic cell interaction and signaling (Estes et al. 2008). These histopathologic end results of HIV infection resemble some of the features of natural aging.

HIV heightens systemic immune activation and inflammation as well. Within a few weeks of infection, there is massive depletion of T cells and Th-17 cells from the gastrointestinal-associated lymphoid tissue (Appay and Sauce 2008). This leads to a breakdown in follicle-associated epithelial tight junctions and continual leakage of microbial products, creating a systemic antigenic burden that induces chronic immune activation and inflammation (Brenchley et al. 2006). Correspondingly, plasma biomarkers of microbial translocation such as lipopolysaccharide (LPS) and soluble CD14 become elevated, and their levels correlate with gut permeability, degree of immune activation, and expression of the pro-coagulant monocyte thromboplastin (Funderburg et al. 2010; Sandler et al. 2011). In addition, HIV directly causes immune activation and promotes release of pro-inflammatory cytokines such as IL-6, IL-1β, and TNF-α as well as pro-coagulants such as cystatin-C and d-dimer (Neuhaus et al. 2010). Importantly, plasma biomarkers of immune activation and inflammation decline markedly with ART but do not normalize (Hunt et al. 2003, 2008; Neuhaus et al. 2010). Other potential sources of chronic antigenic stimulation include co-infections (such as with hepatitis B virus, hepatitis C virus, or cytomegalovirus), thymic dysfunction, and adaptive immune dysregulation through impaired Treg cell function (Hunt et al. 2011; Ho Tsong Fang et al. 2008; Appay and Sauce 2008). Persistent HIV-induced immune activation may affect mtDNA content and confer mitochondrial damage (Maagaard et al. 2008).

Convergence of the effects of normal aging and HIV

As HIV-infected persons age, the independent effects of natural aging and HIV presumably converge to accelerate immune senescence and development of a chronic inflammatory state. Comparisons of immunophenotypic changes in HIV-infected individuals and HIV-uninfected elderly provide quantitative estimates of the impact of this convergence. For example,

naive CD8+ T cell frequencies in HIV-infected individuals approximate those in HIV-seronegative individuals 20–30 years older (Kalayjian et al. 2003), and the frequency of CD31+ CD4 T cells (reflecting recent migration from the thymus) in HIV-infected individuals resembles that of HIV-uninfected individuals 17–28 years older (Rickabaugh et al. 2011). Along the same line, telomeres in CD4 and CD8+ T cells of HIV-infected patients with a median age 37 years have lengths similar to those of HIV-seronegative patients 38 years older (Bestilny et al. 2000).

Selected non-AIDS events in aging HIV-infected adults

Confluence of the immuno-inflammatory effects of HIV and natural aging is also postulated to accelerate development of non-AIDS disorders involving the cardiovascular, nervous, and musculoskeletal systems, among others. In a recent study, age-related, non-infectious comorbidities (including cardiovascular disease, hypertension, diabetes mellitus, bone fractures, and renal failure), were more prevalent in HIV-infected patients compared with the general population in all age strata evaluated (Guaraldi et al. 2011a, b). The prevalence of polypathology, defined as presence of two or more non-infectious comorbidities, was similar in HIV-infected patients aged 41–50 years and uninfected persons aged 51–60 years.

Cardiovascular system

Cardiovascular events are the leading cause of mortality among older adults in the general US population. As HIV-infected patients are now living longer, myocardial infarction (MI) and other age-associated cardiovascular diseases have emerged as important health concerns. Many of these processes, namely MI (Hsue et al. 2004a, b; Matetzky et al. 2003; Triant et al. 2009, 2007; Vittecoq et al. 2003; Klein et al. 2002; Durand et al. 2011; Lang et al. 2010), cerebrovascular disease (Rasmussen et al. 2011; Corral et al. 2009), carotid disease (Hsue et al. 2004a, b), and peripheral arterial disease (Ye et al. 2010), develop earlier in HIV-infected patients compared to the seronegative population. Indeed, approximately 50% of HIV-infected patients manifest more advanced coronary age as measured by coronary artery calcium score than would be predicted by their biologic age (Guaraldi et al. 2009), while established coronary calcification progresses faster in the context of HIV infection (Guaraldi et al. 2011a, b). The observed increases in vascular disorders are not fully explained by the high rates of traditional risk factors for atherosclerosis (i.e., dyslipidemia, diabetes, smoking, obesity, and hypertension (Adeyemi et al. 2008; Crum-Cianflone et al. 2010)) in older HIV-infected persons (Triant et al. 2007).

Evidence suggests that HIV itself predisposes to premature atherosclerosis and resultant cardiovascular morbidity. Atherosclerosis, the precursor of many cardiovascular events, is a chronic inflammatory condition of blood vessels (Hansson and Hermansson 2011). Since HIV induces chronic inflammation, immune activation, and hypercoagulability, the endovascular microenvironment in HIV-infected persons tends to be pro-atherogenic. Consistent with this, levels of CRP, a cytokine mediator of endovascular inflammation, are elevated in HIV-infected patients (Jong et al. 2010) and correlate with the incidence of dyslipidemia (Masiá et al. 2007), MI (Triant et al. 2009), and mortality (Mangili et al. 2011; Tien et al. 2010). Furthermore, HIV-associated T cell changes, such as increased activation of CD8+ and CD4 cells and senescence of CD8+ cells, are associated with development of carotid artery lesions (Kaplan et al. 2010).

ART use is associated with improved endothelial function (Torriani et al. 2008), and continuous ART use, as compared to interrupted ART use, may protect against cardiovascular events (Phillips et al. 2008). On the other hand, ART itself may predispose to cardiovascular risk through increased dyslipidemia and insulin resistance, especially if the latter are left untreated (Friis-Møller et al. 2007). Thus, more precise assessments of the cardiovascular risks and benefits of prolonged ART are needed to guide patient care (Baker et al. 2009).

Cancer

Rates of AIDS-defining cancers such as invasive cervical cancer, certain lymphomas (including primary central nervous system (CNS) lymphoma), and Kaposi's sarcoma have decreased by greater than three-fold in the modern ART era; in contrast, rates of prostate, colon, and other non-AIDS-defining cancers (NADC) have increased approximately three-fold (Shiels et al. 2011). The increase in NADC is partly due to longer exposure to cancer risk factors as a result of decreased mortality from opportunistic infections. Thus, virally mediated cancers such as anal cancer (from human papilloma virus infection), hepatocellular cancer (from hepatitis B or C virus infection), and lymphoma (from Epstein–Barr virus infection) have remained prominent among malignancies diagnosed in recent years (Vogel et al. 2011; Silverberg et al. 2009). Cumulative time with low CD4 counts (<200 cells/mm^3) appears to be an important risk factor for the development of cancers associated with oncogenic infections (Kesselring et al. 2011).

Research suggests that HIV itself influences the incidence and severity of NADC. Notably, some NADC, such as lung (Shiels et al. 2010), anal (Shiels et al. 2010), liver (Berretta et al. 2011), and colon (Chapman et al. 2009) cancers, may present earlier and at more advanced stages in HIV-infected patients (Ruiz 2010; Chapman et al. 2009),

though these trends are not consistently seen for other cancers (Shiels et al. 2010). In addition, HIV-infected individuals have an increased risk for lung cancer, the most common cause of NADC in the HIV population (Shiels et al. 2011), even after controlling for tobacco use (Kirk et al. 2007). Mechanisms for an independent HIV effect on the pathogenesis of NADC are yet to be fully elucidated; possibilities include HIV-associated defects in immune surveillance, chronic inflammation, and immune activation. Nevertheless, age is an important complicating factor. The estimated number of lung cancers in US AIDS patients younger than 50 years has remained stable over time, but among those older than 50 years, the number increased from 35 in 1991 to 283 in 2005 (Shiels et al. 2011).

Nervous system

HIV-associated neurocognitive disorders (HAND) encompass a spectrum of neurologic dysfunction spanning asymptomatic neurocognitive impairment, mild cognitive disorder, and HIV-associated dementia (HAD) (Antinori et al. 2007). The prevalence of HAD was as high as 50% in the pre-ART era (Sacktor et al. 2001). While HAD has substantially declined in the ART era, HAND persists in up to 50% of treated patients (Heaton et al. 2010), and the burden is greatest in those over 50 years old (Valcour et al. 2004; Becker et al. 2004). In addition to neurocognitive impairment, older HIV-infected individuals are at risk for other neurologic derangements, such as distal sensory neuropathy and extrapyramidal motor anomalies (Watters et al. 2004; Valcour et al. 2008).

Neurocognitive deterioration is partly driven by neurotoxic factors, such as substance abuse (Byrd et al. 2011), vitamin B12 deficiency (Beach et al. 1992), and hepatitis C virus coinfection (Vivithanaporn et al. 2010) that are prevalent in the HIV-infected population. In addition, age-related, metabolic changes affecting cardiovascular risk, such as hypertension (Becker et al. 2009; Wright et al. 2010), hypercholesterolemia (Wright et al. 2010), and diabetes (Watters et al. 2004; Becker et al. 2004) predispose to neurocognitive decline through accelerated cerebrovascular disease (Becker et al. 2009). Furthermore, HIV is associated with deposition of abnormal proteins (i.e., amyloid, tau, and alpha synuclein) in the CNS, and this process may be potentiated by older age (Anthony et al. 2006; Khanlou et al. 2009; Achim et al. 2009) and/or ART use (Green et al. 2005; Anthony et al. 2006). The role of these proteins in HAND pathogenesis is incompletely characterized. Other host factors, such as apolipoprotein E ε4 genotype, may contribute to HIV-related neurodegeneration, but the exact mechanism of this remains unclear as well (Chang et al. 2011).

HIV infection and chronic inflammation are also important in the pathogenesis of HAND. HIV reaches the CNS very early after infection (Tambussi et al. 2000), establishing chronic infection in microglia and a variety of other cells, some of which later become sanctuaries for the virus (Kramer-Hämmerle et al. 2005; Spudich et al. 2005). Additionally, HIV-infected monocytes may continuously traffic to the CNS from peripheral reservoirs (Valcour et al. 2010). Mechanisms by which HIV induces neurotoxicity have been reviewed elsewhere (Nath and Geiger 1998). Although ART can broadly reduce the heightened gene expression that underlies harmful immuno-inflammatory changes (Borjabad et al. 2011), low-level viral replication can continue despite ART, leading to chronic local inflammation and immune activation, which can hasten neuronal and synaptic–dendritic dysfunction and death (reviewed in Valcour et al. 2011). Markers of chronic inflammation include elevated levels of choline (Harezlak et al. 2011; Chang et al. 2004), a nervous system inflammatory marker, and myoinositol (Chang et al. 2004), a glial-cell activation marker, in the basal ganglia and white matter of HIV-infected patients. This CNS neurochemical profile is similar to that of the normally aging brain (Chang et al. 1996). Neuroimaging studies reveal similar functional metabolic derangements in HIV-infected patients and seronegative patients who are 15 years older that are thought to be mediated by chronic inflammation and oxidative stress (Ances et al. 2010). Finally, high LPS levels due to microbial translocation may contribute to trafficking of inflammatory cells, including activated monocytes, into the CNS in patients with HAD (Ancuta et al. 2008).

Taken together, these data implicate multiple shared factors (such as cardiovascular risk factors, abnormal protein deposition, inflammation and immune activation) in the pathogenesis of age- and HIV-related neurocognitive impairment. Consistent with this, some neurocognitive disorders occur more frequently in HIV-infected patients than would be expected from either aging or HIV infection alone, suggesting that additive or synergistic interactions may exist between these variables (Cysique et al. 2011; Valcour et al. 2008; Sacktor et al. 2010). Prevention and treatment of HAND will require a focus on each of these potential precipitants. Importantly, neurocognitive dysfunction is strongly predicted by the nadir CD4 count before ART treatment (Heaton et al. 2011, 2010), leading some to hypothesize that early ART initiation could be neuroprotective (Wright 2009; Heaton et al. 2011). It also suggests that ART has limited restorative effects once neurologic damage has occurred. Choice of ART appears to influence the degree of neuronal recovery and neurocognitive improvement (Winston et al. 2010).

Bone health

Bone mineral density (BMD) peaks at approximately 30 years of age (Kroger and Laitinen 1992) after which there is a decline that accelerates during menopause in

women. Over two million fragility fractures (i.e., fractures that occur after a fall from a standing height) occur annually in the USA (Burge et al. 2007). These fractures are strongly associated with aging, result in total costs of approximately $17 billion annually, and contribute significantly to morbidity and mortality in old age (Burge et al. 2007). Osteoporosis, the underlying abnormality in patients with fragility fractures, is up to four times more prevalent in HIV-infected persons than the general population (Brown and Qaqish 2006), and is of increasing socioeconomic concern as the HIV-infected population continues to age.

Comorbid conditions associated with HIV infection, such as heroin use and hepatitis C infection, are correlated to bone density loss in the elderly (Sharma et al. 2010), and cumulative exposure to these, along with other traditional risk factors such as vitamin D deficiency, hypogonadism, and tobacco use, contribute to reduced BMD in aging HIV-infected patients. However, among patients over 55 years of age, HIV infection is associated with decreased BMD even when controlling for other risk factors, including age, sex, and body mass index (Jones et al. 2008). The role of HIV in bone loss is likely linked to the osteoclast stimulating effects of proinflammatory cytokines such as IL-6 and TNF-α which are induced by the virus (Kwan et al. 2004; Siggelkow et al. 2003). Interestingly, initiation of virtually any ART regimen is accompanied by at least 1–2% decline in BMD (Gallant et al. 2004). Most of this decline occurs within the first 48 weeks of ART (Gallant et al. 2004).

Frailty

Frailty, a syndrome comprising weakness, exhaustion, unintentional weight loss, decreased strength, and/or slowness, is frequently observed in aging adults and associated with adverse outcomes (Fried et al. 2001) including mortality (Desquilbet et al. 2011). Older HIV-infected patients exhibit high rates of a frailty-related phenotype (FRP), the development of which may be accelerated by approximately 10 years in HIV-infected men (Desquilbet et al. 2007). The high burden of other chronic comorbidities (Fried et al. 2001; Ruiz and Cefalu 2011) and hypogonadism may promote frailty, but contribution of HIV itself has been suggested. Supporting this, lower CD4 count is associated with the FRP (Desquilbet et al. 2009).

Conclusions and future research priorities

While successful ART has diminished the morbidity and mortality due to HIV-related illnesses, a new challenge to address the aging of the HIV-infected population has paradoxically arisen. Normal aging and HIV infection are associated with interwoven immuno-inflammatory phenomena, suggesting that the two processes may potentiate each other. Consistent with this, many age-related comorbidities present earlier and more aggressively and progress more rapidly in HIV-infected patients compared with the general population. As the prevalence of these comorbidities increases with aging of the HIV-infected population, research priorities must evolve to reflect this. Research should focus on utility of early ART initiation, earlier screening for (and optimal treatment of) comorbidities, and strategies to control residual systemic inflammation and immune activation during virologically suppressive ART. Given the increasing number of elderly HIV-infected patients and the associated expected rise in the burden of age-related comorbidities, addressing the aforementioned issues from both individual and public health perspectives is essential.

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