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Rosuvastatin Slows Progression of Subclinical Atherosclerosis in Patients with Treated HIV Infection

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Abstract

Objective—To determine the effect of statins on the progression of subclinical atherosclerosis in a population of HIV-infected adults on antiretroviral therapy.

Design—Double-blind, randomized clinical trial

Methods—SATURN-HIV was a 96-week double-blind, randomized clinical trial of 10 mg daily rosuvastatin (n=72) versus placebo (n=75) in a population of HIV-infected subjects on stable antiretroviral therapy with LDL-cholesterol 130mg/dL (3.36mmol/L) and evidence of heightened T-cell activation (CD8+CD38+HLA-DR+ 19%) or increased inflammation (high sensitivity C-reactive protein 2mg/L (19mmol/L)). Change in common carotid artery IMT (CCA-IMT) was the primary outcome. Secondary outcomes were changes in LDL and coronary artery calcium (CAC).

Results—Median (Q1, Q3) age was 46 (40, 53) years; 78% were male and 68% African American; 49% were on a protease inhibitor. Mean (95% CI) change in LDL was –21 (–27 to –15) mg/dL [–0.54 (–0.70 to –0.39) mmol/L] in the rosuvastatin arm. In a multivariable linear mixed-effects model, assignment to statin was associated with 0.019mm (95% CI: 0.002–0.037mm) less progression of CCA-IMT over 96 weeks. We did not find substantial effect modification by level of inflammation or immune activation biomarkers, except for a borderline statistically significant interaction for soluble vascular cell adhesion molecule (p=0.065). There was no difference in CAC change (p=0.61).

Conclusions—Rosuvastatin effectively lowers LDL and appears to substantially slow progression of CCA-IMT in patients with treated HIV infection. Future study is needed to

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Conflicts of Interest: AS and RG have no disclosures.

Supplemental Digital Content 1

Supplemental Digital Content 2

Supplemental Digital Content 3

Supplemental Digital Content 4

CTL wrote the first draft of the manuscript and performed all vascular ultrasound measurements. AS performed statistical analyses. RG made substantial intellectual contributions to the cardiac CT aspects of the study. GAM designed the study and supervised all aspects of the trial. All authors participated in the analysis and interpretation of trial data, and all reviewed the manuscript for intellectual content.

determine whether subjects with higher levels of inflammation or immune activation derive greater cardiovascular benefit from statin therapy.

Keywords

HIV; statin; inflammation; carotid intima-media thickness; coronary artery calcium

Introduction

Inflammation is a fundamental driver of atherosclerosis, and patients with inflammatory autoimmune disease are at high risk of atherothrombotic cardiovascular (CV) events[1]. Similarly, HIV infection is characterized by chronic inflammation and immune activation[2] and a 1.5–2-fold higher risk of myocardial infarction that persists despite effective antiretroviral therapy (ART)[3]. In this population, numerous observational studies have associated circulating biomarkers of inflammation and immune activation with arterial inflammation[4], subclinical carotid disease[5, 6], high risk coronary plaque[7, 8], and CV events[9]. It remains unclear, however, whether anti-inflammatory therapies might slow progression of atherosclerosis and reduce events in HIV infection.

Statins are HMG-CoA reductase inhibitors that lower low-density lipoprotein (LDL) concentrations and dramatically reduce the risk of CV events in the general population[10]. This reduction in events may be due to an anti-inflammatory effect that is independent of LDL lowering[11]. Yet, for patients with higher levels of systemic inflammation, such as systemic lupus erythematosus (SLE) or rheumatoid arthritis (RA), there is mixed evidence that statins reduce progression of subclinical vascular disease or CV events[12–18].

The **Stopping Atherosclerosis and Treating Unhealthy Bone with Rosuvastatin in HIV** infection (SATURN-HIV) study was designed to test whether statin therapy would reduce progression of atherosclerosis in an HIV-infected population on ART with evidence of heightened inflammation or immune activation and low LDL. In pre-specified interim analyses, we have previously shown that rosuvastatin reduces soluble markers of inflammation and cellular markers of monocyte and lymphocyte activation[19–21]. In this study, we report the results of the primary outcome of carotid intima media thickness (IMT) progression and the secondary outcome of coronary artery calcium (CAC) score progression over 96 weeks.

Methods

The SATURN-HIV study was a double-blind, randomized controlled trial of 10mg daily rosuvastatin versus matching placebo with a primary outcome of common carotid artery IMT progression from 0 to 96 weeks. Secondary outcomes included 96-week changes in lipids and CAC score, as well as inflammation and metabolic outcomes. All participants were 18 years of age without known coronary disease or uncontrolled diabetes, and on stable ART for at least 3 months with HIV-1 RNA <1,000 copies/mL. Similarly to the JUPITER (Justification for the Use of Statins in Prevention-an Intervention Trial Evaluating Rosuvastatin) study in HIV-uninfected adults[10], we included participants with LDL-cholesterol 130mg/dL (3.36mmol/L) and evidence of increased inflammation and/or T-

cell activation (high sensitivity C-reactive protein $\geq 2\text{mg/L}$ ($\geq 19\text{mmol/L}$) and/or CD8+CD38+HLA-DR+ T-cells $\geq 19\%$). Nineteen per cent CD8+CD38+HLA-DR+ is the median level of patients successfully treated with ART and the 75th percentile for HIV-uninfected controls at our site. Additional inclusion and exclusion criteria are listed in Supplemental Table 1 (Table, Supplemental Digital Content 1). Randomization was stratified by use of protease inhibitors and by presence or absence of CAC at study screening. All participants provided written informed consent, and the study was approved by the Institutional Review Board of University Hospitals Case Medical Center (Cleveland, Ohio). The study was registered on the clinicaltrials.gov website (NCT01218802).

Self-reported demographics and medical history were obtained along with a targeted physical exam including height, weight, waist, and hip measurements. Blood was drawn after at least a 12-hour fast for glucose, insulin, and lipoproteins. HOMA-IR was calculated from the fasting glucose and insulin measurements[22]. Ten-year Framingham Risk Score was calculated using a published risk calculator[23]. HIV-1 RNA level and CD4+ cell count were obtained as part of routine clinical care. Study participants and their physicians were blinded to laboratory values measured for this study; however, they were not blinded from laboratory values checked for clinical purposes during the study period.

Carotid Ultrasound

At baseline, 48, and 96 weeks, all participants underwent high resolution ultrasound scanning of the carotid arteries on a Philips iU22 with L9-3 MHz linear array transducer (Philips Healthcare; Andover, MA, USA) using the consensus protocol of the American Society of Echocardiography[24]. The distal one centimeter of the common carotid artery (CCA) was imaged at three angles (anterior, lateral, posterior) bilaterally. Far-wall CCA-IMT was measured offline by a single reader (CTL; blinded to treatment assignment and participant characteristics) using semi-automated edge-detection software (Medical Imaging Applications; Coralville, IA, USA). The mean-mean CCA-IMT (mean of 6 segments) was used for all analyses because of its superior reproducibility compared to other segments. Cine clips of the bilateral CCA, internal carotid arteries, and external carotid arteries were used to identify the presence of any plaque, defined as IMT $>1.5\text{mm}$ or $>50\%$ thicker than the adjacent vessel. Using this protocol, reproducibility for mean-mean CCA-IMT measurements at our site is high, with intraclass correlation coefficients ranging from 0.961–0.968.

Cardiac Computed Tomography

At baseline, 48, and 96 weeks, all participants also had a non-contrast computed tomography (CT) scan of the chest for coronary artery calcium scoring. All scans were performed on a 64-slice multidetector CT scanner (Somatom Sensation 64, Siemens Medical Solutions USA) with $30 \times 0.6\text{mm}$ collimation, 330ms rotation time, and 120kV tube voltage. Three-millimeter slices were obtained from the carina to the diaphragm with prospective ECG gating at 60% of the R-R interval. Calcified coronary lesions were defined as areas of ≥ 6 pixels with density >130 Hounsfield units (HU). A single reader (RG; blinded to treatment assignment and participant characteristics) quantified total coronary calcium score using the Agatston method.

Biomarkers of inflammation and immune activation

Several biomarkers of systemic inflammation, monocyte activation, endothelial activation, and coagulation were measured in plasma at the baseline visit. Interleukin-6 (IL-6), soluble tumor necrosis factor- α receptors I and II (sTNFR-I and II), soluble vascular cell adhesion molecule-1 (sVCAM-1), soluble intercellular adhesion molecule-1 (sICAM-1), and two soluble markers of monocyte activation (sCD14 and sCD163) were determined by ELISA (R&D Systems; Minneapolis, MN, USA). Plasma cystatin C, high sensitivity C-reactive protein (hsCRP), and fibrinogen were measured by particle enhanced immunonephelometric assay on a BNII nephelometer (Siemens; Munich, Germany). D-dimer was determined by immunoturbidometric assay on a STA-R Coagulation Analyzer (DiagnosticaStago).

Monocytes and T-cells were phenotyped by flow cytometry as previously described[20]. Three monocyte subsets: (1) CD14+CD16+, (2) CD14^{dim}CD16+, and (3) CD14+CD16- were each quantified as a percentage of the overall monocyte population. T-cell activation was quantified as the percentage of CD4+ or CD8+ cells that expressed both CD38 and HLA-DR. Screening CD8+ activation was measured from fresh whole blood and entry CD8+ activation was measured from frozen PBMCs.

Statistical analysis

Baseline characteristics of demographic variables, HIV parameters, cardiovascular risk factors and subclinical vascular disease were described using median (interquartile range, IQR) for continuous variables or percentage for categorical variables. Differences between groups, rosuvastatin vs. placebo, were tested with t-tests, Mann Whitney tests, or Fisher's exact tests as appropriate.

The primary outcome variable in this analysis was the change in mean-mean common carotid artery IMT (mm) over the study period (96 weeks). The study was powered to detect a mean difference in 0 to 96 week IMT change of 0.118mm with 84% power assuming a sample size of 140 subjects, standard deviation of 0.208mm, and 20% loss to follow-up.

To measure the effects of statin treatment we analyzed the IMT change (baseline IMT value subtracted) outcome variable using flexible linear mixed-effects (LME) models with random intercept and random slope. The random-effects in the model account for variations between individuals in the study and correlations within individual repeated CCA-IMT measurements. For variances of the random-effects, which measure the variability of the longitudinal trajectories between individuals that are unexplained by covariates, we used an unstructured variance-covariance matrix. We estimated unadjusted and adjusted treatment effects using the maximum likelihood method. All candidate covariates (from Table 1) that were significant at 10% level were used to create the final multivariable adjusted model. Although BMI was statistically significantly associated with IMT change at 10% level, it was not included in the final model due to multicollinearity with metabolic syndrome. To further explore the effect of statin treatment on CCA-IMT progression among sub-groups of patients with the highest levels of inflammation and immune activation, we compared the statin treatment effect for patients with the highest quartile of each individual biomarker

(Q4) to all others (Q1-Q3). We then tested for statistical significance of these interactions using linear mixed-effects model as described above.

In this study, a number of subjects withdrew or were lost to follow-up; however, none were due to drug-related adverse events. Detailed dispositions of study subjects are presented in Supplemental Figure 1 and the Results section. We compared the baseline characteristics of subjects with incomplete data to those who completed the study to check for any systematic biases (Supplementary Table 2). Moreover, to test whether differences between subjects with and without missing data affected our results, we created a binary missing data indicator variable. When this missing data indicator variable was used as a covariate in the LME model, we found that the outcomes did not differ significantly at a <5% level. We therefore assumed a missing at random (MAR) mechanism of missingness. The LME model is well-suited to produce unbiased parameter estimates with valid statistical inference when missingness is MAR.

All analyses were conducted using STATA 13.0 (StataCorp; College Station, TX, USA).

Results

Supplemental Figure 1 (Figure, Supplemental Digital Content 2) describes the flow of participants through the SATURN-HIV trial. Of the 202 participants screened, 147 participants met entry criteria and were enrolled (72 into the rosuvastatin arm and 75 into the placebo arm). Twenty-eight participants (9 rosuvastatin; 19 placebo) withdrew or were lost to follow-up prior to the 96 week visit, none due to drug-related adverse events. One participant had missing 96 week carotid data due to poor image quality. Thus, one hundred and twenty-three (84% of participants) had complete 48-week data and 118 (80%) had complete 96-week data. Three participants (two on rosuvastatin) had premature study drug discontinuation but continued study follow-up. One subject in the rosuvastatin arm discontinued study drug at week five due to myalgias and high creatinine kinase. The other subject in the rosuvastatin arm discontinued at week 37 due to a possible exacerbation of neuropathy symptoms.

The baseline characteristics of all 147 participants at entry are displayed in Table 1, and characteristics of the 118 subjects with complete 96-week data are shown in Supplemental Table 2 (Table, Supplemental Digital Content 3). Overall, median age was 46 years; 78% were male and 68% were African American. HIV disease was well-controlled; although a quarter of participants had low-level detectable HIV-1 viremia (>50 but <1000 copies/ml) despite ART. Lipid profiles and 10-year Framingham scores were low risk, but nearly one-quarter of participants had metabolic syndrome and at least a third had carotid plaque by ultrasound or detectable coronary artery calcium. Overall, median (IQR) entry CD8+ activation was lower than screening, likely due to differences in assays being run on frozen vs. fresh samples [28(22–40)% vs. 12(9–18)%, screening vs. entry, $p<0.001$].

Lipid changes

Participants assigned to the rosuvastatin arm achieved a mean (95% CI) reduction in LDL concentration of -24 (-29 to -18) mg/dL [-0.62 (-0.75 to -0.47) mmol/L] by week 24

(Figure, Supplemental Digital Content 4). This approximate 20–25% reduction from baseline was sustained throughout the course of the 96 week study, and was statistically different from the placebo arm at all time points. There was a corresponding 0–96 week reduction in non-HDL concentration [–21(–28 to –13) vs. –3.7(–12 to 4.4) mg/dL; –0.54 (–0.72 to –0.37) vs. –0.10 (–0.31 to 0.11) mmol/L; statin vs. placebo, $p=0.003$] without significant change in HDL [1.1(–1.3 to 3.5) vs. 1.7(–2.6 to 6.1) mg/dL; 0.03 (–0.03 to 0.09) vs. 0.04 (–0.07 to 0.16) mmol/L; statin vs. placebo, $p=0.48$].

Carotid Intima-Media Thickness

In a linear mixed-effects model, assignment to rosuvastatin 10mg daily was associated with an unadjusted 0.021 mm (95% CI: 0.003–0.038 mm) lower IMT change over the 96 week study period compared to placebo. This remained statistically significant after adjustment for age, sex, insulin resistance (HOMA-IR), metabolic syndrome, and protease inhibitor use [0.019 mm (95% CI 0.002–0.037 mm), $p=0.03$; Table 2]. The trajectory of CCA-IMT change over the study period is shown in Figure 1. Within the placebo group, CCA-IMT progressed significantly over the course of the 96 week study, but was unchanged in the statin group. The difference in IMT change between statin and placebo groups was statistically significant at 48 weeks ($p=0.025$) and borderline significant at 96 weeks ($p=0.061$) despite a mean (95% CI) annualized rate of CCA-IMT progression in the placebo group that was slower than anticipated [0.015 (0.005–0.025) mm/yr]. Among the 74 participants ($n=41$ statin; $n=33$ placebo) without carotid plaque at baseline, only 4 developed plaque by week 96, without differences by treatment group [4.9 vs. 6.1%, statin vs. placebo; $p=0.82$].

In an exploratory subgroup analysis, we examined whether subjects with higher baseline inflammation and immune activation would experience greater reductions in IMT progression with statin therapy compared to those with lower levels of inflammation. Figure 2 shows the adjusted statin treatment effect on 96 week CCA-IMT change by high vs. low subgroups of baseline biomarkers (Q4 vs. Q1–3). In linear mixed models with the same covariates as in the primary analysis, there was a borderline statistically significant interaction for sVCAM only (p for interaction = 0.065; all other $p > 0.15$).

Coronary Artery Calcium

The percentage of participants with detectable coronary calcium at week 0 and week 96 by treatment group is shown in Figure 3A. Among the 73 participants ($n=40$ statin; $n=33$ placebo) without detectable coronary calcium at baseline, there was no difference in detectable CAC after 96 weeks of statin [15% vs. 6%, statin vs. placebo; $p=0.19$]. Among the 45 participants ($n=22$ statin; $n=23$ placebo) with detectable CAC at baseline, there was no difference in mean (95% CI) 0–96 week CAC change [Figure 3B; 12 (–2.6 to 28) vs. 37 (8 to 67), statin vs. placebo; $p=0.61$], but statin use was associated with significantly less mean CCA-IMT progression in this subgroup [–0.017 (–0.060 to 0.026) mm vs. 0.041 (0.001 to 0.081), statin vs. placebo; $p=0.023$].

Discussion

This is the first randomized, placebo controlled trial to assess the effect of statin therapy on the progression of subclinical carotid artery disease in a HIV-infected cohort on antiretroviral therapy with baseline LDL less than 130mg/dL ($< 3.36\text{mmol/L}$). In our study, rosuvastatin 10mg lowered LDL by approximately 20–25% and slowed progression of CCA-IMT during 2 years of follow-up. These findings have important implications for the design of future clinical outcomes studies of statin therapy in patients with chronic inflammatory disorders.

In the general population, the JUPITER study showed that rosuvastatin significantly reduces CV events among patients with low LDL if they were also selected for modest elevations in hsCRP[10]. Yet, only 62% of HIV-infected patients who experience cardiovascular events would be recommended for statin therapy using the latest 2013 ACC/AHA guidelines[25, 26]. Furthermore, only 26% of patients with high risk plaque features on CT coronary angiography would meet criteria for therapy[27]. These studies highlight the need to identify biomarkers that not only risk-stratify this population but also identify the patients who are most likely to benefit from statins. We therefore designed our trial to target patients with lower LDL cholesterol, but with elevated markers of inflammation (hsCRP $\geq 2\text{mg/L}$ ($\geq 19\text{mmol/L}$)) and/or CD8+ T-cell activation (CD8+CD38+HLA-DR+ T-cells $\geq 19\%$). In the end, only 13 (6%) of 202 subjects screened were excluded based on these criteria, highlighting the high degree of inflammation and immune activation in this treated HIV-infected population.

Carotid IMT is a surrogate marker of atherosclerotic vascular risk that has been used in clinical practice and in trials of statin therapy to identify patient subgroups that merit more aggressive treatment for primary prevention[24, 28]; however, two IMT trials in patients with SLE did not show any statin benefit on IMT progression[12, 17]. Subsequent secondary analyses of APPLE suggested a statin benefit in patients with higher hsCRP[13] and in subjects without vitamin D deficiency[29].

We hypothesized that similarly to the APPLE study, patients with the highest levels of inflammation would have a greater statin benefit. Although there was a tendency toward greater benefit across many of the biomarkers studied; in adjusted models, we only observed a borderline statistically significant interaction for sVCAM. Interestingly, neither CD8+ T-cell activation nor hsCRP—the biomarkers chosen for inclusion criteria—seemed to modify the statin effect or associate with the magnitude of CCA-IMT change. We do not believe that this can be explained by the exclusion of subjects with low levels of hsCRP, because over half of the participants had an hsCRP < 2.0 [20]. Although these subgroup analyses were pre-specified, the results should be interpreted with caution and should be viewed only as hypothesis generating. Future studies, including secondary analyses of this trial and others, should consider other potential modifiers of the statin effect to identify which patients are most likely to benefit.

Studies conflict about whether statins alter progression of coronary artery calcium[30, 31]. Statins may modify the pattern of CAC (e.g. less spotty calcification) and/or components of

the Agatston score (e.g. increasing density > volume)[32] in a way that promotes plaque stabilization[33]; however, the mechanisms by which this occurs remain unclear[34]. In our study, it is therefore not surprising that we saw no difference in incident new CAC or CAC progression between groups.

For patients with chronic treated HIV infection, statins appear to be safe and effective, as long as important drug-drug interactions with ART are considered[35]; however, there is an urgent need to determine whether statins will reduce clinical cardiovascular endpoints. To our knowledge, only one other placebo controlled trial has assessed the effect of statin therapy on subclinical vascular disease in this population. In a small trial of 40 HIV-infected men with LDL <130mg/dL (3.36mmol/L), Lo and colleagues demonstrated that 20–40mg of atorvastatin reduced total coronary plaque burden (particularly non-calcified plaque) as assessed by CT angiography[36]; however, there was no difference in coronary calcium changes or aortic inflammation measured by F-18-fluorodeoxyglucose positron emission tomography. Our findings are consistent with those of Lo et al. and suggest that HIV-infected patients are likely to gain a cardiovascular outcomes benefit from statin therapy. This hypothesis will be tested in the Randomized Trial to Prevent Vascular Events in HIV (REPRIEVE; reprieve.trial.org).

In this study of subjects without diabetes, we have previously demonstrated worsening of insulin resistance as early as 48 weeks after initiation of rosuvastatin[37]. Large and longer term clinical trials are needed to assess whether an increased risk of diabetes will jeopardize the favorable effect of statins on cardiovascular risk in the HIV-infected population.

Major strengths of our study are the randomized, placebo-controlled design and extensive immunophenotyping of participants. Although it is the largest placebo-controlled statin trial conducted in HIV-infected persons to date, it may have been underpowered to detect clinically significant treatment modification by inflammation or immune activation status. These subgroup analyses were also not adjusted for multiple comparisons and should only be considered hypothesis generating. Our study was also limited by 20% attrition over the 96 week study, which reduced study power. We anticipated this rate of drop-out in our study population, and were powered (at least 80% power) in the planning stage of this study to detect clinically significant changes in the primary CCA-IMT outcome. Although there was differentially more attrition in the placebo group, baseline characteristics of those with complete data remained similar between treatment groups. Lastly, our study included mostly men and African Americans, and may therefore be less generalizable to women and other racial/ethnic groups.

In conclusion, 10mg of daily rosuvastatin lowers LDL by 20–25% and appears to slow progression of carotid IMT in patients with treated HIV infection. Although we did not find definitive evidence of treatment effect modification by inflammation status, this should be examined in larger trials with clinical cardiovascular endpoints in patients with HIV infection or other chronic inflammatory diseases.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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	Rosuvastatin		Placebo		P-value
	Mean change (mm)	95% CI	Mean change (mm)	95% CI	
0-48 Weeks	-0.004	-0.015—0.008	+0.017	0.003—0.031	0.025
0-96 Weeks	+0.003	-0.014—0.021	+0.028	0.008—0.047	0.061

Figure 1.
0–96 week change in carotid intima-media thickness by treatment group. P-value is for between group comparisons. Error bars represent 95% confidence interval.

Figure 2.

Subgroup analysis of the statin treatment effect on carotid intima-media thickness over 96 weeks by baseline inflammation and immune activation status. Data are derived from multivariable adjusted linear-mixed models. Participants with the highest quartile of biomarker (Q4, black) are compared to all others (Q1–3, grey). Point estimates represent the parameter estimate (standard error) for assignment to statin within each subgroup. The p-value for interaction is displayed to the right of the point estimates. T-cell activation is defined as the proportion of CD4+ or CD8+ T-cells that co-express HLA-DR and CD38.

sVCAM-1, soluble vascular cell adhesion molecule; TNFR_{II}, tumor necrosis factor- α receptor II; IL-6, interleukin-6; hsCRP, high-sensitivity C-reactive protein.

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Figure 3.

(A) Prevalence of coronary artery calcium score >0 at baseline and 96 weeks by treatment group; and (B) Change in coronary artery calcium score from 0–96 weeks among those subjects with detectable calcium score at baseline (n=22 statin; n=23 placebo). Lines represent mean (95% CI).

Table 1

Baseline characteristics of study participants by assigned treatment group.

Demographics	Rosuvastatin n=72	Placebo n=75
<i>Age (years)</i>	45 (41, 51)	47 (39, 53)
<i>Male sex</i>	81%	76%
<i>African American race</i>	69%	67%
HIV Parameters		
<i>HIV duration (years)</i>	11 (6, 17)	12 (6, 19)
<i>Current CD4+ count (cells/μl)</i>	608 (440, 848)	627 (398, 853)
<i>Nadir CD4+ count (cells/μl)</i>	173 (84, 312)	190 (89, 281)
<i>Undetectable viral load (<50 copies/ml)</i>	78%	77%
<i>ART duration (years)</i>	5.2 (3.1, 9.9)	5.9 (3.3, 9.6)
<i>Current Protease Inhibitor Use</i>	50%	48%
<i>CD8+CD38+HLA-DR+ T-cells (%)</i>	13 (9.0–19)	11 (8.0–17)
<i>High sensitivity C-reactive protein (mg/L)</i>	1.6 (0.8–4.9)	2.0 (0.7–5.2)
<i>High sensitivity C-reactive protein (mmol/L)</i>	15 (7.6–46.7)	19 (6.7–49.5)
Cardiovascular Risk Factors		
<i>Body Mass Index (kg/m²)</i>	27 (23, 30)	27 (23, 30)
<i>Systolic Blood Pressure (mmHg)</i>	122 (112, 136)	120 (110, 132)
<i>Anti-hypertensive Medication Use</i>	28%	24%
<i>HDL Cholesterol (mg/dL)</i>	47 (38, 58)	46 (37, 57)
<i>HDL Cholesterol (mmol/L)</i>	1.22 (0.98, 1.50)	1.19 (0.96, 1.47)
<i>LDL Cholesterol (mg/dL)</i>	96 (76, 107)	97 (77, 121)
<i>LDL Cholesterol (mmol/L)</i>	2.48 (1.97, 2.77)	2.51 (1.99, 3.13)
<i>Metabolic Syndrome</i>	22%	21%
<i>eGFR_{cr} (CKD-EPI)</i>	99 (85, 117)	100 (87, 118)
<i>HOMA-IR</i>	1.7 (1.0–2.8)	2.0 (1.1–4.4)
<i>Current Smoking</i>	60%	67%
<i>Family History of Myocardial Infarction</i>	33%	29%
<i>Framingham Risk Score (% 10-year risk)</i>	3 (1, 7)	4 (1, 7)
Subclinical Vascular Disease		
<i>Mean-mean common carotid artery IMT (μm)</i>	664 (624, 772)	670 (602, 752)
<i>Carotid plaque</i>	33%	43%
<i>Coronary Artery Calcium >0</i>	33%	40%

Data presented as median (IQR) or percent as appropriate.

All $p > 0.05$ for differences between groups using t-tests, Mann Whitney tests, or Fisher's exact tests as appropriate.

ART, antiretroviral therapy; HDL, high-density lipoprotein; LDL, low-density lipoprotein; GFR_{cr} (CKD-EPI), creatinine-based estimated glomerular filtration rate (2009 Chronic Kidney Disease Epidemiology Collaboration equation); HOMA-IR, homeostatic model assessment of insulin resistance; IMT, intima-media thickness.

Table 2

Multivariable linear mixed model of the statin treatment effect on CCA-IMT change (mm) over the 96-week study period.

	β	95% CI	P-value
Assignment to statin treatment arm	− 0.019	−0.037 to −0.002	0.030
Study week	0.010	0.001 to 0.018	0.030
Baseline age	−0.001	−0.010 to 0.008	0.847
Male sex	−0.013	−0.035 to 0.009	0.252
Baseline HOMA-IR	0.003	−0.006 to 0.013	0.495
Baseline metabolic syndrome	−0.021	−0.044 to 0.003	0.087
On protease inhibitor at baseline	0.011	−0.007 to 0.029	0.224

Covariate selection described in methods section.

CCA-IMT, mean-mean common carotid artery intima-media thickness. HOMA-IR, homeostatic model assessment of insulin resistance.