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Modeling Aging in HIV Infection in Nonhuman Primate Models to Address an Emerging Challenge of the post-ART Era

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Abstract

The advent of antiretroviral therapy (ART) has dramatically improved both quality and length of life for subjects infected with human immunodeficiency virus (HIV), delaying or preventing progression to acquired immunodeficiency syndrome (AIDS). However, the virus induces aging-related changes to the immune system which confound treatment. Additionally, the normal physiologic events that occur during aging lead to deficiencies in immunity which not only exacerbate HIV pathogenesis but also trigger a variety of comorbidities. Here, the synergistic linkage between aging and HIV infection is examined in regard to the immunological and pathological mechanisms that drive both senescence and disease progression. The use of NHPs to investigate potential therapeutic strategies to control the deleterious consequences of aging with HIV infection is also reviewed.

II. Introduction

Aging is the natural progressive functional decline in multiple organ systems [i.e., the immune, cardiovascular, and gastrointestinal (GI) systems], typically occurring after age 50, rendering the individual vulnerable to internal damage and external stress. Age-associated physiological changes are particularly meaningful considerations for HIV patients, as this population is steadily growing older. The advent of ART has increased life expectancy in HIV-infected subjects; however, the infection induces premature age-related changes minimally affected by ART [1, 2]. In 2014, 25% patients with HIV and 39% of HIV-related deaths were aged >55 years [3]. Persistent immune activation (IA) triggers non-AIDS comorbidities and mortality, with diseases typically appearing in the 6th to 7th decade of life, occurring as early as the 4th decade of life in treated HIV-infected subjects [4-8]. Persistent chronic inflammation (INFL) also aggravates AIDS-related comorbidities, including GI dysfunction, which further exacerbate IA [9-17]. Additionally, the ordinary progression of age-related physiologic changes unrelated to HIV infection compromises immunity and

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complicates disease progression, constituting a barrier to treatment, as older patients have higher risk for ART-related toxicities and a lower response overall to ART [18].

Nonhuman primates (NHPs) share multiple attributes with humans, including immunological features. They are outbred and have a long lifespan, lasting two or more decades, making it a model of choice for AIDS research. Simian immunodeficiency virus (SIV) infects different species of Asian macaques and induces AIDS in a manner closely resembling HIV pathogenesis. Conversely, African NHP species which are natural hosts for SIV do not develop gut dysfunction, chronic IA/INFL, or progress to AIDS, despite high viral replication and acute CD4⁺ depletion. The few recorded cases of which have progressed to AIDS all occurred in older individuals who outlived the lifespan of their species, clearly illustrating the effect of age on AIDS progression [19, 20].

NHPs represent a perfect model for studying HIV pathogenesis due to (a) long lifespan, (b) the possibility to perform invasive studies, (c) the remarkable similarities between SIV and HIV infections, and (d) the availability of multiple models with various outcomes of SIV infection to address specific aspects of HIV pathogenesis. Here, we will review the complex reciprocal relationship between aging and AIDS, particularly the interaction between aging, IA/INFL, comorbidities and disease progression.

III. HIV/SIV infections accelerate aging

The failure of HIV-infected subjects to live as long as uninfected persons was once thought to result from ART toxicity; however, a new paradigm emerged in which morbidity and increased fatality stem from persistent IA/INFL. These conditions are directly driving disease progression and death in HIV/SIV infections and induce a plethora of pathologies known as serious non-AIDS-related events (SNAEs) [21-27]. These include cardiovascular disease (CVD), cancer, type II diabetes mellitus, respiratory diseases (e.g., chronic obstructive pulmonary diseases and pneumonia), liver disease, osteoporosis, muscle atrophy, and HIV-associated neurocognitive disorder (HAND) [4, 5, 28-32]. In particular, the comparisons performed by our lab between progressive and nonprogressive NHPs, were instrumental in demonstrating that SNAEs develop in the absence of ART and are determined by IA/INFL.

a. HIV/SIV-induced premature aging of the immune system

During HIV/SIV infection, multiple alterations occur in the quantity and function of immune cells that mimic age associated changes that ensue during normal senescence. In particular, the T-cells bear significant changes related to senescence during HIV/SIV infection. A hallmark of HIV infection is the depletion of CD4⁺ T-cells [33], leading to an inversed CD4/CD8 ratio, which is also a marker of early immune aging, leading to SNAEs and mortality[6]. In SIV-infected macaques, low CD4/CD8 ratio is also predictive of disease progression and advanced immune aging [34]. CD8⁺ cytotoxic T-cells (CTLs) also undergo HIV-induced alterations promoting accelerated aging. CTLs that lack the CD28⁺ costimulatory marker accumulate concomitantly with an increase of the marker p16^{INK4a} and these cells also naturally accumulate during normal aging and have reduced telomerase activity and antiproliferative capabilities [35, 36]. Pathogenic HIV/SIV infections are

characterized by a decrease in the Th17/Treg ratio, which is also observed during the normal aging processes [37, 38]. Th17 cells which are crucial in the maintenance of intestinal mucosal barrier integrity and control of microbial translocation (MT)[39], are preferentially depleted in both blood and gastrointestinal lymphoid tissues during pathogenic SIV/HIV infections [14, 40] and preserved in natural hosts [14, 39]. The severe T-cell alterations observed in HIV/SIV infection predict a reduced capability to fight HIV disease and lead to pervasive and irreversible immune senescence.

Finally, HIV/SIV induces premature senescence of humoral immunity. In SIV-infected rhesus macaques (RMs), the frequency of both switched memory and activated memory B-cells increase progressively with the duration of SIV infection, whereas naïve and unswitched memory B-cell populations gradually decrease, along with IgD; all these alterations are associated with AIDS-induced immune senescence [41].

b. HIV/SIV-induced IA/INFL

Innate activation markers, such as CXCL-10, neopterin, soluble CD163 (sCD163), or soluble CD14 (sCD14) increase in HIV-1-infected subjects, and these markers also increase in elderly subjects even in the absence of HIV infection [42-46]. The levels of CD16⁺ monocytes in HIV-1-infected subjects are equal to those in uninfected subjects 10-14.5 years older, demonstrating that HIV infection leads to aging of the innate immunity, which predicts earlier mortality [46]. Also, the double expression of CD14 and CD16 increases on monocytes during HIV/SIV infection indicating immune senescence, [23, 46-49]. In the T-cells compartment, CD38 and HLA-DR double expression and Ki-67 expression are highly elevated in CD4⁺ and CD8⁺ T-cells [15, 50], which is associated with disease progression [51, 52]. Finally, inflammation markers commonly increase in aging [i.e., IFN- α , IL-6 and CRP] also increase during HIV/SIV infection, predicting higher risk of disease progression and death [53-59]. Collectively, these studies reveal that SIV/HIV-induced chronic IA/INFL mimics aging-associated IA/INFL and leads to premature aging of the immune system and consequent SNAEs. Studies in NHPs have confirmed that these modifications occur regardless of ART and can be independently induced by the virus [60, 61]. Taken together with studies that show how young individuals treated with the new generation of ART still suffer from the major health impacts of accelerated aging [62], our data points to the importance of therapeutically reducing HIV/SIV-triggered IA/INFL. These interventions should be implemented as early as possible after infection to ameliorate the effects of residual IA/INFL that persists even in patients for which ART was initiated very early on during acute HIV infection [63]. This population will receive ART for a more extended period and may be more severely affected by the combined ART-induced toxicity and IA/INFL, thus highlighting the importance of designing preventive and therapeutic strategies to control both organ damage and the development of non-AIDS comorbidities.

c. HIV/SIV-induced gastrointestinal dysfunction

During HIV/SIV infection, GI dysfunction is diagnosed in nearly all patients, being characterized by distinct clinical and histopathologic changes and altered intestinal permeability [13, 17, 64]. These alterations occur early in infection in the gut-associated lymphoid tissue (GALT) harboring CCR5⁺CD4⁺ memory T-cells, the major cell type

targeted by HIV-1. The massive destruction of GALT tissue leads to increased translocation of microbial products, including LPS, from the intestinal lumen to the bloodstream [9, 15]. Microbial translocation (MT) is a major driver of systemic IA/INFL in HIV/SIV infection [9, 60, 65, 66], predicts HIV/SIV disease progression and response to ART [15, 16, 67] and is closely related to SNAEs [16, 60, 68-70]. NHPs provide an ideal model for experimental manipulation of mucosal integrity and invasive investigation of HIV/SIV-associated MT to test new pathogenesis paradigms. Our interventional studies in NHPs confirmed a causative role of the IA/INFL induced by gut dysfunction in the development of CV comorbidities in the context of SIV/HIV infection [65, 71].

d. HIV/SIV-induced hypercoagulability

A hypercoagulable status marked by elevation of D-dimer (2-DD) and tissue factor (TF) expression on monocytes is observed in HIV-infected subjects as well as SIV-infected NHPs [60, 72, 73], representing another source of inflammation. Together with persistent IA/INFL, hypercoagulability induces CVD and accelerated aging of organ systems during HIV/SIV infection.

CVD poses a serious threat to HIV-infected subjects. While its etiology is multifactorial, including comorbid conditions and ART toxicity [29, 74, 75], increased cardiovascular risk in long-term treated elderly HIV subjects calls for better understanding of the relationship between hypercoagulability and IA/INFL. This relationship is bidirectional, potentially bridged by TF and protease-activated receptor (PAR) signaling [76-82]. Its mechanism likely relies on the increased expression of TF on activated monocytes, which is associated with higher levels of 2-DD [83] and thus increasing the risk for cardiovascular complications in HIV-infected individuals [72].

In turn, coagulation activation yields increased levels of proteases, such as thrombin, that interact with PARs to mediate inflammatory responses [77]. Such interactions can activate specific cell receptors on mononuclear cells, endothelial cells and platelets, which further boosts cytokine production (TNF- α and interleukins) and the expression of cell adhesion molecules (i.e., CCL2, ICAM-1, VCAM-1) [84, 85]. INFL can promote coagulation through a positive feedback loop on TF expression: inflammatory signals (AP-1, Erg-1 and NF- κ B) can increase TF expression, enhancing its availability for factor VII (FVII) or FVIIa binding [81].

e. Serious non-AIDS events induced by accelerated aging

The risk of developing SNAEs increases throughout HIV/SIV infection, and oftentimes leads to fatality. CVD incidence in younger HIV-infected individuals is roughly 2-fold higher than in age-matched uninfected subjects [29]. Long-term treated subjects have a greater prevalence of atherosclerosis, vascular dysfunction, myocardial infarction, heart failure than age-matched uninfected adults [86, 87]. As such, CVD is becoming one of the leading causes of non-AIDS death in HIV-infected subjects [58]. Persistent IA/INFL and consequent hypercoagulability lead to increased systemic thrombosis and proatherogenic elevations in serum triglycerides and low-density lipoprotein (LDL), which are major causes of common CVDs [27, 58, 59, 88-90]. While in humans it is difficult to dissect the relative

roles of HIV infection vs. behavioral risk factors (i.e. a diet rich in fat, alcohol, smoking or sedentarism) in producing CVD, in NHPs that do not have such behavioral risk factors, SIV infection is independently associated with cardiovascular pathogenic features, such as thrombotic microangiopathy, and elevated 2-DD, pointing to the role of chronic IA/INFL and hypercoagulability in HIV-related CVD [60].

HIV patients are also more prone to have low bone mineral density (BMD) than healthy age-matched peers, leading to early onset of osteoporosis [28, 91]. Low BMD, typically a disease of elderly, can impact HIV-infected adolescents and young adults, likely due to the alterations of the RANK/RANKL/osteoprotegerin pathway and altered osteoblastic differentiation [30, 92, 93]. IA/INFL markers and osteoprotegerin are elevated when both bone and endovascular damage are present, even in the context of ART [30]. In SIVmac-infected RMs, administration of activin receptor IIB ligand can increase BMD and reduce bone marrow inflammation, and thus protect the RMs from SIV-associated bone loss [94]. As such, SIV-infected NHPs represent a viable option for modeling HIV-associated CVD and osteoporosis and investigating therapeutic interventions to tackle this emerging issue in HIV patients.

Other SNAEs typically associated with aging include progressive muscle atrophy (sarcopenia) due to increased cytokine production (i.e. TNF α) and nutritional deficiencies [10, 95], nonalcoholic fatty liver disease [96], and HIV-associated neurocognitive disorder, a dementia-like condition caused when the virus persists in the central nervous system despite ART, leading to cognitive decline typically seen in much older patients [97]. ART treatment itself can also induce cognitive decline and metabolic disorders, which leads to an increased risk of type II diabetes mellitus [98], another disease associated with aging. Taken together, these comorbidities dramatically complicate outcomes of HIV/SIV infection and necessitate additional treatment modalities, the management of which is paramount in aging patients.

IV. Aging impact on HIV/AIDS

Aging individuals face unique challenges due to compromised immunity, elevated IA/INFL, hypercoagulation, loss of mucosal integrity etc. Each of these conditions is also induced over the natural course of HIV/SIV infection as mentioned previously. Thus, aging may accelerate both disease progression and HIV-associated non-AIDS comorbidities, and eventually cause increased mortality. A case in point is represented by natural hosts: while they do not generally progress to AIDS, sporadic cases of AIDS were documented in these species, the common feature being that they occurred in very old animals that outlived the lifespan of the species [20].

Here, by reviewing the impact of aging on key pathogenic features of HIV/SIV infection, we will dissect the underlying mechanism(s) of how aging can affect the HIV/SIV infection outcome.

a. Impact of immune senescence on the immune responses to HIV infection and vaccination

Aging-related immune senescence leads to reduced responsiveness to pathogens, increased susceptibility to and severity of infections, and decreased efficacy of vaccination [7, 8, 99-101]. These aspects are more important in aged HIV-infected subjects, in which HIV-related accelerated aging tops natural aging processes to increase immunodeficiency and weaken the ability of immune system to combat HIV infection.

The complex phenotypes of age-related immune dysfunction are multifactorial and multilayered, affecting every component of the immune system. Defects in innate immunity are among the most obvious effects of aging and are directly linked to increased frequency of infection. They include: (i) compromised neutrophil functions [102-104], (ii) altered macrophage function [105-110], (iii) mixed effects on natural killer (NK) cells, with a general increase in cytotoxic CD56^{dim} NK cells, decrease in IL-2 and IL-12-mediated chemokine production and consequent skewed T helper (Th) 2 responses [111-113]; (iv) decreased micropinocytosis, phagocytosis, and migration capacities of dendritic cells (DCs), and reduced production of IFN α and IL-12 upon stimulation with TLR agonists (i.e., LPS and single-stranded RNA) [44, 114].

The age-related decline in the TLR function weakens the innate immunity, providing easy access for HIV entry, and increased susceptibility to opportunistic infections and coinfections. Aging of specific innate immune cells may even interact with HIV infection in more intricate ways: aged neutrophils upregulate CXCR4 expression, allowing increased gp120 ligation and entry of CXCR4-trophic HIV into neutrophils [83]. Aged neutrophils share phenotypes with the activated neutrophils, further increasing HIV binding and facilitating infection spread [115, 116]. However, complete understanding of the relationship between aged innate immunity and HIV infection is still lacking.

The adaptive immunity is also heavily impacted by natural aging. A key contributor to immune senescence is thymic involution, which associates progressive reduction of the naïve T-cell output [117, 118]. Thymus function is important for immune reconstitution in HIV-infected subjects [119]. In HIV-infected children, rapid disease progression associates thymic dysfunction and involution [120-122]. In patients on ART, larger thymic size associates higher recovery of CD4⁺ T-cells and more diverse immunological repertoire [119, 123, 124]. Decreased CD4/CD8 ratio, which is also a prognostic marker for HIV/SIV infection as discussed earlier, is also observed in aging RMs [125], potentially due to the reduced CD4 production. Thus, aging-associated decrease of thymic output may partly explain the poor response to ART in elderly patients.

Interestingly, adult AGMs have increased CCR5 expression on CD4⁺ T cells compared with neonates [126]. This increases the pool of SIV target cells, eventually bypassing the protective mechanisms [127] and providing a mechanistic explanation for both increased susceptibility to SIV infection via the mucosal route in adults vs neonates and for the cases of disease progression reported in old individuals of these species [19]. Aging also differentially affects naïve and memory Th17 cell responses, with increased IL-17 production from naïve CD4⁺ T-cells and decreased IL-17 production from memory CD4⁺ T-

cells [128]. A decrease in Th17/Treg ratio, a hallmark of HIV infection, also occurs in older individuals after stimulation with phythaemagglutinin (PHA), accompanying elevated expression of FoxP-3 mRNA and IL-10 [129], which is indicative of a compromised gut health. Altogether, the immunological changes in the T-cell compartment that occur with natural aging likely contribute to the poor clinical outcome observed in elderly HIV patients.

Aging also impacts the B-cells, with a decline of overall B-cell antibody responses [130], and a lower antibody affinity [131]. This is particularly important during HIV/SIV infection, when the early B cell-mediated antibody responses are already ineffective, and directed against nonneutralizing epitopes [132].

In addition to these specific immune alterations, aging can exert an overall immune dysfunction. The self-renewal capacity of hematopoietic stem cells (HSCs) diminishes during aging, due to the accumulation of oxidative damage to DNA and telomeric shortening [133, 134], resulting in a decreasing pool of immune cell progenitors. Additionally, aged HSCs frequently show myeloid differentiation bias [135], with decreased frequency of common lymphoid progenitors [136]. This insufficient self-replenishment of the lymphoid progenitor pool prevents aged HIV-infected subjects from achieving immune recovery while on ART or evading disease progression.

b. Impact of aging-associated IA/INFL and non-AIDS comorbidities in HIV subjects

During aging, immune senescence associates chronic innate IA/INFL (“inflammaging”), characterized by increased production of proinflammatory cytokines (i.e., IL-6 and TNF α), acute-phase proteins (i.e., CRP), reactive oxygen species (ROS), and autoantibodies [43, 137].

Natural aging-associates IA/INFL characterized by altered monocyte phenotype (e.g., increased CD11b expression and decreased CD38, CD62L and CD115 expression), or increased IA/INFL markers (e.g., CXCL10, neopterin and sCD163) [43]. These responses have the potential to exacerbate HIV/SIV-associated monocyte activation and migration that is associated with increases in plasma inflammatory biomarkers that predict morbidity and mortality in chronic HIV/SIV infections [138].

Besides innate immune activation, higher T-cell activation also occurs in adult RMs compared to adolescents, indicating that the age increase is associated with a heightened adaptive immune system activation accompanied with systemic inflammation due to a high production of IL-2, IL-6 and TNF α [125]. Non-AIDS HIV/SIV comorbidities being at least partially triggered by low-grade systemic IA/INFL and/or immune alterations [19], aging-associated and HIV/SIV-associated IA/INFL may potentiate comorbidities and increase mortality in aged HIV-infected subjects on ART.

c. Impact of aging-associated hypercoagulability on HIV-associated IA/INFL and comorbidities

Aging is a risk factor for CVD and thrombotic events [139, 140] and an underlying mechanism is hypercoagulability. Age-induced pro-thrombotic changes include progressive increases of coagulation factor VII, factor VIII, and fibrinogen, as well as prothrombin-

fragment 1+2 (F1+2), thrombomodulin, thrombin-antithrombin III complexes (TAT), fibrin degradation fragments 2-DD and TF [141-144]. A consistent age-related increase of 2-DD also occurs in AGMs [145]. Therefore, it is conceivable that aging-related hypercoagulability worsens the coagulation state described in HIV/SIV infection and may increase the risk of comorbidities.

d. Impact of aging on HIV-related intestinal dysfunction

Natural aging has the potential to worsen HIV/SIV-related gut dysfunction through: (i) alterations of the mucosal immune system, especially through a decline of the phagocytic function of macrophages and dendritic cells, impairing microbial product clearance [44, 109, 146], and age-associated decreases in the Th17/Treg ratio [128]; (ii) tight junction remodeling, with an induction of zonula occluden-1, occludin and JAM-A proteins and a reduction of claudin-2 expression [147]; (iii) Increased proinflammatory cytokines (IFN- γ , IL-1 β and IL-6), which increase gut permeability [147-149]; (iv) microbiome alterations, such as an increase of *Enterobacteriaceae* in frail individuals [150], which correlates with increased sCD14 and IL-1 β production [151]. These alterations result in a “leaky gut”, likely contributing to MT and consequent IA/INFL. These features explain the more rapid HIV disease progression in elderly subjects.

V: Conclusions and areas for future study

Aging and HIV infection closely interrelate in the pathogenesis of AIDS and non-AIDS comorbidities in the post-ART era. While ART significantly improves the lifespan of HIV subjects, HIV-induced premature aging as well as aging-associated changes prominently affect immune function, IA/INFL, intestinal dysfunction, hypercoagulation, impacting multiple organ systems (Figure 1), forming a vicious circle which eventually leads to SNAEs and mortality (Figure 2). Strikingly, rare cases of AIDS progression in SIV-infected natural hosts all occurred in aged subjects, strongly demonstrating the impact of aging on HIV/SIV pathogenesis. Despite many similarities between HIV-induced premature aging and natural aging, they may also impact specific organ systems in subtle and different ways, pointing towards the importance of future research efforts to further elucidate the interplay of both types of aging. Studies to dissect the detailed mechanisms of how aging impacts HIV disease manifestation and investigate potential interventions may be invasive in nature, thus calling for the use of animal models. With long lifespans, the remarkable similarities between simian and human immunity, and comparable pharmacokinetics of therapeutics utilized in HIV and SIV infections, NHPs represent an ideal model of aging and comorbidities.

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Highlights:

- Aging is an emerging issue in the HIV-infected population in the post-ART era
- Aging and HIV infection synergistically drive AIDS and non-AIDS comorbidities
- Rare cases of AIDS progression in SIV natural hosts only occur in aged animals
- NHPs represent an ideal model of aging and comorbidities in HIV infection

Vicious cycle of aging and HIV/SIV infection

Figure 1:
Summary of the adverse effects of natural aging process and SIV/HIV-induced premature aging on immune system and multiple organ systems.

Figure 2:

Aging and HIV/SIV infection form a vicious cycle through the induction of immune dysfunction in addition to alterations of vital organ systems that eventually lead to increased SNAEs and mortality.