HIV and Aging: Parallels and Synergistic Mechanisms Leading to Premature Disease and Functional Decline

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1 Introduction

Why is there a chapter on HIV in a translational science textbook on aging? Effective antiretroviral therapy (ART) has resulted in many people with HIV infection living far beyond what was thought possible just a few years ago [1, 2]. It is estimated that over half of all U.S. HIV-infected persons will be >50 years by 2015 [3, 4], and the success and availability of ART is even leading to an aging HIV-infected population in developing nations [1, 5, 6], emphasizing the need for aging-related research in those countries where HIV burden of illness is greatest [7].

There is marked debate as to whether HIV accelerates aging itself or is an added risk factor for a number of diseases and conditions that lead to an "aged phenotype." Of course, there is no single pathway that defines "aging" – in fact, two recent, excellent reviews [8, 9] emphasize a number of "hallmarks" of aging – biologic changes that accompany aging, but none is clearly "the" causal pathway. Cardiovascular disease (CVD) and many other diseases increase with age, and advancing age is the leading risk factor for CVD. But we generally don't consider CVD risk factors (e.g. hypercholesterolemia) to be conditions that accelerate aging itself. However aging with HIV is different than aging with hypercholesterolemia; a much broader array of illnesses occurs with greater frequency in people aging with HIV (PAWH). This leads not only to prematurity of a single disease, but multiple diseases, as well as decreased physiologic reserve and increased vulnerability to catastrophic illness, hospitalization and death. Functional decline – physical and/or cognitive – often accompanies multi-morbidity or may occur independently, but in either case functional decline is the strongest risk factor for disability and loss of independence, particularly when social and family support structures are lacking. This state of multi-morbidity, vulnerability, functional decline and loss of independence is what we usually view as "old" – or the aged phenotype – and there is no doubt that this phenotype occurs earlier in PAWH when compared to HIV-uninfected persons [10–14]. In this chapter, we will briefly summarize a few examples of age-related serious non-AIDS events (SNAEs) such as CVD and cancer – and geriatric syndromes (functional decline/frailty and multi-morbidity) to highlight the clinical relevance and translational opportunities to link mechanisms to clinical outcomes in PAWH.

2 Increased Prevalence of Age-Related, Serious Non-AIDS Events (SNAEs) in PAWH

While life expectancy has increased markedly for PAWH, this group experiences a greater frequency of age-associated comorbid conditions, such as CVD, non-AIDS-defining cancers (liver, lung, anal), osteoporosis/osteopenia/bone fractures, metabolic syndrome, and neurocognitive dysfunction. These events are termed SNAEs and increasingly robust data suggest they are very common in PAWH, even those

well controlled on ART [15]. CVD and cancer have the most robust database and are therefore examined in greater detail in the following paragraphs.

CVD risk factors and rates of acute coronary syndromes and heart failure are markedly increased in HIV-infected vs. age matched control subjects [16–20], and coronary artery "age" is accelerated on average by about 15 years in treated HIV-infected persons (median duration of ART ~11 years) as assessed by coronary artery calcium (CAC) score comparing PAWH to age-defined norms established in the MultiEthnic Study on Aging (MESA) cohort [21]. Higher levels of C-reactive protein, interleukin-6, and D-dimer have been shown to be significantly associated with an increased risk of all-cause mortality in HIV-infected individuals not on ART, and much of this is cardiovascular mortality [22]. Specific ART drugs also may be causally associated with early heart disease, even after controlling for age and traditional cardiovascular risk factors [23, 24]. Further, lipodystrophy and metabolic syndrome (altered body fat, hyperlipidemia and insulin resistance) are common in HIV-infected patients receiving ART [25, 26]. The redistribution of fat mass and progression to metabolic syndrome (12/100 patient-years) typically occurs within 3 years after the initiation of ART [27], when weight gain is often substantial, thus increasing cardiovascular disease risk. Enhanced cardiovascular "aging" is not limited to coronary artery disease. Left ventricular diastolic dysfunction and increased vascular stiffness [28–30] are more common in HIV-infected subjects versus uninfected, age-matched controls even after controlling for hypertension and other risk factors. Heart failure and atrial fibrillation, typically seen in older adults, is increasingly being reported in younger PAWH [18–20].

As ART use has become widespread, AIDS-defining cancers (Kaposi's Sarcoma, lymphomas) have become less common in this population, but increased survival and perhaps decreased competing causes of AIDS-defining cancer deaths have led to increased numbers of non-AIDS-Defining Cancers (NADC) [31]. A number of NADC occur more frequently in PAWH than age-matched control cohorts [32] and NADC are increasingly a cause of death in PAWH [15]. Initial reports suggested the age of onset of many NADC was much earlier than in those without HIV, but most of this appears to be a cohort effect. PAWH are a younger cohort than the general population [1] so colon, lung or other cancers may appear to only be occurring in younger adults, but there aren't many 70+ year old PAWH so this is often a false impression. As control groups and age-adjustments have been refined, it appears NADC are only minimally "accelerated" with regard to age at diagnosis – perhaps 3–5 years [33] (Table 1). It is important to note that some NADC that are most strongly related to age – breast cancer in women and prostate cancer in men – do not appear to be increased in those with HIV [33, 34], though data are sure to evolve as persons continue to age with HIV infection.

Another way to examine the question of whether HIV directly "ages" individuals or acts in parallel is to assess whether age remains an independent risk factor for SNAEs in PAWH. Within cohorts of PAWH, increased age is an independent predictor of stroke, myocardial infarction, fractures, osteoporosis, diabetes, and non-AIDS associated cancers, while controlling for CD4 count, viral load, intravenous drug use, smoking, and duration of HIV infection [35].

Table 1 Age differences between HIV-infected and HIV-uninfected for select NADC

Select NADC	Median age at diagnosis in AIDS population (years)	Median age at diagnosis in HIV⁻ general population (years)	Apparent difference (years)	Median expected age at diagnosis in HIV⁻ population if cohort limited to the same age distribution as those with AIDS (years)	Real difference (years)
Rectal	46	69	−23	51	−5
Lung	50	70	−20	54	−4
Ovarian	42	63	−21	46	−4
Myeloma	47	70	−23	52	−5

Adapted from [33]

3 Geriatric Syndromes in PAWH

3.1 Multi-morbidity

Despite the success of ART, extensive evidence suggests HIV-infected persons are more likely than their HIV-uninfected counterparts to have multiple comorbidities at a young age. This is perhaps not surprising for illnesses with overlapping risk factors (i.e. hepatitis C, human papillomavirus [HPV]-related cancers), but it is also true across organ systems where intersecting risks are not so clear; early-onset of disease in individual organ systems in PAWH has been observed (e.g. coronary artery disease, arterial stiffness, cerebral blood flow, and bone fractures) [21, 36–39]. Chronic liver and renal diseases are also more common in PAWH compared to HIV uninfected populations [40]. Although behavioral factors such as smoking and illicit drug use are more prevalent in populations of PAWH, controlled studies have shown that these factors do not fully explain the increased risk for age-related conditions such as cardiovascular and liver disease [35, 41, 42]. Where aggressive ART is widely available, 58 % of HIV-infected subjects aged 51–60 have one or more of the following: renal failure, diabetes mellitus, bone fracture, hypertension or overt cardiovascular disease vs. only 35 % of HIV-uninfected controls [10, 35]. The rate of multi-morbidity (> one major chronic illness) at age >50 years is about 2.5 times higher in HIV-infected subjects vs. HIV-uninfected controls [10, 35, 40].

On average, PAWH aged 50 and older have up to three chronic illnesses, in addition to HIV [43] (Fig. 1). Depending on the population, studies have demonstrated increased prevalence of specific comorbidities. The onset of multi-morbidity appears to be accelerated 12–15 years in those with HIV infection [10]. Further, multi-morbidity risk assessments such as the Veterans Aging Cohort Study (VACS) Index derived and validated in HIV-infected subjects correlates with mortality risk and hospitalization [44, 45]. Importantly, the VACS index has now been validated to predict mortality in HIV-uninfected populations [45] demonstrating the generalizability of this integrated measure of cumulative damage to the hematopoietic, immunologic, hepatic and renal systems.

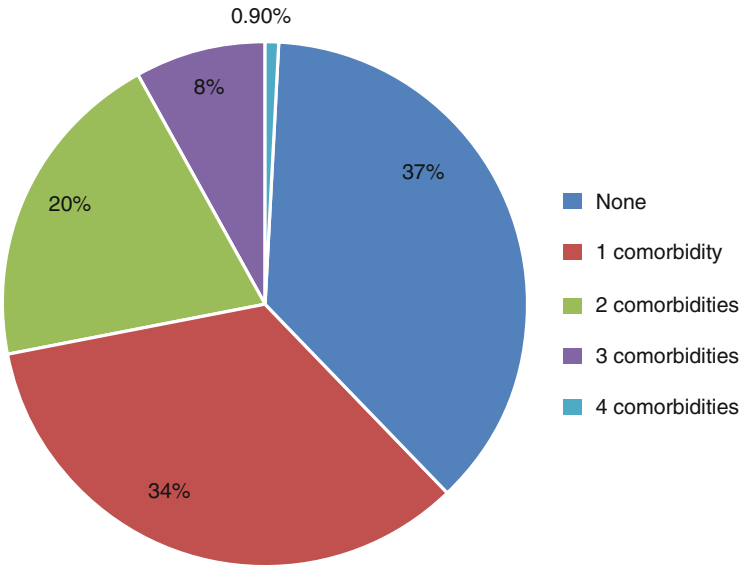

Fig. 1 Prevalence of comorbidity burden, HIV-infected persons age > 50 (Data derived from [10])

3.2 Polypharmacy

In the setting of multi-morbidity, PAWH have increased risks of developing both HIV-associated non-AIDS (HANA) and non-HIV related conditions. Consequently, polypharmacy and increased complexity of care are becoming commonplace in the health management of PAWH, noting that the disease courses may be altered depending on the patient's state of virologic suppression [46]. PAWH who are aged 50 and older are more likely to have at least one medication (in addition to ART) compared to PAWH younger than age 50 [47]. Specifically, older PAWH are more likely to take concurrent cardiovascular, gastrointestinal, and hormonal medications than younger patients [47].

The inherent complexity of polypharmacy translates into potential harm for older patients. In older adults without HIV, polypharmacy is a known risk factor for falls, adverse drug events (ADE) including drug-drug interactions (DDI), morbidity, and mortality [48]. These associations remain true for PAWH but may occur at younger ages compared to people without HIV infection [47–49]. At baseline, older patients are at increased risk for ADE, compared to younger patients. In addition to direct toxicity for the patient, ADE and DDI can mean decreased efficacy of therapy, both for HIV and other comorbidities, especially in the case of protease inhibitor (PI)-based ART [49]. The list of potential DDI is extensive and includes virtually every class of therapeutics, including cardiovascular, gastrointestinal, hematologic, anti-neoplastic, antimicrobial, psychiatric, and endocrine (including inhaled steroids which aren't typically considered to have systemic effects) [47–50]. Predicting

DDI is more challenging due to changes in drug metabolism that occur with normal aging, a process which may be accelerated or accentuated in PAWH. The known increased prevalence of liver and kidney disease in PAWH further complicates prediction and prevention of DDI and ADE [48, 49].

Adherence to ART is extremely important for PAWH and is a predictor of morbidity and mortality for these patients, but a significant challenge for many [49, 51–53]. Similar principles regarding consistent medication use can apply to other chronic illnesses, including the common HANA and non-HIV associated comorbidities which are so prevalent in this population. Recent data suggest that lower pill burden is an important factor in improving adherence and virologic suppression, making awareness (and avoidance if possible) of polypharmacy even more salient [54].

3.3 Frailty

Frailty has been defined and various measures validated in older HIV-uninfected adults, but it is generally agreed to represent increased risk and decreased ability to recuperate from illness and injury. Frailty is increased in HIV-infected vs. age-matched HIV-uninfected controls [13, 55–61]. In those PAWH, there is a high correlation between various measures of frailty validated in seniors, though definitions vary from study to study and the reader should be cautious to assess frailty definitions, cohort effects, and control group definitions when comparing individual rates of frailty between studies [62]. Early research measured the prevalence of frailty using the frailty-related phenotype (FRP) in 55 year old men with HIV infection (infected for less than or equal to 4 years) as equivalent to the prevalence of FRP in men 65 years of age or older without HIV [12]. Onen et al. measured a prevalence of 9 % for frailty in an outpatient HIV clinic (mean age of 41.7 years), which was comparable to the prevalence of frailty in Caucasian Europeans aged 65 years and older [13]. In the same study, investigators measured patient-level characteristics; frailty was associated with socioeconomic status, multi-morbidity, lower education level, longer period of HIV infection, history of opportunistic infection, as well as an increased risk of hospitalization, number of hospitalizations, and inpatient length of stay [13]. Much of the early data suggested frailty in PAWH was associated with uncontrolled HIV/weight loss/wasting, but more recent data suggest frailty in HIV has been associated with obesity and intramuscular adiposity, as seen in HIV-uninfected older persons [59, 61, 63].

Frailty is potentially mediated more by inflammation and body composition than by HIV infection itself. This is compounded by the fact that optimal immune function may be hindered by age-related changes that are independent of virologic suppression [46, 64]. In PAWH, frailty is associated with central obesity, sarcopenia, and increased muscle fat density for age [65]. Oursler et al. showed that, despite ART, physical function in PAWH aged 50 years and older was worse compared to HIV-uninfected people [60]. Regardless of age, HIV-infected patients with chronic pulmonary disease had worse physical function compared to HIV-uninfected peo-

ple, such that a 50 year old person with HIV and chronic obstructive pulmonary disease (COPD) had functional measurements approximating a 68 year old person with COPD, but without HIV [60]. Within populations of PAWH, the prevalence of frailty is increased in people who also use intravenous drugs [43]. Not surprisingly, frail PAWH have a high prevalence of comorbidities, including hypertension, COPD, viral hepatitis, dementia, and cancer; this pattern of multi-morbidity mirrors trends seen in the larger population of PAWH [11].

Beyond the effects that frailty may have on physical health and mental well-being, this phenotype has implications for healthcare delivery and models of care. Guideline-driven care may not be practical or universally applicable to PAWH if their risks of various conditions change at different age breakpoints or based on factors other than what has been measured in the foundational studies. Use of more tailored prediction tools such as the VACS Index may be more applicable due to incorporation of multiple biomarkers [46].

3.4 Neurocognitive Impairment

A full examination of the neurologic manifestations of HIV and even discussion limited to cognitive impairment is beyond the scope of this review. Briefly, 50 % of PAWH will develop an HIV-associated neurocognitive disorder (HAND) [43, 66]. HAND is a spectrum of clinical conditions ranging from asymptomatic neurocognitive impairment (ANI – least severe) to HIV-associated dementia (HAD – most severe, previously known as "AIDS Dementia Complex") [67] (Fig. 2). The symptoms can be largely reversed with ART, but the incidence of HAND is associated with worse adherence. The impact of HAND is marked with HAND being associated with decreased ability to complete daily functions, poorer quality of life, and shorter survival. While the incidence and prevalence of HAND are decreasing due to ART, the incidence and prevalence of ANI and mild neurocognitive disorder (MND) are stable to increasing, spurring a recommendation for universal neurocognitive screening of PAWH [67, 68]. Furthermore, HIV itself may alter brain structure, despite ART, thus, the full expression of HIV-related cognitive disorders may require time to become apparent [69].

3.5 Quality of Life and Mental Health

Compared to HIV-uninfected people, PAWH (ages $\geq$ 50 years) are not as happy, optimistic about aging, or resilient [43, 70]. They also experience more perceived stress, anxiety about the future, and lower quality of physical and mental health [70]. Social isolation, a common occurrence in older adults regardless of HIV status, is associated with increased risk for hospitalization and all-cause mortality. The social networks for older PAWH may shrink due to common age-related factors

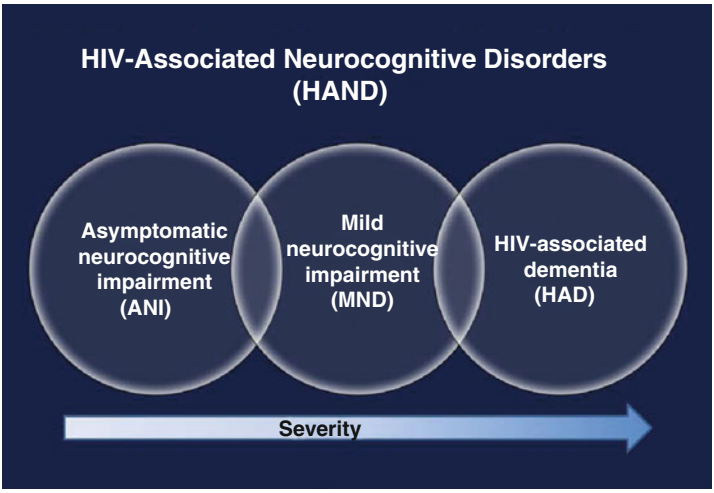

Fig. 2 The spectrum of HIV-associated neurocognitive impairment

(e.g. age-related deaths, limited transportation, geographic isolation) and/or more HIV-specific factors: loss of peers earlier in the HIV/AIDS epidemic, stigma, marginalization in the current make-up of the epidemic [43, 71, 72]. While both HIV-infected and HIV-uninfected older adults may experience social isolation to some degree, HIV infection alone is associated with increased risk and prevalence of social isolation [71].

4 Potential Mechanisms Linking Chronic HIV Infection with Age-Related Conditions

4.1 Immunological Similarities Between HIV Infection and Healthy Aging

The overlapping burden of morbidities and SNAEs in PAWH and aged individuals has led to the hypothesis that similar pathogenic mechanisms are driving the development of these diseases in both populations. Indeed there are many immunological parallels between chronic HIV infection and healthy aging which are summarized in Table 2 and discussed in detail below.

Adaptive Immune Changes

The reduced number of naïve T cells and reduced CD4:CD8 T cell ratio observed in the aged is a hallmark of T cell immunosenescence [73, 74] and also occurs in HIV-infected individuals due in part to thymic involution and reduced regenerative capacity [75, 76]. Low CD4:CD8 T cell ratio is an independent predictor of non-AIDS mortality [77] and cardiovascular disease risk [78, 79] in HIV-infected

individuals, suggesting T cell immunosenescence has important clinical implications in the context of PAWH. Importantly, the majority of HIV-infected individuals on long term ART fail to normalize the CD4:CD8 T cell ratio, despite restoration of CD4+ T cell levels [80]. Elderly HIV-uninfected and HIV-infected individuals also exhibit increased T cell activation (as measured by expression of the activation markers HLA-DR and CD38) [76, 81], an increased susceptibility to spontaneous apoptosis [82, 83] and an expansion of 'senescent' memory CD8+ T cells which lack expression of the co-stimulatory molecule CD28, contain shortened telomeres and exhibit a reduced proliferative potential [84–86]. Expansion of this cell population is thought to be largely driven by chronic antigenic stimulation by cytomegalovirus (CMV), with a large proportion of CD8+ T cells in both HIV-infected and aged individuals being specific for CMV epitopes (discussed further below). However, there are phenotypic differences in the T cells expanded due to HIV infection and those observed in CMV+ HIV seronegative individuals, in that the former show an increased number of transitional memory cells and a reduced proportion of CD28-cells expressing CD57 (a marker of reduced proliferative capacity), with low levels of this population being associated with increased risk of mortality [87]. These observations suggest that although there are many phenotypic similarities between HIV infection and aging, the mechanistic drivers, and thus immunological consequences of, senescent T cell expansion in HIV and aging may be subtly different.

While the above mentioned immunological alterations due to HIV are significantly improved by ART, they typically fail to normalize, and defects including reduced naïve T cell proportions, inverted CD4:CD8 T cell ratios and increased T cell activation largely persist in virologically suppressed HIV-infected individuals (reviewed in [88]). Furthermore, aging appears to impact negatively on the immunological benefit of ART and associated reductions in immune activation, with older HIV-infected individuals exhibiting muted naïve T cell regeneration following ART initiation [89], suggesting immunological aging may heighten HIV-related immune dysfunction in older HIV-infected individuals.

During aging, there is a reduction in the number of both total and memory B cells and defects emerge in class switching and antibody production which are thought to contribute to impaired vaccine response in the elderly [81, 90]. Viremic HIV infection is similarly associated with reduced total and memory B cell numbers together with hypergammaglobulinemia, increased cellular activation and increased susceptibility to apoptosis [91]. ART reverses many of these defects, although virologically suppressed HIV-infected individuals continue to show impaired antibody production, reduced vaccine responses and an incomplete restoration of memory B cells [92, 93]. Markers of HIV disease severity including viral load and immune activation are associated with an increased frequency of regulatory B cells (Bregs), which inhibit CD8+ T cell proliferation and function via a mechanism involving IL-10 and PD-1 [94], which may potentiate immune dysfunction in HIV. Bregs from HIV-infected individuals constitutively express higher levels of IL-6, IL-10 and cellular activation markers, suggesting increased Breg activation in vivo [95]. Interestingly, older HIV-infected individuals show an altered pattern of B cell resto-

Table 2 Comparison of immunological changes observed in HIV infection and aging

	HIV Infection	Aging
T cells	Decreased naïve and increased memory T cells Decreased CD4:CD8 T cell ratio Expansion of senescent CD8+ CD28-T cells Expansion of CMV-specific CD8+ T cells	
B cells	Decreased numbers and proportion of mature/memory B cells Impaired class switching and antibody production, leading to impaired vaccine response	
Monocytes/Macrophage	Impaired phagocytosis Increased proportion CD16+ inflammatory monocytes Increased expression of cellular activation markers Increased TLR4-stimulated cytokine/chemokine production Dysfunctional TLR-responses	
Natural Killer (NK) cells	Expansion of CD56dim population (acute HIV infection only) Impaired cytokine production (modest decline in aging)	
	Increased activation Increased spontaneous ADCC Expansion of CD56- population Impaired cytotoxic potential	
Dendritic cells	Reduced numbers in blood (pDC in HIV and mDC in aging)	
	Impaired response to TLR 7/8 stimulation Increased activation in pDC	Impaired chemotaxis and antigen uptake
Neutrophils	Increased basal activation	Decreased chemotaxis
	Impaired phagocytosis, migration, respiratory burst and intracellular killing	
Inflammation	Increased plasma levels of IL-6, TNF, hsCRP	
Soluble markers of immune activation	Increased plasma levels of CXCL10, sCD14, sCD163, neopterin	
Gut integrity	Increased plasma concentrations of LPS Increased levels of gut permeability markers I-FABP and/or zonulin-1	
Oxidative stress	Increased plasma markers of oxidative stress	
Telomere length	Shortened (PBMC, T cells, monocytes)	

Shaded cells indicate immunological changes which occur in both HIV infection and aging

ration after ART initiation, including expansion of the naïve population to levels greater than those in uninfected individuals [96], suggesting that HIV and age may potentiate immune dysfunction in PAWH. These studies collectively indicate that HIV infection induces a phenotype within the adaptive immune system which resembles age-related immunosenescence and immune dysfunction, and viral suppression associated with ART only partially improves these parameters.

4.1.1 Innate Immune Changes

Immunological similarities are also seen between HIV infection and healthy aging within the innate immune system. Monocytes from both HIV-infected individuals and the elderly show impaired phagocytic function, increased TLR4-mediated production of pro-inflammatory cytokines and chemokines and an increase in phenotypic markers of activation, including an expansion of the inflammatory CD16+ monocyte subset [97–101]. Viral suppression associated with ART appears to normalize some of these changes, such as the proportions of CD16+ subsets, whilst other markers of monocyte dysfunction persist [97, 102]. Elevated levels of soluble plasma monocyte/innate immune activation markers including the chemoattractant CXCL10 (released from IFNγ-stimulated monocytes), neopterin and soluble(s) receptors CD14 and CD163 (shed from activated monocytes/macrophages) are elevated in both the elderly and HIV-infected individuals and although ART reduces the levels of these markers in HIV infection, they fail to normalize [97, 98, 103–107].

An increase in total NK cell number, due to expansion of the $CD56^{dim}$ population occurs during aging and in acute HIV infection [74, 108]. Aging is associated with a minimal impairment of NK cell cytotoxic function and cytokine production [109–111], whilst overall cytolytic activity is impaired in HIV infection (most prominently in viremic infection) which may be due in part to expansion of an anergic $CD56^{neg}$ population in HIV-infected individuals [108]. NK cells from both viremic and virologically suppressed HIV-infected individuals show heightened basal activation [112, 113] and spontaneous ADCC activity [112], whilst cytokine production is impaired [114]. The functionality of neutrophils is similarly impaired in HIV infection as in aging, as evidenced by impaired phagocytosis and oxidative burst but a heightened basal level of activation [115]. The impact of age on the number, activation state and function of dendritic cells remains unclear due to conflicting findings (reviewed in [116]), although chemotaxis and antigen uptake are impaired in aged humans [117, 118] whilst HIV infection is associated with impaired ex vivo response of plasmacytoid dendritic cells to TLR7 ligands [119]. Taken together, these data suggest that a signature of increased activation but dysregulated function is a common effect of both HIV infection and aging on innate immune cells, although much work is required to fully define the extent of these effects. It is important to note that many of the above mentioned age-related immunological changes have been observed in cross-sectional studies of HIV-infected individuals with varying degrees of immunosuppression both prior to and following ART initiation. Future longitudinal studies are required in cohorts of individuals who initiate ART early

and maintain immunocompetence to adequately determine the impact of virologically suppressed HIV infection on age-related immune changes in PAWH.

4.2 Telomere Shortening

The presence of telomeres at the ends of chromosomes protects the DNA from damage and preserves the replicative potential of the cell. Telomere length progressively decreases with age and triggers replicative senescence, which contributes to immunosenescence and immune aging [120]. Telomere shortening is associated with risk of a range of age-related diseases including malignancies [121], cardiovascular/metabolic disease [122–124] and neurocognitive disease [125, 126] (summarized in Table 3 and reviewed in [195]) and has been linked with premature death in a large prospective study in Denmark [123]. HIV infection is associated with heightened telomere shortening within both T cells [85] and monocytes [97]. However, epidemiological links between shortened telomeres and HIV-related co-morbidities have received little investigation to date.

Telomere length is maintained within cells via the action of telomerase and premature telomere shortening in HIV infection may be due to reduced activity of this critical enzyme. The HIV proteins Vpr [196] and Tat [197] have been shown to inhibit telomerase in vitro whilst HIV-infected individuals appear to have an impaired ability to upregulate telomerase in response to cell stimulation [198]. Antiretroviral therapy may also contribute to premature telomere shortening as the nucleos(t)ide reverse transcriptase inhibitor (NRTI) drugs can inhibit the telomerase reverse transcriptase (TERT) component of human telomerase. In vitro studies have shown that even modern, relatively non-toxic NRTIs such as tenofovir and emtricitabine show inhibitory effects on human TERT [199, 200], and can accelerate telomere loss in cultured cells [199] whilst a small cross-sectional study found telomeres from individuals on NRTI-containing regimens were shorter than HIV negative controls and HIV-infected individuals taking non-NRTI containing regimens [200]. NRTIs remain the backbone of ART regimens throughout the world, but the accumulated consequences of decades of NRTI-treatment on oxidative stress and telomere shortening remain to be defined.

4.3 Oxidative Stress

An imbalance between levels of oxidants and anti-oxidants occurs during aging, resulting in increased plasma markers of oxidative stress in the elderly [201, 202] which contribute to immunosenescence and inflamm-aging (reviewed in [203]). HIV infection is also associated with increased levels of oxidative stress, with decreased plasma levels of anti oxidant factors such as glutathione and increased levels of the oxidative stress marker malondialdehyde found in both viremic and

Table 3 Associations between immunological changes occurring during aging/HIV infection and morbidity/mortality

		HIV-infected	General population
	Marker	Outcome/risk factor	
Inflammation			
Cardiovascular/metabolic disease	IL-6	Cardiovascular events [127, 128], obesity [129]	Sudden cardiac death [130, 131], cardiovascular events [131–134]
	hsCRP	Cardiovascular events [127, 128], progression of cIMT [135], metabolic syndrome [136], diabetes [137]	Cardiovascular events [131, 138], insulin resistance [139]
	sTNFRI/II	Obesity [129], diabetes [137]	Cardiovascular events [138]
	TNF	Coronary artery calcium [140]	
Neurocognitive impairment	IL-6	[141]	[132] Future cognitive decline [142]
	hsCRP		[132, 143]
	sTNFR-I/II	[144]	
	TNF		Alzheimer's disease [145, 146]
Malignancies	IL-6, hsCRP	All cancers [147]	All cancers [148]
	D-Dimer	All cancers [147]	
	TNF		All cancers [148]
Bone disease/osteoporosis	hsCRP		Bone mineral density [149], fracture risk [150], future bone mineral density loss [151]
	IL-6		Future bone mineral density loss [151, 152]
	TNF		Future bone mineral density loss [151]
Frailty/disability	IL-6	[153, 154]	[132, 155]
	TNF	[153]	
	CRP	[153]	[132, 156]
Mortality	sTNFRI, hsCRP	[157]	

(continued)

Table 3 (continued)

		HIV-infected	General population
	Marker	Outcome/risk factor	
Loss of gut integrity/microbial translocation			
Cardiovascular/metabolic disease	LPS	Progression of cIMT [158], endothelial dysfunction [159], hypercholesterolemia [160], insulin resistance [160], hypertension [161]	Metabolic syndrome [162]
	LBP		Metabolic syndrome [163]
Neurocognitive impairment	LPS	[141, 164]	
Malignancies	LPS	Non-Hodgkin's lymphoma [165]	
Mortality	IFAB-1, zonulin	[157]	
Monocyte/innate immune activation			
Cardiovascular/metabolic disease	sCD14	Increased cIMT [166], cIMT progression [158], coronary calcification [167], hypertension [161]	Diabetes [169], hypertension [169]
	sCD163	Arterial inflammation [170], non-calcified coronary artery plaques [171]	Atherosclerosis [172], insulin resistance [139, 173, 174], diabetes [175]
	MCP-1	Coronary artery calcium [140]	
Neurocognitive impairment	sCD14	[141, 144, 176, 177]	
	sCD163	[178]	
	Neopterin		Alzheimer's disease [179]
Malignancies	sCD14	Non-Hodgkin's lymphoma [165]	
Frailty/disability	Neopterin		[180]
Mortality	sCD14	[157]	
T cell activation/senescence			
Cardiovascular/metabolic disease	HLADR + CD38+ T cells	Carotid artery plaques [181, 182], carotid artery stiffness [183]	
Bone disease/osteoporosis	T cell activation	Bone mineral density [184]	
Mortality	Low CD8+ CD28- CD57+ T cells	[185]	

(continued)

Table 3 (continued)

		HIV-infected	General population
	Marker	Outcome/risk factor	
Telomere shortening			
Cardiovascular/metabolic disease	Leukocyte telomere length		Increased cIMT [122, 185], risk of myocardial infarction and stroke [122–124], Diabetes [122]
	Monocyte telomere length		Type 2 diabetes [187]
Neurocognitive impairment	Leukocyte telomere length		Dementia [125]
	Monocyte telomere length		Alzheimer's disease [126]
Malignancies	Epithelial cell telomere length		Epithelial cancer [121]
	Telomere length in mucosal tissue		Early stages of gastric carcinoma [188]
Early death	Leukocyte telomere length		[123, 125]
Cytomegalovirus (CMV) infection			
Cardiovascular/metabolic disease	CMV seropositivity		Type 2 diabetes [189], mortality in coronary artery disease patients [190]
	CMV-specific T cells responses	cIMT [191]	
	CMV IgG	Carotid artery disease [192]	
Frailty/disability	CMV IgG		[193]
Mortality	CMV IgG CMV seropositivity		All-cause mortality [193], cardiovascular related deaths [194]

virologically suppressed HIV-infected individuals [204, 205]. High intracellular levels of the antioxidant factors N-acetylcysteine and glutathione inhibit HIV replication in infected cells [206] whilst low levels of these factors are associated with increased NF-kB-mediated transcription of HIV and a heightened ability of the pro-inflammatory cytokine TNF to activate HIV transcription [207], suggesting a positive feedback loop between inflammation and HIV replication. The mechanism responsible for decreased anti oxidant levels in HIV may involve the HIV Tat protein, which has been shown in mouse models to decrease production of anti oxidants and induce mitochondrial damage [208]. Certain antiretroviral (ARV) drugs including PIs and NRTIs increase the production of reactive oxygen from cells treated in vitro [209]. Consistent with this, one study reported higher levels of oxidative stress in ART-treated individuals as compared to both untreated HIV-infected and uninfected individuals, however the HIV-infected individuals in this study had significantly higher levels of a number of confounding factors including concurrent hepatitis C infection [210]. More data from virologically suppressed HIV-infected cohorts with adequate control of variables which may potentially influence oxidative stress are required to determine the impact of oxidative stress on immune aging in the modern ART era.

4.4 Chronic Inflammation and Immune Activation

Increased inflammation is one of the cornerstones of immunological aging and geroscience, and appears to be potentiated by HIV infection. Indeed, chronic inflammation and related immune activation likely has the greatest impact on morbidity and mortality in PAWH in the post-ART era. Inflammaging is a well-documented state of chronic, low-grade inflammation occurring progressively with age and is associated with the development of many age-related morbidities and functional decline in the elderly [211]. Markers of inflammation including IL-6, TNFα and high-sensitivity C-reactive protein (hsCRP) are elevated in both HIV-infected individuals and the elderly [212, 213] and are associated with increased risk of SNAEs including CVD, frailty, malignancies, bone disease and neurocognitive decline. Inflammation is intrinsically linked with cellular activation, and biomarkers of immune activation and inflammation are increasingly being recognised as risk predictors of inflammatory diseases in HIV infection, as they are in the aged (see Table 3). Biomarkers of monocyte/macrophage activation including plasma levels of sCD163 and sCD14 are predictive of age-related diseases including neurocognitive impairment/dementia [141, 176–178], malignancies [165] and also mortality [214] in HIV infection (see Table 3). Chronic monocyte/macrophage activation appears to be particularly relevant for the development of CVD in HIV infection; biomarkers of monocyte activation including the proportion of inflammatory CD16+ monocytes, the expression of monocyte activation markers (i.e. CD11b) and the soluble activation markers mentioned above are associated with atherosclerosis and its progression [158, 159, 215], arterial inflammation [170], coronary calcium score [167] and the presence of non-calcified carotid plaques [171] in HIV-infected

individuals. Importantly, these associations have been made in cohorts of primarily virologically suppressed individuals, suggesting mechanisms other than overt HIV viremia are involved. Indeed, in the post-ART era, markers of inflammation and/or immune activation are emerging as more relevant predictors of disease outcome and death in virologically suppressed individuals than traditional HIV biomarkers such as viral load and CD4+ T cells count [157, 216]. Recent data reporting an association between sCD163 levels and telomere length [217] provide a direct link between monocyte/macrophage activation and potentiation of immunological aging. Given chronic inflammation/immune activation and resultant disease burden are similar between HIV-infected individuals and the aged, the question arises to what extent the mechanisms driving these phenomena are similar in both populations and what contributing factors may be unique to HIV infection.

5 Factors Potentiating Age-Related Changes and Morbidity in HIV-Infected Individuals

The development of SNAEs in PAWH is multifactorial, and typically results from the combined effects of traditional risk factors, HIV-specific effects, and a potentiation of age-related changes (see Fig. 3).

5.1 Traditional Risk Factors

Traditional risk factors for disease development are highly relevant for the aging HIV-infected population, not only as they are often more readily modifiable but also because they may potentiate HIV-specific factors. Many cohort studies report a higher prevalence of smoking amongst HIV-infected participants [218–220], and whilst illicit drug use is higher within certain high risk HIV-infected populations, this variable is often not adequately assessed or controlled for in HIV cohort studies. Relevant to the development of cardiovascular disease, HIV infection is associated with dyslipidemia and metabolic alterations, which are discussed further below.

5.2 Metabolic Alterations

Hyperglycemia occurs in up to 17 % of HIV-infected individuals receiving ART and diabetes mellitus is more common in HIV infected vs seronegative people [221], with some studies reporting up to a fourfold increased risk due to HIV [222]. Insulin resistance in ART-treated HIV infection is largely associated with the use of protease inhibitor antiretroviral drugs, which act to inhibit the glucose transporter Glut-4 [223], although hepatitis C virus (HCV) co-infection, inflammation and immunodeficiency also contribute to insulin resistance and diabetes in HIV infection [221].

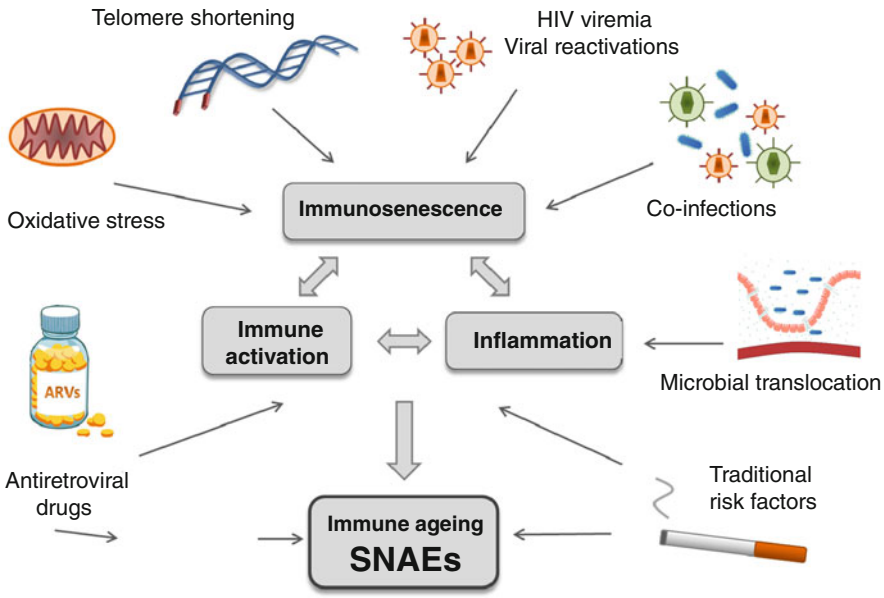

Fig. 3 Mechanism contributing to the pathogenesis of SNAEs in HIV-infected individuals

High glucose levels have been shown to increase the susceptibility of CD4+ T cells in HIV infection in vitro by upregulating the expression of the HIV co-receptor CXCR4 [224], whilst increased expression of Glut-1 on T cells from HIV-infected individuals (irrespective of ART) is associated with T cell activation and immunodeficiency [169]. Taken together, these data suggest that metabolic alterations due to both HIV and its treatment not only increase the risk of co-morbidities such as diabetes, but may also perpetuate HIV replication and immune activation to further drive immune exhaustion and senescence in PAWH.

HIV-related lipodystrophy syndrome is common in HIV infection, and includes lipoatrophy (loss of subcutaneous fat) and dyslipidemia. Lipoatrophy appears to be largely due to PI and NRTI use, particularly the NRTIs stavudine and zidovudine (reviewed in [225]). Whilst HIV infection per se is associated with lipid alterations including high triglyceride and low HDL levels (thought to be due to the effect of inflammation on lipid peroxidation, reactive oxygen species production and vascular changes [226, 227]), the majority of dyslipidemia observed in the post-ART era is due to the specific effects of antiretroviral drugs.

5.3 Antiretroviral Drugs

Although highly effective in inhibiting HIV replication and maintaining immune health, many antiretroviral drugs, particularly the NRTIs, have some degree of toxicity which is at least partially attributable to effects on the mitochondria. The

ability of NRTIs to inhibit HIV reverse transcription is due to structural similarities between NRTIs and endogenous nucleos(t)ides, and whilst nuclear DNA polymerases are not significantly affected by NRTIs, the mitochondrial replicase pol γ is inhibited by NRTIs at physiologically relevant levels, resulting in depletion of mitochondrial DNA and increased oxidative stress (reviewed in [208]). Specifically, zidovudine and stavudine have been shown to increase oxidative stress in a number of cell types including adipocytes and macrophages [228]. As discussed above, NRTIs are also able to inhibit the RT component of cellular telomerase and may potentially contribute to premature telomere shortening. Interestingly, certain NRTIs have recently been shown to be able to inhibit NLRP3 inflammasome-mediated activation of caspase-1 and subsequent production of the pro-inflammatory cytokines IL-1β and IL-18 [229], suggesting NRTIs may have an unexpected influence on cytokine production in HIV-infected individuals receiving these drugs.

HIV-infected individuals treated with ART have a relative risk of CVD of 1.52 (95 % CI 1.35–1.70) compared to untreated individuals [230], suggesting ART may contribute to the pathogenesis of CVD. Indeed, recent use of certain PIs and the NRTIs abacavir and didanosine has been associated with increased risk of myocardial infarction [231, 232] although the association with abacavir was not reproduced in a randomised control trial and remains controversial [233]. The increased risk attributable to PIs is largely due to an effect on lipid levels, as 70–80 % of HIV-infected individuals receiving PI-containing ART regimens show elevated lipid levels [226]. Most PIs (with the possible exception of atazanavir) have been shown to induce dyslipidemia involving increased plasma concentrations of triglycerides, total cholesterol and LDL [234], all of which are known risk factors for cardiovascular disease. The mechanism involves a direct effect of PIs on adipocyte differentiation and also an ability of these drugs to inhibit factors involved in lipid transport and metabolism [227].

Untreated HIV infection results in loss of bone mineral density which contributes to increased fracture risk and osteoporosis (as discussed above), but ART-initiation potentiates this effect and results in a further loss of bone mineral density of approximately 2–6 % within the first 2 years of ART initiation. This effect is thought to be due to disruption of the delicate immunological balance in the bone marrow which governs osteogenesis, and specific antiretroviral drugs including the NRTI tenofovir [235] and the protease inhibitor class of drugs have been shown to potentiate bone loss in ART-treated individuals [236].

The relatively recent introduction of ART, combined with the lengthy and multifactorial pathogenesis of many HIV-related co-morbidities, means that significant associations between specific ARVs and disease outcomes are continuing to emerge. HIV-infected individuals initiating therapy in the early days largely did so with low CD4 counts and received ARVs which have since been phased out due to side effects and toxicities. Thus, ongoing and future longitudinal studies will be critical for evaluating the long term effects of current ARVs on immune changes and the development of age-related diseases in HIV-infected individuals who avoid significant immunological damage by initiating ART at higher CD4 T cell counts.

6 Mechanisms That May Contribute to Chronic Inflammation and Immune Activation in HIV

6.1 Microbial Translocation and Endotoxemia

HIV infection is associated with increased permeability of the gut to microbial products, which translocate across the gut epithelium and eventually into the bloodstream, resulting in increased plasma levels of the bacterial endotoxin lipopolysaccharide (LPS) and bacterial DNA in HIV-infected individuals [237]. The cause of increased gut barrier permeability in HIV infection is due to immunodeficiency and structural defects within the gut-associated lymphoid tissue (GALT) resulting from HIV-mediated T cell depletion [238]. The majority of lymphocytes in the body are contained in GALT, which is an important site for both pathogenesis and persistence of HIV. CD4+ T cells are rapidly depleted from the GALT during primary HIV infection and remain depleted into chronic infection. Studies in Simian Immunodeficiency Virus (SIV)-infected macaques (a pathogenic animal model of HIV infection) have revealed that peak infection of CD4+ T cells in the lamina propria of the gut occurs within 10 days of infection, at which point 93 % of target CD4+ memory T cells are infected [239]. While effective ART suppresses viral replication and restores peripheral CD4+ T cells, gut-associated CD4+ T cells remain depleted years after ART initiation [240]. Interestingly, a subset of HIV-infected individuals who maintain high CD4+ T cells counts and low/undetectable viral loads in the absence of ART (known as long term non-progressors) maintain normal CD4+ T cell levels in the GALT [241], suggesting the importance of this compartment for disease pathogenesis. The mechanism of increased gut permeability in HIV involves epithelial disruption and decreased production of tight junction proteins in the distal portions of the colon [242] which is consistent with increased levels of intestinal fatty acid binding protein (I-FABP; a marker of enterocyte damage) and zonulin-1 (a regulator of tight junction permeability) in the plasma of HIV-infected individuals [157, 243]. The inability to fully restore GALT structure and function despite effective restoration of peripheral T cells by ART means that chronic endotoxemia (elevated levels of LPS in the blood) persists in virologically suppressed HIV-infected individuals. Lipopolysaccharide (LPS) is a potent immune activator which is recognised by toll-like receptor (TLR)-4 expressing cells such as monocytes/macrophages in an immune complex consisting of LPS-binding protein (LBP), the adaptor protein MD2 and either soluble or cell-bound CD14. LPS signalling stimulates the production of pro-inflammatory cytokines including IL-6, TNF and type I interferons. Microbial translocation is considered a significant driver of both HIV disease and related co-morbidities, with gut translocation markers such as LPS, the LPS binding protein LBP and I-FABP/zonulin-1 associated with immune activation and HIV disease progression [237, 244, 245], cardiovascular and metabolic disease [159, 160], neurocognitive impairment [141] and mortality [157, 216].

In contrast to HIV, relatively little is known regarding the effect of age on the integrity of the gut epithelium in humans [246], however work in *Drosophila* has demonstrated that loss of intestinal barrier integrity occurs with aging and is a better

predictor of age-related morbidity and death than chronological age [247]. Increased plasma levels of LPS [98] and LBP [248] in the elderly indicate microbial translocation, may also increase during aging and the inverse association between LBP levels and physical function in the aged [248] suggests it may also contribute to morbidity in this population, although this requires further investigation.

6.1.1 Alterations to the Gut Microbiome

Within the GALT, cytokines including IL-17 and IL-22 play a critical role in maintaining gut integrity and orchestrating the mucosal immune responses to gut pathogens. Depletion of CD4+ T cells from the gut during HIV infection reduces the production of these cytokines and disrupts the delicate mucosal immunological balance. The gut microbiome interacts intimately with mucosal immunity and helps educate and regulate immune cells. Significant alterations are observed in the gut microbiome of HIV-infected individuals, with sequence analysis of bacterial communities from stool/gut mucosa samples revealing an overall increase in genetic diversity, an expansion of *Prevotella* and potentially pathogenic bacteria and a reduced proportion of *Bacteroidia* species [249–252]. Importantly, these changes in microbial communities are associated with inflammation, innate and adaptive immune activation and markers of disease progression in HIV-infected individuals. ART appears to only partially normalize the bacterial composition of the microbiome in a proportion of treated individuals [251]. A higher proportion of bacteria from the order *Lactobacillales* (lactic acid-producing bacteria) in the distal gut of ART naïve individuals has been associated with more favorable immunological parameters including higher pre-ART CD4+ T cells counts and CD4:CD8 T cells ratio but lower viral loads and sCD14 levels [253]. The complex interplay between the gut microbiome, GALT immunity and systemic inflammation/immune activation continues to be elucidated but may reveal an important mechanism of persistent immune dysfunction in HIV which can be targeted therapeutically.

6.1.2 Cytomegalovirus (CMV) and Latent Viral Infections

Accumulative immune stimulation by pathogens and subsequent immune exhaustion is an integral mechanism of immune aging and heightened pathogen burden due to concurrent and reactivated viral infections may hasten this process in PAWH. While CMV-seropositivity rates vary considerably between different countries (ranging from 40 to >90 %), there is a consistent trend of increasing seropositivity with age [254] and CMV is recognized as a significant driver of immunosenescence [255, 256]. CMV infection profoundly shifts the lymphocyte subset proportions towards a differentiated memory T cell phenotype [257, 258]. In aged individuals, the proportion of CD8+ T cells specific for a small number of CMV epitopes can represent up to 27 % of the total CD8+ pool [259], with these cells typically being dysfunctional and exhibiting an immunosenescent phenotype [260]. CMV seropositivity has also been associated with an increased risk of age-related diseases such as cardiovascular disease [261].

CMV disease is a significant cause of morbidity and mortality in HIV-infected individuals with AIDS and/or severe immunodeficiency [262], while asymptomatic CMV infection also appears to potentiate immunosenescence in HIV-infected individuals. CMV infection is almost ubiquitous in the HIV-infected population with seropositivity rates of approximately 95 % [263] and the presence of IgM antibodies suggests viral reactivation/reinfection commonly occurs [264]. Levels of CMV-specific CD8+ T cells are up to twice as high in HIV-infected as in uninfected individuals and persist in ART-treated individuals despite long term virological suppression [265], which is consistent with reactivation and impaired immune control [263]. HIV-infected/CMV seronegative subjects show higher CD4:CD8 T cells ratios and less phenotypic evidence of immunosenescence than HIV/CMV seropositive individuals [266] whilst serum CMV IgG levels, which are increased in HIV-infected individuals, correlate with inflammatory markers [267]. Taken together, these observations suggest that CMV seropositivity may potentiate HIV-related immunosenescence and inflammation and hasten the aging process.

Although ART reduces HIV viral load to near undetectable levels in the plasma, residual HIV replication (up to 20 copies/mL) can be detected in the plasma of the majority of virologically suppressed individuals using ultra-sensitive assays [268]. In addition, ongoing HIV replication may persist at higher levels within anatomical sites such as lymphoid tissue where antiretroviral drugs may fail to penetrate to effective therapeutic concentrations. Reactivation/replication of other latent viruses including Epstein–Barr virus (EBV) and Herpes Simplex Viruses (HSV) also appears to be heightened in HIV-infected individuals, likely due to increased immune activation. HSV-2 reactivation occurs frequently in HIV-infected individuals, is positively associated with HIV viral load [269] and is shed more frequently in HIV-infected vs seronegative individuals [270]. EBV viral loads in HIV-infected individuals are reportedly greater than those in EBV+ HIV-uninfected individuals [271].

Human endogenous retroviruses (HERVs) are a family of replication defective viral elements which comprise up to 8 % of the human genome. Although thought to be largely silent, increased transcription of HML-2 RNA (a member of the HERV-K family) has been demonstrated in PMBCs from HIV-infected individuals [272] and has also been detected at increased levels in plasma in some [273] but not all [272] studies. Increased HERV transcription may be due to heightened immune activation and/or the ability of the HIV Tat protein to activate endogenous retroviral transcriptional elements [274]. Although cause and effect are difficult to delineate, it is clear that heightened inflammation/immune activation and reactivation of latent viral infections may constitute a self-perpetuating cycle contributing to immune exhaustion and immunosenescence in many PAWH.

6.1.3 Concurrent Infections

The development of age-related morbidities in HIV-infected individuals can be influenced by concurrent infection with a range of pathogens. Co-infection with HCV can be up to 90 % in certain high risk HIV+ groups, and is associated with an

increased risk of coronary heart disease [275], osteoporotic fracture [276], and neurocognitive impairment [277], suggesting hepatitis C infection may potentiate the pathogenesis of these conditions. The mechanism of this is unclear, although a potentiation of inflammation and immune activation is likely, and increased levels of pro-inflammatory factors such as IL-6 have been demonstrated in HIV/HCV co-infected, as compared to mono or uninfected individuals [278]. Active HCV infection is also associated with shorter leukocyte telomere length in those with HIV [279]. Taken together, these data suggest that HCV co-infection may further heighten inflammation/immune activation and associated immunosenescence in HIV-infected individuals and potentiate the development of age-related diseases.

HIV-infected individuals co-infected with tuberculosis (TB) have significantly increased pro-inflammatory cytokine production [280] and ART initiation in highly immunocompromised HIV+/TB+ individuals often results in TB-associated immune reconstitution inflammatory syndrome, which results in significant pro-inflammatory cytokine production [281]. Heightened CD4+ T cell activation and pro-inflammatory cytokine production also occurs in malaria co-infection [282]. These observations suggest concurrent infections may further potentiate inflammation due to HIV and aging in co-infected individuals, however further studies are required to elucidate the full impact of these effects on age-related disease outcomes.

7 Potential Treatments/Interventions to Alleviate the Effects of HIV on Aging/SNAEs

The immunological similarities between HIV infection and aging (particularly chronic inflammation and its consequences) suggest that addressing mechanism of aging may alleviate premature aging and disease pathogenesis in HIV-infected individuals. A large number of preliminary trials are underway to address immune activation, inflammation, microbial translocation and other mechanisms of enhanced aging in PAWH, but none has yet demonstrated efficacy in definitive clinical trials [283–287]. If this is accomplished in PAWH, it will have vast implications for aging in general and may be applicable to a much broader population.

8 Concluding Remarks

The success of antiretroviral therapy in preventing AIDS and extending the life span of HIV-infected people has revealed unexpected parallels between the impact of HIV infection and aging on immune function. Current research is only beginning to uncover how HIV may be potentiating age-related changes and the consequences of this for premature aging and increased risk of age-related comorbidities in those living and aging with HIV. It is still unclear whether HIV-associated ‘aging’ is the

result of chronic infection, or whether those infected with HIV at an older age may experience similar effects. Furthermore, the impact of long-term ARV drug use on age-related process remains to be fully elucidated. HIV infection further complicates the many health challenges experienced by aging individuals including multimorbidity, polypharmacy, impaired physical and mental health and reduced quality of life. Uncovering the critical processes which drive age-related changes and identifying therapeutic strategies to ameliorate the residual effects of HIV will be important for ongoing management of the increasingly aging HIV-infected population.

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