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Residual Immune Dysfunction Under Antiretroviral Therapy

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Keywords

HIV; inflammation; non-AIDS comorbidities

Introduction

Prior to the introduction of effective combination antiretroviral therapy (ART), human immunodeficiency virus (HIV) infection was a major cause of death among young adults in the 1980s and early 1990s. The hallmark of HIV infection is CD4+ T cell decline, and if left untreated, the infection typically progresses to acquired immunodeficiency syndrome (AIDS) 8–11 years after seroconversion [1]. The complications of AIDS are well-known and include potentially fatal opportunistic infections (OIs) and certain malignancies, mostly lymphomas, human papilloma virus associated anal or cervical cancer and Kaposi sarcoma. ART has decreased the prevalence of AIDS and lowered mortality rates [2] among people with HIV (PWH). However, even with treatment, the life expectancy of PWH is shorter compared to the general population [3], indicating unmet needs in the understanding and treatment of HIV.

Although HIV/AIDS is widely known as an immunodeficiency state, it is also, if not predominantly, a disease of immune dysregulation. This is demonstrated by the multiple defects in almost every aspect of the immune system and the occasional manifestations of HIV infection as exacerbated or atypical infectious, rheumatologic or autoimmune conditions, seemingly a paradox [4–6]. Evidence of this immune dysfunction persists even after ART-mediated viral suppression. Shortly after ART initiation, it can manifest in the form of immune reconstitution inflammatory syndrome (IRIS), a condition characterized by dysregulated inflammatory responses to co-infection. In contrast, after long-term ART, PWH experience higher rates of liver disease, cardiovascular morbidities, non-AIDS cancers, and other serious non-AIDS events (SNAEs) [7]. This elevated risk for certain chronic diseases is at least partly attributed to the damaging effects of chronic inflammation. Further, some ART-treated PWH demonstrate persistently increased risk for other infections and decreased responses to vaccination. These phenomena indicate that while viral suppression and rise in

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CD4 counts with ART prevents AIDS-related complications, it cannot fully reverse some of the negative consequences of HIV infection on immunological function.

In this article, we will discuss how chronic inflammation and immune dysfunction intersect and prevent full immune recovery and health among PWH even under ART. We will outline possible causes of chronic inflammation and conditions that reflect immune dysfunction, such as IRIS, increased rates of chronic diseases, and poor vaccine responses. Finally, we will discuss additional risk factors for poor health outcomes in this population and strategies for reducing immune dysfunction in PWH.

Evidence of immune dysfunction and chronic inflammation

Studies of Simian Immunodeficiency Virus (SIV) in non-human primates (NHPs) have been valuable for understanding important aspects of HIV pathogenesis. SIV infection progresses and causes an immunodeficiency disease only in Asian NHPs, which are non-natural hosts for the virus, while maintaining a milder course in the natural African NHP host. However, both natural and non-natural hosts develop high levels of viremia and CD4 depletion after SIV infection, suggesting that these factors alone cannot fully account for disease progression in non-natural hosts. Instead, pathogenic infection is distinguished in part by persistent and generalized activation of both the innate and adaptive arms of the immune system in the non-natural host, compared to a transient inflammatory response during acute infection in natural hosts, implicating chronic inflammation in the disease pathogenesis [8].

A large body of evidence indicates that HIV also causes chronic inflammation in humans. The immune activation also triggers coagulopathy, which further exacerbates inflammation [9]. Biomarkers reflecting inflammation and coagulopathy are elevated in PWH, and some strongly associate with poor outcomes. The levels of D-dimer, IL-6, C-reactive protein, and soluble CD14 (sCD14) specifically are important independent predictors of mortality even after controlling for important clinical factors such as age or HIV-related factors such as CD4 counts [10, 11]. In fact, immune activation, commonly assessed by the expression of CD38, HLA-DR, or Ki-67 among T cells, has been demonstrated to be a better predictor of mortality than viral load in some studies [12, 13]. The persistent activation of the innate immune system, often measured by monocyte activation, may be an even stronger predictor of morbidity and mortality than adaptive immune activation during virologic suppression [14]. Although these biomarkers decline with ART, some remain elevated over HIV-uninfected controls even when ART is started very early in acute HIV infection (AHI) [15]. These studies suggest that immune activation and coagulopathy are triggered early in HIV infection, persist despite virologic suppression, and are important independent drivers of poor health outcomes among PWH.

Further support for the role of chronic immune activation in adverse outcomes is derived from studies of elite controllers (ECs). ECs are PWH who are able to spontaneously control viral loads without ART, and most also maintain normal CD4+ T cell counts. However, chronic immune activation also occurs among ECs, who have decreased percentages of naïve cells [16] and elevated monocyte activation markers [17] and soluble inflammatory mediators. Further, some experience declining CD4+ T cells and can develop AIDS despite

consistently low levels of viremia. Compared to those maintaining CD4+ T cell counts, ECs with CD4 decline have increased levels of adaptive immune activation, reflected by the expression of CD38 and HLA-DR among both CD4+ and CD8+ T cells [18]. Markers of innate immune activation, including higher proportions of mature CD14++CD16+ monocytes, are also found in these patients [16]. A subset of ECs remains at elevated risk for SNAEs despite low viral load, implicating persistent immune dysfunction as the driving pathogenic factor.

Causes of chronic inflammation and immune dysfunction

The pathogenesis of chronic inflammation and immune activation in HIV infection appears to be multifactorial. Several viral proteins are highly immunogenic, and acute HIV infection induces inflammatory cytokine production and inflammatory cell death via pyroptosis [19]. Even under ART, which suppresses active viral replication, HIV persists in a small subset of long-lived infected cells termed the viral reservoir. Both cellular reservoirs as well as tissue reservoirs, such as the central nervous system and other anatomical sites with poor ART penetration [20], enable the persistence of latent virus that may continue to trigger the immune system. Activated CD4+ T cells, particularly peripheral PD-1+CXCR3− T follicular helper cells, are enriched for inducible virus, demonstrating an important relationship between immune activation and viral reservoir formation and maintenance [21].

Transient elevations in viremia or “blips” occur among virally suppressed PWH [22], and very low copy numbers can be detected by ultra-sensitive methods, suggesting some degree of persistent replication [23]. Even some of the defective, replication-incompetent proviruses that accumulate under ART are transcriptionally and translationally active, producing viral products that could be the trigger of immune responses [24, 25]. Early initiation of ART results in smaller viral reservoirs as measured by HIV DNA and decreased expression of CD38 and HLA-DR on T cells, supporting a relationship between reservoir size and degree of immune activation [26]. Persistent immune stimulation by the ART-suppressed virus is further supported by the observation that most PWH remain seropositive despite long-term viral suppression. Despite this, in a cohort of early acute PWH who initiated therapy prior to seroconversion and remained seronegative, we did not find evidence of lower inflammatory markers compared to those who became seropositive having evidence of viral transcription [27].

Significant evidence also implicates disturbances to the gut, one of the earliest sites of HIV replication. HIV infection causes the preferential loss of gut CD4+ T cells [28], especially Th17 cell subsets critical for maintaining mucosal integrity. The virus drives downregulation of epithelial cell tight junctions [29] and enterocyte apoptosis, further disrupting barrier function. The result of these effects is the translocation of products of gut bacteria across the bowel wall, evidenced by increased systemic levels of bacterial products, such as lipopolysaccharide (LPS), which contribute to innate and adaptive immune activation [30, 31]. In NHP models, systemic LPS levels do not increase after infection in natural hosts, supporting the role for microbial translocation in pathological infection [30]. These changes to the gut are accompanied by microbiome disturbances, characterized by an overall loss of diversity and a shift to a more pro-inflammatory distribution of gut bacteria [32, 33]. This

includes enrichments in Enterobacteriaceae and Prevotella, both of which have been linked to immune activation [31, 34, 35]. These shifts in species and low gene counts indicative of decreased diversity have been correlated with lower nadir CD4 counts [36]. In addition to this relationship with immunodeficiency, the extent of dysbiosis has further been associated with the degree of immune activation, and an increased number of comorbidities [37]. Importantly, more recently, Prevotella has been linked to sexual practices (receptive anal intercourse) regardless of HIV status [37].

Fibrosis of lymphoid tissues also occurs with HIV infection and contributes to CD4 decline and poor CD4 recovery after ART, setting the stage for immune dysfunction. Collagen deposition in the lymph nodes of PWH is believed to be triggered by TGF-β expression induced by infection. Fibrosis is also observed among ECs and those treated with ART [38], suggesting it can even be induced by very low levels of viral replication. This fibrosis causes disruption of the lymph node tissue architecture, which is hypothesized to impede T cell migration and limit cells' access to growth factors like IL-7 made by fibroblast reticular cells [39]. These effects may be particularly detrimental to naïve populations, which indeed are preferentially lost.

High rates of co-infection with other pathogens among PWH are another important factor. The most important of these may be Cytomegalovirus (CMV), which has high rates of seropositivity and shedding among PWH. Even in HIV-uninfected individuals, CMV infection can drive massive expansion of CMV-specific CD8+ T cells [40], the result of which is restriction of the T cell receptor (TCR) repertoire and inversion of the CD4/CD8 ratio. These effects likely compound immune dysfunction in PWH. CMV shedding has been linked to both CD4+ and CD8+ T cell activation in ART-treated PWH [41, 42] and delayed reservoir decay under ART. Co-infection with hepatitis viruses is also highly prevalent among PWH, and increased immune activation, measured by CD38 expression on both CD4 and CD8 T cells, has been observed among PWH co-infected with Hepatitis C virus [43].

Defective immune reconstitution under ART

After ART initiation, CD4 counts typically continue to rise over the course of years, and the majority of ART-treated PWH achieve suppression of plasma viremia and reconstitution of CD4 T cells. However, some fail to achieve full immunologic recovery, reflected by persistently low CD4 T cell counts despite long-term ART. Roughly 60% of PWH fail to achieve normal CD4 counts of >500 cells/μL after 4 years of ART [44, 45]. Approximately 6% never even achieve CD4 counts >200 cells/μL despite continuous ART for 4 years, and this increases to 25.9% with discontinuous ART use [44]. Incomplete CD4 recovery predicts increased risk of mortality [46], and rates of both AIDS-related events and SNAEs are increased [47, 48]; these include non-AIDS malignancies [46, 49], liver disease [50], and respiratory disease [51].

In addition to discontinuous ART use, initiation of ART during late stages of HIV infection also increases the likelihood of immunological non-response. Most patients starting ART with baseline CD4 counts of >300 or >350 cells/μL achieve reconstitution [45, 52], but persistently low CD4 counts are seen among 25% of those with baseline CD4 <100

cells/μL, even after 7–10 years of ART [45]. Poor responses also correlate with increased levels of innate and adaptive immune activation [53, 54]. CD4 recovery further depends upon thymic size and function [55], and higher baseline collagen deposition predicts poor CD4 reconstitution after ART [56, 57]. Even when peripheral CD4 counts normalize, tissue CD4 populations may not fully recover. Virally suppressed PWH with normal or near-normal blood CD4 counts may exhibit persistently decreased CD4+ T cell numbers in gut-associated lymphoid tissue [58].

Other aspects of CD4+ T cell reconstitution beyond quantitative reconstitution must also be considered. The balance of naïve, effector, and memory T cell populations is also skewed by HIV infection and may not be fully restored by ART. Limited rescue of the naïve CD4+ T cell population occurs with ART among patients who already experienced severe depletion of these populations [59]. Constriction of the CD4+ TCR repertoire is also reflected by depletion of certain TCRBV subfamilies [59]. Finally, CD4+ T cells retain qualitative defects that hinder full functional immune recovery. Antigen-specific responses are impaired, seen in decreased IFN-γ production from *Mycobacterium tuberculosis* (TB)-specific CD4+ T cells [60] and increased CTLA-4 and PD-1 on HIV-infected cells contributing to hypo-responsiveness [61].

Due to concurrent changes among CD8+ T cells, including expansions of terminally differentiated cells [62, 63] and similar depletions of naïve populations, some ART-treated PWH fail to normalize CD4/CD8 ratios even with CD4 reconstitution. Inverted CD4/CD8 ratios and the accumulation of anergic CD28− CD8+ T cells are observed in both aging and HIV infection [64] and are part of an “immune risk” phenotype that predicts death even in the general population [65]. Among PWH, low CD4/CD8 ratios confer an increased risk of SNAEs and non-AIDS mortality, independently of CD4 count [66]. Patients with CD8 counts >2000 cells/μL after 1 year of ART have an increased risk of death compared to those with CD8 counts between 500–1500 cells/μL [67], and increasing CD8 counts may be associated with adverse health outcomes such as myocardial infarction [68]. Functional defects among CD8+ T cells, such as decreased proliferative and cytotoxic activity among HIV-specific CD8+ T cells, also persist despite viral suppression [69, 70].

Persistent disturbances in innate immunity are also apparent, with many studies addressing monocytes. Monocyte activation and inflammasome induction have been implicated in persistent CD4 decline despite ART [71] as well as poor CD4 reconstitution after ART [71, 72]. A subset of monocytes in PWH strongly upregulates expression of tissue factor (TF) and cytokines in response to LPS, even under ART, driving activation of the clotting cascade [73]. Other innate cells are also altered. The percentages of activated HLA-DR+CD38+ NK cells remain elevated despite viral suppression [74], and mature NK cells still exhibit low IFN-γ production after rescue to normal levels with ART [75]. Similarly, neutrophils remain highly activated under ART as evidenced by increased CD11b expression and generation of reactive oxygen species [76], but retain functional defects such as decreased chemotaxis and low fungicidal activity [77]. HIV infection also causes low numbers of dendritic cells (DCs) and decreased cytokine signaling from these cells, and proportions of plasmacytoid DCs may not be restored even with ART [78, 79]. The involvement of innate immune dysregulation is reflected by increased levels of innate immune activation markers in serum,

including neopterin, CXCL10, sCD14, and sCD163, which are not restored to levels seen in age-matched uninfected controls by ART [80, 81].

More recent research also suggests that innate lymphoid cells (ILCs), particularly IL-17 and IL-22 producing colonic ILC3s, are depleted early in HIV infection, not fully restored by ART if initiated after cellular loss, and may contribute to persistent gut barrier dysfunction [82, 83]. Mucosal associated invariant T cells (MAIT cells), particularly those expressing IL-17, are also lost early in HIV infection and do not recover fully in number or in function under ART [84, 85]. HIV infection is further marked by alterations in γδ T cells, with decreased expression of IFN-γ and TNF-α that remains low after ART [86]. These changes may further contribute to impaired mucosal immunity as well as increased susceptibility to other infections, such as TB.

Finally, HIV infection is characterized by persistent defects in humoral immunity, including B cell activation, hypergammaglobulinemia, and changes in B cell phenotypes such as decreased memory populations and increased percentages of exhausted, immature transitional, and other atypical subsets [87]. Certain defects, including decreased B cell proliferation in response to CD4+ T cell help, are ameliorated with viral suppression under ART [88]. Other defects are not corrected despite antiretroviral therapy. Persistently low levels of memory B cell populations and loss of protective antibodies against vaccine antigens contribute to increased risk for certain diseases such as pneumococcal infection even after treatment with ART [89–91].

Inflammatory complications during immune reconstitution

It is clear that the negative consequences of HIV infection on the immune system are not fully reversed by ART. In fact, the initiation of ART itself is sometimes the catalyst that unveils this immune dysfunction. Shortly after starting ART, approximately 20% of patients develop Immune Reconstitution Inflammatory Syndrome (IRIS), a syndrome of clinical worsening following viral suppression that is attributed to the activation of dysregulated responses against underlying co-infections. Most cases occur within the first 2 months of treatment mostly in patients starting therapy with lower CD4 counts [92] and are subcategorized as “unmasking” IRIS, involving a formerly undetected pathogen, or “paradoxical” IRIS, involving a co-infection that had been seemingly adequately treated. The most common pathogens involved are *Mycobacterial* species, *Cryptococcus*, and herpesviruses including CMV. Given the role of immune hyperactivation in IRIS, glucocorticoid therapy is the mainstay of treatment.

Risk factors for the development of IRIS help to illustrate a relationship between immunosuppression, immune activation and immune dysregulation. Lower CD4 nadirs, lower CD4 counts at the time of ART initiation, and lower CD4/CD8 ratios reflective of more severe immunosuppression are all associated with increased risk of IRIS [93–95]. Excess immune activation is also apparent during the time of the IRIS event. One study of IRIS stemming from various pathogens found overall increased levels of IFN-γ during the timing of the IRIS event compared to non-IRIS controls [96]. Levels of IL-6 are also elevated during IRIS arising from TB infection (TB-IRIS) and *Cryptococcal*

meningitis (CM-IRIS) [97, 98]. Patients with TB-IRIS have increased serum TNF and IFN-γ [99] and cells producing cytokine in response to antigen stimulation [100], illustrating involvement of adaptive responses. TB-IRIS patients have higher levels of sCD14, soluble CD163 (sCD163), and soluble tissue factor (sTF) compared to non-IRIS controls at the time of IRIS, correlating with expansion of CD14++CD16− monocytes [97], indicating simultaneous involvement of innate cells. Inflammasome activation has also been implicated in the development of TB-IRIS [101] further suggesting a major role for innate immune dysregulation in IRIS.

Other important risk factors for IRIS include shorter duration of OI treatment and shorter interval between OI treatment and ART initiation [92, 97]. Longer treatment of TB infection has been shown to decrease markers of immune activation and the incidence of IRIS [97]. In CM-IRIS, a higher antigen burden, lower levels of protective Th1 type cytokines, and accompanying increases in less protective Th17 and Th2 type cytokines are associated with increased risk of IRIS [98, 102]. These studies suggest that suboptimal antigen clearance is involved in the pathogenesis. In the context of severe lymphopenia and residual antigen, homeostatic proliferation driven by IL-7, which increases with CD4 lymphopenia and during IRIS events [96], may promote the over-representation of highly activated pathogen-specific CD4+ T cells. Even 6 months after the IRIS event, IRIS patients have increased percentages of effector memory CD4+ T cells and central memory CD8+ T cells [96].

While IRIS due to infectious causes appears relatively soon after ART initiation, autoimmune disease is another complication that can occur during the later stages of immune recovery. Autoimmune thyroid conditions may appear roughly 1.5–2 years after ART initiation and are more common with a history of more severe immunosuppression indicated by low CD4 count [103]. The recurrence of sarcoidosis among PWH with a remote history of this condition has also been reported [104]. Other autoimmune phenomena that have been documented after ART include autoimmune hepatitis [105], Sjogren's syndrome [106], and alopecia [107]. Hypothesized causes of this autoimmunity include residual thymic dysfunction, re-biasing from a Th2 to a Th1 type response, and expansion of self-reactive clones during reconstitution of the CD4+ T cell receptor repertoire.

Major HIV morbidities: cardiovascular disease and others

More chronically, persistent immune dysfunction can manifest as increased rates of non-infectious morbidities. Cardiovascular disease is the leading cause of mortality worldwide, and the prevalence is increasing among PWH despite decreases in the general population [108]. The risk of acute myocardial infarction among PWH is 1.5-fold higher [109], and HIV infection is an independent risk factor for ischemic stroke [110, 111]. Chronic inflammation and immune dysfunction clearly play a role in the pathogenesis of these conditions. Levels of sCD163, sCD14, and CCL2 reflect monocyte/macrophage activation and are correlated with coronary artery stenosis in PWH and the general population [112]. Increased proportions of non-classical CD14+CD16++ and intermediate CD14++CD16++ monocytes, as well as upregulated TF expression on monocytes, are seen in both HIV infection and in patients with acute coronary syndrome who are HIV seronegative [113]. Expression of TF by monocytes correlates with plasma viremia and plasma sCD14 and

can be induced *in vitro* by LPS, suggesting microbial translocation probably contributes to thrombotic disease through activation of monocytes [113]. CMV infection, which is common among PWH, is also linked to atherosclerosis [114].

Some ART medications themselves may be linked to cardiovascular morbidity. Protease inhibitors in particular are linked to hyperlipidemia and hypercholesterolemia [115], the development of atherosclerosis via increased fibrinogen [116], and increased risk of myocardial infarction in some studies [117]. Nucleoside reverse-transcriptase inhibitors (NRTIs) and non-nucleoside reverse-transcriptase inhibitors (NNRTIs) have also been associated in lipid and triglyceride alterations [118]. Certain ART regimes, particularly dolutegravir combined with tenofovir alafenamide fumarate, augment weight gain and obesity [119], contributing to metabolic disturbances that may increase the risk of cardiovascular morbidity. Other known risk factors for cardiovascular and thrombotic diseases, including smoking and comorbidities such as hypertension, are also prevalent among PWH and further contribute to the increased risk.

Liver disease is another important morbidity among PWH, accounting for about 14.5% of deaths [50]. In this population, liver disease is strongly associated with immunodeficiency and co-infection with Hepatitis B and C viruses [50]. Increasing CD4 counts are protective, suggesting beneficial effects of ART. However, unexpectedly, the risk of liver-related mortality has been shown to increase with longer exposure to ART – the exact reasons for this are unclear, and may involve antiretroviral toxicity, particularly with reverse transcriptase inhibitors, and the natural progression of hepatitis over time [50, 120]. Non-alcoholic steatohepatitis (NASH) and non-alcoholic fatty liver disease (NAFLD) also occur at high rates among PWH and are driven by multiple factors in this population, including an association with male gender, NNRTI use, and increased body mass index among others [121, 122].

Renal dysfunction is also observed in PWH, reflected in elevated cystatin C levels compared to uninfected controls [123], and has also been associated with tenofovir usage [124]. Renal and liver diseases combined with poor nutritional status may contribute to Vitamin D deficiency, which is common among PWH and is linked to various other pathologies, including IRIS, osteoporosis, atherosclerosis[125] and accelerated liver disease [126].

Non-AIDS defining cancers (NADCs) have become another leading cause of death among PWH. PWH are at an elevated risk of anal cancers, certain lymphomas, oropharyngeal cancers, and lung cancer, among others [127]. High rates of smoking are observed among PWH, and this represents the greatest risk factor for the development of lung cancer in this population [128]. However, HIV infection remains an independent risk factor for lung cancer [128, 129], and the risk appears to be inversely related to CD4 count. Local tissue damage from dysregulated CD8 responses, increased rates of pneumonia and chronic lung infections, and even direct viral oncogenesis have been proposed as contributing factors with varying degrees of supporting data [130]. Risk of NADCs such as liver cancer and anal cancer are augmented by co-infection with other pathogens, including hepatitis viruses and human papilloma viruses, respectively.

HIV infection also affects the central nervous system, causing neuronal apoptosis and synaptodendritic degeneration, leading to neuropsychiatric impairment in approximately half of PWH [131]. This impairment is common even among PWH treated with ART. While the prevalence of HIV-associated dementia has significantly decreased in the ART era, a similar percentage of PWH meets criteria for milder HIV-associated neurocognitive disorders now compared to in the pre-ART era [131, 132]. Impairment is more common with lower CD4 nadirs [132]. Although cognitive function improves over time with treatment, PWH with advanced immunosuppression still exhibit twice the rate of cognitive impairment compared to the HIV-uninfected population, even after CD4 >200 on ART [133]. These studies suggest that neuropsychiatric impairment is likely established during the peak of immunosuppression and persists despite immune reconstitution.

HIV infection also decreases bone mineral density through direct effects on osteoclasts and osteoblasts as well as inflammation-related impact, resulting in a high prevalence of bone diseases among PWH. Osteoporosis is approximately three times more common among PWH compared to the HIV uninfected population [134]. ART does not seem to ameliorate the effects of HIV on bone density, and some medications such as protease inhibitors may even accelerate the problem; osteoporosis appears to be more common among ART-treated PWH compared to ART-naïve [134], although this finding remains controversial.

Other disorders that are more common among PWH that are likely not fully reversed by ART include pulmonary arterial hypertension [135], which may arise from dysregulated fibroblast activity and growth factor expression during HIV infection [136], and frailty, a phenotype associated with weight loss, exhaustion, and weakness that is typically associated with advanced age [137].

Infections & vaccine responses

OIs decrease significantly with ART, but some PWH remain at risk, particularly those with incomplete CD4 recovery. Compared to the general population, PWH also remain at higher risk of a number of bacterial diseases even with treatment. They are more likely to develop invasive pneumococcal disease [138], a phenomenon attributed to the loss of memory B cells and serologic memory [91]. Globally, TB co-infection also remains a major obstacle. PWH are at higher risk of acquiring TB infection, which has been shown to accelerate the course of HIV [139], and this risk likely remains elevated over the HIV-uninfected population even after treatment with ART [140].

PWH also have high rates of co-infection with other chronic viruses. Co-infection with Hepatitis B and C viruses is common and confers a higher risk of SNAEs [48], in particular liver disease [141]. Infection with certain human papilloma viruses can cause anal, cervical and oropharyngeal cancers, which occur at higher rates among PWH. PWH are also at an increased risk of developing herpes zoster and complications of zoster, even at relatively young ages, a phenomenon associated with poor immune function [142]. As previously discussed, seropositivity rates for human herpesviruses such as CMV and the related Epstein-Barr Virus are also high and may contribute to immune activation and dysfunction.

PWH may also remain at an elevated risk of vaccine-preventable illnesses such as measles, tetanus, and influenza. ART fails to recover protective memory B cell populations, and PWH have poorer responses to immunizations and booster immunizations against certain pathogens [143–146]. Responses to influenza vaccine are perhaps the best studied, and it is now well-documented that low CD4 count is associated with poor responses to influenza vaccination. Low CD4 count is associated with lower peak antibody titers as well as decreased formation of memory B cell responses [147]. ART improves responses to influenza vaccination largely by increasing numbers of CD4 T cells [148]. However, even PWH with CD4 >500 are still less likely to mount antibody responses than HIV-uninfected counterparts [143], and antibody titers remain lower among PWH despite ART. Similar immunological deficiencies are present in both the elderly and among PWH, such as decreased memory B cell and peripheral T follicular helper cell expansion after vaccination [144]. Accordingly, as in the elderly, PWH have improved responses with increased vaccine doses and the addition of adjuvants as outlined below.

Defects in responses to various other important vaccinations are also observed. PWH have decreased seroconversion rates in response to primary Hepatitis B vaccination, and the duration of the response is shorter. Protective antibody levels were only present in roughly 50–66% of vaccinated PWH after 1 year [149, 150], and less than a third of initial responders after two2 years [150]. Adjuvants, higher doses, and additional immunizations can increase seroconversion rates [145, 149, 151]. Loss of protection is also seen earlier among PWH for measles vaccination, a greater proportion of whom have no evidence of measles antibodies 1 one year post-vaccination compared to HIV-uninfected controls [146]. Pediatric studies have shown that while DTaP vaccination induces protective antibodies in ART-treated children, titers may be lower and duration is shorter compared to those observed in HIV-uninfected children [152, 153]. In summary, while PWH may be able to respond to vaccination, particularly after ART treatment, the duration of this response may be limited in both magnitude and duration due to persistent dysfunction among immune cell subsets.

Demographics and lifestyle factors

Persistent immune dysfunction plays a prominent role in the morbidities and poor health outcomes that persist after ART, but lifestyle risk factors are also involved. Although continuous ART has been shown to improve outcomes, medication adherence is unfortunately suboptimal in most cases [154], indicating a critical area for improvement. High rates of tobacco use, injection drug use (IDU), and alcohol use are present among PWH and contribute to various SNAEs including lung cancer, liver disease, and more. These activities have also been associated with poorer adherence to ART and control of HIV [139, 155]. IDU further increases risk of acquiring other chronic infections such as hepatitis B or C viruses. Obesity is also present at high rates among PWH and has been independently linked to monocyte and innate immune activation in PWH [156].

Sex differences may also play a role in HIV-associated outcomes, potentially due to differences in immunological function, drug metabolism, and sociological factors related to sex. It has been frequently observed that women with HIV have lower viral loads [157],

but studies on outcomes after ART are conflicting. Women with HIV may have a decreased risk of certain complications compared to men with HIV, such as dementia and Kaposi sarcoma [158], while experiencing an increased risk of others, such as myocardial infarction [109]. Some data suggest that sex plays a role in risk for disease progression and virologic control after ART, but many of these studies are complicated by differences in medication adherence, drug use, educational and socioeconomic factors.

Finally, social determinants of health also contribute to high rates of morbidity in this population. For example, despite elevated risk of colorectal cancer, PWH are less likely to be up-to-date on screening [159], revealing a need for more rigorous use of preventative health measures in this population. Insurance coverage and stable housing are two factors shown to increase ART usage and decrease mortality rates among PWH [160, 161], and programs to help patients access these resources could have tremendous positive impacts on health outcomes.

Combatting residual immune dysfunction

ART remains the single intervention with the strongest data for reducing morbidity and mortality among PWH. Early initiation of ART can promote robust immune restoration, minimize the size of the viral reservoir [162], decrease the degree of residual inflammation [15], limit mucosal damage, and reduce the extent of lymphoid tissue fibrosis [57]. Therefore, early diagnosis of HIV infection and early initiation of ART, at higher CD4 counts and before advanced disease or severe immunodeficiency, is critically important for limiting immune activation and persistent immune dysfunction.

Because the ART-suppressed virus may still be recognized by the immune system [24, 25], further reductions to the viral reservoir could theoretically minimize chronic immune activation and improve outcomes. Some teams have investigated the use of intensive ART regimens involving an increased number of drugs, but this “mega-ART” approach has not been shown to improve outcomes or accelerate reservoir decay compared to standard ART [163, 164]. The development of effective therapeutic vaccines could also potentially contribute to improved viral control, but trials of candidates in humans have only yielded mixed results [165]. Partial inhibition of glycolysis has been found to dampen viral replication and accelerate the decay of infected cells *in vivo*, suggesting that metabolic pathways could be a promising target to explore for the development of future novel therapies [166].

Other strategies to improve health outcomes have focused on augmenting immune recovery via cytokine therapies, which have had mixed results. Treatment with IL-2 can increase the numbers of CD4+ T cells, but two large randomized controlled trials, Subcutaneous Recombinant, Human Interleukin-2 in HIV-Infected Patients with Low CD4+ Counts under Active ART (SILCAAT) and Evaluation of Subcutaneous Proleukin in a Randomized International Trial (ESPRIT), failed to show any clinical benefit [167]. Treatment with recombinant human IL-7 can also increase numbers of both CD4+ and CD8+ T cells [168], and in particular naïve and central memory CD4+ T cells [169], but it remains unclear if this confers any clinical advantage. These cytokines have further been used as part of “shock and

kill" strategies to reactivate the latent viral reservoir to increase susceptibility to therapies targeting active replication [170, 171].

Other approaches have attempted to dampen immune activation with medications directly acting against the inflammation or against its causes. The immunosuppressive agent hydroxychloroquine decreases percentages of activated T cells and monocytes and increases proportions of naïve cells among PWH [172], and the immunomodulatory drug leflunomide was similarly found to decrease markers of T cell activation in untreated PWH in a randomized trial [173]. HIV-associated gut mucosal disruption has been targeted with probiotics, which have shown some effects on reversing immune dysfunction [174]; lactoferrin, which had no effect [175]; and with sevelamer, a drug previously observed to decrease microbial translocation in hemodialysis patients. Sevelamer did not decrease various measures of microbial translocation or immune activation in PWH, but lowered levels of sTF and cholesterol, suggesting potential cardiovascular benefits [176]. Antifibrotic drugs have been investigated for their potential to counteract lymphoid collagen deposition. Pirfenidone has been shown to decrease collagen synthesis from fibroblasts *in vivo* [177] and improve CD4+ T cell reconstitution in SIV models [178], but lisinopril, also tested for its anti-fibrotic properties, had no effect on reversing fibrosis, dampening inflammation, or decreasing HIV reservoirs [179]. Losartan also failed to decrease inflammation or improve CD4 counts [180]. Given the role of co-infections in chronic immune activation, a study investigated the effect of treating subclinical CMV infection with valganciclovir and found that it decreased the rates of CMV DNA positivity and the levels of CD8 T cell activation [181].

Finally, because of the prominence of HIV-associated coagulopathy and its relationship with inflammation and adverse outcomes, many trials have studied the use of anticoagulants in PWH. The Targeted Anticoagulation Therapy To Reduce Inflammation and Cellular Activation in Long-Term HIV Disease (TACTICAL-HIV) trial found that giving a low dose of the direct factor Xa inhibitor edoxaban for four months significantly lowered D-dimer levels but had no effect on markers of inflammation [182]. A shorter course of the thrombin receptor antagonist vorapaxar did not significantly decrease markers of immune activation or coagulation in the Attenuation of D-dimer Using Vorapaxar to Target Inflammatory and Coagulation Endpoints (ADVICE) study [183]. Treatment of PWH with statins and aspirin have been shown to decrease markers of T cell and innate immune activation [184–186]. The Randomized Trial to Prevent Vascular Events in HIV (REPRIEVE), a large prospective study comparing pivastatin to control for prevention of major adverse cardiac events in PWH, is currently underway [187].

Although the development of ART is still one of the triumphs of modern medicine, the evidence of persistent immune dysfunction even among early treated PWH indicates that challenges in the understanding and treatment of HIV infection remain. Decades of studies have increased our knowledge of the multiple factors that drive and sustain the chronic immune activation and inflammation in ART-treated PWH, which is closely linked to the higher burden of certain non-infectious morbidities in this population. As we continue to learn more about the pathogenesis of persistent immune dysfunction under ART, health outcomes in PWH could be improved now by early diagnosis and treatment, cancer

screenings and other age-appropriate monitoring, lifestyle interventions to decrease high risk behaviors, increased availability of social resources, and control of coinfections such as HCV and comorbidities.

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