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## Statins to improve cardiovascular outcomes in treated HIV infection

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### Abstract

**Purpose of review**—To evaluate evidence that statins reduce cardiovascular risk in patients living with HIV

**Recent findings**—Moderate to high dose atorvastatin and rosuvastatin appear to reduce non-calcified coronary plaque volume and slow progression of carotid intima-media thickness in patients with treated HIV infection. Expected lipoprotein changes with statins on the background of modern ART are similar to the general population. In addition to lipids, the statin benefit may be mediated in part by improvements in vascular inflammation and levels of T-cell and monocyte activation. One concern is the potential for rosuvastatin to cause insulin resistance. Decisions to prescribe statins must be done in the context of global risk assessment, but traditional risk calculators such as the Framingham risk score or the ACC/AHA pooled-risk equations underestimate risk in this population. Furthermore, many patients with subclinical disease would not be recommended for statins according to the most recent ACC/AHA guidelines.

**Summary**—Statins are likely to improve cardiovascular outcomes for patients with HIV, but results of the first outcome study are not expected until 2020. In the meantime, clinicians should individualize statin prescriptions, and should consider using more potent statins (rosuvastatin, atorvastatin, and pitavastatin) when possible.

### Keywords

statin; HIV; inflammation; lipids

### Introduction

The cardiovascular complications of HIV/AIDS have evolved considerably since the early years of the epidemic. Pericarditis and dilated cardiomyopathy—common in the 1980's and 90's—are now rarely seen in the setting of effective antiretroviral therapy (ART). Yet despite effective viral suppression with ART, atherosclerotic cardiovascular disease (CVD)

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events such as myocardial infarction (MI) and ischemic stroke occur more commonly in HIV-infected patients compared to uninfected controls[1, 2]. Proposed mechanisms of this increased risk in HIV have been recently reviewed[3] and include metabolic dysfunction, direct vascular effects, immune activation, and chronic “inflammaging” (Figure 1). Initial epidemiologic studies from the early 2000’s associated antiretroviral drugs, particularly protease inhibitors, with risk of MI[4], but newer generations of these drugs have proven to be less toxic[5]. In light of data from the SMART study and others, the current consensus is that ART has a net cardiovascular benefit[6].

How can we now further reduce the risk of cardiovascular disease in patients with chronic treated HIV infection? Recent attention has focused on statins (HMG-CoA reductase inhibitors) because of their proven benefit to reduce cardiovascular events in the general population, and because of their highly touted “pleiotropic” effects on inflammation and vascular health. Although initially developed to reduce LDL cholesterol, statins have been shown to dramatically reduce the relative risk of MI even in patients with relatively normal LDL levels[7]. Furthermore, the risk reduction is related to the magnitude of reduction in markers of chronic inflammation[8]. Despite the interest in this area, there are currently few data on the cardiovascular benefits of statins in an HIV-infected population.

In this paper, we review recently published studies of the cardiovascular benefits of statins in treated HIV infection and explore some of the potential mediators of this benefit. We also provide an update of current evidence and a framework for how clinicians might approach prescribing statins to patients living with HIV.

## Statins to improve CVD outcomes

In general, for patients who have had a myocardial infarction or acute coronary syndrome (ACS), intensive statin therapy reduces the risk of future major adverse cardiovascular events including cardiovascular death, stroke, and all-cause mortality[9] and the benefit is greater for high vs. moderate intensity statin[10]. Therefore, guidelines recommend that all patients with known CVD (including patients with HIV) should be prescribed high-dose statin therapy if tolerated[11]. For primary prevention of cardiovascular events in patients without known CVD, statins also reduce relative risk of vascular events on the order of 20–40%, but the absolute risk reduction is much lower than for secondary prevention[12]. The most impressive results come from the JUPITER trial in subjects with low LDL cholesterol (<130mg/dL) but elevated high-sensitivity C-reactive protein (hsCRP >2.0mg/L)[7]. In this trial, 20mg of rosuvastatin was associated with a 44% [95%CI 31–54%] relative risk reduction in major cardiovascular events.

Trials to reduce cardiovascular events in patients with relatively normal cholesterol were preceded by many trials of statins to reduce surrogate outcomes such as progression of carotid intima media thickness (CIMT). In the METEOR trial, for example, individuals with low Framingham risk score with evidence of CIMT thickening assigned to 40mg of daily rosuvastatin had a lower rate of CIMT progression over 2 years compared to placebo[13].

The data in patients with chronic HIV infection are limited to observational studies or trials that have focused on surrogate outcomes like in METEOR. Retrospective observational

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studies have suggested dramatic benefits of statins on all-cause mortality. In the Johns Hopkins HIV Clinical Cohort, for example, statin use was associated with a relative hazard of 0.33 (95%CI 0.14–0.76) for mortality after multivariate adjustment for HIV factors and pre-ART cholesterol levels. In a large Danish cohort, statin use seemed to be associated with a similar adjusted mortality rate ratio [aMRR 0.34 (95%CI 0.11–1.04)] among individuals with at least one comorbidity in an analysis restricted to observation time without virologic failure[14]. In contrast, statin use was not associated with reduction in time to all non-AIDS-defining events in an analysis of 3601 subjects from the AIDS Clinical Trials Group Longitudinal Linked Randomized Trials (ALLRT) cohort[15]. Prospective observational data are limited to one study that followed 36 patients with hypercholesterolemia and CIMT thickening (CIMT 0.9mm) who were started on 10mg daily rosuvastatin as part of their clinical care[16]. After 24 months of treatment, the investigators reported significant mean (standard deviation) reductions in mean CIMT ranging from –0.21(0.12) mm at the right common carotid to –0.34(0.19) mm at the left internal carotid.

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The first three clinical trials testing the effect of statins on markers of vascular disease were published a decade ago. All used a relatively weak statin (pravastatin 40mg) due to concerns about drug interactions and used brachial artery reactivity testing (i.e. endothelial function) as the outcome. The first was a placebo-controlled, double-blind, crossover trial of 20 patients that demonstrated a trend toward improved flow-mediated dilation (FMD) with pravastatin (0.7% +/- 0.6%, p=0.08)[17]. Another similarly designed trial was conducted among 29 mostly male subjects on protease inhibitor-based ART with total cholesterol levels >5 mmol/L (193mg/dL)[18]. Median (interquartile range) FMD increased from a baseline of 2.0 (1.5–2.6)% to 3.2 (1.9–4.1)% after 8 weeks of statin therapy. In contrast, no difference in FMD change was seen in another similarly sized placebo-controlled trial of pravastatin[19].

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Recently, the results of two larger randomized, double-blind, placebo-controlled trials of more potent statins to improve other surrogate CVD outcomes were reported[20, 21]. Lo et al. randomized 40 HIV-infected subjects on ART to 20mg of atorvastatin titrated to 40mg after 3 months vs. placebo and followed them for 12 months[20]. All subjects had LDL <130mg/dL but also had both subclinical coronary atherosclerosis on coronary CT angiography and increased aortic inflammation by positron emission tomography (PET/CT). There was no change in the primary cardiovascular outcome of aortic target to background ratio (TBR) of fluorodeoxyglucose uptake measured by PET/CT; however, there were dramatic reductions in non-calcified plaque volume measured by coronary CT angiography [–19(–39 to +9)% vs. +20(–7 to +94)%, statin v. placebo, p=0.009] and reductions in the number of plaques with “vulnerable” or high-risk features [fewer low attenuation plaques (p=0.03) and fewer positively remodeled plaques (p=0.04)].

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The SATURN-HIV trial was conducted in 147 patients on ART with low LDL cholesterol (<130mg/dL) and elevated markers of systemic inflammation (hsCRP >2.0mg/dL) OR T-cell activation (CD8+CD38+HLA-DR+ 19%). Subjects were randomized to rosuvastatin 10mg daily vs. placebo and followed for 96 weeks, and randomization was stratified by the use of protease inhibitor and presence of coronary calcifications. The primary outcome of

mean CIMT progression was reduced in the statin arm [+0.003 (95% CI, -0.014 to +0.021) mm vs. +0.028 (+0.008 to 0.047) mm, statin vs. placebo,  $p=0.031$ ][21].

Together, the two most recent trials suggest that there will be a benefit of the more potent statins to reduce cardiovascular events for HIV-infected patients who are otherwise at low risk—the mean 10-year Framingham Risk Score was <7.5% in Lo et al and <5% in SATURN-HIV; however, both studies enrolled mostly men (~80%) and required elevated markers of vascular or systemic inflammation as an entry criteria. The larger REPRIEVE trial will test whether statin therapy reduces cardiovascular events in a more generalizable population of patients on ART with 10-year ACC/AHA risk of <7.5%, but results are not anticipated until 2020. Completed and ongoing trials of statins with non-lipid cardiovascular endpoints are described in Table 1.

## Potential mediators of the statin effect

As shown in Figure 1, there are multiple proposed mechanisms by which HIV infection may increase the risk of cardiovascular disease: (1) metabolic dysfunction, (2) direct vascular effect, (3) immune activation, and (4) chronic inflammaging[3]. Because of their pleiotropic effects, statins are likely to improve cardiovascular outcomes through mediators in each of these categories. In this next section, we will explore recent data on some of these potential mediators.

### Lipids and adiposity

The effects of statins on lipids in treated HIV infection have been recently summarized in a systematic review[22]. Eighteen studies were included in the review, although not all studies reported lipid changes. The authors conclude that atorvastatin, pravastatin, and rosuvastatin are all well-tolerated and efficacious at lowering LDL cholesterol. For example, in a trial that compared atorvastatin 10mg daily, rosuvastatin 10mg daily, and pravastatin 20mg daily in patients on protease inhibitor-based regimens, LDL was reduced by 20%, 25%, and 18%, respectively, after 1 year of therapy[23]. Another trial confirmed the efficacy of more potent statins, showing that rosuvastatin 10mg was nearly two-fold more effective at lowering LDL compared to pravastatin 40mg (-37% vs. -19%, respectively)[24]. Despite some disagreement among experts and observational data to suggest possible “statin resistance” [25, 26], the most recent clinical trials would suggest that the LDL lowering effect is similar to that seen in the general population; however, the lipid response often depends on the background ART use due to drug interactions.

Historically, HIV-infection was characterized by profound changes in body composition previously referred to as lipodystrophy (peripheral fat loss and/or central fat gain) in some patients. Although lipoatrophy is less commonly seen with current ART, the central fat accumulation continues to occur, regardless of ART regimen[27–29] Because HIV-lipodystrophy is associated with alterations in cardiometabolic risk factors, it is possible that improvements in body fat content and distribution may mediate some of the cardiovascular benefit of statins in HIV infection. In a large observational study of the ALLRT cohort, statin use was associated with 0.6cm greater 32-week change in hip circumference after multivariable adjustment[30]. The authors estimate this difference to correspond to a 0.22 kg

difference in limb fat. A randomized trial of pravastatin resulted in a somewhat larger 0.53 kg increase in limb fat compared to placebo over 12 weeks in patients receiving PI-based ART[19]. In contrast, 2 other placebo-controlled randomized trials showed no benefit of pravastatin on peripheral fat gain in patients with clinical lipodystrophy[31, 32]. Recent data from SATURN-HIV similarly showed no effect of rosuvastatin 10mg on peripheral or central fat volumes by DEXA[33]. Expanding on this study, future analyses of the SATURN-HIV trial may shed light on ectopic fat changes after statin therapy[34].

### **Inflammation and immune activation**

Statins have wide-reaching anti-inflammatory and immunomodulatory effects, including influencing both the innate and adaptive immune responses and affecting a variety of biomarkers of systemic inflammation and endothelial dysfunction that are important in CVD[35, 36]. These effects may be particularly beneficial in the HIV-infected population as heightened inflammation and immune activation are thought to play critical roles in CVD development. Studies published to date, however, are conflicting as to whether statin therapy significantly reduces levels of CRP and other inflammatory markers such as interleukins and adhesion molecules in this population[20, 37–41]. The discrepancies are most likely related to different statins used and/or differences among the study subjects.

The two randomized trials previously mentioned[20, 21] have both shown a reduction in lipoprotein-associated phospholipase A<sub>2</sub> (Lp-PLA<sub>2</sub>), a vascular inflammation marker that predicts both primary and recurrent future coronary or cardiovascular events in the general population[42]. The implication of this reduction is unclear, however, as a large Lp-PLA<sub>2</sub> inhibitor trial showed no benefit for time to first major CVD event in the general population[43].

There are also a few studies that have investigated changes in immune activation, exhaustion and/or T-cell function in ART-treated HIV-infected subjects[41, 44–47]. All of these studies showed decreases in some or all of the markers studied with atorvastatin and rosuvastatin, mainly T-cell and monocyte activation; however, the effect on soluble markers of inflammation has been more inconsistent. Further research is needed to determine the significance of these reductions on outcomes of CVD morbidity and death.

### **Other pleiotropic mediators**

Chronic kidney disease is one of the strongest predictors of CVD events in the general population[48] and in patients with HIV[1]. Although statins reduce CVD events in the general population, they appear to have little effect on kidney function decline[49]. In SATURN-HIV, rosuvastatin was associated with improvements in the kidney biomarker cystatin C and creatinine-based estimates of glomerular filtration rate[50].

Other analyses of secondary endpoints in SATURN-HIV suggest a beneficial effect on N-terminal pro-B-type natriuretic peptide[51], a biomarker of cardiac wall stress that predicts both vascular and heart failure events, but there was no effect on the expression of two well-known transcriptional mediators of vascular inflammation—Krüppel-like factors 2 and 4[52].

Future translational studies should further investigate statin mechanisms in the setting of chronic inflammatory diseases such as treated HIV. Placebo-controlled study designs will be possible in low-risk individuals at least until the results of the REPRIEVE study are known. Such mechanistic studies should also consider the value of HIV-uninfected persons as negative controls and persons with inflammatory polyarthropathies as positive controls.

## Risks and side effects of statin therapy

Statins used at recommended doses in HIV-infected individuals have a relatively low risk of side effects comparable to the general population in most studies[24, 39, 53]. The most serious side effect is rhabdomyolysis[54], but this is rare. For example, over 96 weeks in SATURN-HIV, there were no cases of rhabdomyolysis and only 3 participants (2 statin and 1 placebo) discontinued study drug due to myalgias[55]. Additionally, there was no change in creatinine kinase and a trend toward increased lean body mass in the rosuvastatin arm. The implications of the increased diabetes risk with statins is concerning for the HIV population, however. A single study (SATURN-HIV) to date has investigated this side effect in HIV-infected subjects and showed a >50% increase in insulin resistance after only 48 weeks of rosuvastatin therapy[56].

## Who should be prescribed statins?

Prescribing statins to reduce the risk of CVD in patients with HIV infection should always be done in the context of global cardiovascular risk assessment; however, few studies have described the performance of commonly available risk calculators for the HIV-infected population. Recent studies from North American cohorts suggest that these risk calculators have reasonable discrimination (c-statistics 0.65–0.75) in HIV-infected populations, but underestimate risk for MI[57, 58] and stroke[59] with observed:expected ratios of ~1.25[57, 58]. This underestimation of risk is most significant for patients who are categorized as low risk (<7.5% 10-year risk)[57]. Thus, HIV-specific calculators have been proposed. Friis-Moller et al. used the D:A:D cohort to construct a risk model that incorporates current use and duration of specific ART drugs[60]. In the derivation cohort, the prediction tool had better discrimination and calibration when compared to the Framingham Risk Score[60], but in other cohorts, the model performs similarly to Framingham and other risk calculators[57, 58]. Another model that may more accurately assess CVD risk in patients living with HIV is the Veterans Affairs Cohort Study (VACS) Index. Although extensively studied as a predictor of mortality[61], it is less well-validated as a CVD risk estimator[62].

In 2013, the American College of Cardiology (ACC) and the American Heart Association (AHA) issued joint heart disease and stroke prevention guidelines that focus on lifestyle, obesity, risk assessment, and treatment of cholesterol[11, 63]. Instead of recommending target LDL goals, the new cholesterol treatment guidelines identified four types of patients that would benefit from statin therapy: (1) high LDL >190mg/dL; (2) history of known CVD; (3) diabetes; and (4) 40–75 years old with a >7.5% 10-year risk of CVD. The guidelines were released together with a new calculator to predict risk that was created using pooled data from multiple cohort studies[63]. Although some have argued that the pooled cohort equations overestimate risk for some patients, there is emerging evidence that they

underestimate risk in patients with HIV[57]. For example, although the new guidelines expand recommendations for statin use above what would have been recommended by the Adult Treatment Panel (ATP III) guideline, nearly 40% of HIV-infected patients who have a CVD event would not have been recommended to receive statin therapy prior to the event under either of these guidelines[64]. Similarly, the ACC/AHA guidelines recommend statins for a larger number of HIV-infected patients with high risk plaque features by coronary angiography compared to ATP III; however, statins would not be recommended by either guideline for nearly three-quarters of patients with high risk plaque features[65].

In 2015, the National Lipid Association issued recommendations for patient-centered management of dyslipidemia that re-affirmed the importance of treating to target cholesterol levels[66]. In Part 2 of the recommendations, expert panels were convened to create specific recommendations for at-risk populations. The expert panel concluded that HIV-infection should be considered a major risk factor for CVD, which can be used to determine absolute risk category and corresponding treatment goals[67]. These recommendations include an update on statin interactions with ART based on recent studies[68–70] and suggested that more potent statins such as rosuvastatin, atorvastatin, and pitavastatin are generally preferable to the less potent pravastatin. To further assist the clinician in navigating drug-drug interactions, we have compiled an overview in Table 2. The National Lipid Association has previously reviewed these interactions in more detail[67, 71]. Table 2 displays significant interactions with protease inhibitors including ritonavir, cobicistat, and non-nucleoside reverse transcriptase inhibitors. Except for cobicistat-boosted elvitegravir, there are no significant statin interactions with integrase inhibitors or entry inhibitors.

Considering the relative merits of these guidelines and others (e.g. European Society of Cardiology), it is important for the clinician to take an individualized approach to statin prescriptions for patients living with HIV. For each patient, expected absolute risk reductions should be weighed against potential risks and side-effects. This discussion of risks and benefits should result in a mutual decision between patient and provider about whether to start a statin.

## Conclusion

Recent studies have sparked new interest in the potential of statins to improve cardiovascular outcomes in patients living with HIV/AIDS. But are statins a magic bullet? Our opinion is that while clearly more study is needed to determine which patients will benefit, efforts must be made to increase use in patients for whom there is a clear indication. In 2009, less than 40% of HIV-infected veterans who met ATP III recommendations for lipid-lowering therapy actually received it [72]. With expanded recommendations under ACC/AHA guidelines, these numbers are likely to be even lower. Clinicians should strongly consider having a discussion about statins with patients in the context of how to live well with HIV in the modern treatment era.

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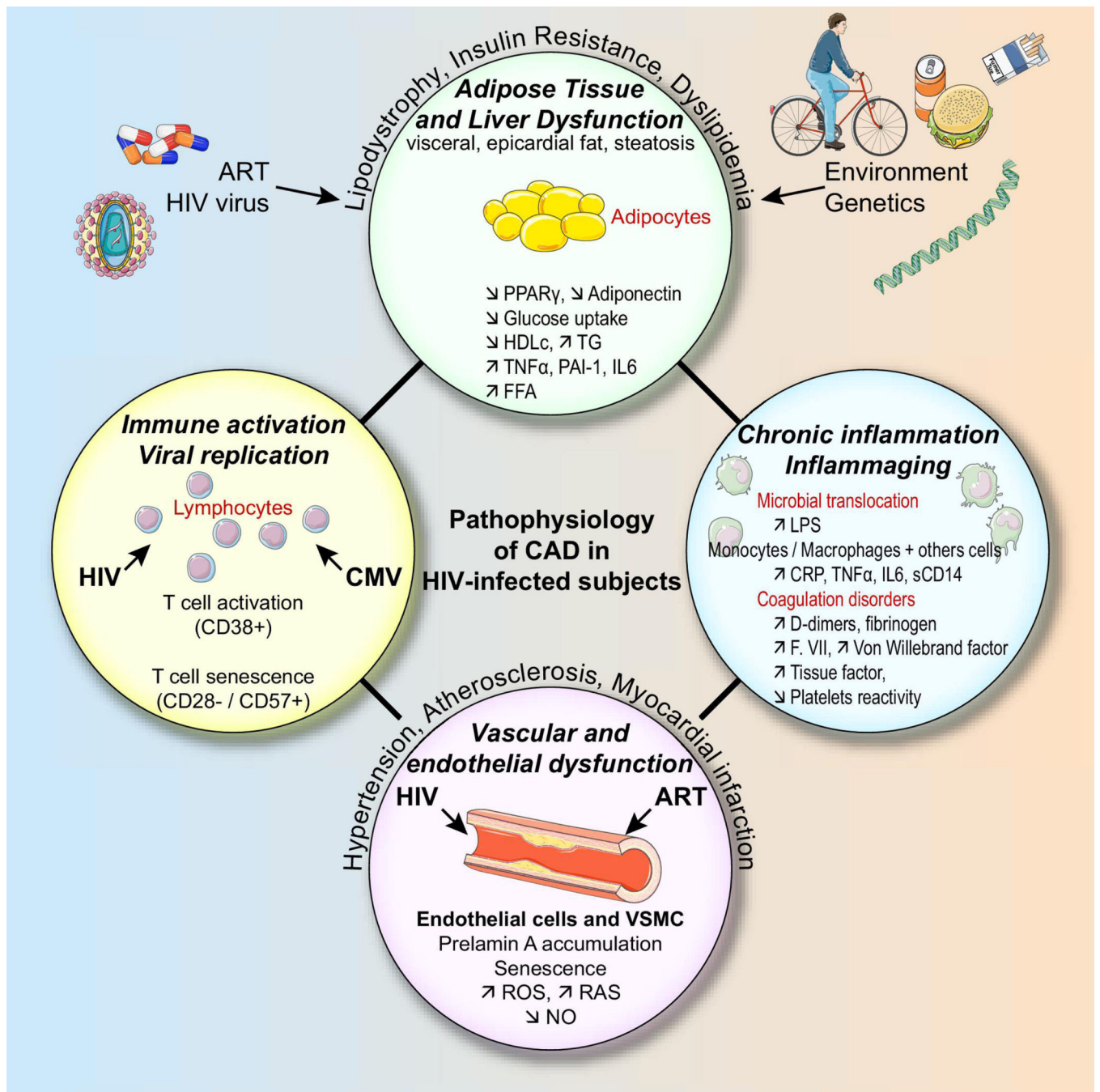
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### Key Points

- Single-centered randomized clinical trials suggest that moderate to high dose atorvastatin and rosuvastatin reduce the burden of subclinical carotid and coronary atherosclerosis in patients with treated HIV infection, but the results of a multicenter cardiovascular outcomes study (REPRIEVE) are not expected until 2020.
- In treated HIV, the cardiovascular benefit of statins may be mediated in part by reductions in atherogenic lipoproteins, but also by reductions in vascular inflammation and immune activation.
- There may be a risk of insulin resistance and diabetes with certain statins, and this should be assessed further in future studies.
- Statins should be prescribed in the context of global risk assessment, keeping in mind that commonly used risk calculators tend to underestimate risk in patients with treated HIV infection.
- Clinicians should consider the more potent statins (atorvastatin, rosuvastatin, and pitavastatin) whenever possible, while being aware of modest drug-drug interactions.



**Figure. Proposed mechanisms of increased cardiovascular risk in chronic HIV infection**  
 Reproduced with permission from Boccara et al.[3]

**Table 1** Randomized clinical trials of statins to improve vascular measures and clinical CVD outcomes in HIV-infected adults on ART

<b>(A) Completed</b>									
Clinicaltrials.gov Identifier	Year Completed	Population**	N	Intervention	Duration	Surrogate CVD outcome	Main Results	References	
N/A	2004	On stable PI; total cholesterol >3.36mmol/L and either triglycerides >3.88mmol/L or HDL <1.07mmol/L	20	Pravastatin 40mg vs. Placebo	8 weeks	FMD	Trend toward improved FMD with pravastatin (p=0.08)	Stein et al.[17]	
N/A	2006	On stable PI; total cholesterol >5mmol/L (193mg/dL)	29	Pravastatin 40mg vs. Placebo	8 weeks	FMD	Improved FMD in statin arm vs. no change in placebo.	Hurlimann et al.[18]	
NCT00227500	2006	Men >18yrs; Stable PI; Total cholesterol >6.5mmol/L (251mg/dL)	33	Pravastatin 40mg vs. Placebo	12 weeks	FMD	No difference in FMD change	Mallon et al.[19]	
NCT00965185	2014	Stable ART; <i>subclinical</i> coronary athero by CTA AND aortic inflammation by PET; LDL 70–130mg/dL	40	Atorvastatin (20–40mg) vs. Placebo	12 months	Coronary CTA plaque features; Aortic TBR*	Reduced non-calcified plaque volume and # of high risk plaques; no difference in aortic TBR change	Lo et al.[20]	
NCT01218802	2014	Stable ART; LDL <130mg/dL; hsCRP >2 or elevated CD 8+ T-cell activation	147	Rosuvastatin 10mg vs. Placebo	96 weeks	CIMT; FMD; CAC	Reduced 48 and 96 week CIMT progression; no difference in CAC change	Longenecker et al.[21]	

<b>(B) Ongoing</b>									
Clinicaltrials.gov Identifier	Estimated Completion	Population	N	Intervention	Duration	CVD outcome(s)			
NCT01881971	2016	Stable ART; COPD	30	Rosuvastatin vs. Placebo	24 months	CIMT; FMD			
NCT02081638	2017	Elite Controller or ART >4 yrs	80 <sup>†</sup>	Open label Aspirin 81mg vs. Atorvastatin 40mg	9 months	Carotid MRI			
NCT01813357	2017	Stable ART; FRS 10–15%	102	Rosuvastatin 20mg vs. Placebo	24 months	CIMT; FMD			
NCT02234492	2018	>40yrs; ART >2 yrs; FRS 10–20%; LDL <4mmol/L (<155mg/dL);	82	Open label Rosuvastatin 10mg vs. usual medical care	6 months	Coronary Flow Reserve <sup>‡</sup> ; Vascular TBR*			
NCT02344290	2020	40–75yrs; stable ART; <7.5% 10yr risk	6500	Pitavastatin 4mg vs. Placebo	42–72 months	MACE; Coronary CTA substudy			

\* Measured using 18-fluorodeoxyglucose positron emission tomography (18-FDG PET/CT)

\*\* Population includes most important inclusion/exclusion criteria; full criteria available at [clinicaltrials.gov](http://clinicaltrials.gov) or in the published manuscript

<sup>†</sup> 40 elite controllers; 40 treated progressors

<sup>‡</sup> Measured using myocardial contrast echocardiography

PI, protease inhibitor; CTA, computed tomography angiography; TBR, Target to background ratio; CIMT, carotid intima-media thickness; FMD, flow-mediated dilation of the brachial artery; CAC, coronary artery calcium; COPD, chronic obstructive pulmonary disease; FRS, Framingham Risk Score; MACE, major adverse cardiovascular events (CVD death, nonfatal myocardial infarction, unstable angina hospitalization, coronary or peripheral arterial revascularization, nonfatal stroke or transient ischemic attack, urgent peripheral arterial disease ischemic event)

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**Table 2**

Antiretroviral drug interactions with commonly used statins

	<b>PI</b>	<b>Cobicistat</b>	<b>NNRTI</b>
<b>Atorvastatin</b>	↑↑ Do not exceed 20–40mg X with TPV/r	↑↑ Do not exceed 20–40mg	↓ EFV and ETR ↔ RPV
<b>Rosuvastatin</b>	↑↑ LPV/r and ATV/r Do not exceed 10–20mg ↑ DRV/r	↑ Do not exceed 10–20mg	↔
<b>Pitavastatin</b>	↔	↔	↔
<b>Pravastatin</b>	↔ ↑ DRV/r	↔	↔ ↓ EFV
<b>Simvastatin</b>	X	X	↓

This table is compiled from multiple sources and is meant to be a simplified overview. For details, please refer to the following review articles [67, 71].

↑ = mild increase in statin concentration; ↑↑ = moderate increase; X = contraindicated due to strong interaction; ↓ = decrease; ↔ no to minimal interaction

PI, protease inhibitor; NNRTI, non-nucleoside reverse transcriptase inhibitor; r, ritonavir; TPV, tipranavir; LPV, lopinavir; ATV, atazanavir; DRV, darunavir; EFV, efavirenz; ETR, etravirine; RPV, rilpivirine