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Review

Mechanisms of Cardiovascular Disease in the Setting of HIV Infection

Priscilla Y. Hsue, MD

University of California San Francisco (UCSF), Zuckerberg San Francisco General Hospital, San Francisco, California, USA

ABSTRACT

Although the initial reports of increased cardiovascular (CV) disease in the setting of advanced AIDS were reported approximately 30 years ago, advances in antiretroviral therapy and immediate initiation of therapy on diagnosis have transformed what was once a deadly infectious disease into a chronic health condition. Accordingly, the types of CV diseases occurring in HIV have shifted from pericardial effusions and dilated cardiomyopathy to atherosclerosis and heart failure. The underlying pathophysiology of HIV-associated CV disease remains poorly understood, partly because of the rapidly evolving nature of HIV treatment and because clinical endpoints take many years to develop. The gut plays an important role in the early pathogenesis of HIV infection as HIV preferentially infects CD4+ T cells, 80% of which are located in gut mucosa. The loss of these T cells damages gut mucosa resulting in increased gut permeability and microbial translocation, which incites chronic inflammation and immune activation. Antiretroviral therapy does not cure HIV infection and immune abnormalities persist. These abnormalities correlate with mortality and CV events. The effects of antiretroviral therapy on CV risk are complex; treatment reduces inflammation and other markers of CV risk but

RÉSUMÉ

Même si les premiers signes d'augmentation des maladies cardiovasculaires (CV) en présence du SIDA au stade avancé ont été rapportés il y a environ 30 ans, les progrès réalisés en matière de traitement antirétroviral et l'instauration immédiate du traitement au moment du diagnostic ont transformé ce qui était jadis une maladie infectieuse mortelle en problème de santé chronique. En conséquence, les types de maladies CV survenant en présence d'une infection par le VIH sont passés des épanchements péricardiques et de la cardiomyopathie dilatée à l'athérosclérose et à l'insuffisance cardiaque. La physiopathologie sous-jacente des maladies CV associées au VIH demeure mal comprise, en partie parce que le traitement du VIH a évolué rapidement et que l'élaboration des critères cliniques nécessite de nombreuses années. L'intestin joue un rôle important au début de la pathogenèse de l'infection par le VIH, car le virus infecte préférablement les lymphocytes T CD4+, dont 80 % se trouvent dans la muqueuse intestinale. La perte de ces lymphocytes T endommage la muqueuse intestinale, augmentant ainsi la perméabilité intestinale et permettant la translocation microbienne, ce qui favorise l'inflammation chronique et l'activation immunitaire. Le traitement

With the advent of antiretroviral therapy (ART), the life expectancy of persons living with HIV increased dramatically and now approaches that of the general population.[1]

With this increased lifespan, non-AIDS comorbidities including cardiovascular (CV) disease (CVD) have emerged as key contributors to mortality.[2] As specific ART drugs and the timing of initiation of treatment have evolved, so have the CV conditions occurring in the setting of HIV. In the pre-ART era, the first reports of CVD in HIV were pericardial effusions,[3-5] followed by dilated cardiomyopathy.[6-8] These structural abnormalities were attributed to poorly controlled HIV,[8] older nucleoside reverse transcriptase inhibitors (NRTI),[9] and infectious complications.[10]

In the initial reports of coronary artery disease associated with HIV infection, the coronary disease was attributed to dyslipidemia from protease inhibitors (PIs);[11,12] however, the risk of CVD, including myocardial infarction (MI),[13] peripheral arterial disease,[14] and heart failure,[15] remains significantly higher than in the general population, and cannot be blamed mainly on PIs. As discussed elsewhere in this issue,[16] traditional risk factors are more common in HIV and include hypertension,[17] dyslipidemia,[16] cigarette smoking,[18] metabolic syndrome,[19] diabetes,[19] and chronic kidney disease.[20] Recently, a large meta-analysis (80 studies, 790,635 individuals living with HIV, and an aggregate follow-up of 3.5 million person-years) reported that the risk of CVD has increased 2-fold in HIV and that the global burden of CVD has tripled over the past 20 years.[21,22]

Understanding the mechanisms for CVD in HIV is a necessary first step that will lead to optimal prediction of individuals at risk, leading to early intervention to prevent

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Corresponding author: Dr Priscilla Y. Hsue, Room 5G1 Cardiology, Zuckerberg San Francisco General Hospital, 1001 Potrero Avenue, San Francisco, California 94110, USA. Tel.: +1-415-206-8257; fax: +1-415-206-5447.

E-mail: priscilla.hsue@ucsf.edu

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induces lipid abnormalities, most commonly hypertriglyceridemia. On a molecular level, monocytes/macrophages, platelet reactivity, and immune cell activation, which play a role in the general population, may be heightened in the setting of HIV and contribute to HIV-associated atherosclerosis. Chronic inflammation represents an inviting therapeutic target in HIV, as it does in uninfected persons with atherosclerosis.

antirétroviral ne guérit pas l'infection par le VIH, et les anomalies immunitaires persistent. Ces anomalies ont une corrélation avec la mortalité et les événements CV. Les effets du traitement antirétroviral sur le risque CV sont complexes; le traitement réduit l'inflammation et d'autres marqueurs du risque CV, mais induit des anomalies lipidiques, le plus souvent sous forme d'hypertriglycéridémie. Au niveau moléculaire, les monocytes/macrophages, la réactivité plaquettaire et l'activation des cellules immunitaires, qui jouent un rôle dans la population générale, peuvent être augmentés en présence du VIH et contribuer à l'athérosclérose associée au VIH. L'inflammation chronique représente une cible tentante dans le traitement du VIH, comme chez les personnes non infectées atteintes d'athérosclérose.

disease.[23] Understanding the pathophysiology of CVD in HIV is also required for the development of optimal therapies to treat HIV-associated CVD. Almost certainly the risk factors contributing to this disease process have changed as the HIV epidemic has changed. A clear understanding of how HIV infection causes CVD remains elusive, and a critical challenge for researchers, clinicians, and persons living with HIV. The factors contributing to the mechanisms of CVD in HIV and their inter-relationships will be discussed in the remainder of this article.

Overview of Mechanisms Contributing to CVD in HIV

The atherosclerosis that develops in persons living with HIV shares important commonalities with atherosclerosis in uninfected persons. This review focuses on the unique mechanisms of atherosclerosis in HIV, most of which interact with and amplify the mechanisms operative in "ordinary" atherosclerosis. The mechanisms contributing to CVD in the setting of HIV are listed in Table 1, and their inter-relationships are depicted in Figure 1.

Leaky Gut and Microbial Translocation

The gut plays an important role in the early pathogenesis of HIV infection.[24,25] HIV preferentially infects CD4+ T cells, 80% of which are located in gut mucosa. The loss of these T cells damages gut mucosa resulting in "leaky gut," as illustrated in Figure 2. (Leaky gut plays an important role in many medical conditions, including autoimmune diseases.) Leaky gut alters the intestinal microbiome,[25-27] increases gut permeability, and allows microbial products to cross into the bloodstream, a phenomenon termed "microbial translocation." Microbial translocation incites chronic downstream inflammation and immune activation.[25-27] Depletion of gut CD4+ T cells persists into the chronic phase of HIV infection despite effective ART.

Microbial translocation appears to play an important role in CV risk both in individuals with and without HIV infection. Lipopolysaccharide, a product of microbial translocation, stimulates monocytes to produce soluble CD14, a marker that is independently predictive of mortality in HIV.[28] In the general population, the gut microbiota-derived metabolite trimethylamine-N-oxide (TMAO) has been reported to be a new marker for CV risk, being associated with increased mortality, CV events, cerebrovascular events,[29,30] and heart failure.[31] However, studies of TMAO in HIV have yielded conflicting results. Higher TMAO levels have been linked to thicker carotid intima-media thickness (IMT)[32] and greater coronary plaque burden,[33] but in another study, the relationship to coronary artery stenosis was the opposite from expected.[34]

Various interventions targeting the gut including sevelamer,[35] rifaximin,[36] probiotic administration,[37] and mesalamine[38] have not consistently lowered inflammatory markers or T-cell activation in HIV. This suggests that other strategies may be needed to impact chronic inflammation in the setting of HIV.

Table 1. Factors contributing to the pathogenesis of CVD in HIV

Traditional CV risk factors
• Hypertension, lipid abnormalities, cigarette smoking, metabolic syndrome, diabetes, chronic kidney disease
Leaky gut and microbial translocation
T-cell activation and cytomegalovirus coinfection
Antiretroviral therapy
Chronic inflammation
Platelet abnormalities

CV, cardiovascular; CVD, cardiovascular disease.

T-cell Activation and CMV Coinfection

Although successful ART controls HIV, the virus persists in a latent reservoir; thus, treatment must be continued indefinitely but HIV infection is not cured.[39] Immune dysfunction and inflammation improve with ART, but the restoration is partial and immune abnormalities persist.[40,41] Whether these persistent immune abnormalities, as assessed by T-cell activation, correlate with future CV events is unclear. In 1 case-controlled study, higher levels of inflammatory and coagulation markers, including interleukin-6 (IL-6), soluble tumor necrosis factor receptor I, kyrurenine-to-tryptophan ratio, and D-dimer, were associated with the occurrence of non-AIDS defining events including MI and stroke, but T-cell activation was not.[42]

How might we explain the failure of T-cell activation to correlate with CV events in the setting of HIV infection? One possibility is that "upstream" factors proximal to HIV infection have less influence than "downstream" inflammatory and coagulation markers that are closer to the CV events. Another possibility is that the impact of T-cell activation on CV events

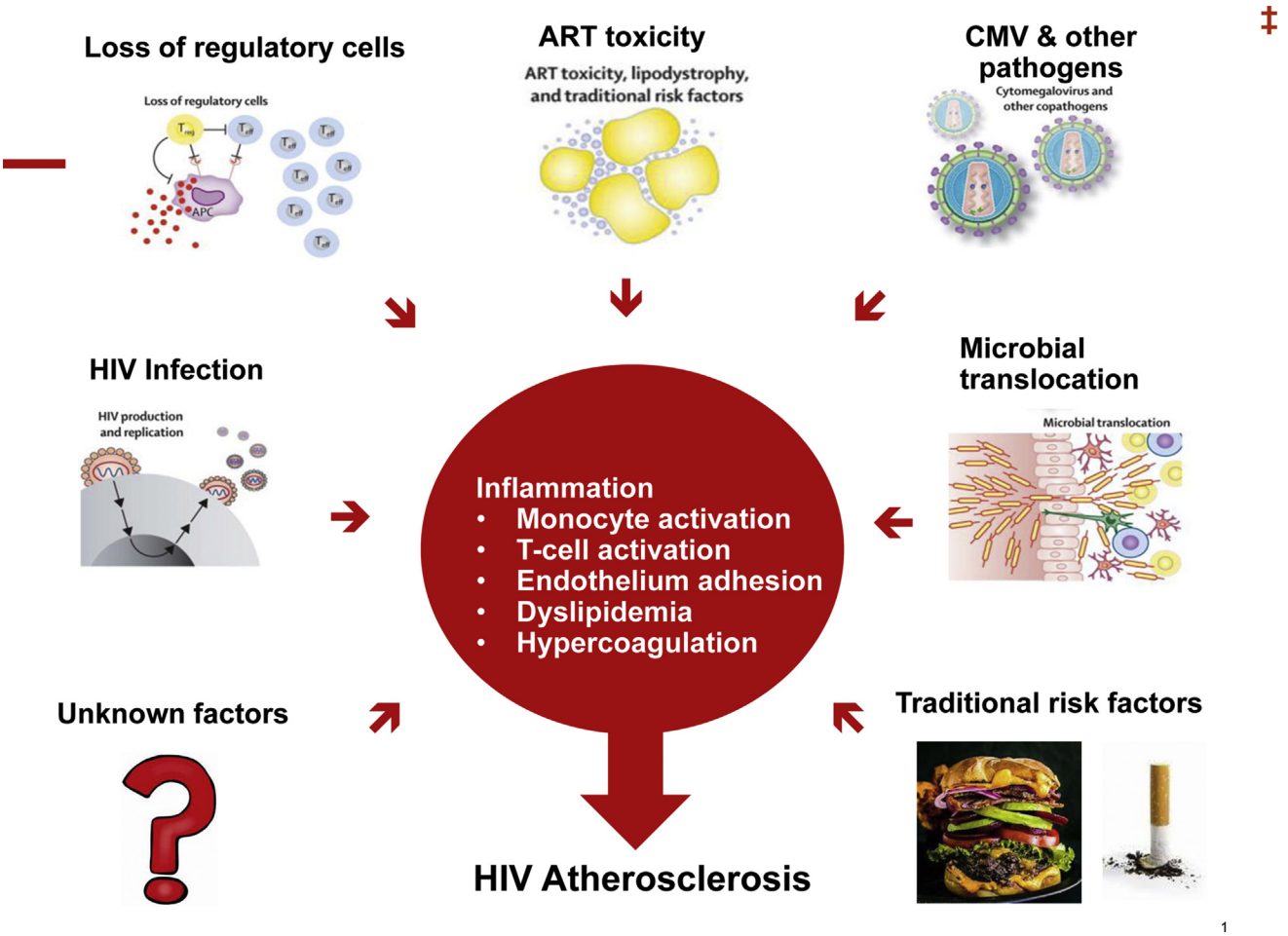

Figure 1. Mechanisms leading to atherosclerotic cardiovascular disease with human immunodeficiency virus (HIV) infection. This schematic figure illustrates the multiple and complex mechanisms leading to HIV-associated atherosclerosis in people living with HIV. While HIV infection is controlled by antiretroviral medication, HIV is not cured and thus persons living with HIV must take antiretroviral medications chronically. Antiretroviral therapy (ART) suppresses HIV infection and may improve T-cell abnormalities, but even in the setting of effectively treated HIV infection, abnormalities in immune activation and chronic inflammation persist, which are strongly predictive of atherosclerosis. HIV infection causes immune dysfunction and loss of regulatory T-cells. Concomitant cytomegalovirus (CMV) infection, also is a strong driver of immune activation and CV risk in HIV. HIV infection depletes immune cells in the gut, making it susceptible to microbial translocation, which produces downstream proinflammatory responses that favour the development of pro-atherosclerotic vascular damage. Traditional risk factors, including cigarette smoking, hypertension, and metabolic issues, are also more common in the setting of HIV infection. The degree of cardiovascular risk associated with HIV infection is not fully explained by known risk factors, so as-yet unidentified contributors may also exist. The final common pathway of all risk contributors in HIV includes chronic inflammation, mediated via monocyte/macrophage activation, T-cell activation, vascular dysfunction, dyslipidemia, and hypercoagulation.

in HIV may be mediated by an effect on microvascular disease. In support of this hypothesis, our group has recently reported that impaired T-cell activation in treated subjects with HIV correlated with impaired reactive hyperemia, a marker of microvascular disease.[43] An additional bit of evidence linking immune activation to CV outcomes relates to cytomegalovirus (CMV)-specific immune responses. These CMV-specific responses underlie immunologic aging in HIV[44] and are independently predictive of carotid IMT in HIV.[45,46]

Although controversial, CMV infection has been associated with an increased risk of CVD in the general population[47] and with coronary atherosclerosis in cardiac transplant recipients.[48] It is possible that CMV-associated immune responses play a key role in the development of atherosclerosis in persons living with HIV.

Severity of HIV Disease and CVD

The hallmark of HIV infection is CD4+ T-cell depletion. Early studies reported an association between nadir CD4 count, a maker of advanced immunodeficiency, and surrogate markers of atherosclerosis such as carotid IMT[49] and arterial stiffness.[50] Shortly thereafter, low CD4+ T-cell count was linked to incident MI in 2 large HIV cohorts.[51,52] Using more stringent adjudication criteria, lower CD4 count and

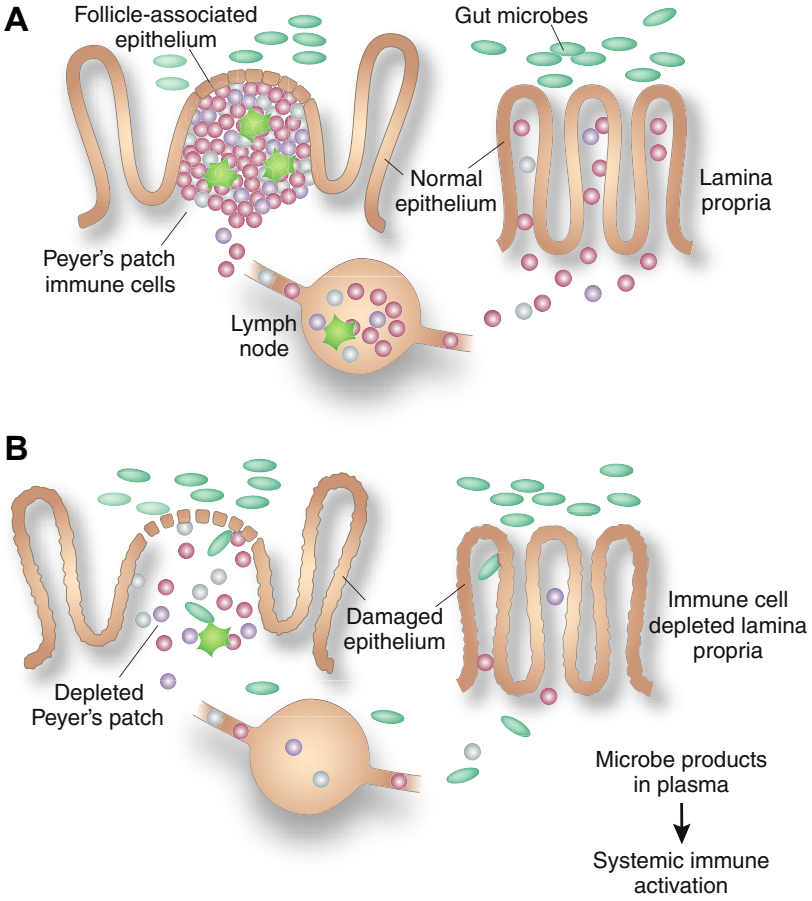

Figure 2. (**A**) Normally functioning gut endothelium with abundant immune cells. Gut microbes do not cross the lamina propria. (**B**) The consequences of HIV infection, with marked depletion of immune cells, leaky gut, and microbial translocation. Microbial products in the plasma cause systemic chronic immune activation. Reprinted from Brenchley et al.,[25] with permission from Springer Nature. © 2006 Springer Nature.

detectable HIV RNA levels were both associated with an increased risk for type 1 MI in the North American AIDS Cohort Collaboration.[53]

A low CD4/CD8 ratio is a hallmark of a collection of T-cell defects related to aging, termed immunosenescence.[54] A low CD4/CD8 ratio is a predictor of mortality in the general population.[54] After initiation of ART, an important proportion of HIV-infected individuals with adequate CD4+ T-cell recovery will have a persistently low CD4/CD8 ratio. A low ratio has been predictive of mortality and non-AIDS events, including CV events, in some[54,55] but not all studies.[56] It has been suggested that monitoring this ratio might be clinically useful because it is a marker of persistent immune dysfunction, inflammation, and increased CV risk.[54]

Impact of ART on CV Risk in HIV

The drugs approved for the treatment of HIV infection are listed according to class in Table 2. The precise impact of ART on CV risk is complex and not simple to evaluate for a number of reasons: (1) 3 to 4 drugs are given in combination to attain viral suppression; (2) continuous treatment resulting in viral suppression reduces CV risk, yet specific drugs increase risk; (3) the increase in risk associated with ART may be mediated by lipid abnormalities, other metabolic disturbances, or other poorly understood mechanisms such as antiplatelet effects; (4) an increased CV event rate may not be apparent until after years of treatment; and (5) newer drugs with more favourable lipid and metabolic profiles are replacing older, more toxic ART.

Although the benefits of ART on HIV disease itself begin shortly after starting therapy and are easy to monitor using CD4 count and HIV viral load, initial studies evaluating the effects of ART and CV risk were mixed. A large cohort study from the US Veterans Affairs included 36,766 HIV-infected individuals treated between 1993 and 2001.[57] The introduction of ART was associated with a precipitous decline in mortality with no increase in CV or cerebrovascular events. However, soon thereafter, the Data Collection on Adverse Events of Anti-HIV Drugs (DAD) Study Group reported a 26% relative increase in the rate of MI per year of ART exposure.[58] The DAD study included a cohort of over 23,000 individuals and more than 36,000 person-years of observation. In a follow-up study, the DAD group reported that exposure to PIs specifically was associated with an increased risk of MI that was only partly explained by PI-induced dyslipidemia.[59]

Table 2. Antiretroviral therapy for HIV infection

Protease inhibitors
• Atazanavir, darunavir, fosamprenavir, ritonavir, saquinavir, tipranavir
Nucleoside reverse transcriptase inhibitors
• Abacavir, emtricitabine, lamivudine, tenofovir, zidovudine
Non-nucleoside reverse transcriptase inhibitors
• Doravirine, efavirenz, etravirine, nevirapine
CCR5 antagonists
• Maraviroc
Integrase inhibitors
• Dolutegravir, raltegravir
Fusion inhibitor
• Enfuvirtide
Pharmacokinetic enhancer
• Cobicistat
Postattachment inhibitor
• Ibalizumab

In the **S**trategies for **M**anagement of **A**nti**r**etroviral **T**herapy (SMART) study, the episodic use of ART, the drug conservation strategy, was compared with continuous ART, the viral suppression strategy.[60] During 16 months of follow-up, the episodic use of ART was associated with an increased risk of death and opportunistic infections, including an increase in CV events ($P = 0.05$). Inflammatory and coagulation biomarkers in SMART, namely IL-6 and D-Dimer, were strongly related to all-cause mortality, suggesting that this was the mechanism whereby intermittent ART increased the risk.[61]

When ART first became available, it was withheld until the CD4+ count fell below a specific level. The **S**trategic **T**iming of **A**nti**r**etroviral **T**herapy (START) study established that starting ART when the CD4+ count exceeded 500 cells/mm^3 yielded better results compared with waiting until the CD4+ count fell below 350 cells/mm^3.[62] Early initiation of ART in START was not associated with an increase in CV event rates, a finding that was unsurprising given the young age of the study population, the relatively short duration of follow-up, and the paucity of CV events. Subsequent studies from START evaluating the effect of early ART on predictors of CV risk showed no effect on arterial elasticity,[63] an increase in low-density and high-density lipoprotein cholesterol, and a reduction in the need for antihypertensive medication.[64]

The NRTI abacavir has been controversial. Recent or current use of the abacavir was associated with an increased risk of MI in a report from the DAD study with a relative rate of 1.90, 95% confidence interval 1.47-2.45.[65] Current or recent use, but not cumulative use was associated with the increased MI risk. This increased risk was not confirmed in most other studies or in meta-analyses.[66,67] The possible increased CV risk of abacavir has been attributed to increased thrombosis,[68] increased platelet reactivity,[69] and endothelial dysfunction.[70]

Newer forms of ART have been compared using surrogate markers for CV events. Between PIs, carotid IMT progressed more slowly among individuals initiating atazanavir as compared with darunavir.[71] This finding presaged a report from the DAD study, now with over 49,000 study participants followed for a median of 7 years, showing that the cumulative use of ritonavir-boosted darunavir but not ritonavir-boosted atazanavir was associated with an increased risk of CV events.[72] It has been postulated that the increase in serum bilirubin levels associated with atazanavir use may be cardioprotective, as bilirubin was demonstrated to be inversely associated with CVD in a cohort with and without HIV.[73]

Switching ART from PIs to integrase inhibitor therapy[74] does not appear to impact endothelial function despite improvement in lipid profiles.[75] Long-term studies will be required to evaluate the impact of integrase inhibitors on CV events. Although recently studies have reported high rates of heart failure in the setting of HIV,[1] the mechanism underlying this risk remains unclear. Regimens including PIs were associated with a lower left ventricular ejection fraction, increased CV mortality, and a higher rate of heart failure readmissions in a recent single-centre cohort study of individuals with HIV and heart failure.[76]

Chronic Inflammation and CVD in HIV

Inflammation plays an important role in atherogenesis both in individuals with and without HIV infection, and is currently being intensively investigated as a target of therapy. A strong association has been shown in HIV cohorts between inflammatory and coagulation markers and mortality,[56] CVD,[77] fatal CVD,[78] and non-AIDS events.[79] It is generally assumed that a therapy that does not reduce inflammatory markers is unlikely to reduce CV events, at least through an anti-inflammatory mechanism. Intensification of ART using CCR5 inhibitors or integrase inhibitors does not appear to significantly impact inflammatory markers,[80,81] suggesting that other interventions will be required in the setting of effectively treated HIV infection.

In the general population with CVD, a monoclonal antibody to interleukin-1β (IL-1β), canakinumab, significantly reduced inflammatory markers including IL-6 and hs-CRP without any effect on low-density lipoprotein cholesterol.[82] These changes were associated with a significant reduction of recurrent CV events as compared with placebo. Interestingly, anti-inflammatory therapy with canakinumab also reduced total cancer mortality, incident lung cancer, and lung cancer mortality.[83] In further analysis of the data, individuals who achieved an hs-CRP level of < 2 mg/L when treated with canakinumab had a 25% reduction in major CV events, a 31% reduction in CV mortality, and a 31% reduction in all-cause mortality, whereas no reduction in these endpoints was observed among individuals who failed to achieve this level of hs-CRP reduction.[84] Similarly, on-treatment IL-6 reductions were associated with a large, statistically significant reduction in CV endpoints.[85]

The effect of anti-inflammatory treatments on inflammatory markers in the setting of HIV has been mixed. Statins have not been shown to consistently lower hs-CRP, IL-6, or D-dimer levels,[86-88] nor did a short course of aspirin therapy in a placebo-controlled study.[89] Modelling studies have suggested that a reduction of IL-6 and D-dimer could translate to a 37% reduction in the risk of serious non-AIDS events or death in HIV.

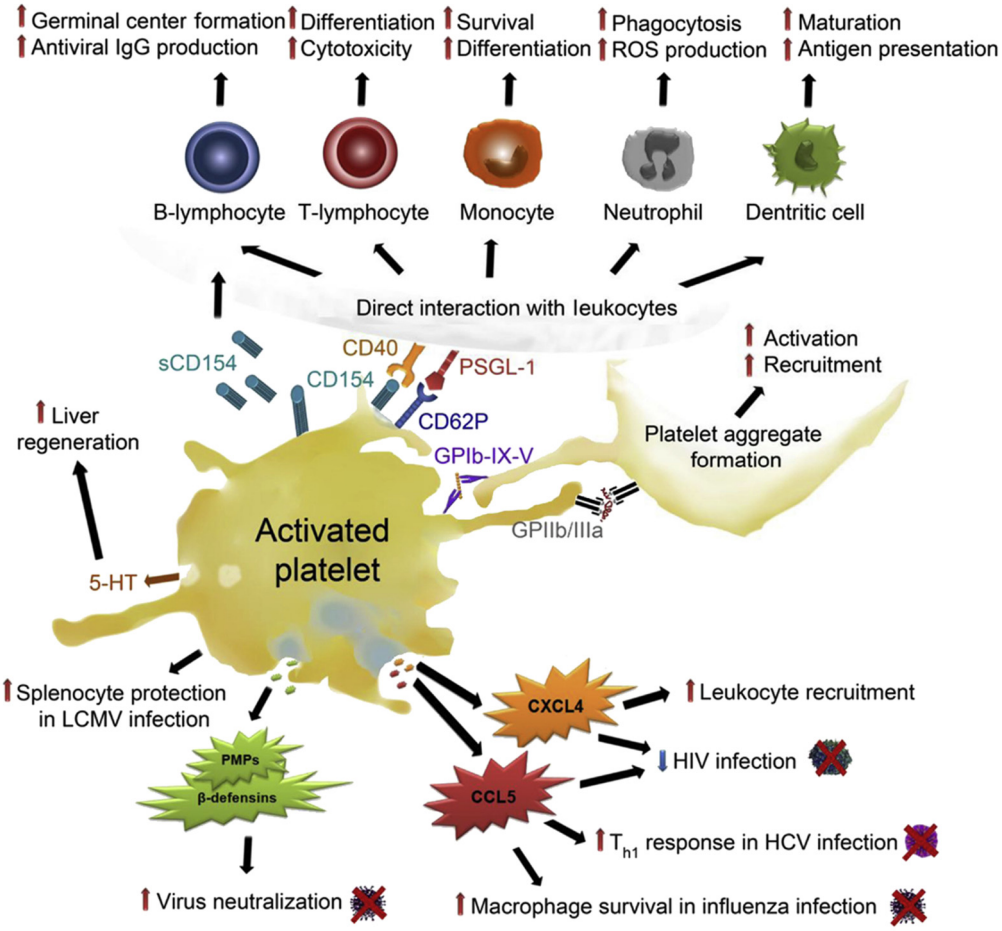

Figure 3. Effects of activated platelets on virus infection. On activation, platelets release their α-granules, containing high amounts of CXCL4, which upregulates coagulation and leukocyte recruitment. Moreover, CXCL4 decreases HIV infection but enhances liver fibrosis. CCL5, another α-granule-derived chemokine, also decreases HIV infection. Platelets release PMPs and β-defensins from their α-granules, which mediate virus neutralization. They protect splenocytes from necrosis in LCMV infection. Platelet dense granules contain 5-HT, which enables not only liver regeneration but also hepatitis B virus and HCV infection. Platelet activation leads to the expression and release of CD154 and CD62P, which allow direct interaction between platelets and leukocytes. Platelet interaction with B-lymphocytes enhances germinal centre formation and antiviral IgG production. Platelets trigger T-lymphocyte differentiation and cytotoxicity as well as survival and differentiation of monocytes. In neutrophils, platelet adhesion stimulates ROS production and boosts phagocytosis. Platelet interaction with dendritic cells promotes their maturation and facilitates antigen presentation. Finally, platelet activation results in interaction and activation of further platelets, which triggers platelet aggregation and amplifies the above-described processes. 5-HT, serotonin; CCL5, chemokine (C—C motif) ligand 5; CXCL4, C—X—C chemokine ligand 4, GP, glycoprotein; HCV, hepatitis C virus; LCMV, lymphocytic choriomeningitis virus; PMP, platelet antimicrobial peptide; PSGL-1, P-selectin (CD62P) glycoprotein ligand-1; ROS, reactive oxygen species; sCD154, soluble CD154/CD40 ligand; Th1, T-helper lymphocyte type 1. Reproduced from Assinger[99] with permission by Creative Commons Licence (CC BY 4.0).

Our group has evaluated the impact of low-dose methotrexate in HIV. We found no effect on inflammatory markers or endothelial function but a significant decrease in CD8+ T cells and a decrease in arterial echogenicity.[90,91] In a recent large trial among 4786 patients with previous MI or multivessel coronary disease, plus either diabetes or metabolic syndrome, low-dose methotrexate did not lower IL-1β, IL-6, or hs-CRP levels, and did not reduce CV events.[92]

In contrast, in a small study of persons with HIV, IL-1β inhibition using canakinumab had no impact on CD4, CD8, or HIV RNA levels but significantly reduced IL-6 and hs-CRP.[93] Canakinumab treatment also significantly inhibited both arterial and bone marrow inflammation in this study. As yet, no other intervention in HIV has been reported to lower IL-6 or hs-CRP, and no clinical endpoint studies evaluating the impact of lowering inflammation in HIV have not been performed. Nevertheless, this therapeutic area remains promising for its potential to reduce CV events in those living with HIV.

Platelet Function in HIV

Platelets play an important role in the immunologic response to infection[94] and in the inflammatory activity that contributes to atherogenesis.[95] The HIV virus is internalized and sheltered by platelets, and platelets disseminate the virus throughout the body.[96] Circulating platelet leukocyte

aggregates are increased in treatment-naïve individuals with HIV infection, and these aggregates correlate with CD4 count and viral load.[97] In response to viruses and other stimuli, platelets are activated, undergo morphologic changes, and release α-granules, leading to increased expression of molecules such as P-selectin.[98,99] Lipopolysaccharide, a circulating product of microbial translocation, also stimulates platelets, through a mechanism related to IL-1β.[100] The complex actions resulting from platelet activation are depicted in Figure 3.

In the setting of treated HIV infection, platelet function is altered,[101] probably as a consequence of chronic inflammation.[102] However, ART can directly affect platelet function; for example, the PI ritonavir has been shown to stimulate platelet production of proinflammatory mediators such as prostaglandin E_2.[103] Specific ART drugs have sometimes been reported to have either salutary or harmful effects on platelet reactivity in one study but not another. For example, the integrase inhibitor raltegravir reduced platelet hyper-reactivity in one study[104] but not in another.[105] As previously discussed, whether the NRTI abacavir causes an increased risk of MI is controversial. In one study[69] but not in another,[106] abacavir increased platelet reactivity.

Morphology of Atherosclerosis in HIV

The differences between HIV-related atherosclerosis and "ordinary" atherosclerosis extend to morphologic differences. Studies using different imaging techniques show that atherosclerosis in the setting of HIV has distinct features.[107] Using intravascular ultrasound in individuals presenting with ACS, those living with HIV had lower plaque burden, higher prevalence of hypoechoic plaques, and a higher incidence of subsequent CV events.[108] Using computed tomographic angiography, noncalcified plaque is more common and extensive in individuals with HIV compared with controls.[109] Multiple studies have reported greater carotid IMT in the setting of HIV.[110] This has been associated with higher levels of inflammatory markers[111] and higher mortality.[112,113] As assessed by fluorodeoxyglucose-positron emission tomography/computed tomography, persons living with HIV have higher levels of arterial inflammation, which is related to makers of macrophage activity,[114] and also higher levels of bone marrow activity, which was strongly related to HIV disease characteristics.[115]

Individuals living with HIV also have impaired endothelial function as assessed by brachial artery flow-mediated vasodilation.[43] This endothelial dysfunction improves after initiation of ART[116] and may be related to T-cell dysfunction.[50] Using magnetic resonance imaging, cardiac fibrosis has been reported in persons living with HIV,[117] and appears to be related to inflammation.[118]

Conclusions

The etiology of HIV-associated CV disease remains elusive many years after the initial clinical reports. The underlying mechanisms have likely shifted during this time to reflect changes in ART and timing of initiation of ART. Although traditional CV risk factors clearly play a role, HIV-specific features including ART and chronic inflammation/immune activation are also clearly implicated in the pathogenesis of CVD in HIV. Future studies including basic investigations of the molecular mechanisms underlying this disease process, translational proof-of-concept approaches to identify key therapeutic targets, and finally clinical-outcome studies are all needed to move this field forward.

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Disclosures

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