Immunosenescence and Ageing in HIV

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Abstract

HIV was the prime killer of youth and severely limited life expectancy until recently, when potent antiretroviral therapy reduced both morbidity and mortality. However, treatment did not normalize patient life span. Despite effective therapy, immune recovery is incomplete. Reconstitution of CD4 T cells occurs, but a residual altered immune phenotype persists with long-term clinical consequences. Death in these patients frequently occurs from the same comorbidities causing death in the elderly. Their lingering laboratory and clinical phenotype is very characteristic of immune ageing, a process that is referred to as immunosenescence.

HIV disease has been proposed as a model of accelerated immunosenescence. The mechanisms driving this acceleration are not clear and likely multifactorial. Host responses and attempts at restoration of immunity, as well as a long-term damaged immune environment, appear to be linked to ageing complications. During treatment with antiviral therapy, premorbid conditions not only remain but also find fertile ground to exploit the underlying compromised host landscape.

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The immune system, despite undetectable plasma HIV RNA, is not quiescent. A chronic subclinical inflammatory state often persists. It remains to be determined if this inflammation is driven by very low-grade expression of HIV antigens or by persistent antigenic challenge from secondary comorbidities or both. The net effect is the early emergence of a remodeled ageing phenotype with many of the features and impairments found in the very elderly. Although the mechanisms in HIV-associated immunosenescence are likely multiple and complex, growing evidence supports the concept that CMV plays a central role.

Keywords
Ageing · Immune homeostasis · Chronic inflammation · Immunosenescence · Comorbidities · HIV · CMV · Immune risk phenotype

Introduction

This chapter will review HIV-associated changes in ageing and immunosenescence. HIV has been proposed as a model of accelerated immunosenescence. The mechanisms of rapid ageing are likely multifactorial and for the most part unclear. In the context of this disease, determining if ageing and comorbidities are a cause or effect of immunosenescence is very important. Studying the temporal changes in HIV disease has potential to shed light on how the reshaping of the immune system from chronic inflammation in a persistently altered immune landscape affects long-term health and longevity.

Overview of Ageing and HIV

HIV/AIDS is one of the world's most significant public health challenges. Over the last 30 years, untreated HIV disease has generated previously inconceivable levels of morbidity and mortality among individuals of childbearing age. Most of the 70 million people who have been infected with the HIV virus have been young and half have died (World Health Organization 2017). Reversing this trend has been the unprecedented antiretroviral therapeutic efficacy that began with the introduction of triple drug combinations two decades ago (Deeks et al. 2013).

Successful reduction of death rates in middle- and high-income countries brought the hope of longevity. Treated individuals with undetectable plasma HIV-1 could potentially have a life expectancy approaching that of the general population (Samji et al. 2013). Unfortunately, this has not been the case. Along with HIV control, a high prevalence of cardiovascular, bone, metabolic, neurocognitive, and other ageing comorbidities was noted. These comorbidities have shortened patient life spans (Guaraldi et al. 2011; Hemkens and Bucher 2014).

The reasons for the appearance of the newly recognized obstacles to the quality of life, healthy ageing, and longevity have been unclear. From a biologic perspective,

life is characterized by a continuum of dynamic changes that encapsulate time within a complex set of cellular, tissue, and organ processes. These time-dependent alterations evolve over the years as a consequence of health challenges, healing, and rejuvenation. The totality of modifications in cell metabolism, phenotype, function, and tissue remodeling define what we term as ageing.

Maintenance of long-term good health in the elderly requires overall long-term normal cellular and tissue function, in particular an immune system that is regulated and ready to respond. Chronic deviations from natural homeostatic states have ageing consequences. The loss of immune homeostasis in HIV disease occurs early in infection; it is profound and persists even years after optimal suppression of HIV-1 plasma RNA (Ndumbi et al. 2013, 2014a). Renewal and repair is critical for homeostasis to occur. In HIV disease homeostasis is impacted at multiple cell and organ levels. The affected lymphoid organs include the gut, the thymus, the spleen, lymph nodes, and the bone marrow. All of these organs not only undergo substantial damage, but they also rapidly become remodeled in the process. Untreated HIV, with time, leads to an exhaustion of lymphopoiesis (Sauce et al. 2011), loss of lymphocyte homeostasis, and a depletion of CD4 T cells. Effective HIV therapy in part replenishes the peripheral blood CD4 T cell pool. However, the loss of CD3+ (T cell) homeostasis and an abnormally low CD4:CD8 ratio, for the most part, remain. These ongoing abnormalities are indicative of a residual dysregulated state (Sauce et al. 2011; Ndumbi et al. 2014a).

With chronic HIV infection, T cells encounter persistent and recurring antigen and inflammatory signals. Even with adequate viral suppression, immune activation can be substantial and lasting. This inflammatory state not only persistently maintains an altered homeostasis and an abnormal naive and memory T cell phenotype; it also leads to a deterioration of T cell function. With loss of normal effector function, multiple inhibitory receptors are expressed on T cells resulting in the expression of negative regulatory pathways and altered transcriptional control. These changes promote and establish T cell exhaustion, which becomes clinically evident as an inefficient control of infections and tumors (Wherry and Kurachi 2015). The progressive reduction in immune capacity and long-term altered homeostasis characterize the immunosenescence in HIV, a process mostly observed in aged individuals.

The HIV virus is a unique human pathogen that specifically targets host defense. It is unquestionably a master of immune perturbation as it engages, activates, drives, and exhausts immune responses, leading to profound and permanent immune damage. Because of the very dynamic state HIV creates, it is unclear if immunosenescence is a direct consequence of retroviral pathology or results from uncontrolled secondary chronic inflammation. The transformed immune setting of potent activation, dysregulation, and deficiency may be permissive of recurrent secondary antigenic challenges. These antigenic encounters would in turn lead to chronic subclinical low-grade inflammation promoting the clinical expression of comorbidities.

Most human herpes viruses can be chronic sources of antigen. Other immune stimuli could possibly arise from papilloma virus, metabolic, neoplastic, cardiovascular, and neurocognitive origins. Latent herpes group pathogens such as varicella-

zoster virus are frequently found as HIV coinfections and tend to reactivate. Their impact on the maintenance of low-grade inflammation is unknown. Varicella-zoster virus remains latent in neural ganglia, reactivation episodes manifest as herpes zoster, and the frequency of reactivation increases with age, possibly as a consequence of immunosenescence. CMV infection potentiates the effect of ageing on VZV reactivation rate. While a negative association between CMV infection and VZV antibody titers occurs in young individuals (Ogunjimi et al. 2014).

Since 1950 the number of centenarians has doubled each decade in industrialized countries. The odds of living to 100 have increased from 1 in 20 million to 1 in 50 for females in low-mortality nations (United Nations 2015). This remarkable change in global longevity did not arise from evolutionary occurrences in the human genome but rather from the composite effect of improved hygiene, global vaccination programs, antimicrobials, and better medical care. The reduction in morbidity and mortality noted in recent generations quite possibly resulted from fewer early life events from infections and inflammation.

Ageing is invariably defined as a natural and inevitable time-dependent process of biologic remodeling. However, it is also most often accompanied by declining health, physical function, and quality of life. Although ageing is considered to be a natural process, the rate of the physiologic decline is often determined by lifestyle and environmental factors that in part promote chronic low-grade systemic inflammation. These include an unhealthy diet high in carbohydrates and fat, lack of exercise, obesity, smoking, drug abuse, and chronic viral infections.

Although indolent chronic inflammation is linked to many diseases of ageing, the intracellular mechanisms that are responsible in driving this process are largely unknown. Damage to molecular and cellular mechanisms, such as mitochondrial dysfunction, can play an important role. Inflammasomes can potentiate inflammation in response to pathogen signals from infectious disease or from danger signals coming from cellular and metabolic stress. Both signals lead to the production of interleukin-1β and IL-18. These interleukins accelerate atherosclerosis and plaque vulnerability in animal models (Whitman et al. 2002) and play a role in the pathophysiology of acute coronary syndromes (Blankenberg et al. 2002). Interleukin-18 is a strong predictor of cardiovascular death in stable and unstable angina (Blankenberg et al. 2002).

Older individuals can exhibit constitutive expression of IL-1β, nucleotide metabolism dysfunction, and elevated oxidative stress. Elevated levels of these pro-inflammatory cytokines are linked to cardiovascular disease (Duewell et al. 2010), hypertension (Fearon and Fearon 2008), malignancy (Zitvogel et al. 2012), cognitive decline, frailty (Youm et al. 2013), as well as degenerative diseases (Sardi et al. 2011). Until recently, it was not known whether inflammasomes were activated in human ageing and if they contributed to the onset of age-associated disease. Making use of large data sets from a longitudinal cohort, it was possible to identify expression of specific inflammasome gene modules that stratified older individuals into two extremes. The first group had constitutive expression of IL-1, nucleotide metabolism dysfunction, elevated oxidative stress, and high rates of hypertension and arterial stiffness. The second did not express IL-1 in a constitutive fashion and lacked the

dysfunctional characteristics. IL-1 expression was consistently elevated over a 5-year period in individuals who were hypertensive and exhibited other comorbidities of ageing. Metabolomic data identified circulating adenine and N^4-acetylcytidine, nucleotide-derived metabolites, capable of priming and activating the NLRC4 inflammasome, which in turn induced IL-1β, activating platelets and neutrophils (Furman et al. 2017).

Very limited data are available on the role of inflammasomes in HIV infection and ageing. It is tempting, however, to speculate that the above innate immune mechanisms may in part initiate or maintain HIV-associated comorbidities. Both canonical NF-Kβ and inflammasome activation have been demonstrated to generate pro-inflammatory cytokines in HIV-infected persons (Ahmad et al. 2002; Stylianou et al. 2003; Chattergoon et al. 2014).

Il-18 is a pleotropic cytokine exerting a spectrum of biologic effects. In synergy with IL-12 and IL-15, it induces interferon-γ from NK and T cells. These cytokines in turn regulate naive T cells promoting their differentiation to effector subsets. IL-18 may play a role in the pathogenesis of AIDS and cancer through the fratricidal killing of NK cells (Iannello et al. 2009; Terme et al. 2011). Antiretroviral therapy reduces but does not normalize IL-18 to physiologic plasma levels (Samarani et al. 2016).

High levels of plasma IL-18 are found in patients from the time of their HIV seroconversion and correlate with HIV viral load (Song et al. 2006). In a cohort of patients from low- and middle-income countries, those with high pretreatment levels of IL-18 and sCD14 that failed to normalize levels with therapy tended to develop clinical failure (Balagopal et al. 2016).

Extensive loss of immune homeostasis occurs with ageing. This loss is possibly the end result of a progressive time-dependent and complex derangement of regulatory processes. The affected mechanisms are those that normally coordinate metabolic, intracellular, and adaptive cellular responses in order to maintain host cell and tissue function in a challenged immune environment.

Immunosenescence begins early in life. The term was coined at a clinical level in 1969 when it was described as a constellation of age-related changes in the immune system resulting in a greater susceptibility to infection and reduced responses to vaccination (Walford 1969). Later the definition was amended to include the concept of age-associated biologic dysregulation contributing to morbidity and mortality. This was largely because of a recognition of a greater incidence or reactivation of infections, autoimmunity, and cancer (DelaRosa et al. 2006).

Currently the immunosenescence phenotype is viewed as a consequence of continuous cellular attrition from chronic antigenic stress, accumulation of memory and effector T cells, reduction of naive T cells, a shrinking T cell repertoire, and shortened telomeres. The term does not impart a specific functional or a mechanistic designation. The main functional features of this insidious process are an impaired ability to respond to new antigens, occurrence of unsustained memory responses, a greater propensity for autoimmune disorders, and a lingering low-grade systemic inflammation (Goronzy and Weyand 2013).

Similar patterns of T cell senescent phenotypes and comorbidities have been identified in HIV infection in young or midlife patients. These profiles are in many

ways alike to those found in HIV-uninfected, very elderly, individuals (Hadrup et al. 2006; Deeks and Phillips 2009; Guaraldi et al. 2011; Bachi et al. 2013; Boccara et al. 2013). Despite the apparent association with an ageing immune profile, no definitive proof exists that the skewed immune phenotype in HIV is the cause of an accelerated or precocious onset of comorbidities.

Premature ageing can occur in individuals thymectomized in childhood. It is, however, unknown to what degree the "functional thymectomy" seen in HIV disease affects rate of ageing. The elderly and those with uncontrolled HIV are susceptible to pneumococcal infection (Meiring et al. 2016), possibly from splenic dysfunction. Although it has been long recognized that splenectomy is a major risk for pneumococcal sepsis in the general population, it is unknown if removal of the spleen affects ageing. In a longitudinal study of HIV-infected individuals, prior to the availability of antiretroviral drugs, a surprisingly significant survival advantage and viral burden reduction were noted with splenectomy (Bernard et al. 1998; Tsoukas et al. 1998). The CD4+ T cell receptor repertoire diversity is compromised in spleens of aged mice (Shifrut et al. 2013). Reduced T cell receptor diversity in the elderly is an important cause of immune dysfunction and has also been an important issue in HIV as well. Patients with low CD4 counts often have disruptions in V-beta repertoire that do not appear to resolve with treatment. Very little is known about splenic and thymic function in the elderly. In rats, changes in expression of genes involved in cell signaling and immune function occur in the spleen and thymus of older animals (Sidler et al. 2013).

Time-dependent remodeling of a variety of nonlymphoid tissue also occurs in HIV. Early in the epidemic, when no treatments had yet to be discovered, HIV-infected patients visually seemed to age rapidly. The ageing features occurred in the context of a syndrome of AIDS wasting. The syndrome had altered body characteristics that resembled those found in very old frail individuals. The features included sunken cheeks, prominent nasolabial folds, temporal muscle atrophy, skeletal muscle loss, and frailty. With the introduction of the initial mono and dual nucleoside reverse transcriptase inhibitor combinations of HIV drugs, the issue of tissue remodeling and ageing became even more prominent. Several anthropomorphic changes reminiscent of body changes in the elderly were noted (Tchkonia et al. 2010). These included the loss of subcutaneous fat and visceral adiposity, prominent facial nasolabial folds, muscle fatigue, and loss of muscle mass, as well as frailty. A social stigma was attached to these body changes, as the altered body features could readily identify and label those who were HIV-infected. In order to minimize side effects, clinical trials were conducted with an aim at reducing drug exposure. The rate of CD4 T cell decline determined the tolerated length of treatment interruptions. Although this approach led to less drug side effects, transient therapeutic disruptions even for a short time had long-term negative consequences. The landmark SMART study demonstrated that intermittent use of antivirals, rather than continuous use, was associated with higher levels of plasma and cell activation markers and an increased risk of cardiovascular disease when compared to continuous use of therapy (El-Sadr et al. 2006). Antiretroviral-associated toxicity thus only partially explained

the increasing prevalence of comorbidities that have also been referred to as non-AIDS-defining illnesses.

Predictive blood-derived biomarkers and diagnostic imaging techniques in young to midlife individuals with HIV have been useful in the identification of a spectrum of ageing comorbidities, including early onset of osteoporosis, atherosclerosis, and neurodegenerative diseases (Lo et al. 2010; Guaraldi et al. 2011). Unfortunately, biomarkers have yet to be developed and validated in order to identify those undergoing immunosenescence.

Not surprisingly there is substantial commonality in underlying inflammatory disorders and the types of comorbidities found in the elderly. The most common life-threatening comorbidities of older individuals are those resulting from atherosclerosis, namely, myocardial infarction and stroke. Patients with HIV; autoimmune diseases, including systemic lupus erythematosus, rheumatoid arthritis, psoriasis, and multiple sclerosis (Symmons and Gabriel 2011; Christiansen 2012; Nikpour et al. 2013; Kwa and Silverberg 2017); as well as chronic inflammatory conditions such as type II diabetes and inflammatory bowel disease (Pedicino et al. 2013; Wu et al. 2017) are more likely than age-matched healthy controls to have atherosclerosis and high rates of cardiovascular events. Overall cardiovascular risk includes not only each individual's physiologic state; it also involves environmental, lifestyle, and genetic factors. In normal individuals, at an interindividual level, cardiovascular disease susceptibility and age of onset vary substantially. Although numerical age is closely tied to cardiovascular risk, the variability in risk, as a function of age, may be dependent on the length and level of chronic inflammation and the presence of immunosenescence.

Molecular and Cellular Mechanisms Contributing to Immunosenescence in HIV

Multiple molecular and cellular mechanisms of ageing may be involved in the development of the immunosenescence in HIV disease. Possibilities include progressive DNA damage, mitochondrial dysfunction, stem cell exhaustion, genomic instability, epigenetic changes, loss of proteostasis, telomere shortening, loss of telomerase activity, activation of p38 mitogen-activated protein (MAP) kinase, and restricted cellular regeneration. The following section will examine some of these mechanisms.

Syndromes of premature ageing have defects in DNA repair pathways (Burtner and Kennedy 2010; Cavanagh et al. 2012). The high copy number and mutation rate of mitochondrial DNA (mtDNA) make it a possible marker of cellular injury and ageing. Mitochondrial damage in HIV has been studied extensively because of the toxic effects of the first-generation antiretroviral therapies. Cells normally identify and respond to DNA damage through DNA strand vigilance. DNA double-strand breaks can be challenging. When breaks occur, the cell either activates cell cycle arrest to allow for repair or undergoes apoptosis if the damage is not repairable. Specific data on ageing and DNA repair mechanisms in HIV are lacking. In

rheumatoid arthritis, DNA repair pathway defects make naive CD4 T cells more susceptible to apoptosis and thus accelerate immune system ageing (Shao et al. 2009). DNA damage accumulates in normal individuals past the age of 70. The accrual of damaged lymphocyte mitochondrial DNA, in that age group, likely plays an important role in immunosenescence (Ross et al. 2002; Park and Larsson 2011). Elevated oxidative stress increases the rate of mitochondrial DNA damage. The accumulation of mtDNA mutations further potentiates oxidative stress and cell apoptosis.

HIV is known to activate mitochondrial enzymes leading to mitochondrial dysfunction and apoptosis of cells. In addition to damage specifically ascribed to viral pathogenesis, the use of certain antiretroviral drugs is also associated with mitochondrial dysfunction. The subsequent long-term clinical manifestations of mitochondrial damage affect many organ systems and cause hematologic toxicity, myopathy, neuropathy, nephrotoxicity, pancreatitis, and other potentially life-threatening problems. Drug toxicity has often been the cause of HIV treatment discontinuation.

Lipodystrophy, one of the most frequently encountered side effects, is linked to use of protease inhibitors as well as nucleoside analog reverse transcriptase inhibitors. It is characterized by loss of subcutaneous fat in the face, limbs, and buttocks (lipoatrophy) and/or abnormal central fat accumulation in the trunk and abdomen (lipohypertrophy). Multiple studies have shown mitochondrial impairment in those with lipodystrophy, particularly in those also suffering from abdominal lipoadiposity and fatty liver. Visceral obesity is an important risk factor for cardiovascular and neurovascular disease and dementia. It is associated with insulin resistance and metabolic syndrome, both of which are factors in ageing.

HIV patients treated with nucleoside analog antiretroviral drugs acquire somatic mtDNA mutations over time, much like those noted later in life due to normal ageing. Genetic polymorphisms play a role in longevity; mtDNA single nucleotide polymorphisms (SNPs) influence the regulation of oxidative phosphorylation, reactive oxygen species (ROS) production, and apoptosis. In a study involving several large HIV cohorts, mtDNA haplogroups J and U5a were elevated among those who had accelerated progression to AIDS and death. Haplogroups Uk, H3, and IWX on the other hand were highly protective against disease progression (Hendrickson et al. 2008).

Results of genome-wide analysis of peripheral blood mtDNA mutations in HIV-treated individuals indicated that use of nucleoside analog reverse transcriptase inhibitor (NRTI) drugs allowed for permissive mutagenesis in vivo. These studies provided evidence that novel mtDNA sequence variation arose within individuals over a relatively brief period. The findings were consistent with models of upregulated cellular oxidative stress, along with inhibition of protective DNA repair mechanisms (Martin et al. 2003). Ultra-deep resequencing-by-synthesis, along with single cell analyses, suggested that the increase in somatic mutation was not due to increased mutagenesis. It was rather due to accelerated mtDNA turnover which can lead to the clonal expansion of preexisting age-related somatic mtDNA mutations and downstream biochemical defects (Payne et al. 2011).

Mitochondrial DNA content in adipose tissue is increased in untreated HIV infection and decreased in patients on stable therapeutic regimens, whereas these changes are not noted in muscle or PBMCs. Patients with clinical lipoatrophy, and those on zidovudine, stavudine, or didanosine, have significantly lower mtDNA content in adipose tissue. Studies suggested that HIV leads to increases in mitochondrial content in adipose tissue and supported the role of NRTI-linked adipose tissue toxicity in the development of peripheral fat wasting. Mitochondrial DNA proliferation in adipose tissue may exist as a direct compensatory response to HIV-related mitochondrial toxicity or in response to HIV immune activation and inflammation. NRTI therapy can potentiate the initial damage, leading to mitochondrial toxicity syndromes. Expression of two activation markers, HLA-DR and CD38, on T cells correlate with mitochondrial DNA levels in adipose tissue. This suggests that the same process that was responsible for activation marker expression can possibly account for the changes in mitochondrial DNA (Morse et al. 2012). There have been conflicting reports of mitochondrial DNA depletion in PBMCs of HIV-infected adults, regardless of antiretroviral therapy.

It appears that intracellular damage accumulates with ageing, reaching a critical point that affects cellular function. Ageing cells project a deleterious profile of a "senescence-associated secretory phenotype" (SASP) (Bhatia-Dey et al. 2016). Ultimately, it leads to tissue breakdown and macroscopic remodeling that characterizes ageing. Senescence may thus be a precondition for anatomical ageing and may in part explain the gradual nature of a process which is invisible during most of its progression.

In senescent human cells, constitutive activation of p38 MAP kinase decreases induction of telomerase and lymphocyte proliferative activity following activation. Studies of p38 activation revealed that a metabolic sensor, 5′-monophosphate-activated protein kinase (AMPK), induced it. In turn it was activated by intracellular adenosine triphosphate (ATP). Glucose deprivation of normal cells induces p38 and AMPK resulting in similar decreases in telomerase activity and cell proliferation to those seen in T cell senescence. Interestingly, this process can be reversed by inhibition of these kinases suggesting that modulation of nutrition may be a way to enhance immunity in the aged (Chang and Pearce 2016). Senescent CD8 cells are limited to using glycolysis to generate ATP, in contrast to non-senescent cells that also use oxidative phosphorylation for normal cellular function (Henson et al. 2014). Inhibiting p38 signaling in CD8 senescent cells leads to increased autophagy, clearance of dysfunctional mitochondria, and reduced reactive oxygen species. Despite the improvement in mitochondrial function, glycolysis still remains the preferred pathway in energy production. In addition to T cell senescence, natural killer cell dysfunction occurs with ageing. The killer cell lectin-like receptor G_1 ($KlRG_1$) inhibitory receptor activates AMPK and inhibits NK cell function as part of ageing.

Epigenetic change is another mechanism in the development of cellular senescence. Differentiation of immune cells occurs without any specific change in genome. Ageing, on the other hand, may in part be due to the accumulation of nuclear and mitochondrial DNA mutations, posttranslational histone modifications,

and chromatin remodeling. Increased histone acetylation and decreased methylation are known age-related epigenetic alterations.

An epigenetic clock based on 353 dinucleotide markers known as cytosine phosphate guanines (CpGs) has the ability to measure natural DNA methylation levels (Horvath 2013). The clock has been used to determine the biological age of cells, tissues, and organs, and it predicts all-cause mortality in the elderly (Marioni et al. 2015a). Additionally, it correlates with physical and mental fitness in late life (Marioni et al. 2015b). DNA methylation levels are thus favorable biomarkers of ageing since chronological age determines DNA methylation levels in human tissues and cells. In an epigenetic study of HIV infection, a significant increase in DNA methylation in brain and blood tissue was observed (Horvath and Levine 2015). The findings were consistent with known clinical manifestations of accelerated ageing in well-controlled HIV. It remains to be seen if the epigenetic clock can serve as a useful tool in the design of therapeutic strategies targeting the prevention of HIV-associated cardiovascular and neurocognitive disorders.

Methylation levels of peripheral blood mononuclear cells in age-matched HIV-1-infected and HIV-1-uninfected individuals demonstrated that HIV-1 infection accelerated age-related methylation by 13–14 years. This finding suggests that HIV-1-associated ageing has similar functional and epigenetic changes that accompany normal ageing (Rickabaugh et al. 2015). Epigenetic approaches have mostly been attempted in HIV as part of an effort to eradicate viral reservoirs using histone deacetylase inhibitors. Of importance to those with HIV and ageing comorbidities is the possible reversibility of the epigenetic changes through pharmacologic avenues. In addition to animal model epigenetic experiments, in humans resveratrol has been studied as a means of repairing epigenetic and mitochondrial dysfunction.

Telomeres are chromatin tips located at the ends of chromosomes. Their length is a measure of cellular senescence and a biomarker of ageing. Telomeres shorten and become susceptible to damage with age (Blackburn et al. 2006). Telomerase is a specialized DNA polymerase necessary for telomere repair following cell division. Loss of telomerase activity can be seen with ageing. Deficiency of telomerase activity in humans causes a variety of age-related issues such as premature gray hair, pulmonary fibrosis, liver disease, and aplastic anemia (Armanios and Blackburn 2012).

In HIV disease, shortened telomeres in the CD8 + CD28- cell memory subset correlate with poor proliferative potential and with replicative senescence (Effros et al. 1996). A study of South Africans with a mean age of 40 years revealed that telomere length was significantly shorter in the HIV-infected than in the HIV-seronegatives (Pathai et al. 2013). In a cross-sectional study, sorted into CD31 + CD4+ and CD31-CD4+ T cell subsets from HIV-infected individuals, telomere length was evaluated using real-time PCR. The study found that HIV-1 infection was associated with shortened telomeres notably in the naive CD4+ T cell subset (Rickabaugh et al. 2011).

In addition to the genome and epigenome, cellular ageing also involves the accumulation of damaged macromolecules that include proteins and lipids. Protein homeostasis, also known as proteostasis, is critical for the maintenance of healthy

tissues. Damage to proteins independently contributes to cellular ageing. If protein replacement is slow, then damaged or misfolded proteins form stable non-degradable toxic complexes. These molecules in turn may trigger age-related diseases (Douglas and Dillin 2010). Very little is known about proteotoxicity in untreated HIV disease. It is interesting, however, that nelfinavir, an HIV protease inhibitor, previously in broad use, is being repositioned as a cancer therapeutic. The rationale is that it similarly induces endoplasmic reticulum stress and apoptosis, inhibiting proliferation in a variety of cancer cells. It is being evaluated in numerous cancer clinical trials. The association of nelfinavir exposure with cancer incidence in HIV-positive individuals was studied, but no reduction in cancer incidence was found (Boettiger et al. 2016). The impact of protease inhibitors in accelerating cellular senescence in HIV-treated patients has not been evaluated.

$P16^{INK4a}$ is a protein mediator of cellular senescence in T cells (Nelson et al. 2012) that decreases replicative capacity. Its protein expression increases with age and during infections. It can be induced as a direct consequence of T cell activation as noted in HIV disease (Migliaccio et al. 2005). Because this protein has potential to cause premature ageing and immune dysfunction, levels of p16 expression were studied in chronically infected HIV patients. An increase in per-cell p16 protein expression was found to be discordant with chronological ageing. In the CD4 compartment, p16 expression levels were restored by successful antiretroviral therapy. This was not the case for the CD8 T cell compartment possibly indicating ongoing cell activation or cellular exhaustion.

Despite the varied mechanisms that contribute to immunosenescence in HIV, specific biomarkers of ageing are limited and are not at the point of clinical utility. Confounding factors that may impact on the use of these ageing biomarkers during HIV infection include effects of antiretroviral therapy, modifiable lifestyle risk factors like smoking, substance abuse, alcohol, and viral hepatitis. There is thus an unmet need for validation of biomarkers of ageing in evaluating immunosenescence in HIV and for the understanding of age-related comorbidities.

The Immune Risk Phenotype and HIV

Immune ageing in the elderly is characterized by changes in T cell subset profiles, as well as alterations in immune function. Changes in phenotype include increases in circulating CD8 T cells and expansions of CD4 and CD8 memory cells, a phenomenon termed as "memory inflation." CD28 which is constitutively expressed on T cells is downregulated progressively during chronic infections and with ageing. The predominant lifelong antigen-specific T cell memory clones in humans are those that arise from chronic human cytomegalovirus (CMV) infection (Olsson et al. 2000) whose prevalence increases with age (Dollard et al. 2011).

The "immune risk phenotype" (IRP) is comprised of the above immune abnormalities and was initially described in 2001 (Pawelec et al. 2001). In the absence of HIV infection, this phenotype identified cytomegalovirus-infected octogenarians with immunosenescence and a high short-term risk for all-cause mortality. The

inverted CD4:CD8 ratio, a very important surrogate marker of disease progression in untreated HIV infection, is also an important IRP component associated with CMV IgG seropositivity (Turner et al. 2014). The IRP and shortened telomeres are both markers of biological ageing and are independently associated with morbidity and mortality (Cawthon et al. 2003; Strindhall et al. 2013; Turner et al. 2014). Notwithstanding that the IRP, a senescent phenotype, identifies poor outcomes in the elderly, there are only limited data on the prevalence and clinical significance of the IRP in immune disorders.

Chronic inflammation and aberrant immunity frequently occur in the elderly. In some, it is manifested as autoimmune disease and metabolic and degenerative disorders. The same comorbidities in much younger individuals share many immune features of the IRP of the aged, yet it is unknown if there is a common unifying mechanism involved in their development. In addition there are clinical and laboratory similarities noted in younger individuals with autoimmune diseases with those found in elderly non-HIV-infected individuals. Similarities in immune phenotypes and comorbidities also characterize immune deficiencies, including the immune deficiency caused by HIV. Patients with common variable immune deficiency (CVID) often have autoimmunity and evidence of B and T cell immune deficiency. They also display an ageing B cell phenotype and an inflated T cell memory pool (Stuchly et al. 2017). The prevalence of CMV in primary immune deficiencies can be high, and patients with CVID often express phenotypic and functional characteristics of the IRP. The component role of CMV in the development of the immunosenescence profile in these patients with preexisting immune aberrations is not clear.

Definitive proof that the T cell immune senescence observed in HIV disease is a direct consequence of HIV retroviral pathology is lacking. The early onset of the comorbidities frequently seen in the elderly during the course of treated HIV disease has been well recognized.

From the very beginning of the HIV epidemic, the hallmarks of infection have been a progressive CD4+ T cell depletion and an inversion of the CD4:CD8 T cell ratio. The initial reports of AIDS at the onset of the epidemic seemed to implicate CMV as the cause of these T cell abnormalities (Gottlieb et al. 1981). When HIV was identified as the etiologic agent of AIDS, the CD4 loss and T cell dysregulation were then solely attributed to HIV. The prevalence of CMV in those with HIV is very high. Therefore, logic would dictate that in those coinfected with HIV, a portion of the immune abnormalities could conceivably be attributed to CMV. Individuals at high risk for HIV can have evidence of immune dysregulation which in part can be attributed to non-HIV pathogens prevalent in those groups. In HIV, effective antiretroviral therapy increases CD4+ T cell counts (Moore and Keruly 2007); however, this improvement does not necessarily reflect long-term immune recovery. Even with effective treatment, most individuals maintain a profound and persistent immune dysregulation as defined by a low CD4:CD8 T cell ratio (Ndumbi et al. 2014a, b). In a sample of 6673 HIV-infected adults enrolled in a Canadian Observational Cohort study, less than 10% of those successfully treated normalized their CD4:CD8 T cell ratio (Leung et al. 2013). The abnormally low CD4:CD8 T cell ratio and other residual immune abnormalities in successfully treated HIV patients

resemble component abnormalities that define the immune risk phenotype (Ferguson et al. 1995; Pawelec et al. 2001). Treatment of those with HIV does not include concurrent use of anti-CMV drugs. It is therefore not inconceivable that residual CMV activity in well-controlled HIV in the context of residual immune compromise could account for persistence of some of the immune abnormalities.

One interesting study of adjuvant CMV treatment in HIV-treated individuals was conducted at a single site. The hypothesis for the CMV treatment was that asymptomatic cytomegalovirus (CMV) replication might contribute to ongoing immune activation in the setting of successful antiviral treatment of HIV. The aims were to determine if CMV therapy could reduce immune activation and improve blunted CD4 recovery. Thirty HIV-infected CMV-seropositive individuals with low CD4 counts (<350 cells/mm) on effective antiretroviral therapy were randomized to treatment with either valganciclovir, an oral anti-CMV drug, at a dose of 900 mg daily, or placebo for 8 weeks with a follow-up 4-week observation period. The primary outcome of the study was change in percentage of activated CD8+ T cells at the end of treatment. CMV DNA remained detectable at the end of the study in most of the placebo-treated participants but in none of the valganciclovir-treated participants indicating expected CMV suppression. Furthermore, valganciclovir-treated patients had significantly greater reductions in CD8 activation at the end of therapy and the observation period than did those treated with placebo (Hunt et al. 2011). These findings indicate that CMV is a cause of chronic immune activation in HIV disease and may be contributing to immunosenescence. With CMV control in HIV, there may be long-term beneficial clinical consequences in terms of a reduction in comorbidities.

An association was established between the IRP and increased risk of mortality among the aged (Wikby et al. 2005; Wikby et al. 2006). In longitudinal studies, elderly individuals with an IRP had increased susceptibility to infections, reactivation of latent pathogens, and decreased responses to vaccination (Saurwein-Teissl et al. 2002; Plonquet et al. 2011; Stowe et al. 2012) reflecting an age-related loss of T cell function. In addition to the initially described phenotypic and serologic changes, the IRP has also been associated with a depletion of naive T cells, an expansion of terminally differentiated memory T cells, the expression of markers of replicative senescence such as CD57 and KLRG-1, as well as the production of proinflammatory cytokines (Wikby et al. 2002, 2006; Zanni et al. 2003; Focosi et al. 2010).

An important feature of cellular senescence is the shortening of telomeres at the ends of chromosomes (Hayflick 1965). Chronic CMV infection contributes to telomere attrition in circulating T cells (van de Berg et al. 2010). Telomere length has not yet been extensively investigated in relation to the IRP. A comprehensive evaluation of the IRP in successfully treated HIV revealed that individuals with an IRP had shorter telomeres than those with no IRP. Furthermore, telomere length in HIV patients lacking an IRP was comparable to uninfected controls. HIV-infected subjects with an IRP exhibited a significantly higher frequency of TNF-α-producing CD8+ T cells and a reduced proportion of CD8+ naive T cells. The IRP status was also associated with a highly significant upregulation of the replicative senescence markers CD57 and KLGR1, on the surface of CD8 + T cells but not on the surface of

CD4+ T cells (Ndumbi et al. 2014a). Taken together, these data indicate that HIV-infected individuals exhibiting the IRP have an increased degree of cellular senescence compared to their non-IRP counterparts. This is of particular importance considering that short lymphocyte telomere length has been repeatedly associated with poor clinical outcomes in other disease states such as diabetes, cancer, and cardiovascular disease (Fitzpatrick et al. 2007; Olivieri et al. 2009; Willeit et al. 2010). HIV-infected individuals with an IRP phenotype may also be at higher risk for age-related comorbidities than those that do not exhibit IRP features. Despite the small group of HIV-infected individuals studied, none of those lacking an IRP experienced cardiovascular disease, while 70 percent of those with an IRP had a documented cardiovascular event as defined by the occurrence of an acute coronary syndrome (myocardial infarction, diagnosed unstable angina, or stroke) (Ndumbi et al. 2014a).

In view of the above findings relating to the IRP, it would appear that there is an important role for CMV in T cell senescence. CMV infection has a prevalence of approximately 50% among middle-aged adults, increasing to 85–90% in the elderly (Olsson et al. 2000). Among Asians prevalence is higher. In elderly Singaporeans, it is as high as 99%. In an elderly US Latino population above the age of 60, it was 95%. Those in the top quartile with respect to anti-CMV IgG antibody titres have higher all-cause mortality and cardiovascular mortality and higher proinflammatory cytokine levels for TNF-α and IL-6 (Roberts et al. 2010). High anti-CMV antibody levels could possibly reflect more frequent CMV reactivation and replication as well as higher proinflammatory cytokine levels. Although active CMV infection is not a direct cause of acute coronary syndromes, CMV infects endothelial cells and thus may be an early step in the cascade of events leading to arteriosclerotic plaque formation (Libby 2002). Very few human studies have been able to demonstrate a direct viral effect on blood vessels nor have CMV genes been consistently found in arteriosclerotic plaques. On the other hand, both cellular and humoral responses to human CMV have been shown to be associated with atherosclerosis (Libby 2002; Haarala et al. 2012; Ji et al. 2012; Sacre et al. 2012). Stochastic episodes of transient viral gene expression occur during CMV latency, and they drive memory T cell pool expansion specific for CMV (Chidrawar et al. 2009; Seckert et al. 2012). These cells have short telomeres in keeping with T cell senescence (Derhovanessian et al. 2010). The phenotype is one of the terminally differentiated effector memory cells that are CD57+ and produce high levels of IFN-γ (Miyazaki et al. 2008).

HIV-infected individuals have a higher prevalence of CMV infection and are possibly more likely to develop an IRP at an earlier age than uninfected individuals. They also have an increased risk of acute myocardial infarction (Currier et al. 2003) and advanced subclinical cardiovascular disease (Boettiger et al. 2016) than age-matched uninfected persons. Precisely how HIV infection, CMV infection, and IRP lead to cardiovascular abnormalities is still incompletely understood. In a study of approximately 600 HIV-infected and 100 HIV-uninfected women with a median age over 40 years, anti-CMV IgG levels were associated with carotid artery stiffness as measured by carotid artery distensibility (Parrinello et al.). Markers of immune activation and markers of immunosenescence such as the percent of CD28-

CD57 + CD4+ and CD8+ T cells were also associated with arterial stiffness (Kaplan 2011a, b, pp 507–508).

Less is known regarding the prevalence of CMV positivity in other chronic inflammatory conditions compared with age-matched controls. Although several studies have found a weak though not significant association between CMV and risk of multiple sclerosis, it is unknown whether CMV IgG-seropositive individuals with autoimmune disorders or immune deficiency as part of an IRP phenotype are more likely to have clinical evidence of cardiovascular disease (Sundqvist et al. 2013).

Despite the importance of CMV in IRP development, the prime role of CMV in immunosenescence is still undergoing some debate (Solana et al. 2012; Fulop et al. 2017). The initial large studies in the very elderly were conducted in one country. They have not been replicated in other elderly populations, nor have they been carried out in HIV cohort studies. Thus the results of these studies cannot be generalized. The IRP does not take into account nutritional and psychologic stress. Biomarkers of inflammation such as IL-6 and hCRP have been independent of the IRP. Chronic infections other than CMV may play an independent and confounding role. These infections are fairly ubiquitous affecting half of the world population. They include commonly found pathogens such as *Helicobacter pylori*, hepatitis B and C, and EBV. Offspring from long-lived families enrolled in the Leiden Longevity Study had significantly lower circulating levels of terminally differentiated CD8+ T cells. Of interest, latent CMV in these individuals was also not associated with lower naive T cells. Data from this cohort implicate genetic factors in longevity and suggest that either lower CMV reactivation occurs in the offspring predisposed to longevity or very good CMV control happens during reactivation.

Nevertheless, striking changes in the immune profile of chronologically young healthy adults infected with CMV suggest it may bring about primary aspects of immunosenescence (Turner et al. 2014). Biomarkers of immunosenescence confirm that similar effects of CMV infection in the elderly such as the accumulation of late differentiated/effector memory T cells, increased inflammation, and poorer immune responses to novel antigens also occur in healthy young adults.

There is a strong link between CD4 + CD28- T cells and CMV infection in other illnesses. Renal transplantation studies have demonstrated that the emergence and expansion of CD4 + CD28- T cells in CMV seronegative graft recipients directly result from infection by a CMV-seropositive graft. Mortality after renal transplantation is mainly due to cardiovascular disease (CVD), infections, and malignancies. In patients with arteriosclerosis, the immunosenescence CD4+ CD28- phenotype is strongly correlated with frequency of acute coronary syndromes, clinical outcomes, and response to statins in reducing recurrence of unstable angina, myocardial infarction, or death (Liuzzo et al. 2007).

In HIV-infected children, the impact of CMV coinfection was most apparent on CD8+ T cells with little impact on the CD4+ T cell subsets. Compared to the HIV monoinfected children, those with CMV coinfection had significantly lower naive (CD8 + CD62L + CD45RA+) and a higher percentage of terminally differentiated (CD8 + CD95 + CD28-) T cells (Kapetanovic et al. 2015). It remains to be seen if the above phenotypic alterations in children and young adults will later in life lead to

clinically relevant immunosenescence changes, comorbidities, and functional deficiencies of ageing.

HIV Comorbidities and Immunosenescence

Atherosclerosis is the most frequently encountered comorbidity in HIV disease. Furthermore, atherosclerosis is a major global cause of mortality and morbidity and will become the leading cause of death within this decade (Bonow et al. 2002). The elderly have the highest incidence of stroke and myocardial infarction. Nonelderly individuals with HIV have a higher than expected rate of cerebrovascular and cardiovascular mortality even after control of a higher prevalence of modifiable risk factors. The SMART study was the first to reveal a high risk of cardiovascular events in HIV patients that were not maintained on sustained antiretroviral therapy (El-Sadr et al. 2006). This suggested that uncontrolled HIV-associated inflammation was the cause of the events. Atherosclerosis is a lifelong inflammatory process occurring progressively with ageing. It has a strong genetic component, is influenced by lifestyle, and is characterized by stiffness and progressive narrowing of the arteries. Chronological age is the most important contributor to overall cardiovascular risk.

The initial concept in the development of atherosclerosis involved a "response to injury" model (Ross et al. 1977). It proposed that atherosclerotic lesions were the result of "injury" to the arterial endothelium. It postulated that the damage created by the injury altered endothelial cell-cell attachment. Forces derived from the shear in the flow of blood resulted in desquamation of endothelium followed by adherence, aggregation, and release of platelets at the sites of injury. Ultimately, these events would lead to thrombus formation and arterial occlusion with subsequent distal ischemic damage.

The turn of this century saw a different model emerge with a radical shift in paradigm regarding the pathophysiology of atherosclerosis, incurring an underlying inflammatory etiology. New perceptions evolved because of improved immune laboratory assays, refinement in concepts of ageing, improvements in vascular imaging technology, a better understanding of the roles of diet and metabolism, and the immune mechanisms involved in inflammation. Because of these developments, there is accumulating clinical evidence pointing to a greater role for chronic inflammation in the development of atherosclerosis. Indeed, high sensitivity C-reactive protein (hCRP), an inflammatory downstream surrogate marker, is currently in wide clinical use as a cardiovascular risk assessment tool.

Although atherosclerotic vascular changes to arteries begin early after puberty, most clinical events happen decades later. Cardiovascular risk is multifactorial and progressively increases after the age of 55. In addition to age as a risk factor, lifestyle is thought to be very important. Prevention today focuses greatly on control of lifestyle factors such as diet, exercise, smoking, and obesity. Some risks associated with the development of atherosclerosis are modifiable; these are hypercholesterolemia, hypertension, diabetes, and smoking. Others are non-modifiable and include

family history, male gender, and advanced age (Wilson et al. 1998). Until recently, it was not known if the modifiable factors were associated with chronic inflammation. Now it is very clear that these lifestyle factors are capable of creating and maintaining the systemic low-grade inflammation associated with arteriosclerosis. Cholesterol crystals, hyperglycemia, and possibly smoking can directly trigger innate immunity through intracellular macromolecular protein complexes called inflammasomes and in this process maintain chronically activated auto-inflammatory pathways.

Inflammasomes are composed, in part, of nucleotide-binding oligomerization domain-like receptors (NLRs), and they are triggered by the presence of pathogens or cellular stress (Martinon et al. 2002). The intracellular events lead to cleavage of caspase 1 and the downstream production of IL-1β and IL-18, two potent inflammatory cytokines (Wilson et al. 1998; Mandrup-Poulsen 2010). Blood levels of plasma IL-1β are elevated in older people (Furman et al. 2013) and are associated with increased risk of cardiovascular disease (Duewell et al. 2010), cancer (Zitvogel et al. 2012), degenerative diseases (Sardi et al. 2011; Scrivo et al. 2011), and functional decline (Youm et al. 2013). Elevated and persistent expression of particular inflammasome gene modules is known to occur in older individuals. Individuals belonging to these modules have a more frequent occurrence of high blood pressure, arterial stiffness, chronic levels of inflammatory cytokines, metabolic dysfunction, oxidative stress, and a lack of familial longevity than those in other noninflammatory modules (Furman et al. 2017).

The most common clinical presentations of coronary artery disease are acute coronary syndromes; these are a consequence of events that lead to unstable atherosclerotic plaque, plaque rupture, and intravascular thrombus formation. This sequence of events creates acute narrowing or occlusion of arteries. Clinically, the narrowing or occlusion is manifested as unstable angina, myocardial infarction, or sudden death.

In the initial stages of the atherosclerotic process, the immune system facilitates changes in the arterial intima. The creation of atherosclerotic plaque requires monocyte-macrophage involvement in generating foam cells by the uptake of oxidized low-density lipoprotein (oxLDL) (Lowenstein 2004; Hansson 2005; Hansson 2009; Ward et al. 2009). Arteriosclerotic plaque development appears to involve both the innate and adaptive immune systems (Edfeldt et al. 2002; Andersson et al. 2010; Duewell et al. 2010). Advanced and unstable atherosclerotic plaque usually takes years to present clinically. Given the proinflammatory state that HIV creates, it is not surprising that atherosclerosis in untreated HIV is accelerated.

Activated T cells in atherosclerotic lesions produce IFN-γ stimulating smooth muscle cells, reducing collagen production and cell proliferation. This cytokine also triggers macrophages resident in the intima to produce downstream mediators including metalloproteases, collagenases, tissue factor, and other prothrombotic elements that together collectively compromise plaque stability and lead to thrombus formation. The inflammatory cascade is triggered by adaptive host responses to specific antigens (oxLDL and heat shock proteins) or via innate mechanisms involving pattern recognition by Toll-like receptors, which are abundant in atherosclerotic

lesions. The antigenic trigger for the initial step in the development of atherosclerosis is not known. T cells appear to play a dominant role. In the whole process, CD4+ T cells are abundant in the plaque infiltrate and produce proinflammatory cytokines. There is evidence that CD8 T cells may exacerbate plaque inflammation and disease. T regulatory cells (Tregs), on the other hand, suppress atheroma formation but are not able to control the CD4 + CD28- T cells that occur with high frequency during ageing.

Epidemiological studies suggest that acute coronary events are preceded by a decade of activated innate and adoptive immunity in the context of long-term inflammation (Kinlay et al. 1998; Lagrand et al. 1999; Ross 1999; Morrow and Ridker 2000). It is therefore reasonable to hypothesize that the chronic triggering of T cells may stem from chronic latent viral infections such as HIV, CMV, and other viruses that undergo intermittent reactivation. The expanded CD8 + CD28- and CD4 + CD28- T cell subsets may be markers as well as drivers of chronic immune inflammation. The low CD4:CD8 ratio may also be a consequence of chronic CD8 T cell activation and memory cell expansion.

In an attempt to examine when and where in the course of human history atherosclerosis appeared, 4000-year-old mummies underwent whole-body CT scans. The 137 mummies came from four different geographical regions that included ancient Egypt, ancient Peru, southwest America, and the Aleutian Islands. A diagnosis of arteriosclerosis was ascribed if calcified plaque was present in the wall of coronary arteries. Surprisingly most individuals had evidence of atherosclerosis at a relatively early age. Even more intriguing was that these individuals likely lived on a fruit, nut, vegetable, and berry diet. In view of a healthy diet and lack of smoking tobacco, the possible causes of early arteriosclerosis were perplexing. The authors concluded that high levels of chronic infection and inflammation in pre-modern conditions, could have promoted the precocious inflammatory aspects of atherosclerosis (Thompson et al. 2013).

In addition to HIV, a high degree of chronic inflammation and aberrant immunity is found to occur in patients with autoimmune diseases and other immune deficiency disorders. Patients with systemic lupus erythematosus, rheumatoid arthritis, and multiple sclerosis or with HIV disease are more likely than age-matched healthy persons to have evidence of atherosclerosis (Roman et al. 2003; Christiansen 2012; Iaccarino et al. 2013; Jadidi et al. 2013; Mavroudis et al. 2013; Nikpour et al. 2013). Since atherosclerosis is an inflammatory condition common to those with aberrant immunity, there may be a unifying immune mechanism to the development of the vascular pathology.

T lymphocytes and macrophages are directly involved in the formation and destabilization of atherosclerotic plaques. T cells in atherosclerotic lesions are activated to produce IFN-γ (Hansson et al. 1989) stimulating smooth muscle cells, such that they lose their ability to produce collagen and to proliferate. This cytokine also triggers the macrophage to generate downstream mediators, thereby impacting the stability of atherosclerotic plaques (Libby and Hansson 1991; Edfeldt et al. 2004). This inflammatory cascade can be triggered by antigens or by pattern

recognition receptors, including Toll-like receptors on vessel cells and macrophages. These receptors are abundant in atherosclerotic lesions (Edfeldt et al. 2002, 2004).

The most common presentation of coronary artery disease is the acute coronary syndrome. It occurs as a result of unstable atherosclerotic plaque with rupture in the coronary arteries and the subsequent formation of a thrombus, leading to acute narrowing or occlusion of an artery. At a clinical level, these events present as unstable angina, myocardial infarction, or sudden death (Hansson 2005).

The antigenic triggers for atherosclerosis are not known, but there is evidence that they may be part of an autoimmune response to oxLDL and that heat shock protein may also be involved (Frostegard et al. 1990, 1992; Xu et al. 1993). The most abundant cell type in plaque inflammatory infiltrates is the CD4 + CD28- T cell that produces proinflammatory cytokines (Robertson and Hansson 2006). CD4 + CD28- cells accumulate preferentially in unstable plaque and not in stable lesions. NKT cells are also present (Bendelac et al. 2007).

In individuals, with recurrent ischemic coronary episodes and no immune-mediated illnesses, the CD4 + CD28- T cell subset has prognostic significance for myocardial infarction or death (Liuzzo et al. 2007). Interestingly, statins preferentially lowered blood lipids and reduced morbidity and mortality almost exclusively in those with high circulating CD4 + CD28- T cell levels (Brugaletta et al. 2006). There is evidence that CD8 T cells may exacerbate plaque inflammation and disease (Olofsson et al. 2008). Tregs, on the other hand, can suppress atheroma formation but are not able to control CD4 + CD28- proinflammatory cytokine production or aberrant effector function. Epidemiological studies suggest that acute coronary events are preceded by a decade of activated innate and adoptive immunity in the context of long-term inflammation (Kinlay et al. 1998; Lagrand et al. 1999; Ross 1999; Morrow and Ridker 2000).

It is reasonable thus to hypothesize that the chronic triggering of T cells may stem from predominately latent viral disorders such as with CMV, HIV, and other chronic infectious agents that undergo intermittent reactivation. This process of intermittent immune activation and proliferation ultimately leads to virus- and antigen-specific memory pools. The expanded CD8 + CD28- and CD4 + CD28- senescent T cell subsets may be markers, as well as drivers, of chronic immune activation, and a low CD4:CD8 ratio may also be one of the sequelae of chronic immune activation. Very few attempts have been made to identify the component contribution to this process from individual viruses. For example, most reports on the role of CD4 + CD28- T lymphocytes in patients with rheumatoid arthritis and CVD did not look at the CMV infection status of those they studied. Similar investigations in HIV disease on the proinflammatory memory pool phenotype have similarly not attempted to evaluate the individual contribution of HIV and of CMV. This lack in ability to distinguish the relative viral effects on immunosenescence likely stems from the high prevalence of CMV in both HIV disease and in autoimmune syndromes, making it difficult to obtain the required comparator HIV-infected CMV-negative cohort sample sizes.

Multiple mechanisms appear to contribute to the increased prevalence of CVD in HIV infection. A higher frequency of traditional CVD risk factors is well recognized, as is, the dyslipidemia associated with antiretroviral treatment. These factors alone

however do not fully explain the excess CVD risk. T cell activation and macrophage activation and immunosenescence appear to play a role. Arterial inflammation which is independently associated with the development of CVD events in non-infected individuals is increased in HIV-infected individuals, even after controlling for traditional CVD risk factors. Even with suppression of HIV-1 RNA to below limits of detection, highly effective antiretroviral treatment fails to cure HIV infection. Latently infected cells continue to produce virions within lymphoid reservoirs. Based on the hypothesis that the inflammatory pathways associated with lymph node inflammation may be related to pathways that potentiate arterial inflammation in HIV-infected individuals, a case-control study in men, with and without HIV, having a median age of 53 years was conducted. It measured HIV viral activity and persistence, circulating inflammatory biomarkers, and arterial and lymph node inflammation. Measures of HIV disease activity were strongly associated with lymph node inflammation but not with arterial inflammation, suggesting that the arterial and lymphoid inflammation did not share underlying pathways of immune activation (Tawakol et al. 2017).

In addition to atherosclerosis, there are other comorbid conditions in HIV disease that may be associated with immunosenescence. Studies on the relationship of HIV immunosenescence and non-AIDS malignancies are very few. AIDS-defining malignancies demonstrate well-documented sequelae of profound immunosuppression in late-stage untreated HIV disease. These malignancies with underlying viral etiologies include Kaposi's sarcoma, non-Hodgkin lymphoma, and cervical cancer. Tumor growth in these malignancies occurs under conditions of severe immune dysregulation and deficiency. A number of non-AIDS-defining cancers have been described that are almost exclusively consequences of long-term chronic viral infections. These include HPV-associated anal cancer, hepatic cancer from HCV or HBV, and EBV-driven Hodgkin's disease. They occur during the CD4 T cell reconstitution phase of HIV therapies and may contribute to subclinical chronic inflammation. There is a striking similarity in the types of cancers found in controlled HIV with those found following organ transplantation and iatrogenic immunosuppression. All these malignancies that appear under immunosuppressive conditions are generated during chronic viral infections and have associated immunosenescence phenotypes.

The prevalence of osteopenia, osteoporosis, and fractures in controlled HIV is very high. The most likely explanation is the negative effect of antiretroviral medication. In a meta-analytical review of cross-sectional studies, osteoporosis in HIV-infected individuals was found to be more than three times greater compared with those that were HIV-uninfected. Treated individuals particularly those exposed to the protease class of antiretrovirals have a higher prevalence of reduced bone mineral density (BMD) and osteoporosis compared with controls. Vitamin D deficiency is increased in a variety of conditions including chronic infection. The use of a fixed-dose combination tenofovir-emtricitabine has been associated with lower hip BMD, and the difference was more pronounced in those with low vitamin D blood levels (Klassen et al. 2016). In addition to the impact of therapy, subclinical chronic inflammation may be a potentiating or even a causative factor in the process.

Unfortunately, there are conflicting data on differences in bone mineral density or vitamin D status in untreated HIV-positive patients, at different disease stages compared to HIV-negative subjects. Furthermore, animal model studies on the concept that phosphate and vitamin D metabolism participate in the regulation of ageing suggested a pathologic role of vitamin D in regulating abnormal mineral ion metabolism and soft-tissue anomalies in mice (Ohnishi et al. 2009). No studies on the role of vitamin D, HIV, and immunosenescence have been reported. In healthy females over the age of 60, unexpectedly, higher levels of vitamin D correlated with decreased frequencies of naive CD8 T cells during early ageing, suggesting that higher levels of 25(OH) vitamin D accelerate CD8 T cell senescence (Hwang et al. 2013).

Immunosenescence and cognitive decline are common markers of ageing. Neurocognitive disease is also increasingly common in HIV patients, yet little is known about immunosenescence in this HIV-associated comorbidity. Soluble immune factors such as cytokines, chemokines, as well as viral proteins can diffuse into the central nervous system and may affect neurons and cause cognitive decline. In a rat model, HIV-1gp120 induced neuronal apoptosis. In addition to direct viral cytopathic effects, a link between CD4+ T cells and cognitive performance has been proposed. Effector memory CD4+ T cells have been demonstrated to be strongly associated with cognitive performance in a healthy senior cohort. Patients diagnosed with probable Alzheimer disease and cognitive deficits according to the mini-mental examination had significantly lower levels of CD4+ naive T cells (CD45RA+) and an increase in the activated/naive CD4+ T cell ratio (CD45RO+/CD45RA+) compared with age-matched cognitively healthy individuals. This suggests that cognitive deficits in HIV disease may also be associated with alterations in the CD4+ T cell compartments. Interestingly, instead of finding a phenotype of premature immunosenescence associated with expanded clones of CMV-specific CD8 cells in Alzheimer disease, a significantly lower proportion of CMV-specific cells were found compared to normal controls. There were no differences in CD4/CD8 ratio or total lymphocyte count that could have explained the difference in CMV specificity nor any obvious signs of more advanced immunosenescence in the Alzheimer disease group (Serre-Miranda et al. 2015).

Conclusion

Antiretroviral therapy has been a major success in treating and possibly reducing the spread of HIV. It is now increasingly clear that the future challenges in the care of patients with HIV will not be in control of the virus itself. The major focus in the future will continue to be the management of multiple comorbidities. These conditions have strong associations with ageing and immunosenescence. If HIV is a model of accelerated ageing, it remains to be seen if the lessons learned from the study of this disease will provide benefit for the general population.

Although chronic inflammation leads to immunosenescence in the clinical phenotype of early aging in HIV, the process by which it occurs is incompletely

understood. Molecular mechanisms in chronic inflammation require further exploration. Additional studies of immune homeostasis, cell regulation and signaling and understanding of T cell function and phenotype are also required. Larger-scale cohort studies in HIV may shed light on T cell immunosenescence, as defined by the immune risk profile. Such studies also have potential for understanding the epigenetic factors, the biological clock, and the specific contributions of the herpes group of viruses in the development of atherosclerosis and other comorbidities of ageing.

Tools for the benchmarking of biological age and in risk assessment will be important. Although a variety of inflammatory and immune activation markers have been evaluated sporadically, there is a need to validate markers of ageing in the context of HIV. Furthermore strategies to reduce the incidence of immunosenescence could include much earlier initiation of HIV therapy as well as attempts to comprehensively screen and control latent viral infections. Lastly by understanding the mechanisms involved, targeted therapies might be possible in order to arrest immunosenescence, rejuvenate immune function, and even reverse ageing.

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