Published in final edited form as:

AIDS. 2017 June 01; 31(Suppl 2): S137–S146. doi:10.1097/QAD.0000000000001444.

Geriatric Syndromes: New Frontiers in HIV and Sarcopenia

Kellie L Hawkins^a, Todd T Brown^b, Joseph B Margolick^c, and Kristine M Erlandson^a

^aUniversity of Colorado, Aurora, CO

^bJohns Hopkins School of Medicine, Baltimore, MD

^cJohns Hopkins Bloomberg School of Public Health, Baltimore, MD

Abstract

HIV infection, in many circumstances, can now be managed as a chronic disease due to the marked increase in life expectancy since the introduction of combination antiretroviral therapy (cART). As the patients who first had access to cART age into their 50s and 60s, the effects of chronic HIV infection on health have become an important research focus in HIV infection. People living with HIV appear to exhibit an earlier occurrence of some aging-related conditions compared to people without HIV, in part due to higher rates of co-morbidities, high risk behaviors (e.g., smoking, substance use), chronic immune activation, inflammation and ART-specific factors. Some studies have even suggested an earlier than expected appearance of the “geriatric syndromes”, which are complex medical syndromes of older adults that are associated with morbidity and mortality. The geriatric syndromes include a wide variety of disease processes ranging from incontinence and dementia to impairments in physical function. This review will focus on one geriatric syndrome, sarcopenia, in older HIV-infected populations and its relation to other aging syndromes, including frailty and falls. The contribution of HIV itself, ART exposure, and specific comorbidities, and the importance of early recognition and prevention of these aging syndromes will be highlighted.

Keywords

sarcopenia; HIV; geriatric syndromes; frailty; falls

Introduction

With the advent of potent cART, the average lifespan of an HIV-infected person now approaches that of the general population^[1]. In many major US cities the percentage of people living with HIV infection who are age 50 or older approaches or has surpassed 50%^[2, 3]. The age of 50 years is often used in the HIV literature as a cut-point when describing aging and HIV and is a consequence of epidemiological data rather than biologic reasons. In terms of aging, similar trends are expected to follow in the developing world with the markedly improved roll-out of cART. Identifying and addressing the unique needs

Conflicts of Interest:

TTB has served as a consultant to Gilead Sciences, Merck, BMS, EMD-Serono, and Theratechnologies. KME has received research funding from Gilead Sciences, and has served as a consultant to Gilead Sciences and Theratechnologies.

of this aging population are paramount to ensuring a healthy and thriving HIV-infected community in the future.

HIV infection is associated with earlier occurrence or greater incidence of many conditions that occur with aging^[4, 5], including cardiovascular disease, liver disease, depression, and neurocognitive impairment. Consequently, a higher incidence of multimorbidity and polypharmacy among HIV-infected people, in particular with advancing age, is observed relative to the general population^[6]. Perhaps some of the most striking evidence of the aging process in HIV infection is the occurrence of conditions strongly related to age, such as geriatric syndromes. Geriatric syndromes, including sarcopenia, frailty and falls, are common, interrelated medical conditions that generally occur in older adults. Geriatric syndromes are unique in that they do not fit into one disease category and, because of this, can be challenging to address. The mechanisms underlying the development of geriatric syndromes among HIV-infected aging adults receiving cART are multifactorial, but thought to be strongly driven by chronic immune activation and the inflammation that persists despite effective suppression of HIV replication^[7, 8]. The increased prevalence of chronic conditions and multimorbidity that occur with older age regardless of HIV status further contributes to the development of geriatric syndromes. Importantly, geriatric syndromes are associated with significant morbidity and mortality, and can be difficult to reverse; thus early recognition and prevention are paramount.

This review will focus on the syndrome of sarcopenia, and its contribution to the development of two additional geriatric syndromes: frailty and falls. These distinct geriatric syndromes (sarcopenia, frailty, falls), and the comorbidities that contribute to their development, may occur more frequently among HIV-infected aging adults than in the general aging population. The importance of early recognition and prevention will also be explored. It should be noted that currently assessment of sarcopenia is mainly used in the research setting, because quantification of muscle mass is difficult to obtain in the usual clinical setting. However, physiologic sarcopenia is a normal aging process and is associated with loss of function^[9].

Sarcopenia

In the general population, rate of muscle loss is highly dependent on age and existing muscle mass. As a generalization, muscle mass declines by approximately 1–2% per year after age 50^[10, 11]. Women undergo an accelerated loss of muscle mass at an earlier age than men, beginning at the time of menopause^[12]; however, it appears men lose more muscle mass over the course of their lifetime compared to females^[13]. Sarcopenia is defined by a decline in both quality and quantity of muscle^[14], and is a major contributor to decline in physical function and development of frailty with aging^[15, 16]. Although there is no international consensus on the operational definition of sarcopenia^[14], a well-accepted definition based on muscle mass alone uses an appendicular skeletal mass index (ASMI) defined as either appendicular lean mass, measured by dual energy X-ray absorptiometry (DXA)^[17], or appendicular skeletal muscle mass measured by MRI (ASM)^[18], both adjusted for height^[19, 20]. A value more than two standard deviations below the mean SMI is considered indicative of sarcopenia^[19]. Newer definitions, however, have favored inclusion of measures

of both muscle mass and muscle strength or physical function^[21], and some definitions further adjust for the body mass index (BMI)^[22]. Sarcopenia has been identified as a major problem with aging, as evidenced by the recent creation of an International Classification of Diseases (ICD)-10 code for it^[23]. Because of variability in the definition (with or without measures of physical function or body mass index), age of the study population, and comorbidities of the study population, the prevalence of sarcopenia can range from 1 to 33% of the underlying population [24–27]. Indeed, determination of the prevalence of sarcopenia in the general older adult population is an area of ongoing investigation.

Sarcopenia has recently been recognized as an emerging issue in HIV infection. The deleterious effects of both HIV and ART on muscle have been studied extensively, especially in the pre-cART and early cART eras. Early in the HIV epidemic, prior to the initiation of ART, a myopathy associated with HIV was noted as a rare complication of HIV infection^[28]. Subsequently, a myopathy was observed with zidovudine, and was attributed to toxic effects on mitochondria^[29, 30]. Other nucleoside reverse transcriptase inhibitors (NRTIs) therapies are also implicated in mitochondrial dysfunction and are thought to interfere with replication of mitochondrial DNA (mtDNA) because they inhibit γ -DNA polymerase, the enzyme responsible for replication of mtDNA^[29]. Ongoing depletion or mutation of mitochondrial DNA can result in dysfunctional cellular respiration and clinical manifestations ranging from impaired exercise tolerance to profound lactic acidosis, most notably with the early NRTIs (zidovudine, zalcitabine, didanosine and stavudine)^[31]. Additionally, studies of the early NRTIs showed that ART-induced oxidative stress and depletion of L-carnitine in skeletal muscle may further contribute to muscle dysfunction^[32, 33]. Even contemporary cART regimens are associated with mitochondrial dysfunction. A small study found depletion of mtDNA in the subcutaneous fat of patients taking ART that contained currently used NRTIs, including tenofovir disoproxil fumarate (TDF) and abacavir^[34]; although this finding was observed in fat rather than skeletal muscle, the results would be expected to reflect more systemic mitochondrial changes. Indeed, in vivo ATP metabolism in resting muscle mitochondria, as measured by magnetic resonance spectroscopy, was abnormal in a study of 23 HIV-infected individuals on NRTI-based contemporary cART (96% with complete viral suppression) relative to age and sex-matched HIV-uninfected individuals; post-exertion (ATP re-synthesis) did not differ^[35]. In addition to mitochondrial dysfunction, muscle fibrosis may contribute to impaired myocyte function. For example, in a recent study genes related to muscle aging (p21/Cip1 and p16INK4a) and fibrosis (TGF β 1, CTGF, COL1A1 and COL1A2) were upregulated in HIV-infected men on cART (all with HIV RNA < 10,000 copies/mL) compared to an -uninfected group of healthy, sedentary men, and expression of these genes was correlated with the degree of fibrosis in the muscle as measured by collagen deposition^[36].

These findings at the cellular level may explain the loss of muscle strength and physical function, a composite outcome including strength, neurologic function, and coordination to carry out routine activities, that is reported in the cART era among aging, HIV-infected individuals. In the French Agency for AIDS and Hepatitis Research (ANRS) CO3 Aquitaine Cohort (n=324), 53% of subjects performed poorly in the five-times sit-to-stand test (5STS), a test of lower limb muscle performance^[37]; a longer duration of HIV diagnosis, but not of use of cART, was associated with poorer performance on the 5STS. Recent findings in the

Multicenter AIDS Cohort Study (MACS) have suggested that both strength and gait speed decline faster after age 50 to 60 among HIV-infected compared to HIV- uninfected men, adjusted for viral suppression and other HIV-related factors, indicating an accelerated functional decline even with treated HIV infection^[38, 39]. Importantly, loss of muscle strength and function is a major component of frailty, and is typically clinically apparent before loss of muscle mass^[17].

Few studies have looked at combined measures of both muscle mass and function, or at changes in muscle mass longitudinally in people with HIV infection. In a cohort of middle-aged, ART-treated HIV-infected adults in Colorado, we found that 50% of adults with physical function impairment also met the SMI criteria for sarcopenia^[40]. Similarly, in a small study of 33 HIV-infected individuals on cART (>90% of whom were virally suppressed), the risk of sarcopenia was 5.2-fold higher compared to HIV-uninfected, healthy individuals (n=60), after adjusting for age and BMI, though the uninfected population studied was not specifically risk factor-matched to the HIV-infected population^[41]. ART initiation or change among younger, HIV-infected individuals has tended to result in an increase in lean body mass (LBM), even with older treatment regimens (primarily zidovudine- or stavudine-based)^[42–45], despite the potential for the thymidine NRTIs to induce mitochondrial toxicity^[46, 47]. Similarly, increases in LBM are seen with initiation of nearly all contemporary ART regimens, with minimal differences between ART regimens^[48, 49]. Observational cohorts have nearly all shown stable^[50] or increased LBM among those who remain on ART^[51–53], although few studies have included older adults. The Study of Fat Redistribution and Metabolic Change in HIV Infection (FRAM) found that HIV-infected men had less skeletal muscle area by MRI compared to HIV-uninfected individuals, while HIV-infected women had slightly higher skeletal muscle than the HIV-uninfected individuals. Over time, however, the rate of age-associated loss of skeletal muscle was similar regardless of HIV serostatus. Of note, in this study population the median age was 42, and less than 25% of patients were older than 45 years^[54]. In the AIDS Clinical Trials Group (ACTG) Study A5318, we found a significantly greater decline in LBM over 7 years among HIV-infected individuals on cART (86% virally suppressed) compared to HIV-uninfected, age- and sex-matched controls with similar reported physical activity levels, following an initial increase in LBM with ART initiation^[55].

In addition to the loss of muscle function and mass, sarcopenia is also characterized by changes in muscle quality. As muscle strength and mass decline with aging, fat within and surrounding skeletal muscle increases^[56–58], both in conjunction with and independent of generalized obesity. In fact, among the general population, the greatest disability is observed in those who are both sarcopenic and obese^[59]. The associations between obesity and sarcopenia in HIV appear to vary by the BMI of the cohort, by sex, and by age. One study of virologically suppressed, HIV-infected individuals noted an age-adjusted protective association (OR=0.8) between obesity and a low skeletal muscle index (total skeletal muscle mass/height²: 10.75 kg/m² for males and 6.75 kg/m² for females)^[60]. In contrast, other studies have found a strong association between impaired physical function (a marker of sarcopenia) and increased overall or trunk fat^[61, 62].

Fatty content within skeletal muscle, as measured by MRI or CT-based density, has also been associated with both physical function impairment and falls in older adults, independent of other fat depots and independent of muscle mass^[63]. The effects of fat within muscle are multifold: adipocyte cytokines (e.g., IL-6) may be deleterious to muscle, adipocyte-myocyte cross-talk may impact myocyte differentiation and growth, and adipocytes within the muscle bundle may directly interfere with contractility of muscle fibers.^[64] We recently reported that ART initiation is associated with significant increases in skeletal muscle fat with minimal gains in skeletal muscle lean area^[65]. In a cross-sectional study within the MACS, we found more skeletal muscle fat with increasing age among HIV-infected men, independent of body fat distribution, compared to HIV-uninfected men^[66]. A small study of 40 community-dwelling HIV-infected individuals in Rochester, NY reported an association between impaired physical function and the ratio of intramuscular to total body fat^[61]. Furthermore, among HIV-infected persons, exercise interventions have led to significant improvement in muscle fat, providing evidence of the reversibility of these findings^[67, 68]. In summary, ART- and HIV-associated impairments in muscle strength, mass and quality are common and, as will be described, contribute to risk of frailty, falls, and disability with aging among HIV-infected persons.

Frailty

Frailty, a syndrome that is easier to recognize than to define, represents a vulnerability to adverse health outcomes and is heavily influenced by, but not equivalent to, sarcopenia. A consensus definition of frailty has not been reached, and multiple operational definitions are cited throughout the literature, making frailty in one population difficult to compare to that in other populations^[69]. The frailty phenotype developed by Fried et al. is one of the most frequently referenced definitions of frailty and is based on evaluation of five physiologic domains (slowness, weakness, low activity, weight loss, and exhaustion), with categorization of individuals as robust (0 domains impaired), pre-frail (1-2 domains impaired), or frail (3 or more domains impaired)^[70]. The frailty index proposed by Rockwood et al. is composed of a large list of conditions and comorbidities, often easily obtained through routine clinical and laboratory monitoring, with an accumulation of deficits past a defined proportion considered to reflect a frail state. The Rockwood Index is measured on a continuous scale and various cut-points have been proposed for a state of frailty^[71]. These are two of the most commonly employed definitions of frailty, but many other definitions have been used based on the setting and available patient characteristics^[72].

An overlap between HIV infection and frailty was first recognized early in the HIV epidemic, when the clinical manifestations of advanced HIV infection mirrored those of aging, with profound wasting and fatigue, and an underlying inflammation and immune compromise^[73]. Indeed, prior to the availability of ART, HIV-infected men in the MACS were 9 times more likely to have a frailty-related phenotype compared to HIV-uninfected men (13.9% vs 1.5% prevalence)^[74]. Although a low CD4 cell count has been observed to be a strong risk factor for frailty among both HIV-infected women (in the Women's Interagency HIV Study (WIHS)) and HIV-infected men (in the MACS)^[75, 76], subsequent studies in the era of cART have continued to demonstrate a higher prevalence of frailty among HIV-infected compared to HIV-uninfected populations, though lower than in the pre-

cART era^[77]. Other studies have found an association between frailty and AIDS but not HIV infection itself^[78]. Importantly, frailty prior to ART initiation was independently predictive of AIDS or death (adjusted HR 3.8)^[79].

The development of frailty in people with HIV infection shares many of the risk factors for frailty in people without HIV infection, but with the addition of many additional burdens unique to people with HIV, including but not limited to prior and current ART toxicities, more pronounced immune system dysfunction, and greater chronic inflammation^[7, 8, 29]. As summarized recently^[80], multiple studies have identified an association between frailty and specific co-morbidities and behaviors common in HIV infection, including low muscle mass, low bone density, neurocognitive impairment, depression, viral (particularly hepatitis C) co-infection, and smoking^[40, 78, 81–86]. Interestingly, a recent study in African-American and Hispanic, post-menopausal women noted that total body fat, but not lean body mass, was associated with frailty in adjusted models in HIV-infected participants^[87]. The accumulation of these co-morbidities contributes to the development of a frail state with limited physical activity, weakness, and fatigue. Frail individuals are then more apt to limit activity, further worsening the weakness, slowness, and underlying comorbidities. This may then exacerbate other syndromes, further contributing to physical disability and resulting in a vicious cycle that is difficult to reverse^[88]. This cycle highlights the need to better define frailty in people with HIV infection and to institute early interventions, as discussed in the treatment and prevention section, to slow the cycle (Figure 1 and 2).

Falls

Among older adults, falls are one of the most common reasons for emergency room visits and loss of independence^[89]. Given the multimorbidity, polypharmacy, and other risk factors for falls in older HIV-infected individuals, identification of recurrent fallers and reduction in risk of falling are key clinical issues in the care of older HIV-infected adults. Importantly, even in middle-aged HIV-infected individuals, the incidence of falls may near that of older (≥ 65 years) adults: we found that 30% of study participants aged 45–65 years had had at least 1 fall in the previous year and that the odds of falling increased considerably for each additional co-morbidity reported^[90]. Within the WIHS, HIV infection itself was not a risk for falls, but factors affecting cognition, including depression, neuroactive medications, and cognitive complaints, were strongly associated with falls^[91].

Falls pose a particular concern among aging HIV-infected adults because of a higher prevalence of low bone mineral density (BMD) and fractures compared to the general, HIV-uninfected population^[92–97]. Incident fractures were 1.58-fold more likely, and fragility fractures 1.35-fold more likely, in HIV-infected vs uninfected individuals in a pooled analysis^[93]. Similarly, in a population-based nationwide Danish study, risk of fracture among HIV-infected participants was 1.5 times that of the general population, with the greatest risk seen in HIV/HCV coinfection (2.9 times greater risk than that of the general population)^[94]. It should be noted that a limitation of the above data is lack of studies that include HIV-uninfected populations that are risk factor-matched. The risk of low BMD in people with HIV infection is multifactorial and due in part to a high prevalence of traditional risk factors for low BMD. HIV- and ART-specific factors also play a role: in a combined

analysis of ART-naïve individuals initiating ART, a CD4+ T-cell count <50 cells/μL at ART initiation was significantly associated with more bone loss (vs. 500 cells/μL) after ART initiation in adjusted models^[92]. One of the strongest ART-associated risk factors is the use of TDF, particularly during the first 3 years of therapy^[95]. However, even in a cohort of ARV-naïve patients initiated on a TDF-sparing regimen, 5% decrease in total BMD was noted in 15% of participants after 96 weeks of therapy^[97]. Data on long-term rates of BMD decline after the first 96 weeks of ART are limited to a recent study that found accelerated decline of BMD in the lumbar spine but not the hip among HIV-infected people on cART (86% with viral suppression) compared to age and sex-matched HIV-uninfected individuals with similar reported physical activity levels but differing mean BMI (27 kg/m² vs 29 kg/m², respectively)^[96].

Bone and muscle arise from the same progenitor cells^[98], are influenced by similar metabolic pathways including those involving growth hormone and insulin-like growth factor^[99], and are similarly affected by both physical activity for growth and bed rest for atrophy^[100]. Low total body weight and low BMD are strongly associated, as demonstrated in a large meta-analysis of studies of HIV-infected populations, and well-established in the general population^[101, 102]. LBM is also strongly associated with higher BMD in patients initiating ART, and with less loss of BMD following ART initiation^[48]. Lower LBM but not HIV or treatment-associated factors is associated with long-term decline in BMD^[55]. In a cohort of virologically suppressed, HIV-infected individuals aged 45–65 years on cART in Colorado, both low LBM and low BMD were found among participants with impaired physical function or frailty^[40]. In the same cohort, physical function was a strong risk factor for falls,^[103] and for each additional criterion of the Fried frailty phenotype that was satisfied, the odds of sustaining a fall increased by 3.1-fold^[103]. Further understanding of the relationships between sarcopenia, frailty, falls, and fracture risk in HIV can guide development of interventions for prevention or treatment.

Quality of Life and Disability

The impact of sarcopenia, frailty, and falls on the health of the HIV-infected population is profound. As people age with HIV, reducing this impact will be critical to limiting disability and maximizing quality of life (QoL). The cumulative effects of sarcopenia, frailty, and falls can lead to impairments in the ability to complete higher-level or even simple daily activities, resulting in disability. Disability refers to a physical or mental impairment that reduces ability to carry out usual activities of daily living (toileting, feeding, etc) or instrumental activities of daily living (managing finances, medications, appointments, shopping, etc)^[104]. Disability in HIV infection has been linked to older age, low CD4 cell count, depression, low physical activity, and neurocognitive decline^[40, 105–108] and these risk factors for the development of disability overlap with those for the other geriatric syndromes such as frailty, sarcopenia, and falls.

HIV infection and older age have both been independently associated with reduced health-related QoL^[109–111]. Older HIV-infected individuals report more social isolation and psychological distress than their younger counterparts^[112]. In contrast, among middle-aged and older HIV-infected adults, faster gait speed and chair rise time were associated with

improved physical and mental QoL^[113]. Monitoring QoL measures may help identify those at greatest risk for physical function decline and disability.

Treatment and Prevention

Sarcopenia, frailty, and falls are complex geriatric syndromes due to impairment in multiple underlying pathways. The pathogenesis and potential treatment targets of geriatric syndromes can be conceptualized by considering processes that promote aging, such as the recently-envisioned Pillars of Aging^[114, 115]. Within the Pillars, mechanisms of aging including metabolism, inflammation, stress maladaptation, proteostasis, cellular senescence, macromolecular damage, and epigenetics are intertwined^[114, 115]. While it is tempting to target a single pathway within the Pillars to understand mechanisms or test interventions, suppression or enhancement of one component of this web may lead to overcompensation by other pathways^[114, 115]. Figure 3 incorporates the overarching ideas of the Pillars of Aging into a model that highlights processes common to aging with or without HIV infection, and the processes that may be unique to or exaggerated in aging with HIV infection, such as chronic immune activation and inflammation, mitochondrial toxicity and dysfunction, and accelerated telomere attrition^[116, 117]. Within the HIV-specific “Pillars of Aging”, pathogenesis, prevention, and treatment of geriatric syndromes can be considered in the context of multiple other processes, and therapeutics would ideally target multiple pillars simultaneously.

Data are limited in people with HIV infection, but extrapolating from the general aging population, complete reversal of clinically apparent sarcopenia or frailty is exceedingly difficult. Significant loss of muscle function and mass can occur within days, and repeated episodes of illness or hospitalization can lead to reset of a lower baseline level of function^[118]. Intensive interventions such as early physical rehabilitation and nutritional supplementation may help attenuate losses, but complete recovery of function or reversal of frailty is uncommon^[119]. In the general older population, increased physical activity and structured exercise (both aerobic and anaerobic) have been shown to slow this age- or event-associated loss of muscle function and mass^[120–123] and the development of frailty. Similarly, physical activity and exercises promoting balance (i.e., tai chi, yoga) can decrease risk and fear of falling^[124, 125]. A novel monoclonal antibody therapy directed against myostatin, a potent negative regulator of muscle growth, has increased muscle mass and strength in both young and old mice after 4 weeks of therapy and holds promise as an agent to further investigate as a therapeutic option for sarcopenia^[126, 127]. A Phase 2 study in older adults, however, demonstrated increases in LBM but not in muscle strength or physical function^[128]. To the best of our knowledge, no interventions outside of exercise have been proven as effective for the prevention and treatment of sarcopenia, frailty, and falls.

Ultimately, a better understanding of the pathogenesis of syndromes associated with aging including sarcopenia, frailty, and falls will lead to more effective prevention and treatment interventions. In this regard, incorporating measures of muscle function/mass or frailty into interventional studies of HIV-infected populations is likely to provide important insights into the potential pathogenesis of, or test potential treatment strategies for, these geriatric syndromes. For example, a substudy of REPRIEVE (a large randomized, controlled trial

designed to determine whether statin therapy can prevent cardiovascular disease (CVD) events in low-CVD risk HIV-infected individual (based on current risk-assessment guidelines) will investigate the impact of a reduction in inflammation through randomized pitavastatin therapy on muscle function of middle-aged HIV-infected persons^[129]. Similar opportunities to test muscle function in interventional trials in younger populations or with novel therapeutics may offer important insights into pathogenesis and prevention of geriatric syndromes.

Conclusion

Recognition and management of geriatric syndromes are of increasing importance as the HIV-infected population ages. Sarcopenia is part of a cycle that can lead to frailty, falls, and further loss of function, perpetuating the cycle. The implications of geriatric syndromes and loss of function on quality of life are marked. Studies that simultaneously explore multiple pathways, seek to understand early muscle dysfunction in younger HIV-infected individuals, and interventional studies that include sarcopenia, frailty, and falls as outcomes are needed. As geriatric syndromes are difficult to reverse, a focus on prevention is likely to have the greatest clinical impact.

Acknowledgments

This work was supported by National Institutes of Health grants K23 AG050260 to KME, K24 AI120834 to TTB, U01 AI35042 to JBM, and T32 HL116276-02 to KLH.

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Figure 1.
Relationship of sarcopenia, frailty, falls, and functional limitation.

Figure 2.

Theoretical trajectories of differing rates of development of geriatric syndromes and further decline in physical function among older, HIV-infected adults, stratified by baseline physical function. The red line represents the trajectory of an individual beginning with a lower level of muscle mass or physical function. The individual undergoes multiple insults with age due to illness, hospitalizations, falls, or other stressors. Theoretically, this individual is unable to completely recover following these episodes and quickly passes a threshold of clinical weakness, onset of a geriatric syndrome, and ultimately death. In an individual starting at a higher level of physical function, repeated insults may either fail to significantly impede physical function (green line), or impact function but with a longer time to clinically apparent weakness and onset of a geriatric syndrome (blue line).

Figure 3.

[114, 115] ¥: The HIV-specific Pillars of Aging are processes common to aging with or without HIV infection, and the processes that may be unique to or exaggerated in aging with HIV infection (highlighted). *Residual HIV viremia, co-infections and gut microbial translocation included under the larger umbrella of chronic inflammation and immune activation. ** Shorter leukocyte-telomere-length (a marker of aging) has been noted in HIV infection. ***Detailed in the “sarcopenia” section of this review. ¥ This figure was adapted from figure 1 in the reference¹⁰⁴ and¹⁰⁵ with permission of the authors and publisher, license number 4032010426699 and 4026641471571, respectively.