HHS Public Access

Author manuscript

Curr Opin HIV AIDS. Author manuscript; available in PMC 2017 March 01.

Published in final edited form as:

Curr Opin HIV AIDS. 2016 March ; 11(2): 216–225. doi:10.1097/COH.0000000000000227.

Immune Activation and Cardiovascular Disease in Chronic HIV Infection

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Abstract

Purpose of review—To describe the potential contribution of immune activation in the pathogenesis of HIV-associated cardiovascular disease (CVD)—a leading cause of morbidity and mortality among HIV positive persons with access to antiretroviral therapy (ART).

Recent findings—We review recent literature that suggests abnormalities in both adaptive and innate immunity contributes to CVD risk among persons with HIV infection. In particular, potentially atherogenic T-cell mechanisms include persistent high-level T-cell activation (and associated pro-inflammatory mechanisms), as well as the presence of co-pathogens (e.g., CMV) providing an ongoing stimulus for cytotoxic T-cell responses. More recent data has then emphasized the potential impact of monocyte/macrophage-mediated inflammation and injury within atherosclerotic lesions. The pathology driving innate immune activation many not fully reverse with ART treatment, highlighting the need for interventions that target inflammation as a CVD prevention strategy.

Summary—Premature CVD among persons with HIV infection is due, in part, to persistent abnormalities in immune activation and systemic inflammation despite viral suppression. Prevention strategies for persons with HIV infection include those that target traditional CVD risk factors as well as newer candidate treatments with potential immunomodulatory benefits.

Keywords

HIV; cardiovascular disease; Immune activation

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Conflict of Interests: CTL has received research funding from Bristol-Myers Squibb and Medtronic Philanthropy. CS and JVB have no conflicts.

Off-Label Use: This review discusses the ongoing investigation of the following drugs for off-label indication of decreasing inflammation and immune activation in patients with HIV infection: methotrexate, tocilizumab, canakinumab, pentoxifylline, salsalate, rosuvastatin, atorvastatin, pitavastatin, aspirin, telmisartan, losartan, metformin, Omega-3 fatty acids.

Introduction

Soon after effective antiretroviral therapy (ART) became available in the mid-1990's, the first case reports of acute myocardial infarction in young HIV-infected men on combination ART were published in the Lancet[1]. In the nearly two decades since, we have developed a greater understanding of the epidemiology and mechanisms of cardiovascular disease (CVD) among those with HIV infection. Recent reviews in this journal have summarized this evolving field in terms of the epidemiology and risk factors for CVD in HIV[2] and whether early ART might reduce CVD risk[3].

Currently, it is now recognized that chronic HIV infection is associated with higher risk for a broad spectrum of cardiovascular diseases that includes not only myocardial infarction[4], but also stroke[5], heart failure[6], and sudden cardiac death[7]. Furthermore, the HIV-associated risk appears to be at least as high in women as it is in men[8]. Pathogenesis studies of subclinical CVD suggest that individuals with HIV-infection may have a greater prevalence of high-risk features within coronary artery plaques,[9, 10] and potentially significant myocardial steatosis and fibrosis[11, 12]. Despite the relative increased CVD risk, absolute event rates remain low in this relatively young population—approximately 0.5 CVD deaths per 1000 person years among 65,000 patients in Europe and North America[13]. Some reports have even described event rates that approach HIV-negative cohorts, possibly due to heightened awareness and more aggressive risk factor modification[14, 15]. Ultimately, CVD event rates are likely to increase, potentially more rapidly, as the treated HIV-infected population continues to age[2].

Traditional risk factors remain important mediators of CVD in the HIV-infected population. For example, smoking is highly prevalent and is associated with a higher risk of MI in HIV infection compared to an uninfected control population[14]. Cardiometabolic risk factors such as hypertension, dyslipidemia, and diabetes are also common in HIV infection, partly attributable to certain antiretroviral medications, and associated with cardiovascular events.[4, 16-18] However, newer ART drugs have more favorable cardiometabolic profiles[19], and some data suggest ART initiation with modern regimens may reduce risk for the metabolic syndrome[17]. Ultimately, with availability of well-established approaches to target traditional risk factor modification, an important unmet need in the field remains understanding and targeting non-traditional risk factors. In particular, chronic inflammation and immune activation persist despite effective ART and appear to contribute to subclinical disease and CVD events, similar to what is seen in patients with inflammatory autoimmune diseases such as rheumatoid arthritis or psoriasis. In this review, we will explore recent evidence of how adaptive and innate immune mechanisms relate to CVD among individuals with HIV infection, as well as review potential strategies to mitigate CVD risk by reducing immune activation.

Adaptive Immune Mechanisms

CD4+ T-cell depletion and dysfunction, and chronic CD8+ T-cell activation, are hallmarks of HIV infection. Greater T-cell proliferation and turnover among HIV infected when individuals is a central components of AIDS pathogenesis[20]. Recent research has focused

increasingly on understanding the implications of changes in adaptive immunity for CVD and other end-organ disease risk. **Figure 1** provides schematic context for how the cellular arms of adaptive immunity can have differential effects on atherogenesis.

Associations between CD4+ T-cell depletion and cardiovascular risk have been widely reported on [9, 21-28]. In the HIV Outpatient Study cohort, CD4 < 500 cells/mm^3 was an independent risk factor for cardiovascular disease events that was as dangerous as smoking or high LDL[21]. Similar data show associations between lower nadir CD4 and other measures of preclinical CVD including higher left ventricular mass, increasing intima–media thickness, and lower brachial artery flow-mediated dilation[9, 22]; however, the D:A:D (Data collection on Adverse events of Anti-HIV Drugs) study failed to show a strong linear relationship between current CD4 count and a broad composite of CVD outcomes, although most events were less frequent among those who did not experience immune depletion [23]. Data from the Kaiser Permanente System are consistent with this, showing that MI rates for HIV+ persons with CD4 counts >500 cells/mm^3 were similar for HIV infected and uninfected persons [24]. In summary, while severe immune depletion (e.g., at CD4 counts <200 cells/mm^3) may contribute to premature CVD, more recent literature suggests this relationship may be less clinically relevant among those with immune preservation. In support of this notion, the Strategic Timing of AntiRetroviral Therapy (START) trial failed to show that immediate ART treatment specifically reduced CVD events among ART-naïve HIV positive patients with CD4 counts >500 cells/mm3, despite reductions in a number of other AIDS and non-AIDS clinical events [29].

Another potentially important contributor to CVD pathogenesis relates to activation of the adaptive immune response. Concurrent with CD4 depletion, high-level and persistent CD8+ T-cell activation is a key feature of the natural history of HIV infection [30]. Both a higher absolute CD8+ T-cell count as well as a lower CD4:CD8 ratio, have been associated with a greater degree of coronary plaque by CT angiography and an increased risk of MI among HIV-infected individuals[28, 31]. In sentinel data by Kaplan et al, higher frequencies of immune activation and senescent CD8+ T-cells phenotypes were associated with higher prevalence of carotid artery lesions, even among patients on ART with effective viral suppression[32]. Mechanisms accounting for persistent CD8+ T-cell activation despite clinically undetectable HIV viral loads, may include both a persistent anti-HIV response as well as stimulation from other prevalent co-pathogens such a cytomegalovirus (CMV) [33, 34]. In a cross-sectional comparison, Hsue et. al. reported higher carotid intima-media thickness (CIMT), inflammation, and T-cell activation among HIV infected versus uninfected persons, though only CMV-specific T-cell responses were independently associated with CIMT in adjusted analyses [35]. The potential importance of CMV-specific T-cell activation for HIV-associated CVD pathogenesis has since been supported by data demonstrating that CMV IgG titers predict greater carotid artery lesions, and that CMV-specific CD4+CX3CR1+ T-cells may contribute to greater CIMT progression via mechanisms that induce arterial wall inflammation [36, 37].

Cumulatively, these data emphasize that ongoing abnormalities in adaptive immune likely contribute to increased atherosclerosis during chronic HIV infection. Research has largely focused on T-cell activation, associated pro-inflammatory mechanisms, and the potential

influence of co-pathogens (e.g., CMV) providing an ongoing stimulus for cytotoxic T-cell responses (CTL; **Figure 1**). To date, the potential loss of anti-atherogenic adaptive immune responses (e.g., T-regulatory and B-cell responses) has not been extensively studied as a potential driver of HIV-associated CVD risk. Although one recent study from sub-Saharan Africa demonstrated that subjects with HIV have a profile of natural auto-antibodies that has been associated with increased risk of cardiovascular disease in the general population and patients with auto-immune disorders.[38] Further research is needed to both explore these underlying mechanisms, as well as to identify treatment strategies that further improve immune recovery and normalize immune activation.

Innate Immune Mechanisms

Innate, or non-specific, immunity is well known to be a central feature of atherosclerosis pathogenesis **(Figure 2)**.[39] The general sequence involves adherence of circulating monocytes to vessel walls with infiltration into nascent plaques, where, as tissue macrophages, they may perpetuate tissue injury via release of pro-inflammatory cytokines and/or evolve into cholesterol rich ‘foam cells’. Recent data have demonstrated that the spectrum of immunologic abnormalities during HIV infection, including treated disease, also includes activation of innate immunity (e.g., monocytes) and associated consequences for systemic inflammation and the development of premature CVD.[40-45]

Multiple studies have now demonstrated that HIV infection is associated with higher frequencies of activated monocyte subsets; i.e., so called intermediate (or ‘pro-inflammatory’, CD14+CD16+) and non-classical (or ‘patrolling’, CD14dimCD16+) monocytes.[43-48] CD16+ monocyte subsets may also be more permissive to infection by HIV.[49] Funderburg et. al. demonstrated that the frequency of pro-inflammatory intermediate monocytes among HIV+ persons were correlated with viral load, CD8+ T-cell activation, CD4+ T-cell declines, and interleukin-6 levels.[44] Compared to HIV uninfected persons, the frequency of patrolling non-classical monocytes were also elevated among HIV infected persons, but also persisted among those with viral suppression.[44] In this study, the frequency of both intermediate and non-classical monocytes was similar between HIV viremic patients and those without HIV infection but who presented for cardiac catheterization with acute coronary syndrome (ACS).[44] Consistent with these data, higher frequencies of CD16+ monocytes (intermediate and non-classical phenotypes) among 436 HIV+ patients (SUN Study) were associated with greater subsequent progression of coronary artery calcium (CAC), independent of traditional and HIV risk factors.[50]

Although the functional characteristics of CD16+ (intermediate and non-classical) monocyte phenotypes remain controversial, these subsets exhibit properties that promote atherogenesis [48, 51-53]. Specifically, the patrolling non-classical phenotype may act as a ‘patrolling’ subset that has greater affinity for vascular surfaces and migration into atherosclerotic lesions [51, 52]. The intermediate monocyte phenotype appears to be functionally more pro-inflammatory, with greater cytokine release after stimulation.[48, 51, 53] CD16+ monocytes then localize to tissues sites of inflammation and fibrosis, with transendothelial migration facilitated by CX3CL1.[54] Epidemiologic data from HIV-uninfected participants at risk for CVD (n=951) also demonstrates that the intermediate monocyte phenotype independently

predicts higher risk for subsequent CVD events (i.e., myocardial infarction, stroke or CVD-death).[55] Elevated levels of CD16+ monocytes among those with HIV infection, and their associations with CVD risk measures, suggests that innate immune activation may function largely to amplify key aspects of atherogenesis.

Numerous recent HIV studies of soluble plasma biomarkers have supported the notion that monocyte-related inflammation has CVD consequences for HIV+ patients.[42, 56-61] Soluble CD14 and CD163 levels, both reflecting monocyte activation, have been associated with greater carotic intima media thickness,[56, 57] calcified and non-calcified coronary plaque,[57-60] and arterial wall inflammation (estimated via FDG-PET imaging) among HIV-positive patients.[61] Recent non-human primate data using SIV infection further implicate monocyte/macrophage activation by demonstrating that cardiac pathology and myocardial fibrosis was associated with greater numbers of CD163+ monocytes as well as mycocardial macrophages overall.[62]

In summary, the current literature supports the notion that monocyte/macrophage-mediated inflammation and injury within atherosclerotic lesions are amplified in the context of HIV infection. Additional HIV associated monocyte abnormalities, related to impaired cholesterol efflux by foam cells and pro-coagulant effects (e.g., related to platelet-monocyte complexes), then further contribute to CVD risk.[63-65] For example, monocytes from HIV + subjects are more likely to become foam cells, have decreased expression of the cholesterol transporter ABCA1, and show impaired cholesterol efflux[66]. Dysfunctional HDL appears to further impair reverse cholesterol transport from macrophages, but this improves with ART[64]. The pathology driving innate immune activation and other monocyte abnormalities are likely related to both indirect effects from an ongoing HIV immune response, as well as due to permanent damage to the immune system—e.g., damage to mucosal lymphatic tissue and epithelial integrity leading to greater translocation of microbial products that drive innate immune responses.[44, 67] In this context, treatment interventions that target non-specific innate inflammation broadly may be more effective as a CVD prevention strategy.

Immune-based Strategies to Mitigate Risk

The accumulating observational evidence that immune activation is associated with CVD risk in persons with treated HIV infection suggests that therapies targeting these mechanisms—whether immunomodulatory drugs or proven CVD prevention therapies with anti-inflammatory effects—may have a cardiovascular benefit. Table 1 lists a number of completed and ongoing trials of immune targeted therapies that have included measures of subclinical vascular disease as surrogate outcomes of cardiovascular risk. In addition to the studies in Table 1, there are other trials that aim to improve outcomes such as immune function and tissue fibrosis, which would also be expected to influence cardiovascular risk.

Methotrexate (MTX) is a competitive dihydrofolate reductase inhibitor that modifies progression of rheumatoid arthritis primarily by reducing T-cell activation, but it also appears to have a beneficial effect on mortality in this population[72]. In light of this observation, the Cardiovascular Inflammation Reduction Trial (CIRT, www.thecirt.org) was

designed to test whether low-dose MTX will prevent CVD events in the general population. Similarly, a pilot study of 200 HIV-infected participants (NCT01949116) will evaluate the safety of low-dose MTX and its effect on endothelial function—results are anticipated in 2016. Other "biologic" agents (i.e. monoclonal antibodies that block cytokines or cytokine receptors) approved for the treatment of autoimmune disease are being tested in HIV-infected patients. Such agents include the interleukin-6 receptor antagonist tocilizumab (NCT02049437) and the interleukin-1 antagonist canakinumab (NCT02272946). Although dramatic reductions in immune activation are expected, whether the benefits will outweigh the significant risks is unclear. A worrisome precedent is that the tumor necrosis factor-α (TNF-α) antagonists etanercept and infliximab were associated with worse outcomes in trials to improve advanced heart failure [73, 74]. In contrast, interleukin-1 receptor antagonism improved heart failure outcomes in smaller studies[75, 76]. Less potent anti-inflammatory drugs salsalate and pentoxifylline have been poorly tolerated and/or have no meaningful effect on endothelial function in small trials of HIV positive participants[68-70].

Many traditional CVD prevention treatments also have 'off-target' anti-inflammatory effects that may partly mediate their CVD benefits. Chief among these are the statins, whose 'pleiotropic' anti-inflammatory properties are highly touted. Recent studies have reported on subclinical vascular outcomes of statins in the HIV-infected population and the potential effect modifying and mediating roles of inflammation and immune activation[77, 78]. Atorvastatin 20mg titrated to 40mg after 3 months reduced non-calcified plaque volume and high-risk coronary plaque features compared to placebo in a trial of 40 HIV positive participants on ART, who had evidence of subclinical coronary atherosclerosis at baseline and elevated vascular inflammation measured by PET-CT[77]. In the SATURN-HIV trial, rosuvastatin 10mg slowed progression of carotid intima-media thickness among 147 subjects with elevated hs-CRP and/or heightened CD8+ T-cell activation. Similar to HIV studies of atorvastatin[79-82], rosuvastatin reduced T-cell activation and exhaustion markers over 48 weeks in SATURN-HIV[83]. Markers of innate immune activation such as soluble CD14 and the proportion of tissue factor-positive non-classical ($CD14^{dim}CD16^{+}$) monocytes were also reduced with rosuvastatin[83]. Furthermore, baseline interleukin-6 levels and $CD14^{dim}CD16^{+}$ monocytes were inversely associated with IMT change in the statin group, and the statin benefit on IMT progression was greatest among subjects with higher levels of baseline markers of inflammation and immune activation[78].

Despite being at high risk, recent data suggest that nearly 75% of HIV infected subjects with high risk plaque features on coronary CTA would not be recommended to receive statin therapy by current guidelines[84]. Thus, the Randomized Trial to Prevent Vascular Events in HIV (REPRIEVE; reprievetrial.org) recently began enrolling 6500 HIV positive participants without a current indication for a statin (10-year ACC/AHA risk <7.5%) in an outcomes trial of pitavastatin vs. placebo. Results are expected in 2020.

Other drugs used for CVD prevention may also have beneficial effects on inflammation. Aspirin reduces relative risk of CVD events by about 10-20% in the general population[85], and also appears to rapidly reduce immune activation in subjects on ART[86]. Ongoing trials of aspirin will further explore its immune and vascular effects in HIV-infected populations (Table 1), but whether the reduction in CVD and other (e.g. cancer) events as

primary prevention will outweigh the risks of bleeding remains unclear. Omega-3 fatty acids modestly improve markers of systemic inflammation, but do not appear to have any effect on endothelial function in one small study[71].

Finally, drugs that act to reduce activation of the renin-angiotensin-aldosterone system (RAAS) may reduce CVD events through multiple pathways including reduction of inflammation and tissue fibrosis. RAAS activation may be worsened by protease inhibitors[87] and is associated with visceral adiposity and insulin resistance in HIV-infected subjects[88], but few clinical trials of RAAS blockade have been conducted in this population. Lisinopril reduced hsCRP and TNF-α despite sub-optimal adherence in one small pilot trial[89]. Telmisartan may ameliorate visceral adiposity in subjects on ART[90], but did not improve FMD in another underpowered pilot (NCT01578772). Telmisartan's effect on tissue fibrosis and inflammation is being tested in a 48-week open label trial of 44 participants on ART (NCT01928927). Two ongoing larger randomized placebo-controlled trials (NCT02049307 and NCT01852942) will evaluate similar inflammation and tissue fibrosis outcomes for losartan; another will test the effect of losartan on carotid IMT progression (NCT01529749).

Summary and Conclusions

Chronic HIV infection is characterized by persistent abnormalities in both adaptive and innate immunity, despite clinically suppressed viral load with effective ART. Drivers of this high-level immune activation remain diverse and may differ between individuals, though the consequences appear to fuel systemic inflammation and amplify well-described pro-atherogenic mechanisms. Treatment strategies with potential to mitigate HIV-associated CVD risk are currently an area of active investigation. Candidate interventions undergoing clinical trials include those that target traditional CVD risk factors, that have broad non-specific anti-inflammatory properties, and/or that target a specific underlying mechanism driving HIV-associated immune activation.

Acknowledgements

None

Financial support and sponsorship: This work was supported in part by the National Institutes of Health (K23 HL123341 to CTL; R01 AG045032 and R01 HL126542 to JVB).

References

1. Henry K, Melroe H, Huebsch J, et al. Severe premature coronary artery disease with protease inhibitors. Lancet. 1998; 351:1328. [PubMed: 9643798]
2. So-Armah K, Freiberg MS. Cardiovascular disease risk in an aging HIV population: not just a question of biology. Curr Opin HIV AIDS. 2014; 9:346–354. [PubMed: 24824885]
3. Longenecker CT, Triant VA. Initiation of antiretroviral therapy at high CD4 cell counts: does it reduce the risk of cardiovascular disease? Curr Opin HIV AIDS. 2014; 9:54–62. [PubMed: 24275676]
4. Freiberg MS, Chang CC, Kuller LH, et al. HIV Infection and the Risk of Acute Myocardial Infarction. JAMA Intern Med. 2013:1–9.
5. Sico JJ, Chang CC, So-Armah K, et al. HIV status and the risk of ischemic stroke among men. Neurology. 2015; 84:1933–1940. [PubMed: 25862803]

6. Butt AA, Chang CC, Kuller L, et al. Risk of heart failure with human immunodeficiency virus in the absence of prior diagnosis of coronary heart disease. Arch Intern Med. 2011; 171:737–743. [PubMed: 21518940]
7. Tseng ZH, Secemsky EA, Dowdy D, et al. Sudden cardiac death in patients with human immunodeficiency virus infection. J Am Coll Cardiol. 2012; 59:1891–1896. [PubMed: 22595409]
8*. Womack JA, Chang CC, So-Armah KA, et al. HIV infection and cardiovascular disease in women. J Am Heart Assoc. 2014; 3:e001035. [PubMed: 25324353] [Epidemiologic studies documenting a 1.5 to 2-fold increased risk of CVD in patients with HIV have historically included mostly male subjects. This study from the Veterans Aging Cohort Study (VACS) confirmed the hazard for CVD in women (HR=2.8) is at least as great if not greater than in men.]
9. Post WS, Budoff M, Kingsley L, et al. Associations between HIV infection and subclinical coronary atherosclerosis. Ann Intern Med. 2014; 160:458–467. [PubMed: 24687069]
10. Zanni MV, Abbara S, Lo J, et al. Increased Coronary Atherosclerotic Plaque Vulnerability by Coronary Computed Tomography Angiography in HIV-Infected Men. Aids. 2013
11. Thiara DK, Liu CY, Raman F, et al. Abnormal Myocardial Function Is Related to Myocardial Steatosis and Diffuse Myocardial Fibrosis in HIV-Infected Adults. J Infect Dis. 2015
12. Holloway CJ, Ntusi N, Suttie J, et al. Comprehensive cardiac magnetic resonance imaging and spectroscopy reveal a high burden of myocardial disease in HIV patients. Circulation. 2013; 128:814–822. [PubMed: 23817574]
13. Ingle SM, May MT, Gill MJ, et al. Impact of risk factors for specific causes of death in the first and subsequent years of antiretroviral therapy among HIV-infected patients. Clin Infect Dis. 2014; 59:287–297. [PubMed: 24771333]
14. Rasmussen LD, Helleberg M, May MT, et al. Myocardial infarction among Danish HIV-infected individuals: population-attributable fractions associated with smoking. Clin Infect Dis. 2015; 60:1415–1423. [PubMed: 25595744]
15. Klein DB, Leyden WA, Xu L, et al. Declining relative risk for myocardial infarction among HIV-positive compared with HIV-negative individuals with access to care. Clin Infect Dis. 2015; 60:1278–1280. [PubMed: 25595743]
16. Armah KA, Chang CC, Baker JV, et al. Prehypertension, hypertension, and the risk of acute myocardial infarction in HIV-infected and -uninfected veterans. Clin Infect Dis. 2014; 58:121–129. [PubMed: 24065316]
17. Krishnan S, Schouten JT, Atkinson B, et al. Changes in metabolic syndrome status after initiation of antiretroviral therapy. J Acquir Immune Defic Syndr. 2015; 68:73–80. [PubMed: 25321179]
18. Tien PC, Schneider MF, Cox C, et al. Association of HIV infection with incident diabetes mellitus: impact of using hemoglobin A1C as a criterion for diabetes. J Acquir Immune Defic Syndr. 2012; 61:334–340. [PubMed: 22878421]
19. Srinivasa S, Grinspoon SK. Metabolic and body composition effects of newer antiretrovirals in HIV-infected patients. European journal of endocrinology / European Federation of Endocrine Societies. 2014; 170:R185–202. [PubMed: 24523497]
20. Sodora DL, Silvestri G. Immune activation and AIDS pathogenesis. Aids. 2008; 22:439–446. [PubMed: 18301056]
21. Lichtenstein KA, Armon C, Buchacz K, et al. Low CD4+ T cell count is a risk factor for cardiovascular disease events in the HIV outpatient study. Clin Infect Dis. 2010; 51:435–447. [PubMed: 20597691]
22. Hsue PY, Deeks SG, Hunt PW. Immunologic basis of cardiovascular disease in HIV-infected adults. J Infect Dis. 2012; 205(Suppl 3):S375–382. [PubMed: 22577211]
23. Sabin CA, Ryom L, De Wit S, et al. Associations between immune depression and cardiovascular events in HIV infection. Aids. 2013
24**. Silverberg MJ, Leyden WA, Xu L, et al. Immunodeficiency and risk of myocardial infarction among HIV-positive individuals with access to care. J Acquir Immune Defic Syndr. 2014; 65:160–166. [PubMed: 24442222] [In the Kaiser Permanente system, risk of myocardial infarction was similar in HIV-infected subjects with a CD4+ T-cell count >500 cells/ml when compared to HIV-uninfected subjects.]

25. Baker JV, Peng G, Rapkin J, et al. CD4+ count and risk of non-AIDS diseases following initial treatment for HIV infection. Aids. 2008; 22:841–848. [PubMed: 18427202]
26. Freiberg MS, Chang CC, Kuller LH, et al. HIV infection and the risk of acute myocardial infarction. JAMA internal medicine. 2013; 173:614–622. [PubMed: 23459863]
27. Triant VA, Regan S, Lee H, et al. Association of Immunologic and Virologic Factors With Myocardial Infarction Rates in a US Healthcare System. J Acquir Immune Defic Syndr. 2010
28. Lang S, Mary-Krause M, Simon A, et al. HIV Replication and Immune Status Are Independent Predictors of the Risk of Myocardial Infarction in HIV-Infected Individuals. Clin Infect Dis. 2012
29**. Group ISS. Initiation of Antiretroviral Therapy in Early Asymptomatic HIV Infection. N Engl J Med. 2015 [Early initiation of ART at CD4+ count >500 cells/ml led to lower risk of serious non-AIDS events overall compared to initiation at <350 cells/ml, although CVD events were few (total and not different between groups [HR(95%CI) 0.84 (0.39-1.81)].]
30. Papagno L, Spina CA, Marchant A, et al. Immune activation and CD8+ T-cell differentiation towards senescence in HIV-1 infection. PLoS Biol. 2004; 2:E20. [PubMed: 14966528]
31. Lo J, Abbara S, Shturman L, et al. Increased prevalence of subclinical coronary atherosclerosis detected by coronary computed tomography angiography in HIV-infected men. Aids. 2010; 24:243–253. [PubMed: 19996940]
32. Kaplan RC, Sinclair E, Landay AL, et al. T Cell Activation and Senescence Predict Subclinical Carotid Artery Disease in HIV-Infected Women. J Infect Dis. 2011; 203:452–463. [PubMed: 21220772]
33. Hunt PW, Brenchley J, Sinclair E, et al. Relationship between T cell activation and CD4+ T cell count in HIV-seropositive individuals with undetectable plasma HIV RNA levels in the absence of therapy. J Infect Dis. 2008; 197:126–133. [PubMed: 18171295]
34. Naeger DM, Martin JN, Sinclair E, et al. Cytomegalovirus-specific T cells persist at very high levels during long-term antiretroviral treatment of HIV disease. PLoS One. 2010; 5:e8886. [PubMed: 20126452]
35. Hsue PY, Hunt PW, Sinclair E, et al. Increased carotid intima-media thickness in HIV patients is associated with increased cytomegalovirus-specific T-cell responses. Aids. 2006; 20:2275–2283. [PubMed: 17117013]
36. Parrinello CM, Sinclair E, Landay AL, et al. Cytomegalovirus immunoglobulin G antibody is associated with subclinical carotid artery disease among HIV-infected women. J Infect Dis. 2012; 205:1788–1796. [PubMed: 22492856]
37. Sacre K, Hunt PW, Hsue PY, et al. A role for cytomegalovirus-specific CD4+CX3CR1+ T cells and cytomegalovirus-induced T-cell immunopathology in HIV-associated atherosclerosis. Aids. 2012; 26:805–814. [PubMed: 22313962]
38. Huck, DM.; Okello, E.; Mirembe, G., et al. American Heart Association Scientific Sessions. Orland, FL, USA: 2015. Role of Natural Auto-antibodies among Ugandans with Rheumatic Heart Disease and HIV..
39. Libby P, Ridker PM, Hansson GK. Inflammation in atherosclerosis: from pathophysiology to practice. J Am Coll Cardiol. 2009; 54:2129–2138. [PubMed: 19942084]
40. Neuhaus J, Jacobs DR Jr. Baker JV, et al. Markers of inflammation, coagulation, and renal function are elevated in adults with HIV infection. J Infect Dis. 2010; 201:1788–1795. [PubMed: 20446848]
41. Armah KA, McGinnis K, Baker J, et al. HIV Status, Burden of Comorbid Disease and Biomarkers of Inflammation, Altered Coagulation and Monocyte Activation. Clin Infect Dis. 2012; 55:126–136. [PubMed: 22534147]
42. Crowe SM, Westhorpe CL, Mukhamedova N, et al. The macrophage: the intersection between HIV infection and atherosclerosis. J Leukoc Biol. 2010; 87:589–598. [PubMed: 19952353]
43. Martin GE, Gouillou M, Hearps AC, et al. Age-associated changes in monocyte and innate immune activation markers occur more rapidly in HIV infected women. PLoS One. 2013; 8:e55279. [PubMed: 23365694]
44. Funderburg NT, Zidar DA, Shive C, et al. Shared monocyte subset phenotypes in HIV-1 infection and in uninfected subjects with acute coronary syndrome. Blood. 2012; 120:4599–4608. [PubMed: 23065151]

45. Hearps AC, Maisa A, Cheng WJ, et al. HIV infection induces age-related changes to monocytes and innate immune activation in young men that persist despite combination antiretroviral therapy. Aids. 2012; 26:843–853. [PubMed: 22313961]

46. Scherberich JE, Nockher WA. CD14++ monocytes, CD14+/CD16+ subset and soluble CD14 as biological markers of inflammatory systemic diseases and monitoring immunosuppressive therapy. Clin Chem Lab Med. 1999; 37:209–213. [PubMed: 10353463]

47. Wilson EM, Singh A, Hullsiek KH, et al. Monocyte Activation Phenotypes Are Associated with Biomarkers of Inflammation and Coagulation in Chronic HIV Infection. J Infect Dis. 2014

48. Belge KU, Dayyani F, Horelt A, et al. The proinflammatory CD14+CD16+DR++ monocytes are a major source of TNF. J Immunol. 2002; 168:3536–3542. [PubMed: 11907116]

49. Ellery PJ, Tippett E, Chiu YL, et al. The CD16+ monocyte subset is more permissive to infection and preferentially harbors HIV-1 in vivo. J Immunol. 2007; 178:6581–6589. [PubMed: 17475889]

50**. Baker JV, Huppler Hullsiek K, Singh A, et al. Immunologic predictors of coronary artery calcium progression in a contemporary HIV cohort. Aids. 2014; 28 [Demonstrated that greater frequency of activated monocytes (e.g., CD16+) predicted subsequent progression of coronary artery calcium among n=436 HIV positive persons.]

51. Ziegler-Heitbrock L. The CD14+ CD16+ blood monocytes: their role in infection and inflammation. J Leukoc Biol. 2007; 81:584–592. [PubMed: 17135573]

52. Ancuta P, Rao R, Moses A, et al. Fractalkine preferentially mediates arrest and migration of CD16+ monocytes. The Journal of experimental medicine. 2003; 197:1701–1707. [PubMed: 12810688]

53. van de Veerdonk FL, Netea MG. Diversity: a hallmark of monocyte society. Immunity. 2010; 33:289–291. [PubMed: 20870168]

54. Aspinall AI, Curbishley SM, Lalor PF, et al. CX(3)CR1 and vascular adhesion protein-1-dependent recruitment of CD16(+) monocytes across human liver sinusoidal endothelium. Hepatology. 2010; 51:2030–2039. [PubMed: 20512991]

55. Rogacev KS, Cremers B, Zawada AM, et al. CD14++CD16+ monocytes independently predict cardiovascular events: a cohort study of 951 patients referred for elective coronary angiography. Journal of the American College of Cardiology. 2012; 60:1512–1520. [PubMed: 22999728]

56. Kelesidis T, Kendall MA, Yang OO, et al. Biomarkers of microbial translocation and macrophage activation: association with progression of subclinical atherosclerosis in HIV-1 infection. J Infect Dis. 2012; 206:1558–1567. [PubMed: 23066162]

57*. Longenecker CT, Jiang Y, Orringer CE, et al. Soluble CD14 is independently associated with coronary calcification and extent of subclinical vascular disease in treated HIV infection. Aids. 2014; 28:969–977. [PubMed: 24691204] [Soluble CD14, a biomarker of monocyte activation, was associated with subclinical vascular disease (coronary calcification, carotid intima-media thickening, and endothelial dysfunction) among n=147 subjects on ART.]

58. Burdo TH, Lo J, Abbara S, et al. Soluble CD163, a novel marker of activated macrophages, is elevated and associated with noncalcified coronary plaque in HIV-infected patients. J Infect Dis. 2011; 204:1227–1236. [PubMed: 21917896]

59. Fitch KV, Srinivasa S, Abbara S, et al. Noncalcified Coronary Atherosclerotic Plaque and Immune Activation in HIV-Infected Women. J Infect Dis. 2013

60*. McKibben RA, Margolick JB, Grinspoon S, et al. Elevated levels of monocyte activation markers are associated with subclinical atherosclerosis in men with and those without HIV infection. J Infect Dis. 2015; 211:1219–1228. [PubMed: 25362192] [Soluble CD14 and CD163, another biomarker of moncyte activation, were both associated with subclinical coronary plaque in the Multicenter AIDS Cohort Study.]

61. Subramanian S, Tawakol A, Burdo TH, et al. Arterial inflammation in patients with HIV. JAMA. 2012; 308:379–386. [PubMed: 22820791]

62. Walker JA, Sulciner ML, Nowicki KD, et al. Elevated numbers of CD163+ macrophages in hearts of simian immunodeficiency virus-infected monkeys correlate with cardiac pathology and fibrosis. AIDS research and human retroviruses. 2014; 30:685–694. [PubMed: 24524407]

63. Feeney ER, McAuley N, Halloran JA, et al. The expression of cholesterol metabolism genes in monocytes from HIV-infected subjects suggests intracellular cholesterol accumulation. J Infect Dis. 2013; 207:628–637. [PubMed: 23204179]

64. Lo J, Rosenberg ES, Fitzgerald ML, et al. High-density lipoprotein-mediated cholesterol efflux capacity is improved by treatment with antiretroviral therapy in acute human immunodeficiency virus infection. Open forum infectious diseases. 2014; 1:ofu108. [PubMed: 25734176]

65*. Liang H, Duan Z, Li D, et al. Higher levels of circulating monocyte-platelet aggregates are correlated with viremia and increased sCD163 levels in HIV-1 infection. Cellular & molecular immunology. 2015; 12:435–443. [PubMed: 25109683]

66*. Maisa A, Hearps AC, Angelovich TA, et al. Monocytes from HIV-infected individuals show impaired cholesterol efflux and increased foam cell formation after transendothelial migration. Aids. 2015; 29:1445–1457. [PubMed: 26244384] [In this novel in-vitro model of atherosclerosis, HIV-infected monocytes were more likely to form foam cells and demonstrated impaired reverse cholesterol transport.]

67. Brenchley JM, Price DA, Schacker TW, et al. Microbial translocation is a cause of systemic immune activation in chronic HIV infection. Nat Med. 2006; 12:1365–1371. [PubMed: 17115046]

68. Gupta SK, Mi D, Dube MP, et al. Pentoxifylline, inflammation, and endothelial function in HIV-infected persons: a randomized, placebo-controlled trial. PLoS One. 2013; 8:e60852. [PubMed: 23593327]

69. Hileman CO, Carman TL, Gripshover BM, et al. Salsalate is poorly tolerated and fails to improve endothelial function in virologically suppressed HIV-infected adults. Aids. 2010; 24:1958–1961. [PubMed: 20613460]

70. Gupta SK, Johnson RM, Saha C, et al. Improvement in HIV-related endothelial dysfunction using the anti-inflammatory agent salsalate: a pilot study. Aids. 2008; 22:653–655. [PubMed: 18317009]

71. Hileman CO, Carman TL, Storer NJ, et al. Omega-3 fatty acids do not improve endothelial function in virologically suppressed HIV-infected men: a randomized placebo-controlled trial. AIDS Res Hum Retroviruses. 2012; 28:649–655. [PubMed: 21870979]

72. Wasko MC, Dasgupta A, Hubert H, et al. Propensity-adjusted association of methotrexate with overall survival in rheumatoid arthritis. Arthritis and rheumatism. 2013; 65:334–342. [PubMed: 23044791]

73. Mann DL, McMurray JJ, Packer M, et al. Targeted anticytokine therapy in patients with chronic heart failure: results of the Randomized Etanercept Worldwide Evaluation (RENEWAL). Circulation. 2004; 109:1594–1602. [PubMed: 15023878]

74. Chung ES, Packer M, Lo KH, et al. Randomized, double-blind, placebo-controlled, pilot trial of infliximab, a chimeric monoclonal antibody to tumor necrosis factor-alpha, in patients with moderate-to-severe heart failure: results of the anti-TNF Therapy Against Congestive Heart Failure (ATTACH) trial. Circulation. 2003; 107:3133–3140. [PubMed: 12796126]

75. Abbate A, Kontos MC, Abouzaki NA, et al. Comparative safety of interleukin-1 blockade with anakinra in patients with ST-segment elevation acute myocardial infarction (from the VCU-ART and VCUART2 pilot studies). The American journal of cardiology. 2015; 115:288–292. [PubMed: 25482680]

76. Van Tassell BW, Arena R, Biondi-Zoccai G, et al. Effects of interleukin-1 blockade with anakinra on aerobic exercise capacity in patients with heart failure and preserved ejection fraction (from the D-HART pilot study). The American journal of cardiology. 2014; 113:321–327. [PubMed: 24262762]

77**. Lo J, Lu MT, Ihenachor EJ, et al. Effects of statin therapy on coronary artery plaque volume and high-risk plaque morphology in HIV-infected patients with subclinical atherosclerosis: a randomised, double-blind, placebo-controlled trial. The Lancet HIV. 2:e52–e63. [PubMed: 26424461] [Among 40 HIV+ subjects on ART with evidence of subclinical coronary atherosclerosis and elevated vascular inflammation at baseline, atorvastatin 20mg titrated to 40mg decreased non-calcified coronary plaque volume and high risk features compared to placebo, but did not reduce vascular inflammation by PET/CT.]

78. Longenecker, CT.; Jiang, Y.; Debanne, SM., et al. Rosuvastatin Arrests Progression of Carotid Intima-Media Thickness in Treated HIV.. 22nd Conference on Retroviruses and Opportunistic Infections (CROI); Seattle, WA, USA. 2015;

79. Ganesan A, Crum-Cianflone N, Higgins J, et al. High dose atorvastatin decreases cellular markers of immune activation without affecting HIV-1 RNA levels: results of a double-blind randomized placebo controlled clinical trial. J Infect Dis. 2011; 203:756–764. [PubMed: 21325137]

80. Nakanjako D, Ssinabulya I, Nabatanzi R, et al. Atorvastatin reduces T-cell activation and exhaustion among HIV-infected cART-treated suboptimal immune responders in Uganda: a randomised crossover placebo-controlled trial. Tropical medicine & international health : TM & IH. 2015; 20:380–390. [PubMed: 25441397]

81. Overton ET, Sterrett S, Westfall AO, et al. Effects of atorvastatin and pravastatin on immune activation and T-cell function in antiretroviral therapy-suppressed HIV-1-infected patients. Aids. 2014; 28:2627–2631. [PubMed: 25574964]

82. De Wit S, Delforge M, Necsoi CV, Clumeck N. Downregulation of CD38 activation markers by atorvastatin in HIV patients with undetectable viral load. Aids. 2011; 25:1332–1333. [PubMed: 21508802]

83*. Funderburg NT, Jiang Y, Debanne SM, et al. Rosuvastatin Reduces Vascular Inflammation and T-cell and Monocyte Activation in HIV-Infected Subjects on Antiretroviral Therapy. J Acquir Immune Defic Syndr. 2015; 68:396–404. [PubMed: 25514794] [A 48-week interim analysis of SATURN-HIV demonstrated reductions in T-cell and monocyte activation with 10mg of daily rosuvastatin. These findings expand on previous studies showing reductions in T-cell activation with atorvastatin.]

84*. Zanni MV, Fitch KV, Feldpausch M, et al. American College of Cardiology/American Heart Association and 2004 Adult Treatment Panel III cholesterol guidelines applied to HIV-infected patients with/without subclinical high-risk coronary plaque. Aids. 2013; 2014; 28:2061–2070. [PubMed: 25265074] [Nearly 75% of patients with HIV infection who had subclinical features of “high-risk” coronary plaque would not be recommended for statin therapy under the most recent 2013 American College of Cardiology and American Heart Association guidelines on the treatment of dyslipidemia for the prevention of CVD.]

85. Seshasai SR, Wijesuriya S, Sivakumaran R, et al. Effect of aspirin on vascular and nonvascular outcomes: meta-analysis of randomized controlled trials. Arch Intern Med. 2012; 172:209–216. [PubMed: 22231610]

86. O'Brien M, Montenont E, Hu L, et al. Aspirin Attenuates Platelet Activation and Immune Activation in HIV-1-Infected Subjects on Antiretroviral Therapy: A Pilot Study. J Acquir Immune Defic Syndr. 2013; 63:280–288. [PubMed: 23406976]

87. Boccara F, Auclair M, Cohen A, et al. HIV protease inhibitors activate the adipocyte renin angiotensin system. Antivir Ther. 2010; 15:363–375. [PubMed: 20516556]

88. Srinivasa S, Fitch KV, Wong K, et al. RAAS Activation Is Associated With Visceral Adiposity and Insulin Resistance Among HIV-infected Patients. J Clin Endocrinol Metab. 2015; 100:2873–2882. [PubMed: 26086328]

89. Baker JV, Huppler Hullsiek K, Prosser R, et al. Angiotensin converting enzyme inhibitor and HMG-CoA reductase inhibitor as adjunct treatment for persons with HIV infection: a feasibility randomized trial. PLoS One. 2012; 7:e46894. [PubMed: 23082133]

90. Lake JE, Tseng CH, Currier JS. A pilot study of telmisartan for visceral adiposity in HIV infection: the metabolic abnormalities, telmisartan, and HIV infection (MATH) trial. PLoS One. 2013; 8:e58135. [PubMed: 23516440]

Key Points

- HIV infection is associated with excess CVD due to multiple factors, some of which are immunologic in nature.
- Alterations in adaptive immunity, reflected in T-cell activation and dysfunction, likely contribute to HIV-associated CVD.
- The CVD consequences of persistent abnormalities in innate immunity, commonly assessed via measures of monocyte activation, may be particularly relevant during treated HIV disease when adaptive immunity has recovered to some degree.
- While effective treatment exists for traditional risk factor modification, CVD prevention strategies that target inflammation and immune activation are lacking though a number of promising candidates are under investigation.

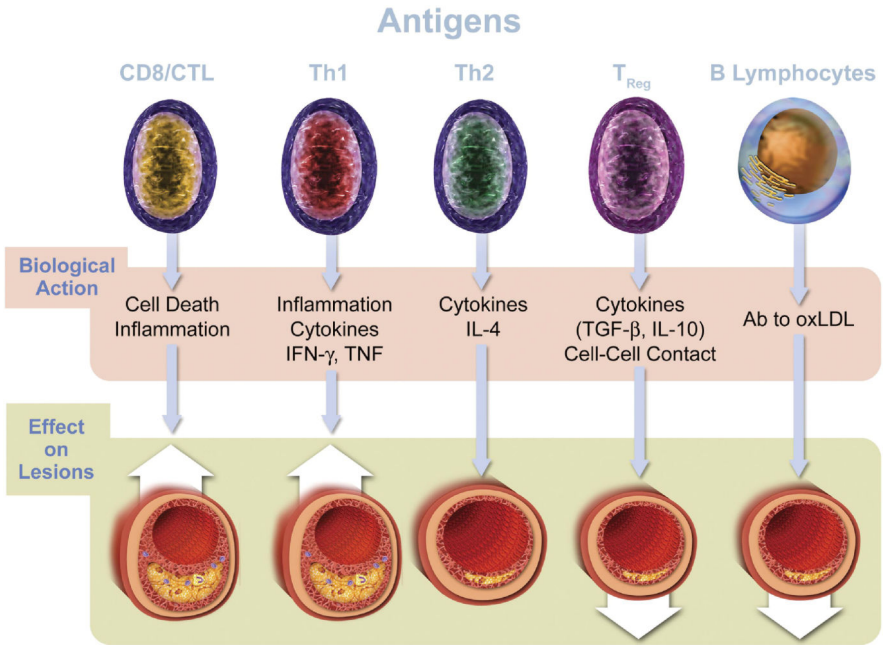

FIGURE 1. Adaptive immunity in atherosclerosis

T and B lymphocytes may positively or negatively influence atherosclerotic plaque through direct action on lesions or through inflammatory cytokine production. Emerging observational data have linked CD8+ and CD4+ T-cell activation to subclinical vascular disease and adverse outcomes among those with HIV infection; relatively less is known about the role of T_{Reg} or B lymphocytes in the context of HIV disease. Reproduced with permission from Libby et al.[39]

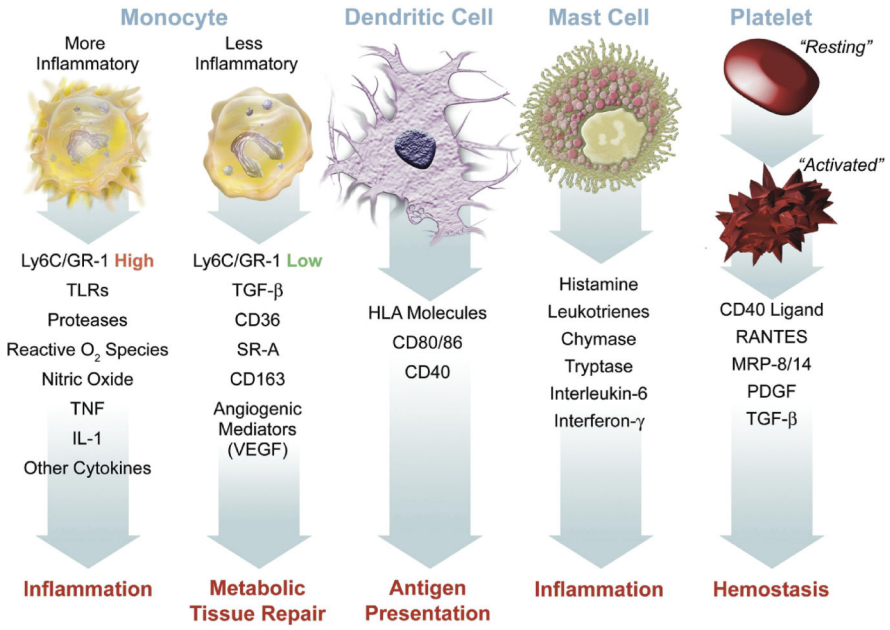

FIGURE 2. Innate immunity in atherosclerosis

Elements of the innate immune system, particularly monocytes and macrophages, drive atherosclerosis and the inflammation that leads to unstable atherothrombotic syndromes. Current literature has demonstrated that HIV infection activates monocytes, impairs reverse cholesterol transport from foam cells, and promotes thrombus formation through platelet-monocyte interactions. Reproduced with permission from Libby et al.[39]

Table 1

Clinical trials to reduce immune activation and vascular risk

This table of completed and ongoing trials of immunomodulatory therapies or cardiovascular risk modifying drugs with anti-inflammatory effects includes only trials with subclinical vascular outcome measures. Trials of anti-inflammatory and anti-fibrotic drugs without vascular outcome measures are not included in this table but are discussed in the text.

Intervention	Identifier	Population	Design	Size	Subclinical Vascular Outcome(s)	Status
Immunomodulatory Therapies						
Methotrexate	NCT01949116	>40yrs on ART with mod-high CVD risk	Placebo RCT	200	FMD	Recruiting
Tocilizumab (IL-6 receptor Ab)	NCT02049437	18-60yrs on ART with CD4 200-500	Placebo crossover RCT	36	FMD; hyperemic VTI	Recruiting
Canakinumab (IL-1β Ab)	NCT02272946	>40yrs on ART with high CVD risk	Placebo RCT	110	FMD; Aortic TBR	Not yet open
Pentoxifylline	NCT00864916	>18yrs; all started ART at study entry	Placebo RCT	26	FMD	Completed[68]
Salsalate 4gm	NCT01046682	>18yrs; on ART	Open label RCT	40	FMD	Completed[69]
Salsalate 3gm	N/A	>18yrs: NOT on ART	Single arm Open label	11	FMD	Completed[70]
CVD Risk Modifying Drugs with Anti-Inflammatory Effects						
Rosuvastatin 10mg	NCT01218802	>18yrs; on ART with LDL<130 and elevated hsCRP or CD8+ activation	Placebo RCT	147	Carotid IMT; FMD; CAC	Completed
Rosuvastatin 10mg	NCT02234492	>40yrs; On ART with 10-yr CVD risk 10-20% and LDL <155	Open-label RCT	82	Coronary flow reserve; Aortic TBR	Recruiting
Rosuvastatin 20mg	NCT01813357	>18yrs; On ART with 10-15% 10-yr CVD risk	Placebo RCT	102	Carotid IMT; FMD	Recruiting
Rosuvastatin	NCT01881971	18-80yrs; On ART with COPD	Placebo RCT	30	Carotid IMT; FMD	Ongoing; not recruiting
Atorvastatin 20/40mg	NCT00965185	18-60; on ART with coronary plaque and high aortic TBR	Placebo RCT	40	Coronary plaque volume and high risk features by CT; Aortic TBR	Completed
Pitavastatin 4mg	NCT02344290	40-75yrs; on ART with <7.5% 10-yr ASCVD risk	Placebo RCT	6500	MACE; Coronary plaque volume and high risk features	Recruiting
ASA 81mg vs. Atorvastatin 40mg	NCT02081638	>18yrs; elite controller compared to persons with >4yrs of ART	RCT	80	Carotid MRI	Recruiting
ASA 325mg	NCT02401269	18-70yrs; on ART without diabetes or heart disease	Placebo RCT	100	RHI and FMD	Recruiting
ASA 100 or 300mg	NCT02155985	>18yrs; on ART	Placebo RCT	121	FMD	Ongoing; not recruiting

Intervention	Identifier	Population	Design	Size	Subclinical Vascular Outcome(s)	Status
Telmisartan 80mg	NCT01578772	>50yrs; on ART with one or more risk factors for CVD	Placebo RCT	17	FMD	Completed; not published
Losartan 100mg +/− switch to RAL	NCT01529749	>18yrs; on ART as tenofovir DF, emtricitabine, and efavirenz	Placebo RCT; 2×2 factorial	48	Carotid IMT	Recruiting
Metformin 1000mg	NCT02383563	>45yrs; on ART	Open label RCT	12	Total coronary plaques by CT	Recruiting
Lovaza (OM-3 FA) 2gm	NCT01001767	18-70yrs; on ART	Placebo RCT	35	FMD	Completed[71]

CVD, cardiovascular disease; yrs, years; ART, antiretroviral therapy; RCT, randomized controlled trial; FMD, flow-mediated dilation of the brachial artery; IL, interleukin; Ab, antibody; VTI, velocity time integral; TBR, target to background ratio; LDL, low-density lipoprotein; hsCRP, high-sensitivity C-reactive protein; IMT, intima-media thickness; CAC, coronary artery calcium; COPD, chronic obstructive pulmonary disease; ASCVD, atherosclerotic cardiovascular disease; MACE, major adverse cardiovascular events; ASA, aspirin; MRI, magnetic resonance imaging; RHI, reactive hyperemic index; RAL, raltegravir; DF, disoproxil fumarate; OM-3 FA, omega-3 fatty acids.