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HIV PATHOGENESIS AND TREATMENT (AL LANDAY, SECTION EDITOR)

Metabolic Consequences of HIV: Pathogenic Insights

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Abstract With the advances in antiretroviral therapy (ART), HIV infection has been transformed into a chronic medical condition that can be effectively managed like diabetes or hypertension. For HIV care providers, the focus of care for many patients has shifted from prevention of opportunistic infection and AIDS-related conditions to age-related cardiometabolic comorbidities, including cardiovascular disease, diabetes, obesity, and frailty. Numerous reports have highlighted that these diseases are occurring at an earlier age among HIV-infected persons. However, there is an ongoing debate regarding the role of HIV infection, ART, and other factors that may underlie the accelerated occurrence of these diseases. Herein, we review the epidemiology of the US HIV epidemic with regards to several metabolic comorbidities and address mechanisms that likely contribute to the current nature of HIV disease.

Keywords HIV · AIDS · Metabolism · Inflammation · Frailty · Cardiovascular disease · Diabetes · Mitochondria · Pathogenesis · HIV pathogenesis · Antiretroviral therapy (ART) · Chronic medical condition

Introduction

Antiretroviral therapy (ART) has revolutionized HIV care, resulting in expanding populations with well controlled HIV infection but a growing list of comorbidities that require a significant amount of time and resources to manage [1, 2•, 3]. Though challenges in the HIV treatment cascade still exist and require further improvement [4], patients are now also increasingly affected by numerous other chronic diseases, including cardiometabolic disorders (coronary artery disease, diabetes, hypertension). HIV-infected patients further face growing prevalence of low bone mineral density, frailty, and obesity that threaten to undermine the gains in quality of life achieved with widespread ART use [2•, 5–7]. Among the scientific community there is a healthy, ongoing debate about the role of HIV infection in the accelerated development of these comorbidities. Is the virus directly altering the natural history of these diseases, or are other environmental and behavioral factors the key drivers? Is there a differential effect of HIV and ART on the development of these comorbidities? Does HIV impact metabolic function and the inflammatory response?

There are numerous hypotheses that have been suggested, including: persistent HIV antigenemia or viremia, dysregulated adaptive immune system, alterations in the innate immune system, microbial translocation, co-infecting viral pathogens, alterations in the microbiome, toxic effects of ART, or concomitant comorbidities such as a sedentary lifestyle or tobacco and substance abuse. Given the complexity of the human organism, the interaction of numerous factors contributes to any given disease state. Herein, we review the current literature regarding the pathology of metabolic disturbances observed in HIV-infected individuals. We highlight key metabolic comorbidities and provide available evidence of how HIV infection contributes, directly or indirectly, to their exacerbation.

HIV Infection is Associated with Higher Chronic Disease Prevalence and Multimorbidity

Multimorbidity, the clustering of two or more chronic medical conditions, is extremely common among elderly persons and has been associated with polypharmacy, reduced functional capacity, reduced quality of life, and increased mortality [8, 9]. Kim and colleagues recently reported that 65 % of patients followed at a large HIV clinic met the criteria for multimorbidity [10•]. Notably, older age, higher CD4 cell counts and obesity

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were independent factors related to multimorbidity. The accelerated presence of multimorbidity has been confirmed from an independent European cohort, although the authors suggest that the highly heterogeneous nature of their HIV-infected cohort makes definitive pathogenesis complicated to attribute to any specific factor [11•, 12]. What about specific metabolic comorbidities?

Cardiovascular Disease

Observational studies have revealed that HIV infection confers a 1.5-2 times increased risk of dying from acute myocardial infarction that remains after controlling for traditional CVD risk factors [9]. Ongoing HIV viremia is clearly a risk for progressive atherosclerosis [13, 14]. The Strategies for Management of Antiretroviral Therapy (SMART) Study demonstrated that persons who remained on continuous ART (i.e., remained virologically suppressed) had markedly reduced CVD endpoints than those persons who underwent treatment interruption [15, 16]. Data from the CDC-funded Study to Understand the Natural History of HIV Infection (SUN) confirmed that uncontrolled viremia independently was associated with progressive atherosclerosis as measured by carotid intima media thickness [17].

However, even with controlled viremia, CVD remains elevated in the HIV population [18•, 19•]. The Data Collection on Adverse Events of Anti-HIV Drugs (D:A:D) study implicated the metabolic toxicities of early ART protease inhibitors, which were independently associated with CVD. The effect was attenuated after accounting for lipid abnormalities [20]. Studies assessing more current ARVs consistently demonstrate a beneficial effect of ART on surrogate markers of atherosclerosis [21]. Does this improvement relate strictly to controlled viremia, or some other factor such as an improvement in the generalized inflammatory state?

Atherosclerosis is an inflammatory process; the accumulation of inflammatory macrophages, deposition of oxidized lipids, and ongoing plaque formation ultimately lead to acute myocardial infarction [22, 23]. Progression of atherosclerosis was more rapid over an average two-year follow-up among HIV-infected patients compared to controls, even among those with controlled viremia [24]. The multiplicative effects of HIV-related chronic inflammation, microbial translocation, and mitochondrial function discussed below could all contribute. However, HIV-infected individuals also present with high prevalence of traditional risk factors of CVD that are associated with inflammation, including tobacco use, substance abuse, dyslipidemia, and obesity [10•, 13]. Additional investigation into the independent and interactive contributions of HIV infection, host genetics, environment and behavior are required to determine the best course of treatment for CVD risk reduction and whether interventions for the general population are effective in the setting of HIV infection.

Diabetes Mellitus

Several groups have reported a high diabetes prevalence (ranging 9-14 %) among HIV-infected patients in the United States, with a higher diabetes risk in both HIV-infected men and women [10•, 11•]. HIV-infected men in the Multicenter AIDS Cohort Study (MACS) had a four times greater prevalence of diabetes than uninfected men [25]. When compared to uninfected control groups, HIV-infected individuals also present with higher levels of insulin resistance [26, 27]. Traditional risk factors such as race/ethnicity, smoking status, and obesity are associated with diabetes risk in HIV-infected patients, and a focus on modifiable risk factors such as smoking could aid with diabetes prevention and control [28].

While traditional risk factors have a significant impact on diabetes risk, HIV infection and ART therapy are recognized as independent risk factors for diabetes. HIV-1 proteins directly contribute to insulin resistance via several tissue-related alterations, including attenuation of peroxisome-proliferator-activated receptor-γ (PPAR-γ) and increased sensitivity to glucocorticoids [29, 30]. HIV-associated lipoatrophy is also a risk factor for pancreatic β-cell dysfunction that exacerbates insulin resistance. Additionally, insulin resistance is a side effect of many ART regimens, particularly PI-based regimens that interfere with glucose uptake [31]. Newer HIV ART induce less insulin resistance and thus are considered more metabolically friendly [32].

Do traditional pharmaceutical and lifestyle treatments improve glycemic control and diabetes risk in HIV-infected individuals? One weight loss study observed that HIV-infected women experienced less improvement in metabolic outcomes than uninfected women, despite similar weight loss [33]. When using metformin, HIV-infected patients with diabetes also experience less improvement in HbA1c levels than uninfected individuals with diabetes [34]. While part of this blunted response was attributable to PI use, it is likely that chronic HIV-related inflammation also plays a role in this limited response to traditional therapies [35•].

Low Bone Density/Osteoporosis

HIV infection and ART, particularly ART initiation, have been associated with low bone mineral density (BMD) and accelerated BMD loss. Numerous studies report higher rates of fractures than expected for any given age with HIV infection [5, 36–38]. While several factors are associated with accelerated bone loss, some key mechanistic features have recently been identified. HIV infection in childhood or adolescence, before peak BMD has been achieved, is associated with a significant reduction in BMD (as measured by DXA) and a marked reduction in the quality of bone by assessment of trabecular BMD and cortical thickness (as measured by

qualitative CT scanning) [39•, 40]. These data suggest that HIV infection undermines normal bone formation.

Other key mechanisms of low BMD have also been explored. ART initiation is consistently associated with a 3-6 % loss in BMD in the first 48 weeks after therapy, with TDF-containing regimens having the greatest impact. Grant and colleagues recently confirmed in the AIDS Clinical Trial Group that advanced HIV disease, particularly having CD4 count<50 c/mm^3 and high plasma HIV viral loads, was associated with the greatest loss of BMD following ART initiation, suggesting that starting ART earlier in the course of disease can limit this metabolic complication [41]. At CROI 2013, Titanji reported that dysregulated B cells were strongly associated with bone loss [42]. In their evaluations, B cells from HIV-infected persons, but not HIV seronegative controls, had reduced levels of osteoprotegerin (OPG) expression and increased expression of receptor activator of nuclear factor kappa-B ligand (RANKL). RANKL binds to osteoclasts stimulating bone resorption, while OPG binds to RANKL to prevent osteoclast activation. By altering the expression of these key regulatory proteins, HIV infection tips the balance of bone regulation to excess resorption and BMD loss.

Beaupere and colleagues evaluated the effects of HIV proteins and two ritonavir boosted PIs (ATV/r and LPV/r) on osteoblast formation from mesenchymal stem cells (MSC) [43•]. Both HIV proteins and PIs increased oxidative stress in the MSC with subsequent loss of proliferative capacity and decreased differentiation into mature osteoblasts. Again, the effects of HIV and certain ARVs tip the balance of bone homeostasis toward excessive bone loss. Interestingly, the detrimental effects of the boosted PIs was at least partially reversed by the addition of pravastatin by a reduction in farnesylated pre-lamin A, a marker of cellular aging.

Frailty

While wasting syndrome was recognized frequently in the pre-ART era, frailty has emerged as a frequent comorbidity for virologically suppressed patients and occurs at a markedly earlier age among HIV-infected persons [6, 44, 45]. The frailty syndrome is characterized by multisystem dysregulation with decreased muscle mass and physical strength, unintentional weight loss, decreased reported energy and physical activity. In the geriatric literature, this phenotype is correlated with increased morbidity (loss of independence, falls, and disability) and mortality [46]. In the MACS cohort, prevalence of frailty was higher among HIV-infected men compared to HIV negative men with the most striking difference in the persons≥age 50 [44]. Additional research in HIV-infected persons confirms that markers of chronic inflammation are elevated in both HIV-infected and geriatric patients with the frailty phenotype [47, 48•].

Uncontrolled HIV Viremia is Bad

Clearly, we are seeing an increased prevalence of aging-related metabolic diseases in HIV-infected populations. Uncontrolled HIV viremia contributes not just to the progression to AIDS and its complications, but also to an increased risk of non-AIDS related comorbidities (Table 1) [49•]. Specifically, the SMART study confirmed that persons with strategic treatment interruption were at greater risk for cardiovascular disease, renal disease, and liver disease [15]. These surprising results provided greater clarity that the ongoing inflammatory response to persistent HIV viremia had consequences beyond the immune system. Hence, current HIV treatment guidelines recommend treatment for patients with higher CD4 cell counts [50]. Clearly, the process of uncontrolled viremia has been shown to induce these metabolic derangements in many different ways.

Table 1 Summary of pathogenic insights and important areas of research

Persistent viremia and antigenemia
• Poorly controlled viremia is associated with greater risk for cardiometabolic diseases. [15].
• Continued viral replication is observed even among elite controllers with low levels of plasma HIV RNA, suggesting that even this group maintains a chronic inflammatory state. [108•].
Microbial translocation
• Chronic immune activation is promoted via depletion of CD4 T cells. [56–59].
• HIV-1 infection contributes to significant alterations in the gut microbiome that promote a pro-inflammatory state [62–64].
Insulin resistance and metabolic function
• HIV-1 infection contributes to insulin resistance via tissue-related alterations in PPAR-γ signaling, glucocorticoid sensitivity, and for pancreatic β-cell dysfunction. [29–31].
• HIV-infected patients experience less improvement than uninfected controls in metabolic outcomes with standard lifestyle and pharmaceutical treatments for diabetes. [33, 34, 93].
• HIV infection is associated with degradation of the outer mitochondrial membrane, with contributes to chronic inflammation, frailty, and cardiometabolic diseases. [47, 48•, 66, 67].
• Elevated resting energy expenditure is observed in HIV-infected individuals, and is associated with the infection itself rather than ART side effects. [72–74].
Future questions for research
What factors contribute to persistent viremia that can be targeted to decrease systemic inflammation?
How does HIV-1 contribute to alterations in the gut microbiome, and which strategies are effective at promoting a healthy gut microbiome despite HIV infection?
Can mitochondrial function be maintained/restored in HIV-infected individuals?
What lifestyle and pharmaceutical interventions are realistic and cost-effective to treat cardiometabolic diseases in infected patients?

PPAR-γ , peroxisome-proliferator-activated receptor-γ; ART, antiretroviral therapy

Does HIV Infection Accelerate the Aging Process?

In the geriatric literature, the development of chronic medical conditions has been related to chronic "sterile" inflammation throughout the body [51]. An area of intense research to prevent these aging-related diseases has focused on the role of cellular senescence. Cellular senescence occurs in response to potential oncogenic insults to cells and also is seen at sites of tissue and wound healing [52]. Thus, senescent cells generally serve a useful anticancer and wound healing purpose in the young organism. Unfortunately senescent cells are resistant to apoptosis. As they accumulate, these metabolically active cells secrete a senescence–associated secretory phenotype (SASP), comprised of numerous pro-inflammatory biomarkers that contribute to the development of tissue damage and age-related comorbidities [53].

The responsiveness of adaptive immunity, specifically T cell function, is a key feature of a functional immune system. One of the primary features of aging is the accumulation of terminally differentiated memory CD8+ T cells. Notably in the geriatric literature, this accumulation of senescent T cells is associated with chronic CMV infection [54]. Similar to CMV, chronic HIV infection is associated with increasing numbers of terminally differentiated senescent CD8+ T cells in response to chronic antigen stimulation. Even with suppressive ART, the proportion of senescent T cells remains similar to that reported in older HIV-negative adults. Furthermore, and more importantly, the alterations in lymphocyte populations remains associated with end organ disease even in the setting of HIV treatment. This topic has recently been reviewed extensively elsewhere [55]. The persistently elevated levels of pro-inflammatory cytokines in suppressed HIV infection are not solely attributable to these changes in the adaptive immune system; we must also consider the alterations in the gut environment and microbial translocation, the changes in cellular bioenergetics, and the role of insulin resistance.

Microbial Translocation and the Gut Microbiome

Due to the constant surveillance of the intestinal flora, the gut-associated lymphoid tissue (GALT) serves as the largest reservoir for lymphocytes in the body [56]. The profound depletion of CD4 T cells from the GALT during acute HIV infection causes catastrophic changes in the gut mucosal integrity facilitating bacterial translocation, augmenting trafficking of inflammatory cells to the GI tract, and promoting chronic immune activation [57–59]. With ART, the level of peripheral T cell activation decreases but fails to return to levels seen in HIV uninfected persons [60, 61]. Interestingly, T cell activation in the GALT is not significantly reduced with ART, leading to ongoing inflammation in the gut mucosa [62]. Following HIV-1 infection, individuals also have a shift in their gut microbiome to one that consists of a greater proportion of Gram negative bacteria with enhanced potential to induce systemic inflammation [62, 63]. This dysbiosis has been confirmed in a recent analysis by Vujkovic-Cvijin and colleagues who observed a significantly altered microbiome composition in HIV-infected patients compared to uninfected controls [64].

Microbial Translocation Alters Lipoproteins as Well

Lipopolysaccharide (LPS), a cell wall component of Gram-negative bacteria, is a common marker of microbial translocation. LPS binds to Toll-like receptor 4 (TLR-4) and induces robust activation of both adaptive and innate immune responses. In addition to this direct immune activation, excessive circulating LPS contribute to another proinflammatory effect: HDL consumption. HDL particles play a critical role in cholesterol clearance. These scavenger molecules transport excess cholesterol particles from tissues, endothelial plaques, and macrophages to the liver where they are ultimately disposed in the feces [65]. HDL also serves as the primary particles in circulation that bind and clear LPS. While this process protects the human organism from an acute bacterial infection, with chronic bacterial translocation as in HIV infection, it likely leads to marked alterations in the clearance of pro-atherosclerotic cholesterol molecules. Thus, a well described consequence of HIV infection, low HDL cholesterol, may have significant ramifications for the progression of aging-related disease, particularly atherosclerosis.

Mitochondrial Function

Adequate mitochondrial reserve capacity is essential for cell function, yet preliminary evidence implicates certain ART medications, and potentially the HIV virus, in promoting mitochondrial toxicity and dysfunction. Host genetics determine baseline mitochondrial function, and naturally occurring variations in mitochondrial DNA of HIV-infected individuals are associated with the rate of progression of HIV disease. Activity of HIV-1 viral protein R (Vpr) is associated with a decrease in the number of CD4+ T cells and contributes to host cell death via a cascade effect resulting in damage of the mitochondrial outer membrane [66]. Our understanding of the impact of HIV infection on mitochondrial function remains limited, however, with significant gaps in knowledge that could alter clinical care related to the impact of HIV on mitochondrial dysfunction/toxicity and the interactive role of HIV virus and mitochondrial function on the aging process in infected individuals.

One area of recent study has been a greater understanding of the bioenergetics of T cell regulation. In response to antigenic

stimulation, naïve T cells are activated, proliferate, and differentiate into effector T cells. These effector cells undergo metabolic reprogramming to clear whatever pathogenic process is ongoing. The changes are marked by an increase in glycolytic rate, increase in synthesis of proteins, lipids and nucleic acids, and a decrease in mitochondrial mass [67]. With resolution of the pathogen, the effector cells die, leaving memory cells which have lower metabolic states and utilize oxidative phosphorylation for metabolic demands. In the setting of persistent antigen (Ag) stimulation, the population of effector cells remains high and serves as a driver of inflammation and excess reactive oxygen and nitrogen species which further serve to cause tissue damage and ultimately end organ disease. Thus, persistent Ag stimulation from the chronic HIV infection and microbial translocation both serve to facilitate immune activation, excessive reactive oxygen species (ROS) and end organ disease.

HIV Infection Alters Body Composition and Metabolism

HIV infection is associated with loss of subcutaneous adipose tissue in the face, extremities, and buttocks (lipoatrophy) [68]. A significant gain of central visceral adipose tissue (lipohypertrophy) has also been reported, though not all follow-up studies show this association [69, 70]. An excess of circulating fatty acids due to the inability of lipoatrophic tissues to store energy, as well as the hormonal/cytokine secretory response of adipose tissue to HIV infection, contributes to chronic inflammation and may alter the body's metabolism as previously reviewed [71]. One area that has been evaluated but not extensively reviewed is the alteration of metabolic rates with HIV infection.

The etiology of metabolic rate alterations with HIV infection remains unclear. Most studies confirm that resting energy expenditure (REE), the amount of kilocalories required to maintain basic bodily functions during rest, is elevated by 10-30 % in HIV-infected patients [72, 73]. REE may be correlated with increasing CD4+ T-cell counts, and it remains elevated among women on ART with undetectable viremia, implicating HIV infection itself rather than effects of ART in contributing to a higher metabolic rate among HIV-infected individuals [74]. Several mechanisms, including body composition changes and opportunistic infections contribute to but do not fully explain elevated REE with HIV infection. Lipoatrophy accompanied by an altered adipose tissue hormone/cytokine secretion, along with evidence of increased REE with overfeeding in HIV-infected individuals but not uninfected controls, suggests a role of adaptive thermogenesis (metabolic inefficiency in response to environmental changes) in elevating REE. However, brown fat, a type of adipose tissue associated with higher REE in uninfected patients, was not found in HIV-infected men with severe lipoatrophy [75]. The etiology of elevated REE with HIV infection is of great clinical significance, as a higher REE may impair gain of muscle mass, lead to increased production of reactive oxygen species by mitochondria, and increase systemic inflammation hypothesized to contribute to chronic disease risk.

Additional Risk Factors Can Exacerbate the Consequences of HIV Infection

While HIV infection is associated with significant inflammation and a variety of metabolic complications, it often occurs in the context of other factors that amplify the infection's deleterious effects. HIV infection itself can contribute to increased likelihood of a patient experiencing these conditions, resulting in a feedback loop that may require clinical and/or social intervention.

Smoking Smoking and substance abuse are associated with increased CVD, poor ART adherence, and increased mortality. Although smoking rates have declined over time, persons living with HIV continue to smoke at rates 2–3 times higher than the general population [76, 77]. Among HIV-infected populations, smoking has been associated with lower quality of life and many of the age-related comorbidities discussed herein. Importantly, cigarette smoking is associated with a 1.5 times greater risk of mortality [78], and tobacco use is associated with increased T cell activation among HIV-infected individuals [79]. It is likely that the effects of smoking and HIV-related inflammation have additive negative consequences for health management.

Poverty Poverty is both a driver and consequence of HIV infection, and United States residents living below the poverty line are five times more likely than the general population to be HIV-positive. Even those persons in poor communities who live above the poverty line have a 2.5 fold increased risk of HIV infection than persons living in higher income neighborhoods. Furthermore, poverty is also associated with factors that contribute to both HIV infection and poor ART adherence, including homelessness, substance abuse, depression, and food insecurity. Poverty has further been linked to decreased access to health care resources and low health literacy, which can significantly impact HIV treatment outcomes.

Nutrition Adequate nutrition is essential to maintain a functioning immune system in HIV-infected individuals. Food insecurity is a recognized risk factor for HIV, and up to 50 % of currently infected urban patients may be food insecure [80, 81]. It is independently associated with increased mortality, decreased ART adherence, and incomplete virologic suppression [82, 83]. Interventions to improve food security are thus a vital component of HIV care, and investigations

focused on which strategies are most effective at ameliorating food insecurity are greatly needed.

Nutrition strategies can also improve health outcomes for food secure HIV-infected patients. Observational and clinical studies have investigated Mediterranean dietary patterns, Omega-3 fatty acids, and vitamin D intake for their potential roles in CVD and diabetes risk among HIV-infected groups [26, 84, 85]. However, knowledge regarding effective dietary patterns for immune function and chronic disease reduction among HIV-infected groups remains limited. Elucidating dietary patterns to improve nutrition that are realistic and affordable for HIV-infected individuals will be critical for adequate patient care.

Obesity A significant increase in body weight was observed in the decades following ART initiation and now up to 65 % of HIV-infected individuals are considered overweight (body mass index [BMI] 25–29.9) or obese [BMI≥30]) [2•, 86]. The effects of excess adiposity in the context of HIV infection are not well elucidated, though obesity is also associated with increased systemic inflammation and CVD risk [87, 88]. Does the presence of obesity in an HIV-infected individual increase chronic disease risk? Could there be benefits to carrying excess body fat for HIV-infected persons? Does obesity impact HIV-related treatment outcomes? Obesity is associated with higher initial CD4+ cell counts; however, less improvement in CD4+ cell levels following ART initiation among obese patients has been reported [89, 90]. Still others have found no difference in CD4+ counts following ART initiation [91, 92], and the degree to which excess adipose tissue may have an immunomodulatory effect on CD4+ cell recovery remains unclear. Intentional weight loss has not been associated with changes in CD4+ cell count or viral load and can be considered safe for HIV-infected patients; however, improvements in insulin sensitivity were either insignificant or worse compared to uninfected controls [33, 93].

Dental Caries HIV-infected individuals are more likely to experience dental caries compared with uninfected controls, and lower CD4+ cell counts are associated with a greater frequency of rampant caries and periodontal disease [94, 95]. The association of ART with dental caries is unclear, with studies reporting either no impact [95] or increased presence of caries in patients on long-term ART [96]. Poor dental health may exacerbate chronic inflammation and CVD risk [97]; thus adequate dental care is an effective strategy to improve overall health among HIV-infected individuals.

The role of Chronic Viral Hepatitis Multiple reports had been summarized in a meta-analysis showing that co-infected patients have a two-fold higher relative risk (RR) of developing cirrhosis and a six-fold higher RR of developing decompensated liver disease than HCV mono-infected persons [98]. Several population-specific factors may account for this increased risk including ART-direct toxicity (microsteatosis from lactic acidosis, drug-induced hepatitis, hypersensitivity reactions), ART-indirect toxicity (metabolic syndrome and non-alcoholic steatohepatitis [NASH]) and higher prevalence of harmful alcohol ingestion [99, 100]. Additionally, HIV can directly mediate liver fibrosis via different pathways: 1) the external envelope protein of HIV, gp120, induces chemokine receptor-mediated signaling and subsequent activation of hepatic stellate cells (HSCs) and production of fibrogenic cytokines; and 2) HIV depletes intestinal lymphocytes, increasing microbial translocation, which has been correlated with progression of HCV-related liver disease [101–103]. Both viruses increase the production of ROS in HSCs and hepatocytes, and are able to induce oxidative stress in tissues such as liver, muscle, fat and peripheral blood mononuclear cells (PBMCs) [104, 105, 106•]. Oxidative stress plays an important role not only in the pathogenesis of liver fibrosis in infectious hepatitis but also in many other processes including aging, cardiovascular diseases, neurodegenerative disease, and cancer [107]. Co-infection may facilitate a more rapid progression of these non-AIDS comorbidities.

Conclusions

HIV infection confers a chronic inflammatory state that significantly impairs immune function and exacerbates chronic disease risk. The clinical knowledge base for chronic disease prevention and treatment is primarily limited to data obtained from HIV-negative populations, and much work remains to elucidate the mechanistic link between HIV and cardiometabolic diseases as well as to develop effective clinical interventions. Recent studies suggest that current ART regimens may contribute to fewer metabolic disturbances than older generations of therapy, and in fact earlier initiation of ART at higher CD4+ cell counts could be critical to minimize the inflammatory state even among elite controllers [108•]. As the HIV-infected population continues to age and experience multimorbidity, an understanding of the pathogenesis of metabolic complications will be necessary for effective patient treatment outcomes.

Compliance with Ethics Guidelines

Conflict of Interest Amanda L. Willig, and E. Turner Overton declare that they have no conflict of interest

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

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