Invited Review

HIV and Inflamm-Aging: How Do We Reach the Summit of Healthy Aging?

Kerry Sheets, MD, MS; Jason V. Baker, MD, MS

Hennepin Healthcare, Minneapolis, Minnesota, and University of Minnesota, Minneapolis

Abstract: *People with HIV (PWH) are living longer and experiencing a greater burden of morbidity from non-AIDS-defining conditions. Chronically treated HIV disease is associated with ongoing systemic inflammation that contributes to the development of chronic conditions (eg, cardiovascular disease) and geriatric syndromes (eg, frailty). Apart from HIV disease, a progressive increase in systemic inflammation is a characteristic feature of biologic aging, a process described as "inflamm-aging." Inflamm-aging is driven by persistent antigen stimulation and stress, leading to an immune profile characterized by elevated levels of blood inflammatory markers and cellular activation and senescence. Chronic HIV disease is hypothesized to accentuate the immune profile of inflamm-aging, in part through viral persistence in lymphatic tissues, permanent injury impairing immune recovery, the presence of copathogens, gut dysbiosis and microbial translocation, and chromosomal and genetic alterations associated with immune activation. Few strategies exist for safe and effective modulation of systemic inflammation among older PWH. The strongest current evidence supports aggressive management of modifiable risk factors such as lipids, blood pressure, and levels of physical activity. Future inflamm-aging research should be directed toward advancing the implementation of proven approaches, such as physical activity, as well as studying novel mechanisms of, and treatments for, inflamm-aging among PWH.*

Keywords: HIV, aging, inflammation, geroscience

Author Correspondence
Write to Jason V. Baker, MD, MS, Hennepin Healthcare, 701 Park Ave, Mail Code S2, Minneapolis, MN, 55415, or email jason.baker@hcmed.org.

Introduction

Sustained antiretroviral therapy (ART) with viral suppression has extended life expectancy for people with HIV (PWH), and it now approaches that of people without HIV. Some estimates suggest the mortality gap is 10 years or less when comparing persons with and without HIV.[1] However, prolonged survival has been associated with increases in non-AIDS-defining age-related comorbid diseases.[1,2] Atherosclerotic cardiovascular disease (ASCVD), cancer, and other common comorbidities occur 10 or more years earlier among PWH than in those without HIV.[1] Factors contributing to the development of early ASCVD, non-AIDS-related cancers, and other end-organ age-related comorbidities among PWH include higher prevalence of traditional cardiometabolic risk factors, incomplete immune recovery, and ongoing systemic inflammation associated with HIV.[3-5] What has now emerged in contemporary HIV clinical care is a convergence of declining mortality with effective ART treatment, combined with the earlier onset of age-related comorbidities. This means a growing portion of the years lived for PWH involves morbidity and disability from numerous diseases. In this context, there is a crucial need to better understand the development of age-related comorbidities to improve the health of aging PWH.

Inflamm-Aging

"Inflamm-aging" is a term first introduced in 2000 by Franceschi and colleagues, describing the observation that chronic inflammation increases with age and then itself contributes to age-related diseases.[6] The underlying premise is that continuous antigenic load and stress contribute to a progressive increase in inflammatory tone and reduced resiliency (Figure 1).

Broadly, the inflammatory process is a crucial protective response that can neutralize and resolve insults and

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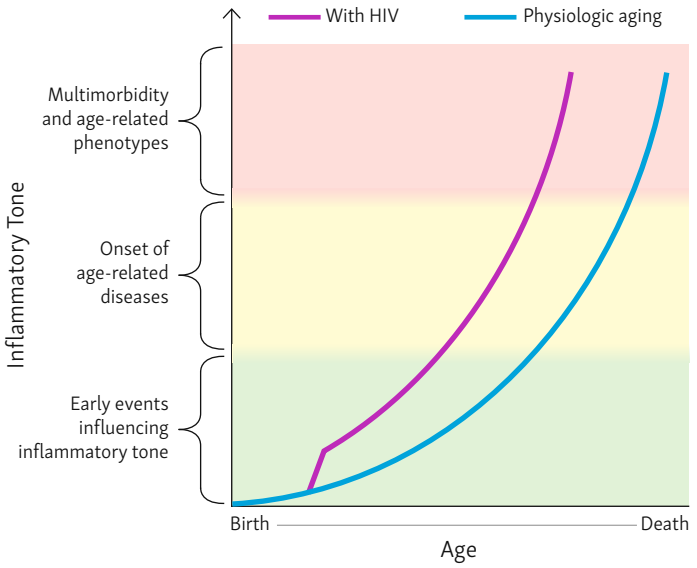

Figure 1. Proinflammatory Tone and Age-Related Disease Risk. Schematic model of inflamm-aging, disease risk, and the influence of HIV. With normal physiologic aging, there is a progressive increase in proinflammatory tone that results from the summation of chronic stimulation and stress with impaired resolution of inflammatory responses. Over time, this process of "inflamm-aging" is associated with the onset of age-related diseases, which then further increase inflammatory tone and additional disease risk resulting in multimorbidity and age-related phenotypes (eg, frailty). HIV disease accentuates this process, the immune profile of inflamm-aging, and ultimately risk for age-related morbidity. Adapted from Franceschi et al.[7]

injury, which is clearly beneficial in the acute setting. However, with lifelong activation, low-grade inflammation becomes progressive and does not fully resolve. Although the concept of inflamm-aging as it was originally proposed had the potential for beneficial or detrimental consequences with advancing age, recent literature has predominantly focused on the hypothesis that progressive inflammation is a characteristic feature of aging that contributes to the development of ASCVD, diabetes, multimorbidity, and frailty.[7-10]

The central factor that provokes and drives inflamm-aging is persistent antigen stimulation and stress, which can arise from a variety of mechanisms.[6-9] Chronic infections or pathogen exposure has been a common focus of research identifying drivers of ongoing immune activation, with examples such as periodontitis, cytomegalovirus, or HIV infection.[11-14] Among PWH, the persistence of HIV within lymphatic tissue reservoirs despite effective ART has been shown to drive chronic immune activation.[15,16] Quite apart from chronic infections, tissue injury or damage from any cause can increase exposure to extracellular debris and oxidized proteins that are recognized by the innate immune system. If not promptly removed, over time an imbalance between self-antigen cellular debris generation and removal can drive inflammation.[17,18]

Gut dysbiosis, reflecting changes in the gut microbiota as well as increased gut permeability, may also be an important driver of inflamm-aging. Advancing age has been associated with a reduction in beneficial commensal flora and an expansion in pathogenic microbiota, a shift that is posited to further impair the mucosal barrier and lead to greater permeability of bacterial products that stimulate innate immune responses and increase inflammatory cytokines in plasma.[19,20] Studies have established that microbial translocation is greater among PWH, in part due to lymphocyte depletion within the gut, and may be an important driver of ongoing immune activation during ART-treated HIV disease.[21]

Behavioral and environmental factors are also increasingly recognized as important factors contributing to chronic stress and inflammatory tone with advancing age. In this context, the concept of metabolic inflammation (or metaflammation) provides a link between nutrient excess and ongoing low-grade inflammation. Evolutionarily, ingestion of nutrients often included concurrent ingestion of pathogens, so innate inflammation became an advantageous response to nutrient exposure. Periods of fasting are important for the resolution of inflammatory response and reducing adiposity, and repetitive or high nutrient exposure can increase physiologic inflammation mediated by metabolic cells.[22] Social determinants of health and environmental stress may also provoke or perpetuate inflammatory responses. Factors such as neighborhood composition or social isolation, exposure to violence, poor dietary patterns or food insecurity, use of or exposure to toxins such as tobacco or alcohol, inadequate health literacy, and limited access to services, can all have a detrimental effect on health and age-related disease risk.[23] Experiences or exposures early in an individual's life (eg, childhood trauma) can then influence innate immune responses as an adult, leading to cumulative effects over a lifetime.[23,24] Given that social determinants of health disproportionately affect PWH, more research is needed to better understand the effect of inflamm-aging as a potential factor further contributing to increased disease risk and health disparities.

Genetic susceptibility and changes that occur during an individual's life can also increase the exposure to inflammatory cytokines and their deleterious effects, and consequently the development of overt end-organ disease with advancing age. For example, polymorphisms

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in cytokine promoter or receptor genes (eg, interleukin [IL]-1, IL-6, or C-reactive protein [CRP]) can influence cytokine levels and their biologic effects.[25,26] Higher levels of circulating cytokines may also be attributed to mutations that occur during one's life. It is well appreciated that mutations accumulate with age, and some of these mutations confer a survival or proliferative advantage on a given cell. Importantly, expansion of these cell lines, or clones, can occur in the absence of malignancy in normal physiologic tissue. The expansion of hematopoietic stem cell clones, without hematologic malignancy, is called clonal hematopoiesis (CH). Clonal hematopoiesis of indeterminate potential (CHIP) refers to a specific subset of CH in which mutations in candidate driver genes occur at greater than a minimum frequency (typically defined by a variant allele frequency ≥2% in a leukemogenic gene). Several of the candidate proliferative mutations in CHIP involve genes that also regulate inflammation; for example, TET methylcytosine dioxygenase 2 deficiency in macrophages leads to increased cytokine production and generation of the inflammasome complex.[27] Epidemiologic data now support that the frequency and type of CHIP are associated with increased risk for ASCVD.[28,29] In summary, CHIP mutations accumulate with age, leading to an expansion of proinflammatory leukocyte clones and increased age-related disease risk.

The Immune Profile of Inflamm-Aging and the Influence of HIV Disease

The immune profile of inflamm-aging is characterized by elevated levels of blood inflammatory markers, ongoing cellular activation, and genetic changes. At the center of these immune changes is chronic activation of the innate immune response managed largely by macrophages that are responding to stimuli, whether triggered by antigens or other stressors, and drive ongoing inflammation and microinjury within tissues.[6] In their original description of inflamm-aging, Franceschi and colleagues termed the chronic activation of macrophage responses "macroph-aging."[6]

In the subsequent decades, characterization of the immune profile of aging has become more complete, including the features of immune senescence. Ongoing cellular stressors can facilitate phenotypic and functional changes known as cellular senescence. Senescent cells are in a state of cell cycle arrest, resistant to apoptosis, and exhibit DNA damage with constitutive signaling and protein synthesis.[10,30] Senescence-associated protein secretion includes proinflammatory cytokines, chemokines, metalloproteases, and other mediators of tissue remodeling. An increase in cell senescence with aging then has secondary effects on immune responses, including dysfunction of epithelial or mucosal barriers (eg, exacerbating microbial translocation), nonresolving innate immune responses, and impaired adaptive immune response and control of chronic infections.[10,31] Overall, immune senescence drives immune dysfunction and elevation in inflammatory markers associated with aging, which can then further perpetuate cell senescence itself through an increased susceptibility to pathogens, DNA damage, and oxidative stress, thereby fueling the cycle of inflamm-aging.

This immune profile of aging and inflammation is accentuated in the context of chronic HIV disease (Figure 1). Blood levels of inflammatory cytokines (eg, hsCRP, IL-6, TNF-α, sTNFR2, sCD14, sCD27, CXCL10, and D-dimer) are higher among PWH than in uninfected controls in numerous cohort studies, with differences persisting despite viral suppression with effective ART treatment.[12,32] Concurrently, the frequency of T-cell activation (CD38+ HLA-DR+) and monocyte activation (CD16+) immune phenotypes is higher among PWH than in uninfected controls, again persisting despite HIV viral suppression.[33-35] Among PWH with viral suppression, the proportion with elevated senescent T-cell phenotypes (CD28− CD57+) is greater than for uninfected controls and also increases substantially with advancing age.[33] The HIV-related mechanisms driving immune activation have been posited to include viral persistence in lymphatic tissues, permanent injury impairing immune recovery (ie, due to lymphatic tissue fibrosis), presence of copathogens (eg, cytomegalovirus), and dysbiosis and microbial translocation.[14-16,21,36] The net result is that chronically treated HIV disease accentuates the immune profile of inflamm-aging, contributing to a steeper trajectory of disease risk.

Immunologic changes in the context of HIV also entail age-related chromosomal and genetic alterations. Whether a consequence of untreated HIV or toxic effects from ART, PWH have been shown to have shorter leukocyte chromosome telomere length and DNA methylation, markers of increased mortality, and earlier onset of age-associated diseases.[37-40] Finally, CHIP (as described above) entails an accumulation of somatic gene mutations that directly contribute to inflammation and is more common among those with vs without HIV.[41,42] Given the proinflammatory effects, the increasing frequency of CHIP provides a potential genetic mechanism by which HIV disease accentuates inflamm-aging and age-related disease risk.

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Inflamm-Aging in the Clinic

Over the past decade, the literature has established that HIV-related systemic inflammation increases risk for a broad spectrum of age-related comorbidities and contributes to mortality from non-AIDS conditions.[43-63] Blood markers of systemic inflammation among PWH have been associated with increased risk for a wide range of chronic conditions including ASCVD, diabetes, cancer, lower bone mineral density, and chronic obstructive pulmonary disease.[49-58] Markers of systemic inflammation among PWH have also been associated with increased risk for geriatric syndromes[64] and adverse aging-related phenotypes including multimorbidity (coexistence of 2 or more chronic conditions in an individual[65]), neurocognitive dysfunction,[59,60] and frailty.[59-63,66]

Geriatric syndromes result from multifactorial etiologies and commonly involve various organ systems. They are sometimes conceptualized as a "final common pathway" in which numerous risk factors, such as organ-specific chronic conditions, and various pathophysiologic pathways interact and result in a syndrome, such as frailty.[64] Geriatric syndromes increase the complexity of clinical care and are associated with increased risk of morbidity and mortality. For example, older PWH with frailty, a state of decreased physiologic resilience, are at increased risk for adverse medical and functional outcomes[67,68] such as hospitalization and nursing home admission. Of relevance, the development and progression of the frailty phenotype in many ways mimics the progression of inflamm-aging (Figure 1). Recovery from acute stressors, such as hospitalization, takes longer for an older adult with frailty, who may never completely return to their prior functional and homeostatic baseline.

Healthy Aging as a Clinical Outcome

A key concept in geriatric care is to solicit and prioritize "what matters most" to each individual. Many older adults place a higher value on functional independence (eg, prevention of morbidity) than on longevity (eg, prevention of mortality). However, many older adults will live for a decade or more with a disability or functional dependence. There is growing recognition that healthy aging, or aging free of substantial morbidity, is an important clinical outcome. Although definitions vary, aging research is increasingly focused on the promotion of healthy life expectancy (years lived in good health), healthspan (survival free of major disease events), and active lifespan (survival free of major disability or dependence)[69] in addition to overall life expectancy[70]

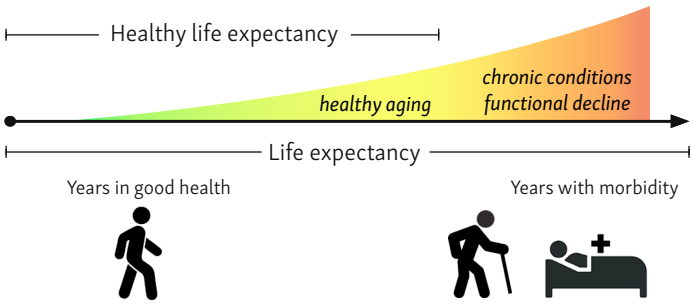

Figure 2. Healthy Aging Focuses on Healthy Life Expectancy. Schematic model of healthy life expectancy and life expectancy. Inflamm-aging is associated with increased morbidity among people with HIV (PWH). Aging research is increasingly focused on the promotion of healthy life expectancy (years lived in good health) in addition to the extension of overall life expectancy. Healthy aging interventions have the potential to increase life expectancy and healthy life expectancy, or importantly, may increase healthy life expectancy more than overall life expectancy, thus compressing the period of morbidity in later life. Treatment of inflamm-aging is likely to be an important component of the promotion of healthy life expectancy and compression of morbidity for PWH. Adapted from Fries et al[71] and Seals et al.[72]

(Figure 2). Healthy aging interventions have the potential to increase life expectancy and healthy life expectancy, or, importantly, may increase healthy life expectancy more than overall life expectancy, thus compressing the period of morbidity in later life.[71] Given the well-documented associations of inflamm-aging with increased morbidity, treatment of inflamm-aging is likely to be an important component of the promotion of healthy life expectancy and compression of morbidity for PWH.

The 5Ms as a Geriatric Framework to Promote Healthy Aging

The 5Ms are a geriatric care framework designed to promote comprehensive, patient-centered care for older adults.[73] The geriatric 5Ms are Mind (eg, cognitive function and mood), Mobility (eg, falls and gait stability), Medications (eg, polypharmacy), Multicomplexity (eg, multimorbidity), and Matters Most to Me. The 5M framework has been adapted to the care of older PWH by Erlandson and colleagues, with the addition of a sixth "M," Modifiable.[74] This sixth "M" emphasizes that although the physiologic history of immune suppression and chronic inflammation is nonmodifiable, addressing modifiable risk factors in later life remains a very important effective strategy to promote healthy aging among PWH.

Examples of strategies that can be modified later in life, and are well known to promote healthy aging,

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include physical activity,[75,76] social engagement,[77,78] and appropriate prescribing, such as avoiding medications that are potentially inappropriate in older adults. For example, walking more in later life, measured in steps per day, is associated with a lower risk of all-cause and cardiovascular mortality. Increased walking is an example of lifestyle physical activity (LPA), self-selected activities of variable exercise intensity that are incorporated into everyday life. LPA overcomes common barriers to structured exercise programs,[79] such as affordability and insufficient time, and may be an important component of healthy aging promotion for older PWH. Loneliness[80] and social isolation[81] are common among older PWH and are associated with the development of geriatric syndromes such as frailty.[82] In addition, connecting older adults with clinical (eg, support groups) and nonclinical (eg, community-based organizations that offer companionship) sources of support may decrease loneliness and increase social engagement.[78] Increases in physical activity and social engagement may also be associated with reductions in inflammation. Aerobic exercise, for example, is associated with reductions in CRP, TNF-α, and IL-6.[83] As such, increased focus on the management of well-established risk factors such as physical inactivity is an important component of the management of inflamm-aging in older PWH.

Pharmacologic treatment of inflammation and inflamm-aging is an active area of study. Recent findings from REPRIEVE (Randomized Trial to Prevent Vascular Events in HIV) among ART-treated PWH aged 40 to 75 years showed that pitavastatin 4 mg daily, compared with placebo, was associated with a 35% reduction in major adverse cardiovascular events (MACE) over a median follow-up duration of 5 years.[84] The reduction in MACE may be accounted for by the lipid-lowering and anti-inflammatory properties of statins. HIV clinical guidelines within the US now recommend moderate or greater intensity statin therapy as primary ASCVD prevention among PWH aged 40 to 75 years.[85]

Geroscience and Healthy Aging for PWH

The field of geroscience observes that age is the largest risk factor for many chronic illnesses, and hypothesizes that treatment of the biologic underpinnings of aging will lead to decreased incidence, prevalence, and severity of chronic disease.[86] Inflamm-aging is considered a "pillar" of biologic and cellular aging.[70] Mechanistic associations of chronic HIV infection with inflamm-aging highlight the relevance and importance of the geroscience framework for reducing mortality and improving healthy aging outcomes for older PWH.

Future inflamm-aging research should be directed to advance implementation of proven approaches, such as physical activity, concurrent with studying novel mechanisms of, and treatments for, inflamm-aging among PWH. Implementation of risk factor modification strategies combined with novel treatments targeting inflamm-aging among PWH has the potential to help older PWH live healthier lives by extending healthy life expectancy with or without extending total life expectancy.

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