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HIV PATHOGENESIS AND TREATMENT (AL LANDAY, SECTION EDITOR)

Inflammatory Co-morbidities in HIV+ Individuals: Learning Lessons from Healthy Ageing

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Abstract Increased life expectancy due to improved efficacy of cART has uncovered an increased risk of age-related morbidities in HIV+ individuals and catalyzed significant research into mechanisms driving these diseases. HIV infection increases the risk of non-communicable diseases common in the aged, including cardiovascular disease, neurocognitive decline, non-AIDS malignancies, osteoporosis, and frailty. These observations suggest that HIV accelerates immunological ageing, and there are many immunological similarities with the aged, including shortened telomeres, accumulation of senescent T cells and altered monocyte phenotype/function. However, the most critical similarity between HIV+ individuals and the elderly, which most likely underpins the heightened risk of non-communicable diseases, is chronic inflammation and associated immune activation. Here, we review the similarities between HIV+ individuals and the aged regarding the pathogenesis of inflammatory diseases, the current evidence for mechanisms driving these processes and discuss current and potential therapeutic strategies for addressing inflammatory co-morbidity in HIV+ infection.

Keywords HIV co-morbidity · Inflammation · Immune activation · Microbial translocation · Monocyte · Immune senescence · Telomere · Resource limited settings · Cytomegalovirus · HIV pathogenesis · Pathogenesis · Treatment · HIV+ infection · Senescent T cells · HIV+ individuals · HIV-positive · Healthy ageing · Co-morbidity

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Introduction

Chronic inflammation is a hallmark of ageing and is recognized as a central mechanism driving many age-related diseases. Indeed, levels of inflammatory markers including IL-6, TNF, and high sensitivity C-reactive protein (hsCRP) are independently associated with non-communicable diseases including cardiovascular disease (CVD), frailty and neurocognitive decline (see Table 1 for summary). HIV infection induces significant inflammation and this is incompletely restored by combination antiretroviral therapy (cART) [1]; elevated levels of inflammatory markers TNF, IL-6 and hsCRP as well as markers of innate immune activation including soluble (s) CD14, sCD163, and CXCL10 persist in combination antiretroviral therapy (cART)-treated individuals despite sustained viral suppression [2-5].

When comparing HIV infection and ageing, the question arises as to whether HIV is accelerating normal immunological ageing processes or whether both conditions result in

Table 1 Associations between inflammatory markers and morbidities in HIV+ individuals and the general population

	HIV+	General population
Cardiovascular disease and risk factors		
LPS	*Measures of CVD*	*CVD risk factors*
	Progression of cIMT [69], Endothelial dysfunction [71]	Metabolic syndrome [160]
	CVD risk factors	
	Hypercholesterolaemia [72], Insulin resistance [72], Hypertension [73]	
LBP		*CVD risk factors*
		Metabolic syndrome [161]
IL-6	*Measures of CVD*	*Measures of CVD*
	Cardiovascular events [25••, 162]	Sudden cardiac death [164, 165]
	CVD risk factors	Cardiovascular events [22, 165-167]
	Obesity [163]	
hsCRP	*Measures of CVD*	*Measures of CVD*
	Cardiovascular events [162] [25••], Progression of cIMT [168]	Cardiovascular events [165, 171]
	CVD risk factors	*CVD risk factors*
	Metabolic syndrome [169], Diabetes [170]	Insulin resistance [172]
D-Dimer	*Measures of CVD*	
	Endothelial dysfunction [25••, 110, 173]	
HLADR+CD38+ T cells	*Measures of CVD*	
	Carotid artery plaques [107] [174]	
	Carotid artery stiffness [108]	
sTNFRI/II	*CVD risk factors*	*Measures of CVD*
	Obesity [163], Diabetes[170]	Cardiovascular events [171]
sCD14	*Measures of CVD*	*CVD risk factors*
	Increased cIMT [175], cIMT progression [69]	Diabetes [64•], Hypertension [64•]
	CVD risk factors	
	Hypertension [73]	
TNF	*Measures of CVD*	
	Coronary artery calcium [176]	
sCD163	*Measures of CVD*	*Measures of CVD*
	Arterial inflammation [26•], Non-calcified coronary artery plaques [40]	Atherosclerosis [177]
		CVD risk factors
		Insulin resistance [172, 178, 179], Diabetes [180]
MCP-1	*Measures of CVD*	
	Coronary artery calcium [176]	
P-selectin (CD62P)	*Measures of CVD*	
	Cardiovascular events [162]	
sVCAM-1	*Measures of CVD*	
	Carotid artery plaques [174]	
Neurocognitive impairment (including HAND)		
LPS	[68, 181]	
IL-6	[68]	[22] Future cognitive decline [182]
hsCRP		[22, 183]
sTNFR-I/II	[184]	
sCD14	[68, 185, 186] [184]	
TNF		Alzheimer's disease [187, 188]

Table 1 (continued)

	HIV+	General population
sCD163	[189]	
neopterin		Alzheimer's disease [190]
Malignancies		
LPS	Non-Hodgkins lymphoma [191]	
IL-6	All cancers [192]	All cancers [193]
hsCRP	All cancers [192]	All cancers [193]
D-Dimer	All cancers [192]	
TNF		All cancers [193]
sCD14	Non-Hodgkins lymphoma [191]	
Bone disease/osteoporosis		
T cell activation	Bone mineral density [58]	
hsCRP		Bone mineral density [48••], Fracture risk [50], Future bone mineral density loss [194]
IL-6		Future bone mineral density loss [194, 195]
TNF		Future bone mineral density loss [196]
Frailty/disability		
IL-6	[134, 196]	[22, 197]
TNF	[196]	
CRP	[196]	[22, 198]
neopterin		[199]

chronic inflammation and increased co-morbidities due to parallel but mechanistically different pathogeneses. This question is critical to inform how best to prevent these conditions both in the setting of HIV infection and in HIV seronegative individuals with underlying low level chronic inflammation. Here we review the similarities in inflammatory disease pathogenesis between HIV+ individuals and the aged, and explore causative mechanisms to identify whether lessons we have learned from healthy ageing can guide prevention of non-communicable co-morbidities in the HIV+ population. We start by defining inflammation and immune activation, as these are commonly confused, then focus on two major age-related morbidities, cardiovascular, and bone disease.

The Relationship between Inflammation, Immune Activation and Immunosenescence

Whilst inflammation and immune activation are intimately related, these two parameters are discrete and are indicated by a distinct set of biomarkers. Inflammation is typically indicated by elevated plasma levels of pro-inflammatory cytokines (e.g., TNF, IL-6) and inflammatory markers such as the acute phase protein hsCRP. Soluble forms of the TNF receptors (TNFRI and TNFRII) are shed following TNF stimulation and are thus used as a biomarker of TNF-activation as levels are higher and more stable than TNF itself. Monocyte/macrophage activation biomarkers include the soluble lipopolysaccharide (LPS) receptor component CD14 (sCD14) which is shed following LPS stimulation [6], and neopterin and CXCL10, which are indicative of IFNγ-mediated activation [7, 8]. The function of the biomarker is not always consistent with how it is interpreted, such as with sCD163 which is used as a biomarker of inflammation-induced monocyte/macrophage activation, although CD163 itself exerts an anti-inflammatory effect [9]. Immune activation is typically measured by cellular markers such as HLA-DR and CD38 on T cells, CD40, CD80, and CD86 on dendritic cells [10] and CD11b on monocytes [11]. Markers of inflammation are often assumed to correlate with cellular activation, although this cannot always be assumed. Finally, chronic immune activation drives immunosenescence, which is indicated by differentiation/senescence markers such as CD57 and loss of CD28, and immune senescence can itself trigger further inflammation (discussed below) and immune dysfunction. The mechanistic links between inflammation, immune activation, and immune senescence (depicted in Fig. 1) likely vary under various pathological states and careful correlative analysis is required to define the most informative biomarkers for HIV-related non-communicable diseases.

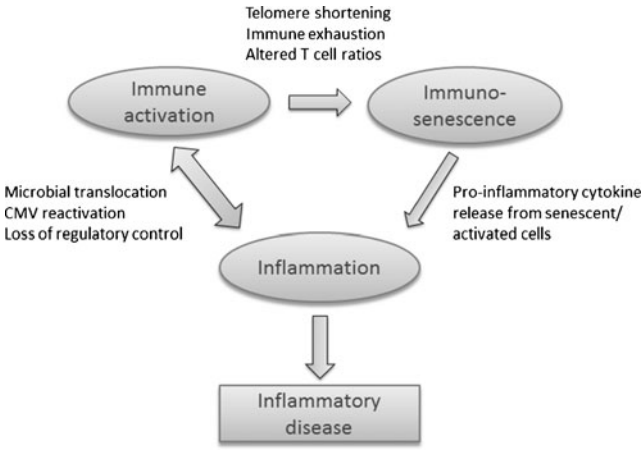

Fig. 1 Relationship between inflammation, immune activation and immune senescence

Cardiovascular Disease

HIV+ individuals have an increased risk of CVD, with a recent meta-analysis estimating the relative risk at 1.61 (95% CI 1.43–1.81) for untreated individuals and 2.00 (1.70–2.37) for those on antiretroviral therapy [12]. This risk is of similar magnitude to that attributed to the traditional CVD risk factors of male sex (HR 1.70; 1.32-2.18) and smoking (HR 2.35; 1.92-2.87) amongst HIV+ individuals in the DAD study [13]. Accurate determination of CVD risk in HIV+ individuals has been confounded by differences in treatment status, virologic suppression and differing adjustment for lifestyle and traditional risk factors. Whilst increased CVD risk persists after adjusting for traditional risk factors [14], the field still requires large-scale studies that adequately control for these and other risk factors known to influence CVD. Part of the increased CVD risk during HIV infection may be attributable to the effects of cART, as the relative risk in cART-treated individuals is 1.52 (95% CI 1.35-1.70) compared to untreated individuals [14]. Certain antiretroviral drugs including protease inhibitors (PIs) and abacavir have been implicated in increased CVD risk [15], however the link between abacavir and CVD remains controversial as associations seen in large cohort studies [16, 17] have not been confirmed in randomized control trials [18], and a recent meta-analyses found no association between abacavir and CVD [19]. Beyond this, there is an increased risk of CVD in HIV+ individuals which cannot be explained by treatment and traditional risk factors.

Chronic inflammation has an established role in the development of CVD in HIV+ and uninfected populations. In the general population, both IL-6 [20] and hsCRP [21] levels predict future cardiovascular events and increases in IL-6 levels in the elderly are associated with increased cardiovascular risk [22]. Interest in the role of inflammation in the development of CVD in HIV infection intensified following the results of the SMART study, which showed that interruptions to cART were associated with higher mortality from non-AIDS events than continuous therapy [23]. These findings were later linked to increased levels of the inflammatory markers IL-6, hsCRP and D-dimer [24]. Further analyses demonstrated that these markers were all independent predictors for future cardiovascular events, even when adjusted for known risk factors [25••].

The mechanism of inflammation-induced CVD involves endothelial activation. Arterial wall inflammation measured in vivo is heightened in HIV+ individuals with no known atherosclerosis compared to matched controls, but similar to HIV uninfected controls with known atherosclerosis, suggesting this may be an early stage in CVD development [26•]. Inflammatory cytokines act on endothelial cells to induce expression of adhesion receptors and increase chemokine production, which in turn promotes attachment and migration of leukocytes, particularly monocytes. A role for the chemokine receptor CCR5 in the development of atherosclerosis in HIV+ individuals is suggested by a link between carotid intima media thickness (cIMT, a clinical marker of atherosclerosis) and CCR5 mRNA levels in circulating leukocytes [27]. The antiretroviral drug maraviroc (a CCR5 antagonist) reduces inflammation-mediated recruitment of monocytes into plaques and inhibits plaque progression in a murine model [28], suggesting its therapeutic potential. However, pilot studies of cART intensification with maraviroc in poor immunological responders have yielded conflicting results regarding its effect on immune activation [29, 30], with one study showing maraviroc actually increased the proportion of HLA-DR+/CD38+ T cells [30]. Some of these discrepancies may be due to differences in immunophenotyping protocols, and further work with validated processing protocols is required to determine the effect of CCR5 antagonists on immune activation.

The migration of monocytes into developing atherosclerotic plaques and their development into inflammatory, lipid–laden foam cells is a critical early step in atherosclerosis (reviewed in [31]). Using an in vitro model of transendothelial migration, we have recently shown that monocytes from HIV+ individuals show an increased propensity to become foam cells and be retained in a model of sub-endothelial plaques (Maisa et al. submitted). This appears to involve both intrinsic alterations to monocytes and soluble factors, as our data shows that blocking TNF ligation ameliorates foam cell formation. These data suggest that in addition to their effects on endothelial activation, inflammatory factors including TNF may also act on monocytes to potentiate early atherogenic processes. Pro-inflammatory CD16+ monocytes, which expand in the blood of both HIV+ individuals [3, 32-34] and the elderly [3, 34-37], have been associated with increased risk of cardiovascular events [38] and peripheral vascular disease [39] in seronegative populations. Amongst viremic HIV+ individuals the phenotype of monocytes, including proportions

of monocyte subsets, is similar to that of uninfected individuals with acute coronary syndrome [33] and levels of sCD163 are associated with non-calcified atherosclerotic plaques in both HIV+ men [40] and women [32], suggesting monocyte activation may contribute to CVD during HIV infection. Together, these data suggest a key role for inflammatory cytokines and monocytes activation in the pathogenesis of CVD in both HIV positive and negative individuals.

Reduced Bone Mineral Density and Osteoporosis

HIV+ individuals also have reduced bone mineral density (BMD) and an increased incidence of osteoporosis (odds ratios of6.4 and 3.7, respectively) [41]. This manifests clinically as a two-four fold increased prevalence of fracture [42] and an increased rate of multiple fractures [43]. Like all HIV co-morbidities, the cause of BMD loss in HIV+ individuals is multifactorial; an increased prevalence of factors known to affect BMD including low body mass index (BMI), smoking, diet and HCV co-infection has confounded quantitation of the HIV-specific effect. However, HIV seropositivity remains significantly associated with reduced BMD after adjustment for factors such as BMI [44]. Vitamin D deficiency is a well known risk factor for bone disease in the general population and although the prevalence of vitamin D insufficiency/deficiency in HIV+ populations is high (50-90%) [45]), it is similar to that of the general population.

Bone modeling is mediated by osteoclasts that resorb bone and osteoblasts that promote bone formation. Osteoclasts are activated via the receptor activator of NFκB ligand (RANKL) that binds to RANK expressed on the osteoclast surface, whilst the decoy receptor osteoprotegerin (OPG) antagonizes RANKL action and promotes bone formation. Osteoclasts/blasts and hematopoetic stem cells are derived from the same bone marrow progenitors and osteoblasts have a significant regulatory effect on function of immune cells (reviewed in [46]). Inflammation deregulates the delicate balance between osteoclast/blast activity; pro-inflammatory cytokines including TNF and IL-6 increase RANKL production, which stimulates osteoclast activity and bone resorption (reviewed in [47]). Further evidence of inflammation in the pathogenesis of osteoporosis is illustrated by hsCRP levels being independently associated with low BMD and fractures [48••, 49]. Immune activation also contributes to altered bone formation, as activated T and B cells produce significant amounts of RANKL. Additionally, LPS is known to stimulate osteoclast production [50]. Both chronic inflammation and immune activation are thus well-recognized mediators of bone loss and reduced BMD is a feature of chronic inflammatory conditions including rheumatoid arthritis [51], inflammatory bowel disease [52], diabetes [53], and chronic hepatitis infection [54]. In this sense, HIV is not unique in inducing inflammation-induced BMD loss, although it remains unclear whether the biochemical processes driving this are identical in chronic inflammatory diseases and in healthy ageing.

In addition to the effects of inflammation and immune activation, HIV-specific factors also induce BMD loss in HIV+ individuals. In vitro and animal studies indicate that viral proteins including gp120 and Vpr can stimulate osteoclast activity and BMD loss [55, 56]. ARV drugs also contribute to BMD loss. cART initiation is associated with a 2-6% loss in BMD within the first 2 years, irrespective of drug regimen. Whilst PIs and tenofovir [44, 57] are associated with increased BMD loss in cART-treated individuals, BMD loss during cART initiation is thought to be primarily due to disruption of the osteo-immunological balance associated with immune-reconstitution. The effect of ARV toxicity and ART initiation on BMD loss has confounded investigation of the relationship between inflammation/immune activation and bone loss during HIV infection and only limited data are available. However, T cell activation and HLA-DR+CD4+/CD8+ T cells are independently associated with low BMD in the setting of HIV infection [58]. Longitudinal analyses, with careful control for the use of tenofovir and PIs, are needed to clarify the association between inflammatory factors and BMD in HIV+ individuals.

Mechanisms Driving Chronic Inflammation and Inflammatory Diseases: Similarities between HIV+ Individuals and the Elderly

The mechanisms contributing to chronic inflammation in HIV+ individuals are multi-factorial and have been recently reviewed elsewhere [1]. Here we focus on three mechanisms which appear to contribute to inflammation and related diseases in both HIV+ individuals and the elderly.

Microbial Translocation

Damage to the gut epithelium during HIV infection is thought to result in increased translocation of microbial products from the gut into the blood stream. The latter contribute to both immune activation and chronic low level inflammation in HIV+ individuals ([2] and reviewed in [59]). Microbial products including LPS [2, 60, 61] and 16s rDNA [62] are elevated in the blood of both untreated and cART-treated HIV+ individuals. The soluble form of the TLR4 co-receptor CD14 (sCD14), is shed from the surface of monocytes upon activation by LPS [63] and we and others have reported that circulating sCD14 levels are also elevated in HIV+ individuals [32, 60, 61]. Levels of LPS, sCD14 and 16s rDNA levels correlate with traditional inflammatory markers including hsCRP [60, 64•, 65], IL-6 [60, 64•, 66], TNF [66], and D-dimer [60, 65], supporting the hypothesis that microbial translocation and

resultant immune activation drive inflammation in the setting of HIV infection.

Following cART initiation, elevated LPS and sCD14 levels decrease [61] but do not normalize [67]. sCD14 and LPS levels reportedly correlate in many [61, 66, 68] but not all [3, 69] studies and recent work suggests that sCD14 and LPS levels may correlate only in patients with low CD4+ T cell counts and high HIV viral loads [65], suggesting these two markers should not be used indistinctly as measures of the same process.

Markers of microbial translocation are predictive of disease progression and mortality in HIV+ individuals [60, 70]. Amongst cART-treated individuals, elevated LPS levels are associated with reduced brachial artery flow mediated dilatation, indicating endothelial dysfunction [71], elevated cholesterol and decreased insulin sensitivity [72]. Prospectively, elevated LPS and sCD14 are independent predictors of future hypertension in cART naïve individuals [73] and of progression of subclinical atherosclerotic plaques amongst treated individuals, but not healthy controls [69]. Collectively, the available data suggest a role for microbial translocation in the development of CVD in HIV+ individuals.

There has been substantially less focus on microbial translocation during healthy ageing although recent evidence suggests its relevance. We and others have reported elevated plasma LPS [35] and sCD14 [67] levels amongst healthy, older individuals. A cross-sectional analysis of over 5000 individuals found an increase in sCD14 with age and demonstrated that baseline sCD14 predicted future cardiovascular events and mortality, independent of traditional cardiovascular risk factors [64•], suggesting a significant role of microbial translocation in the development of CVD in the elderly.

Interpretation of these findings is limited by the difficulty in measuring microbial translocation, particularly the unreliability of LPS assays. The Limulus Amebocyte Lysate (LAL) assay used to measure LPS and PCR amplification of16s rDNA are both highly susceptible to contamination by bacterial products, whilst LPS detection in serum and plasma is limited by the presence of inhibitors. There is substantial variation between individuals [74] and between serum versus plasma [75] regarding the extent to which inhibitors affect LPS detection. Heat inactivation and sample dilution can partially overcome these effects [74, 75]. However, a recent study using HIV+ samples suggested that dilutions of plasma as low as 1:500 (greater than the commonly used dilutions of 1:5–10) may be required to overcome LPS inhibition [74]. The detection of sCD14 is technically more reproducible than that of LPS, however, it is a marker of monocyte activation and thus an indirect measure of microbial translocation. There is also a substantial genetic contribution to sCD14 levels that accounts for 33% of variation [64•]. Thus, methodological differences and variations in assay performance could account for some of the discrepancies observed in the literature.

Telomeres

Telomeres are short, repetitive nucleotide sequences located at the ends of chromosomes, protecting them from degradation. Telomere shortening is a biological marker of ageing; shortened telomeres have been associated with age-related diseases including CVD diabetes and cancers (reviewed in [76] and [77]). A large prospective study of 19,838 subjects in Denmark found modest but significant associations between shortened telomeres and myocardial infarction, ischemic heart disease and early death [78]. Telomere length is an independent risk factor for CVD outcomes in the general population [79]. Telomere length correlates inversely with cIMT after adjustment for age [80] and also with markers of diabetes [81].

Ageing is characterized by an accumulation of late-differentiated T cells with both shortened telomeres and a senescent phenotype (see section below). This population is also expanded in HIV infection [82]. These senescent T cells have a heightened production of TNF, IL-6 and RANKL [83], potentially contributing to chronic inflammation and increased bone resorption in both HIV+ individuals and the aged. It is unclear whether telomere shortening and inflammation are mechanistically connected or whether both are indicative of an associated process, however the two phenomena occur concurrently. Telomere shorting in HIV+ individuals has been reported in T cells [84], and monocytes [35]. Given monocytes are not thought to undergo significant cell division in the periphery, shortened telomeres in peripheral blood monocytes is an unexpected finding and suggests shortening occurs within bone marrow precursor cells, a finding which may have implications for other cell types arising from these precursors including osteoclasts.

The mechanism underlying shortening of telomeres in HIV+ individuals may relate to diminished effects of telomerase (the enzyme responsible for maintaining telomere length) [84]; the normal up-regulation of telomerase in response to cell stimulation is also defective in HIV+ individuals [85]. Nucleot(s)idereverse transcriptase inhibitors (NRTIs) impair telomerase activity both in vitro and in vivo [84, 86]. NRTIs act as substrates for not only HIV reverse transcriptase but also telomerase and mitochondrial DNA polymerase γ (polγ). Our findings from a small cohort study showed that HIV+ patients receiving NRTIs had significantly shorter telomeres than individuals receiving non-NRTI-containing regimens or uninfected controls [86]. Inhibition of the telomerase reverse transcriptase (TERT) may have additional effects independent of telomere length, as the RT component of telomerase helps protect the mitochondria from oxidative stress (reviewed in [87]). The HIV proteins Tat [88] and Vpr [89] can inhibit telomerase in vitro although interestingly, Vpr mutants from long term non-progressors do not degrade TERT [89].

A mechanism of telomerase inhibition that may be common to HIV+ individuals and the elderly is inflammation, as

TNF impairs telomerase activity in CD4+ [90] and CD8+ T cells [91] in vitro. We have also shown that monocytes, including the pro-inflammatory CD16+ monocyte subset, from both young HIV+ individuals and aged seronegative individuals show heightened basal and LPS-stimulated production of pro-inflammatory cytokines and both groups show shortened telomeres [3]. Thus, inflammation-induced telomere shortening and the production of pro-inflammatory cytokines by senescent T cells and activated monocytes may represent a positive feedback loop driving further immune senescence and inflammation in both HIV+ and aged populations.

Cytomegalovirus (CMV)

CMV infection plays a significant role in driving immune ageing and senescence and causes an expansion of late differentiated T cells in aged individuals. In the aged, up to 27% of total CD8+ T cells are specific for a small number of CMV epitopes [92]. Recent findings suggest the expansion of late differentiated CD28- memory T cells previously attributed to ageing is predominantly driven by CMV infection [93••, 94]. CMV infection induces pro-inflammatory cytokine release in vitro and serum CMV IgG levels correlate with inflammatory markers (in [95]). CMV-seropositivity has also been associated with increased risk of CVD [96] and mortality in CVD patients [97].

CMV-specific CD8+ T cells are expanded in HIV+ individuals to almost twice the level as uninfected controls, and this persists despite cART-treatment [98]. In HIV+ individuals, serum levels of CMV IgG are elevated and are associated with subclinical CVD [99, 100], whilst CMV-specific T cell responses are independently associated with cIMT [101]. A study of chronically infected HIV+ individuals in Thailand found 26% of treatment-naïve participants had detectable CMV DNA (a marker of CMV reactivation) [102]. Taken together, these data suggest HIV infection, either directly or indirectly, reactivates CMV and increases the immunological burden resulting from infection with this virus. It is possible that many of the age-related immunological effects of HIV may actually be secondary to, or at the very least confounded by, HIV-induced CMV-reactivation. However whilst direct causality to these diseases, including CVD, has not been demonstrated, inhibition of CMV with valganciclovir therapy in cART-treated HIV+ individuals with low CD4+ T cell counts mediated a significant reduction in CMV DNA and CD8+ T cell activation [103].

Delineating the contribution of CMV to inflammation and immune activation during both HIV infection and ageing is difficult as CMV seropositivity is ubiquitous in both groups (70-80% CMV seropositivity in HIV-negative individuals aged >40 years and >90% in HIV+ individuals) and is rarely controlled for in cohort studies. Serology for CMV has limited value in providing evidence of reactivation. However quantification of CMV reactivation remains challenging as CMV DNA viremia is rarely detected in healthy individuals, is expensive to monitor, and CMV-specific T cell responses do not always correlate with viremia. Whilst CMV-specific T cell responses are more reflective of viral burden and more likely to indicate reactivation than seropositivity a more sensitive and reliable test for CMV reactivation is needed to help clarify the above-mentioned issues.

T-cell Activation and Comorbidities in cART Treated Patients

Immune senescence involves changes to many immune cell types, but is often measured as the accumulation of highly differentiated T-cells, particularly in the CD8+ T-cell compartment (reviewed in [104]. T-cell senescence is characterized by the loss of the co-stimulatory molecules CD27 and CD28, expression of CD57, impaired proliferation, shorter telomeres, as well as the secretion of pro-inflammatory cytokines IL-1, IL-6, and TNF (reviewed in [105, 106]. CD8+ T-cell activation (CD38+HLADR+) and senescence (CD57+CD28-) have been associated with markers of atherosclerosis and vascular dysfunction in cART treated patients [107-109] although more recent studies which adjust for other markers have found markers of innate immune activation to be more important [110-112]. There is also a reported association in cART-treated HIV+ patients between CD8+ T-cell senescence (but not T cell activation) and Kaposi's sarcoma [113]. Although the role of T-cell activation in the development of comorbidities in HIV infection is currently unclear, numerous studies have consistently shown that deficiencies in the number of circulating CD4+ T-cells post-cART is a strong risk factor for multiple age-related co-morbidities including CVD, osteoporosis, non-AIDS related malignancies, and frailty in cART treated individuals [114-118]. These data collectively imply that the adaptive immune system may have a more indirect role in driving clinical end-points in HIV+ individuals.

Ageing with HIV in Resource Limited Settings

The majority of studies investigating age-related comorbidities in HIV+ population have been from developed countries [119-121] and there are limited data from resource-limited settings. However, the prevalence of non-communicable diseases worldwide is high, and is responsible for substantial mortality in both resource rich and poor countries [122-127]. In China, non-communicable diseases account for 80% of all deaths and 70% of total disability-adjusted life-years lost [128]. In North-eastern China, 29% of the urban population has hypertension with adequate control only in 4% [125].

A similarly high prevalence of comorbidities has also been reported among HIV+ individuals living in developing countries. Approximately 70% of over 5000 women recruited for a recent HIV prevention trial in Kwazulu Natal, Africa (median age 27 years) were either overweight or obese [123], with a similar proportion of HIV+ women in South Africa also obese [129] and the prevalence of hypertension among HIV+ individuals in some African countries ranging from 10-45% [130-132]. In HIV+ individuals (median age 37 years) receiving cART in Taiwan, the combined prevalence of osteoporosis/osteopenia was 40% [133]. These data collectively suggest that despite differences in risk exposures between developed and developing country settings, non-communicable diseases are a growing concern and are already presenting a major disease burden both in the HIV+ and uninfected populations in resource limited settings.

Many of the HIV-related risk factors known to be associated with premature aging in HIV including advanced immunodeficiency [116, 117], chronic immune activation and inflammation [134] and chronic co-infections [135, 136] are all prevalent in the resource limited setting [137-141]. Most HIV+ people residing in these countries are from poor socioeconomic backgrounds, an independent factor associated with accelerated aging [142]. Whilst there is improved access to ART, and globally HIV+ patients are living longer, there is generally poor integration of health services in most HIV health care facilities in these settings [143, 144]. Thus patients are likely to present with non-communicable diseases only after the development of significant morbidity. A greater understanding of the extent and risk factors for age-related comorbidities in the HIV+ population in resource limited settings as well as the magnitude of specific pathogenetic factors that may contribute to chronic inflammation and immune activation (e.g., chronic parasitemia) is urgently needed in order to assist public health efforts to integrate non-communicable disease management into existing HIV prevention and treatment programs.

Therapeutics

Preventing inflammatory disease by addressing disease risk factors such as smoking, hypertension, obesity, vitamin D deficiency, are equally important in both the HIV+ and general populations, but given the significant evidence of shared disease pathogenesis, the question arises as to whether different therapeutic approaches are required to specifically target these non-communicable morbidities in HIV+ individuals, or whether we can learn lessons from healthy ageing.

Preventing inflammatory diseases by reducing inflammation seems an obvious approach, although anti-inflammatory drugs are used cautiously in the aged due to adverse effects including gastrointestinal bleeding. Low-dose aspirin is widely used for CVD prophylaxis in the general population; its ability to prevent other age-related inflammatory diseases is unproven. The efficacy of low dose (100 mg daily) aspirin treatment for 5 years in preventing a range of age-related conditions is currently being evaluated in a cohort of 19,000 individuals aged >70 years in the Aspirin in reducing events in the elderly (ASPREE) trial [145]. Results from this study may have relevance also in the HIV+ population. There are promising results from a 1 week trial of low-dose aspirin (325 mg loading dose then 81 mg daily) in 25 cART-treated HIV+ individuals [146•] where a significant reduction in T cell activation and plasma levels of sCD14 but not hsCRP, D-dimer and IL-6, were noted. These anti-inflammatory effects were hypothesized to be secondary to reduced platelet activation and thus monocyte activation, as the aspirin dose used was well below that required to mediate anti-inflammatory effects (3–4 mg daily).

Whilst statins are widely used in the general population as cholesterol-lowering drugs, they also have immunologic and cardioprotective effects including improved endothelial function and reduced T cell activation as well as having anti-inflammatory effects (for review see [147]). Trials evaluating the anti-inflammatory efficacy of statins in HIV+ individuals show mixed results. Rosuvastatin, atorvastatin, and pravastatin can significantly reduce serum IL-6, TNF and hsCRP in cART-treated HIV+ individuals [148], however anti-inflammatory effects of pravastatin were not supported in a further trial [149]. Other studies suggest statins can reduce immune activation without altering markers of inflammation [150, 151]. Statin therapy is associated with reduced all-cause mortality in HIV+ individuals with pre-diagnosed co-morbidity, but the benefit in those without co-morbidity seems less significant [152]. Larger randomized trials in HIV+ individuals are required to clarify their beneficial effect in ameliorating inflammation and inflammatory diseases.

Although chronic endotoxemia is present in both HIV+ individuals and the aged, elevated plasma LPS levels in young HIV+ individuals [3], suggesting that agents that inhibit LPS signaling may be of benefit in these patients. A number of trials have investigated the efficacy of TLR inhibitors chloroquine (CQ) and hydroxychloroquine (HCQ) to reduce immune activation and resultant inflammation. These agents block endosomal acidification and thus activation of the endosomal TLR receptors TLR3, 7, and 9. In a small study, CQ/HCQ reduced CD4+, CD8+ T cell, and CD14+ monocyte activation and plasma LPS and IL-6 levels in cART-treated non-immunologic responders [153, 154]. In contrast, HCQ use in treatment-naïve participants with CD4+ T cell counts >400 cells/ml did not significantly reduce CD8+ T cell activation or

inflammation; in fact CD4+ T cell decline and plasma viral load were significantly increased in the HCQ arm [155]. These results suggest that inhibition of TLR responses in viremic HIV+ individuals may have adverse effects on HIV control and suggest these drugs might only be cautiously used in individuals with virologic suppression.

In addition to increased microbial translocation, HIV+ individuals have an altered gut microbiota, with increased concentrations of *P. aeruginosa* and *C. Albicans* and reduced concentrations of *Bifidobacteria* and *Lactobacilli* (reviewed in [156]). The gut microbiota has significant influence on mucosal immunity, and treatment of SIV-infected macaques with prebiotics in addition to ART improves gastrointestinal immunity [157], although limited data from HIV+ individuals show inconsistent effects on markers of inflammation and immune activation [158, 159]. As rifamycins have an anti-inflammatory effect and can inhibit LPS-induced cytokine production trials are currently underway to determine the efficacy of non-absorbed antibiotics such as rifaximin in reducing microbial translocation during HIV infection. Given the central role that microbial translocation is purported to play in HIV-related inflammation/immune activation, significantly more data on the efficacy of pro/prebiotics and related therapeutics in both viremic and virologically suppressed HIV+ individuals are warranted.

Conclusion

The pathogenesis of inflammation-driven, non-communicable diseases in HIV+ individuals is complex and multifactorial, and whilst there are clear HIV-specific mechanisms contributing to certain co-morbidities, it is equally clear that chronic inflammation drives many of these diseases in HIV+ diseases as well as in healthy ageing. Although the etiologies vary, mechanisms contributing to inflammation such as microbial translocation, immune activation and dysfunction and immune senescence act in parallel in both HIV+ individuals and the aged. Elucidating which manifestations of HIV co-morbidities require novel interventions, and which will benefit from traditional prevention and treatment strategies, is a priority area for research as the HIV+ population ages in both western society and in resource limited settings.

Compliance with Ethics Guidelines

Conflict of Interest Anna C. Hearps, Genevieve E. Martin, Reena Rajasuriar, and Suzanne M. Crowe declare that they have no conflict of interest

Human and Animal Rights and Informed Consent This article does not contain any studies with human or animal subjects performed by any of the authors.

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- • Of importance
- •• Of major importance

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