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# Cardiovascular disease in people living with HIV: Risk assessment and management

# ABSTRACT

Almost 40 million people worldwide are living with human immunodeficiency virus (HIV) infection. With treatment advances, HIV infection is now a manageable chronic disease for those with access to medical therapy. People living with HIV have a significantly higher risk and earlier onset of cardiovascular disease (CVD) owing to chronic inflammation and other biochemical factors, as well as overlapping social determinants of health and nonbiologic risk factors. Knowing that patients living with HIV develop coronary artery disease much earlier than the general population, careful attention must be given to assessment and management of their cardiovascular risk.

# **KEY POINTS**

Because people living with HIV present with coronary artery disease about 10 years earlier than the general population, maintaining a higher index of suspicion for CVD, even in younger patients, is important.

Consider adjusting calculated CVD risk up 1.5 to 2 times and setting lower lipid targets and a lower threshold for starting statin therapy.

Selection of lipid-lowering agents must take into account any potential interactions with antiretroviral therapy medications; a multidisciplinary approach can be helpful. LMOST 40 MILLION PEOPLE WORLDWIDE, including more than 1 million people in the United States, are currently living with human immunodeficiency virus (HIV) infection.<sup>1,2</sup> Over the past 50 years, scientific and policy advances have dramatically improved life expectancy for people living with HIV such that it is now a manageable chronic disease for those with access to medical therapy. As this population ages, clinicians must remain vigilant regarding comorbidities for which they are at heightened risk.

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Specifically, people living with HIV have a significantly higher risk of developing cardiovascular disease (CVD). Globally, this risk is up to 2 times higher compared with individuals without HIV.<sup>3</sup> While the concept that "undetectable equals untransmissible" is a tremendous breakthrough for people living with HIV, it is important for clinicians to remember that increased CVD risk persists even with control of the virus to undetectable levels. Herein, we review the epidemiology and proposed mechanisms of this phenomenon and discuss screening, management, and other considerations in treating people living with HIV.

#### CVD RISK PERSISTS DESPITE VIRAL SUPPRESSION

A model constructed using the data of more than 10,000 individuals being treated for HIV from a cohort of the AIDS Therapy Evaluation in the

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Netherlands suggested that, by 2030, 73% of people living with HIV will be 50 or older and 78% will have been diagnosed with CVD.<sup>4</sup> Irrespective of viral suppression, this population has an increased relative risk of myocardial infarction, ranging from 20% to 100%, compared with people not living with HIV.<sup>5</sup> Studies have shown that patients with HIV are also at increased risk for stroke, sudden cardiac death, heart failure, pulmonary hypertension, and myocardial fibrosis.<sup>3,6-9</sup>

The increased CVD risk in persons living with HIV persists even for patients taking viral suppressive therapies.<sup>10</sup> A virtual cohort of the Veterans Aging Cohort Study—a multisite, longitudinal, prospective study-examined more than 80,000 patients living with HIV and noted that risk for acute myocardial infarction was higher in patients living with HIV in every age group.<sup>11</sup> Importantly, this elevated risk remained when the analysis was restricted to patients with viral suppression. The Veterans Aging Cohort Study was relatively unique in that the patients were all male, the median age was 49 to 50, and 74% to 79% were Black or Latino.<sup>12</sup> Similarly, a meta-analysis found that having HIV conferred a 61% increased relative risk of CVD in those not on antiretroviral therapy (ART).<sup>13</sup> When limited to patients on ART, the relative risk of CVD was 2 times higher compared with patients without HIV.

#### PROPOSED MECHANISMS

The factors that contribute to the increased risk of CVD for patients with HIV infection are varied and not completely understood. Other recent studies reported that chronic inflammation and immune dysfunction persist even when the virus is well controlled.<sup>14</sup>

# Lessons from studies of chronic inflammation in the general population

We know that chronic inflammation is linked to atherosclerosis. JUPITER (Justification for the Use of Statin in Prevention: An Intervention Trial Evaluating Rosuvastatin)<sup>15</sup> showed that rosuvastatin reduced the incidence of cardiovascular events in patients with normal low-density lipoprotein cholesterol (LDL-C) but elevated high-sensitivity C-reactive protein (hs-CRP). Notably, chronic inflammatory biomarkers associated with atherogenesis are elevated in people living with HIV compared with those without HIV.<sup>14</sup>

IMPROVE-IT (Improved Reduction of Outcomes: Vytorin Efficacy International Trial)<sup>16</sup> analyzed the correlation of this dual target (LDL-C and hs-CRP) and the primary composite end point of cardiovascular death, major coronary event, and stroke for patients randomized to simvastatin monotherapy or a combination of simvastatin and ezetimibe.<sup>17</sup> In a substudy that used the IMPROVE-IT data of 18,144 patients who had diabetes mellitus at randomization, simvastatin plus ezetimibe significantly increased the like-lihood of achieving the predefined targets for LDL-C (< 70 mg/dL) and hs-CRP (< 2 mg/L). Further, a recent meta-analysis of randomized controlled trials showed that statins can be effective in reducing hs-CRP in patients with CVD, although further studies are warranted to clearly prove the beneficial effect of statins on hs-CRP.<sup>18</sup>

In a primary analytic cohort of the FOURIER study (Further Cardiovascular Outcomes Research With PCSK9 Inhibition in Patients With Elevated Risk), Bohula et al<sup>19</sup> explored whether the association of inflammation and risk of cardiovascular events persisted even at very low levels of LDL-C. In patients with LDL-C less than 20 mg/dL 1 month after randomization, the 3-year primary event rate for patients with hs-CRP of less than 1, 1 to 3, and more than 3 mg/L was 9.0%, 10.8%, and 13.1%, respectively. This further supports the concept of an inflammatory risk for CVD. A secondary analysis from the CANTOS (Canakinumab Anti-Inflammatory Thrombosis Outcome Study) trial<sup>20</sup> further supported this relationship between hs-CRP reduction and cardiovascular risk reduction.

While IMPROVE-IT, FOURIER, CANTOS, and JUPITER did not specifically focus on people living with HIV, the physiologic lessons learned regarding inflammation and treatment of CVD appear to be generalizable.

#### **HIV-specific mechanisms**

**Hyperlipidemia.** HIV infection itself is associated with a proatherogenic inflammatory state.<sup>21</sup> The prevalence of hyperlipidemia in patients living with HIV ranges from 28% to 80%, compared with 10% to 11% among the general US population.<sup>22,23</sup> Further, REPRIEVE (Randomized Trial to Prevent Vascular Events in HIV),<sup>24,25</sup> a large randomized, 12-country, multicenter trial, found that a daily statin (pitavastatin calcium) reduced major adverse cardiovascular events by 35% compared with placebo in people living with HIV aged 40 to 75 who had low to moderate CVD risk (with normal-range LDL).

**HIV proteins.** Even in patients with undetectable viral load on ART, low-level transcription of HIV genes encoding viral regulatory proteins continues.<sup>26</sup> Such proteins, like transactivator of transcription protein and negative factor, have been shown to induce endothelial dysfunction as well as inflammation.<sup>27</sup> Envelope glycoprotein 120, an HIV surface glycoprotein that helps the



Figure 1. Mechanisms of atherosclerosis and myocardial infarction in people living with HIV.

<sup>a</sup>Traditional cardiovascular risk factors, such as smoking, and older therapies for treating people living with HIV also contribute to the development of atherosclerosis and myocardial infarction.

<sup>b</sup>Markers of microbial translocation from the gut.

HIV = human immunodeficiency virus

Based on information from reference 35.

virus enter target cells, has been shown to stimulate production of the vasoconstrictor endothelin-1, which has been associated with cardiac morbidity and mortality.<sup>28</sup>

**Cytomegalovirus infection.** CD8 T-cell expansion and inflammation linked to cytomegalovirus coinfection is another mechanism that has been proposed for the enduring elevated cardiovascular risk in patients with HIV, even on ART.<sup>29</sup>

**CD4 T-cell depletion and gut microbial translocation.** Depletion of CD4 cells is associated with higher rates of myocardial infarction, ischemic stroke, heart failure, and peripheral artery disease.<sup>5</sup> Replication of HIV in the gastrointestinal tract can severely reduce CD4 cells and thus lead to decreased function of the epithelial barrier.<sup>30</sup> This allows microbial translocation and, in turn, a chronic inflammatory response. It is postulated that both the subsequent susceptibility to opportunistic infections from the depletion of CD4 T cells in the gut mucosa and microbial translocation lead to chronic states of inflammation.<sup>5</sup>

## Nonbiochemical factors

It is important to acknowledge the myriad of nonbiochemical factors that may disparately affect people living with HIV and contribute to CVD risk. Owing to overlapping social determinants of health and other risk factors, the prevalence of cigarette smoking is 2 to 3 times higher in people living with HIV than in those not living with HIV.<sup>31</sup>

Further, transgender people are disproportionately impacted by HIV. The US Centers for Disease Control and Prevention reports an HIV prevalence of 9.2% in transgender people compared with less than 0.5% in adults overall.<sup>32</sup> Studies have noted that metabolic changes asoociated with gender-affirming hormonal treatment may increase the risk of accelerated CVD.<sup>33,34</sup> These factors, along with systemic healthcare factors that contribute to diminished access in these and other vulnerable groups, highlight the complexities of increased CVD risk.

Even after adjusting for these and other various risk factors, however, studies have shown that people with



Figure 2. Pathophysiology of human immunodeficiency virus (HIV)–associated atherosclerotic cardiovascular disease.

Based on information from reference 36.

HIV still have significantly higher CVD risk due to overlapping risk factors. **Figure 1** illustrates the interplay of mechanisms of atherosclerosis and myocardial infarction in patients living with HIV.<sup>35</sup> **Figure 2** shows the proposed pathophysiologic mechanisms involved with HIV-associated atherosclerotic CVD.<sup>36</sup>

#### EARLIER ONSET OF CVD

An early study found that people living with HIV presented with coronary artery disease when they were about 10 years younger than patients without HIV.<sup>36,37</sup> Further studies found these patients were more likely to have low thrombolysis in myocardial infarction risk scores and single-vessel disease but higher rates of restenosis after percutaneous coronary intervention.<sup>36,38,39</sup> The incidence of restenosis after drug-eluting stent placement in patients with HIV was 19% vs 10% in those not living with HIV—with CD8 count and C-reactive protein levels somewhat correlated.<sup>38,39</sup>

#### ART AND COMORBIDITIES

Early studies suggested ART as a possible contributing factor to the increased risk of CVD in people living with HIV. More recent studies, however, have noted that this is not the case with newer ART regimens. Herein, we examine the historical progression of evidence.

#### Dyslipidemia

Combination ART–associated dyslipidemia was first described in patients using protease inhibitors, regimens

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with nucleoside reverse transcriptase inhibitors, and nonnucleoside reverse transcriptase inhibitors, with duration of exposure being associated with increased CVD.<sup>40</sup> Part of this has been attributed to some component of the initial return of appetite and weight gain in these patients once they started ART. The historic DAD (Data Collection on Adverse Events of Anti-HIV Drugs) trial,<sup>41</sup> a comprehensive examination of CVD adverse events associated with ART, found an association between ART and dyslipidemia.

Older ART drugs, including abacavir, ritonavir, and lopinavir, have more cardiotoxic effects, including left ventricular dysfunction or altered lipid or glucose metabolism.<sup>42</sup> Specifically, older protease inhibitors like ritonavir are known to induce hypertriglyceridemia and other adverse effects such as dyslipidemia, hyperglycemia, and overt diabetes mellitus.<sup>42</sup> In addition, protease inhibitors boosted by ritonavir, as well as some first-generation nucleoside reverse transcriptase inhibitors and nonnucleoside reverse transcriptase inhibitors, have been shown to affect lipid parameters, such as increased total cholesterol, LDL-C, and triglycerides.43,44 One study found that exposure to the protease inhibitors lopinavir-ritonavir and indinavir or the nucleoside reverse transcriptase inhibitors abacavir or didanosine was associated with increased risk of myocardial infarction.<sup>42</sup> This risk in patients taking abacavir appears, in some studies, to be linked to increased platelet reactivity and endothelial dysfunction.<sup>36</sup>

Further, different classes of ART can have differing effects on the development of adipose tissue. For example, some integrase inhibitors have been associated with weight gain, and some first-generation nucleoside reverse transcriptase inhibitors and protease inhibitors have been shown to correlate with the development of lipodystrophy.<sup>43,44</sup>

Newer ART medications, such as the C-C chemokine receptor 5 antagonist maraviroc and the integrase inhibitor raltegravir, are more favorable with respect to effect on lipid levels.<sup>22</sup> One recent study showed that switching from a protease inhibitor to the newer integrase inhibitor bictegravir was associated with improvement in lipid markers.<sup>45</sup> In particular, patients with the worst baseline lipid profiles had significant improvements, and those who switched from protease inhibitors to bictegravir also saw improvements in triglycerides. Dolutegravir, another integrase inhibitor, has a more neutral effect on lipids compared with efavirenze or ritonavir-boosted darunavir.<sup>46</sup>

Overall, initiation of ART may negatively impact lipid levels (including LDL, triglycerides, total cholesterol, and high-density lipoprotein), and this change is likely multifactorial. Lipid monitoring in patients living with HIV is imperative for CVD risk reduction.

#### Insulin resistance and metabolic impact

First-generation ART medications were associated with insulin resistance and metabolic syndrome, leading to a higher incidence of diabetes and elevated hemoglobin A1c levels in people living with HIV.<sup>43</sup> Historically, protease inhibitors have been associated with insulin resistance, but these agents may be less commonly used due to other toxicities, such as the possibility of hepatotoxicity, Stevens-Johnson syndrome, or elevated cholesterol, as noted above. First-generation thymidine nucleoside reverse transcriptase inhibitors also impacted fat distribution and caused weight gain, effects that may be responsible for a lingering occurrence of insulin resistance in aging patients who used these medications.<sup>43</sup>

Evidence suggests that certain HIV preexposure prophylaxis regimens may be associated with metabolic changes (although the evidence is from trials that were not specific to people living with HIV).47,48 Specifically, initiation of tenofovir alafenamide fumarate for preexposure prophylaxis was associated with increased risk of hypertension and statin initiation, especially in patients 40 and older.<sup>47</sup> Another study examined tenofovir disoproxil fumarate and emtricitabine and found a modest reduction in cholesterol.<sup>48</sup> The participants in the first study were found to have weight gain, and the participants in the second study were found to have weight loss, which may be the independent driver regarding metabolic impact. These results may further inform future studies on the effects of ART drugs on metabolic function.

#### MANAGEMENT

#### Models underestimate CVD risk

The 2019 American College of Cardiology and American Heart Association guidelines<sup>49</sup> on primary prevention of CVD recognized HIV as a risk factor for CVD based on the presence of chronic inflammation. In doing so, these guidelines acknowledged that standard models for predicting CVD risk systematically underestimate CVD risk for people living with HIV.<sup>10</sup> A recent meta-analysis examined 9 major CVD risk-prediction models and found a general tendency for these models to underestimate risk in these patients.<sup>50</sup>

As such, the guidelines note that individuals living with HIV may benefit from a lower threshold for statin initiation or intensification, particularly those with intermediate risk ( $\geq$  7.5% to < 20% 10-year atherosclerotic CVD risk).<sup>49</sup> Further, consideration of the

underlying HIV diagnosis may help to sway treatment decisions for patients with borderline (5% to < 7.5% 10-year atherosclerotic CVD risk) or intermediate risk.<sup>51</sup>

The American Heart Association scientific statement<sup>52</sup> for prevention and treatment of CVD for people living with HIV suggests that clinicians may consider adjusting calculated CVD risk assessments up 1.5 to 2 times for patients with HIV, particularly for those with certain HIV-associated risk-enhancing factors like prolonged viremia, delayed ART initiation, and low CD4 count. This was more specifically discussed in the European Society for Cardiology guidelines,<sup>53</sup> which also suggest an LDL-C goal of less than 70 mg/dL in people living with HIV.<sup>53</sup>

REPRIEVE, discussed earlier, examined strategies for CVD risk prevention in people living with HIV. The study's results led to the concept that patients living with HIV should begin statin therapy to reduce CVD risk and that this should be individualized and communicated with the patient as part of shared decision-making.<sup>24</sup> However, many patients with HIV who already meet criteria for statin use do not receive a prescription for them (28%) or are prescribed statin therapy below the indicated intensity (12%).<sup>54</sup>

#### Considerations when selecting lipid-lowering agents

Selection of lipid-lowering agents in patients on ART requires attention to potential drug-drug interactions. Ultimately, considerations should be patient- and case-specific and part of a multidisciplinary discussion with infectious diseases and pharmacy colleagues in the broader context of patient care.

Overall, we know that statin therapy can be administered safely in patients on ART.<sup>55</sup> Some illustrative examples can be useful. Lovastatin and simvastatin are contraindicated in patients being treated with protease inhibitors because of the increased risk of rhabdomyolysis.<sup>56</sup> One study suggested a higher risk for atorvastatin in patients taking both protease inhibitors and ritonavir,<sup>57</sup> and the Infectious Diseases Society of America recommends starting with a lower dose of atorvastatin in these patients.<sup>58</sup> Of note, proprotein convertase subtilisin/kexin 9 inhibitors have recently shown promise in reducing atherogenic lipid levels in patients living with HIV and may be of increased utility in the future as investigations continue.<sup>59</sup>

#### A NOTE ON HEART FAILURE IN PATIENTS WITH HIV

There is currently no difference in guidelines regarding treatment of heart failure in people living with HIV and those not living with HIV. Recent studies have,

however, indicated that the increased risk of heart failure for patients living with HIV is not primarily mediated through atherosclerotic disease pathways.<sup>60</sup> With respect to HIV-associated cardiomyopathy, the prevalence of systolic dysfunction has decreased with the spread of ART, but the number of patients with HIV with abnormal diastolic function has increased.<sup>61</sup> One meta-analysis reported systolic and diastolic dysfunction incidence at 8.3% and 43.4%, respectively. in people living with HIV.<sup>62</sup> Direct HIV-induced myocardial damage may have been a predominant driver of systolic dysfunction before the widespread use of ART, hence, a relative decline.<sup>61</sup> Theories to explain the increase in diastolic dysfunction have included higher rates of inflammation, hypertension, or direct impact on myocardium.63

Mechanisms that have been proposed to explain the pathophysiology of HIV-associated cardiomyopathy outside of those behind atherosclerotic risk and acute coronary syndrome are, again, multifactorial.<sup>61</sup> Direct HIV-induced myocardial damage, alluded to above, is one such mechanism. It is theorized that inflammation in the myocardium may contribute to increased left ventricular mass, which is consistent with studies examining similar findings in patients with other types of inflammation, such as systemic lupus erythematosus and rheumatoid arthritis.63 Moreover, chronic inflammation and immune dysfunction may lead to collagen deposition and fibrosis in the myocardium itself.<sup>64</sup> While cardiomyocytes lack HIV-1 receptor proteins (glycoprotein 120 and 24), cardiac interstitial cells may serve as viral reservoirs and mediate inflammation.<sup>61,65</sup> Other mechanisms include negative inotropic effects exerted by proinflammatory cytokines that contribute to reduced systolic function, autoimmune effects, and side effects from some ART medications.<sup>61</sup>

An approach to heart failure risk stratification for patients living with HIV could be beneficial going forward.<sup>66</sup> Chowdhury et al<sup>67</sup> are currently studying whether people living with HIV receive standard of care for heart failure compared with people not living with HIV, which could reveal areas for potential focus in the future.

#### AREAS FOR FUTURE WORK

The link between HIV infection and CVD risk is clear. What remains for discovery are the more granular factors that may increase risk in a subset of people living with HIV and how best to reduce this risk.<sup>6,52</sup> One study examined various biomarkers in people living with HIV in an attempt to create different cluster phenotypes.<sup>68</sup>

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Those in the cardiac phenotype (for example, with elevated interleukin-1 receptor–like protein) were more likely to experience pulmonary hypertension, and those in the inflammatory phenotype (for example, with elevated C-reactive protein and interleukin-6) were more likely to experience diastolic dysfunction. Such studies that examine biomarkers with greater granularity may guide future therapies and screening.

To this end, further studies examining factors associated with HIV infection—including hepatitis C virus coinfection, CD4 count, years of sustained and elevated viral load, history of opportunistic coinfections, timing of ART commencement, and others—are warranted and may yield a more standardized approach to risk analysis and management.

Finally, it is crucial that patients living with HIV be included in trials that study cardiac risk factors to broaden the applicability of evidence to this population. This will greatly aid the collective understanding of how to reduce CVD risk and prevent adverse events in patients living with HIV.

#### REFERENCES

- World Health Organization. HIV. https://www.who.int/data/gho/ data/themes/hiv-aids. Accessed February 14, 2025.
- Centers for Disease Control and Prevention. HIV. https://www.cdc. gov/hiv/index.html. Accessed February 14, 2025.
- 3. Shah ASV, Stelzle D, Lee KK, et al. Global burden of atherosclerotic cardiovascular disease in people living with HIV: systematic review and meta-analysis. Circulation 2018; 138(11):1100–1112. doi:10.1161/CIRCULATIONAHA.117.033369
- Smit M, Brinkman K, Geerlings S, et al. Future challenges for clinical care of an ageing population infected with HIV: a modelling study [published correction appears in Lancet Infect Dis 2015; 15(9):998]. Lancet Infect Dis 2015; 15(7):810–818. doi:10.1016/S1473-3099(15)00056-0
- So-Armah K, Benjamin LA, Bloomfield GS, et al. HIV and cardiovascular disease. Lancet HIV 2020; 7(4):e279–e293. doi:10.1016/S2352-3018(20)30036-9
- Feinstein MJ. HIV, subclinical cardiovascular disease, and clinical progression: insights from immunologic heterogeneity. JAMA 2022; 328(10):931–932. doi:10.1001/jama.2022.15226
- Tseng ZH, Moffatt E, Kim A, et al. Sudden cardiac death and myocardial fibrosis, determined by autopsy, in persons with HIV. N Engl J Med 2021; 384(24):2306–2316. doi:10.1056/NEJMoa1914279
- Barnett CF, Hsue PY. Human immunodeficiency virus-associated pulmonary arterial hypertension. Clin Chest Med 2013; 34(2):283–292. doi:10.1016/j.ccm.2013.01.009
- 9. Hudson JA, Majonga ED, Ferrand RA, Perel P, Alam SR, Shah ASV. Association of HIV infection with cardiovascular pathology based on advanced cardiovascular imaging: a systematic review. JAMA 2022; 328(10):951–962. doi:10.1001/jama.2022.15078
- Triant VA, Perez J, Regan S, et al. Cardiovascular risk prediction functions underestimate risk in HIV infection. Circulation 2018; 137(21):2203–2214. doi:10.1161/CIRCULATIONAHA.117.028975
- Freiberg MS, Chang CC, Kuller LH, et al. HIV infection and the risk of acute myocardial infarction. JAMA Intern Med 2013; 173(8): 614–622. doi:10.1001/jamainternmed.2013.3728
- Justice AC, Dombrowski E, Conigliaro J, et al. Veterans Aging Cohort Study (VACS): overview and description. Med Care 2006; 44(8 suppl 2):S13–S24. doi:10.1097/01.mlr.0000223741.02074.66

#### TAKE-HOME POINTS

- Screening and treatment of CVD should be tailored to patients living with HIV due to their heightened risk profiles.
- Because we know that patients living with HIV develop coronary artery disease much earlier, assessment of CVD risk should be considered along with potentially lower lipid targets and a lower threshold for treatment. Selection of lipid-lowering agents must take into account any potential interactions with ART medications, and a multidisciplinary approach is helpful.
- Careful attention to other cardiovascular pathology is imperative for patients living with HIV, including diastolic and systolic heart failure.

### DISCLOSURES

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- Islam FM, Wu J, Jansson J, Wilson DP. Relative risk of cardiovascular disease among people living with HIV: a systematic review and meta-analysis. HIV Med 2012; 13(8):453–468. doi:10.1111/j.1468-1293.2012.00996.x
- 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(12):1788–1795. doi:10.1086/652749
- 15. **Ridker PM.** The JUPITER trial: results, controversies, and implications for prevention. Circ Cardiovasc Qual Outcomes 2009; 2(3):279–285. doi:10.1161/CIRCOUTCOMES.109.868299
- Cannon CP, Blazing MA, Giugliano RP, et al; IMPROVE-IT Investigators. Ezetimibe added to statin therapy after acute coronary syndromes. N Engl J Med 2015; 372(25):2387–2397. doi:10.1056/NEJMoa1410489
- Giugliano RP, Cannon CP, Blazing MA, et al. Benefit of adding ezetimibe to statin therapy on cardiovascular outcomes and safety in patients with versus without diabetes mellitus: results from IMPROVE-IT (Improved Reduction of Outcomes: Vytorin Efficacy International Trial). Circulation 2018; 137(15):1571–1582. doi:10.1161/CIRCULATIONAHA.117.030950
- Kandelouei T, Abbasifard M, Imani D, et al. Effect of statins on serum level of hs-CRP and CRP in patients with cardiovascular diseases: a systematic review and meta-analysis of randomized controlled trials. Mediators Inflamm 2022; 2022:8732360. doi:10.1155/2022/8732360
- Bohula EA, Giugliano RP, Leiter LA, et al. Inflammatory and cholesterol risk in the FOURIER trial. Circulation 2018; 138(2):131–140. doi:10.1161/CIRCULATIONAHA.118.034032
- Ridker PM, MacFadyen JG, Everett BM, et al. Relationship of C-reactive protein reduction to cardiovascular event reduction following treatment with canakinumab: a secondary analysis from the CAN-TOS randomised controlled trial. Lancet 2018; 391(10118):319–328. doi:10.1016/S0140-6736(17)32814-3
- Lederman MM, Funderburg NT, Sekaly RP, Klatt NR, Hunt PW. Residual immune dysregulation syndrome in treated HIV infection. Adv Immunol 2013; 119:51–83. doi:10.1016/B978-0-12-407707-2.00002-3
- Waters DD, Hsue PY. Lipid abnormalities in persons living with HIV infection. Can J Cardiol 2019; 35(3):249–259. doi:10.1016/j.cjca.2018.11.005

- Li Z, Zhu G, Chen G, et al. Distribution of lipid levels and prevalence of hyperlipidemia: data from the NHANES 2007–2018. Lipids Health Dis 2022; 21(1):111. doi:10.1186/s12944-022-01721-y
- 24. **REPRIEVE**. REPRIEVE: Randomized Trial to Prevent Vascular Events in HIV. https://www.reprievetrial.org/. Accessed February 14, 2025.
- Grinspoon SK, Zanni MV, Triant VA, et al. Performance of the pooled cohort equations and D:A:D risk scores among individuals with HIV in a global cardiovascular disease prevention trial: a cohort study leveraging data from REPRIEVE. Lancet HIV 2025; 12(2):e118–e129. doi:10.1016/S2352-3018(24)00276-5
- Krikke M, van Lelyveld SF, Tesselaar K, Arends JE, Hoepelman IM, Visseren FL. The role of T cells in the development of cardiovascular disease in HIV-infected patients. Atherosclerosis 2014; 237(1):92–98. doi:10.1016/j.atherosclerosis.2014.08.054
- Wang T, Yi R, Green LA, Chelvanambi S, Seimetz M, Clauss M. Increased cardiovascular disease risk in the HIV-positive population on ART: potential role of HIV-Nef and Tat. Cardiovasc Pathol 2015; 24(5):279–282. doi:10.1016/j.carpath.2015.07.001
- Ehrenreich H, Rieckmann P, Sinowatz F, et al. Potent stimulation of monocytic endothelin-1 production by HIV-1 glycoprotein 120. J Immunol 1993; 150(10):4601–4609. pmid:8482849
- Freeman ML, Mudd JC, Shive CL, et al. CD8 T-cell expansion and inflammation linked to CMV coinfection in ART-treated HIV infection. Clin Infect Dis 2016; 62(3):392–396. doi:10.1093/cid/civ840
- Russo E, Nannini G, Sterrantino G, et al. Effects of viremia and CD4 recovery on gut "microbiome-immunity" axis in treatment-naïve HIV-1-infected patients undergoing antiretroviral therapy. World J Gastroenterol 2022; 28(6):635–652. doi:10.3748/wjg.v28.i6.635
- Rahmanian S, Wewers ME, Koletar S, Reynolds N, Ferketich A, Diaz P. Cigarette smoking in the HIV-infected population. Proc Am Thorac Soc 2011; 8(3):313–319. doi:10.1513/pats.201009-058WR
- Centers for Disease Control and Prevention. Issue Brief: HIV and transgender communities. Updated May 16, 2024. https://www.cdc.gov/hiv/ policies/data/transgender-issue-brief.html. Accessed November 6, 2024.
- Poteat TC, Rich AJ, Jiang H, et al. cardiovascular disease risk estimation for transgender and gender-diverse patients: cross-sectional analysis of baseline data from the LITE Plus Cohort study. AJPM Focus 2023; 2(3):100096. doi:10.1016/j.focus.2023.100096
- Aranda G, Halperin I, Gomez-Gil E, et al. Cardiovascular risk associated with gender affirming hormone therapy in transgender population. Front Endocrinol (Lausanne) 2021; 12:718200. doi:10.3389/fendo.2021.718200
- American College of Cardiology. Coronary artery disease in HIV. January 18, 2018. https://www.acc.org/Latest-in-Cardiology/ Articles/2018/01/18/08/57/Coronary-Artery-Disease-in-HIV. Accessed February 14, 2025.
- Hsue PY, Waters DD. HIV infection and coronary heart disease: mechanisms and management. Nat Rev Cardiol 2019; 16(12): 745–759. doi:10.1038/s41569-019-0219-9
- Hsue PY, Giri K, Erickson S, et al. Clinical features of acute coronary syndromes in patients with human immunodeficiency virus infection. Circulation 2004; 109(3):316–319. doi:10.1161/01.CIR.0000114520.38748.AA
- Schneider S, Spinner CD, Cassese S, et al. Association of increased CD8+ and persisting C-reactive protein levels with restenosis in HIV patients after coronary stenting. AIDS 2016; 30(9):1413–1421. doi:10.1097/QAD.00000000001063
- Shlofmitz E, lantorno M, Waksman R. Restenosis of drug-eluting stents: a new classification system based on disease mechanism to guide treatment and state-of-the-art review [published correction appears in Circ Cardiovasc Interv 2019; 12(10):e000044]. Circ Cardiovasc Interv 2019; 12(8):e007023. doi:10.1161/CIRCINTERVENTIONS.118.007023
- Boccara F, Lang S, Meuleman C, et al. HIV and coronary heart disease: time for a better understanding. J Am Coll Cardiol 2013; 61(5):511–523. doi:10.1016/j.jacc.2012.06.063
- Friis-Møller N, Weber R, Reiss P, et al. Cardiovascular disease risk factors in HIV patients—association with antiretroviral therapy. Results from the DAD study. AIDS 2003; 17(8):1179–1193. doi:10.1097/01.aids.0000060358.78202.c1

- Worm SW, Sabin C, Weber R, et al. Risk of myocardial infarction in patients with HIV infection exposed to specific individual antiretroviral drugs from the 3 major drug classes: the data collection on adverse events of anti-HIV drugs (D:A:D) study. J Infect Dis 2010; 201(3):318–330. doi:10.1086/649897
- Lagathu C, Béréziat V, Gorwood J, et al. Metabolic complications affecting adipose tissue, lipid and glucose metabolism associated with HIV antiretroviral treatment. Expert Opinion on Drug Safety 2019; 18(9):829–840. doi:10.1080/14740338.2019.1644317
- 44. Lake JE, Currier JS. Metabolic disease in HIV infection. Lancet Infect Dis 2013; 13(11):964–975. doi:10.1016/S1473-3099(13)70271-8
- Heseltine T, Hughes E, Mathew J, Murray S, Khoo S. The effect of changing to Bictegravir on lipids using real world data: a brief report. J Clin Pharm Ther 2022; 47(12):2182–2187.doi:10.1111/jcpt.13789
- 46. Quercia R, Roberts J, Martin-Carpenter L, Zala C. Comparative changes of lipid levels in treatment-naive, HIV-1-infected adults treated with dolutegravir vs. efavirenz, raltegravir, and ritonavir-boosted darunavir-based regimens over 48 weeks. Clin Drug Investig 2015; 35(3):211–219. doi:10.1007/s40261-014-0266-2
- Rivera AS, Pak KJ, Mefford MT, Hechter RC. Use of tenofovir alafenamide fumarate for HIV pre-exposure prophylaxis and incidence of hypertension and initiation of statins. JAMA Netw Open 2023; 6(9):e2332968. doi:10.1001/jamanetworkopen.2023.32968
- Glidden DV, Mulligan K, McMahan V, et al. Metabolic effects of preexposure prophylaxis with coformulated tenofovir disoproxil fumarate and emtricitabine. Clin Infect Dis 2018; 67(3):411–419. doi:10.1093/cid/ciy083
- 49. Arnett DK, Blumenthal RS, Albert MA, et al. 2019 ACC/AHA guideline on the primary prevention of cardiovascular disease: a report of the American College of Cardiology/American Heart Association Task Force on Clinical Practice Guidelines [published correction appears in Circulation 2019; 140(11):e649–e650] [published correction appears in Circulation 2020; 141(4):e60] [published correction appears in Circulation 2020; 141(4):e774]. Circulation 2019; 140(11):e596–e646. doi:10.1161/CIR.0000000000000678
- Soares C, Kwok M, Boucher KA, et al. Performance of cardiovascular risk prediction models among people living with HIV: a systematic review and meta-analysis. JAMA Cardiol 2023; 8(2):139–149. doi:10.1001/jamacardio.2022.4873
- Feinstein MJ. Science and ART-cardiovascular disease risk assessment in HIV. JAMA Cardiol 2023; 8(2):107–108. doi:10.1001/jamacardio.2022.4880
- Feinstein MJ, Hsue PY, Benjamin LA, et al. Characteristics, prevention, and management of cardiovascular disease in people living with HIV: a scientific statement from the American Heart Association. Circulation 2019; 140(2):e98–e124. doi:10.1161/CIR.0000000000695
- Mach F, Baigent C, Catapano AL, et al. 2019 ESC/EAS guidelines for the management of dyslipidaemias: lipid modification to reduce cardiovascular risk [published correction appears in Eur Heart J 2020; 41(44):4255]. Eur Heart J 2020; 41(1):111–188. doi:10.1093/eurheartj/ehz455
- Cottino MC, Kulig CE, Suh JS, Jimenez HR. Evaluation of statin prescribing practices and predictors of statin underutilization in persons with HIV. J Acquir Immune Defic Syndr 2023; 92(4):334–339. doi:10.1097/QAI.00000000003141
- Feinstein MJ, Achenbach CJ, Stone NJ, Lloyd-Jones DM. A systematic review of the usefulness of statin therapy in HIV-infected patients. Am J Cardiol 2015; 115(12):1760–1766. doi:10.1016/j.amjcard.2015.03.025
- 56. Dubé MP, Stein JH, Aberg JA, et al. Guidelines for the evaluation and management of dyslipidemia in human immunodeficiency virus (HIV)-infected adults receiving antiretroviral therapy: recommendations of the HIV Medical Association of the Infectious Disease Society of America and the Adult AIDS Clinical Trials Group. Clin Infect Dis 2003; 37(5):613–627. doi:10.1086/378131
- 57. Aberg JA, Sponseller CA, Ward DJ, Kryzhanovski VA, Campbell SE, Thompson MA. Pitavastatin versus pravastatin in adults with HIV-1 infection and dyslipidaemia (INTREPID): 12 week and 52 week results of a phase 4, multicentre, randomised, double-blind, superiority trial

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[published correction appears in Lancet HIV 2017; 4(7):e283]. Lancet HIV 2017; 4(7):e284–e294. doi:10.1016/S2352-3018(17)30075-9

- 58. Horberg M, Thompson M, Agwu A, et al; HIV Medicine Association. Primary care guidance for providers who care for persons with human immunodeficiency virus: 2024 update by HIVMA/IDSA. Clin Infect Dis 2024; ciae479. doi:10.1093/cid/ciae479
- Datla S, Kumar S. PCSK9 inhibitors-a new hope for dyslipidemia in HIV. Cardiol Rev 2025; 33(2):112–113. doi:10.1097/CRD.00000000000587
- Go AS, Reynolds K, Avula HR, et al. Human immunodeficiency virus infection and variation in heart failure risk by age, sex, and ethnicity: the HIV HEART study. Mayo Clin Proc 2022; 97(3):465–479. doi:10.1016/j.mayocp.2021.10.004
- Remick J, Georgiopoulou V, Marti C, et al. Heart failure in patients with human immunodeficiency virus infection: epidemiology, pathophysiology, treatment, and future research. Circulation 2014; 129(17):1781–1789. doi:10.1161/CIRCULATIONAHA.113.004574
- Cerrato E, D'Ascenzo F, Biondi-Zoccai G, et al. Cardiac dysfunction in pauci symptomatic human immunodeficiency virus patients: a meta-analysis in the highly active antiretroviral therapy era. Eur Heart J 2013; 34(19):1432–1436. doi:10.1093/eurheartj/ehs471
- Hsue PY, Hunt PW, Ho JE, et al. Impact of HIV infection on diastolic function and left ventricular mass. Circ Heart Fail 2010; 3(1): 132–139. doi:10.1161/CIRCHEARTFAILURE.109.854943

- 64. **Hsue PY, Tawakol A.** Inflammation and fibrosis in HIV: getting to the heart of the matter. Circ Cardiovasc Imaging 2016; 9(3):e004427. doi:10.1161/CIRCIMAGING.116.004427
- Sun K, Li Y-Y, Jin J. A double-edged sword of immuno-microenvironment in cardiac homeostasis and injury repair. Sig Transduct Target Ther 2021; 6:79. doi:10.1038/s41392-020-00455-6
- 66. Freiberg MS, Chang CH, Skanderson M, et al. Association between HIV infection and the risk of heart failure with reduced ejection fraction and preserved ejection fraction in the antiretroviral therapy era: results from the Veterans Aging Cohort Study. JAMA Cardiol 2017; 2(5):536–546. doi:10.1001/jamacardio.2017.0264
- Chowdhury SK, Seo JM, Keller S, Solanki P, Finkel D. 931: Congestive heart failure in persons living with HIV: are we providing standard of care (abstract)? Open Forum Infect Dis 2020; 7(suppl 1):S498–S499.
- Scherzer R, Shah SJ, Secemsky E, et al. Association of biomarker clusters with cardiac phenotypes and mortality in patients with HIV infection. Circ Heart Fail 2018; 11(4):e004312. doi:10.1161/CIRCHEARTFAILURE.117.004312

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