Impact of rosuvastatin on atherosclerosis in people with HIV at moderate cardiovascular risk: a randomised, controlled trial

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Background: People living with HIV-1 (PLHIV) are at increased risk for cardiovascular disease.
Objective: This study aimed to determine if PLHIV would benefit from starting statins at a lower threshold than currently recommended in the general population.
Design: A double-blind multicentre, randomised, placebo-controlled trial was performed.
Methods: Participants (n = 88) with well controlled HIV, at moderate cardiovascular risk (Framingham score of 10–15%), and not recommended for statins were recruited from Australia and Switzerland. They were randomized 1:1 to rosuvastatin (n = 44) 20 mg daily, 10 mg if co-administered with ritonavir/cobicistat-boosted antiretroviral therapy, or placebo (n = 40) for 96 weeks. Assessments including fasting blood collection and carotid–intima media thickness (CIMT) were performed at baseline, and weeks 48 and 96. The primary outcome was the change from baseline to week 96 in CIMT (clinicaltrials.gov: NCT01813357).
Results: Participants were predominantly men [82 (97.6%); mean age 54 years (SD 6.0)]. At 96 weeks, there was no difference in the progression of CIMT between the rosuvastatin (mean 0.004 mm, SE 0.0036) and placebo (0.0062 mm, SE 0.0039) arms (P = 0.684), leading to no difference in CIMT levels between groups at week 96 [rosuvastatin arm, 0.7232 mm (SE 0.030); placebo arm 0.7785 mm (SE 0.032), P = 0.075]. Adverse events were common (n = 146) and predominantly in the rosuvastatin arm [108 (73.9%)]. Participants on rosuvastatin were more likely to cease study medication because of an adverse event [7 (15.9%) vs. 2 (5.0%), P = 0.011].
Conclusion: In PLHIV, statins prescribed at a lower threshold than guidelines did not lead to improvements in CIMT but was associated with significant adverse events.

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**Introduction**

People living with HIV-1 (PLHIV) are at increased risk for cardiovascular disease (CVD) [1].

Traditional risk scores may underestimate risk in PLHIV as they do not take into account the contributions of antiretroviral therapy, chronic inflammation, and immune activation to cardiovascular risk [2]. Thus, their use to determine the need for primary preventive therapy may lead to under-prescription in PLHIV and hence starting statins at a lower threshold than currently recommended in the general population may be appropriate.

This study aimed to determine the effect of rosuvastatin on the progression of atherosclerosis in PLHIV at moderate cardiovascular risk.

**Methods**

A double-blind, randomized, placebo-controlled trial was performed to determine the difference in atherosclerotic progression, estimated by carotid–intima media thickness (CIMT), in PLHIV at moderate cardiovascular risk randomized to rosuvastatin or placebo for 96 weeks.

Participants were recruited from the Alfred Hospital, Melbourne, Australia and from four HIV clinics within the Swiss HIV Cohort Network in Geneva, Lausanne, Bern, and Zurich.

The study was approved by the Alfred Ethics committee (HREC/12/ALF/491-12). Protocol available at DOI 10.26180/5e4344844f1c8. All participants provided written informed consent.

Participants were adults with HIV-1 on antiretroviral therapy with a HIV viral load of less than 200 copies/ml for at least 6 months. All had a Framingham risk score (FRS) of 10–15%. Individuals were excluded if they required a statin according to Australian guidelines (including diabetic patients, those with prior CVD or a serum cholesterol >7.5 mmol/l) [3]. Those with carotid artery stenosis or more than 50% occlusion because of plaque were ineligible, as were individuals who were currently, or had within 6 months, taken lipid-lowering therapy, antplatelets, or had a contraindication to statin use. Individuals with a creatinine clearance less than 50 ml/min or more than Childs B cirrhosis or transaminases three times the upper limit of normal were also excluded.

Participants were randomized 1:1 to oral rosuvastatin (20 mg daily) or matched placebo, using block randomization, stratified by country, with a variable block size (range 2–6). The sequence was generated by an independent statistician and conveyed to study pharmacists who had no direct participant contact, all other study team members and participants were blinded. Participants who were taking ritonavir or cobicistat received dose reduced rosuvastatin (10 mg). The rosuvastatin was encapsulated in a gelatin capsule (blue for the 20 mg and red for the 10 mg) with identical blue and red placebos created by encapsulating sucrose within the same capsules.

Participant demographics and medical history were obtained through self-report and a review of medical records. The FRS was calculated using an online calculator (https://www.mdcalc.com/framingham-risk-score-hard-coronary-heart-disease).

Participants were evaluated at baseline, weeks 12, 24, 48, 72, and 96. Laboratory assessments were performed including full blood count, liver function, renal function, electrolytes and creatinine kinase, along with HIV viral load and CD4+ T-cell count, were measured at each visit, with inflammatory markers [interleukin 6 (IL-6) and high-sensitivity C-reactive protein (hsCRP)] measured at baseline and week 96. Fasting blood collection were performed following an overnight fast at screening, baseline, weeks 24, 48, and 96 for lipid and glucose levels.

CIMT was recorded at weeks 0, 48, and 96. 2D (B-Mode) high-resolution ultrasound digital images were obtained at the common carotid artery (CCA), internal carotid artery (ICA), and carotid bulb on both sides. Images were sent to a core laboratory who read all scans in parallel, blinded to treatment allocation, using semi-automated edge detection software (Carotid Analyser, Medical Imaging Applications LLC, Coralville, Iowa, USA). The reported CIMT is the average of the two sides. The CIMT was measured at the end of diastole as determined by simultaneous ECG recordings with measurements made 0–1 cm from the carotid bulb in 1 cm length segments from the far wall of the CCA.

The primary outcome measure was the change from baseline to week 96 in CIMT.

Secondary outcomes measures included the incidence of adverse events, the change from baseline to week 48 in CIMT, and the change in lipid levels at weeks 48 and 96.

A Data Safety and Monitoring Board (DSMB) reviewed an interim analysis (blinded to allocation) at week 48.
predefined criteria for early cessation included a significant adverse event rate or statistically significant difference in CIMT progression of more than 0.16 mm between arms, neither of which was met.

**Statistical analysis**

Assuming a CIMT progression rate of 0.080 mm over 96 weeks in the placebo arm and near-stabilization of CIMT (95% relative reduction) with rosuvastatin, we assumed an effect size of 0.076 mm (SD 0.09 mm) [4]. With an alpha threshold of 1% and a power of 90%, and 15% lost to follow-up over 96 weeks, an initial total study population of 102 was targeted. This was reduced to 84 individuals with the support of the DSMB in August 2016 because of slow recruitment. With 84 participants, the study had 90% power to detect a difference of 0.076 mm between treatment arms at week 96 (alpha 5%).

The intention-to-treat population included all individuals who received a dose of study medication. The per-protocol set was participants without a major protocol deviation, defined as the absence of any CIMT assessment, participants on placebo who received any doses of rosuvastatin, and participants in the rosuvastatin arm who ceased rosuvastatin or transitioned onto open label statin.

The primary outcome was assessed using linear mixed models fitted via restricted maximum likelihood (REML) method with fixed effects for treatment allocation, time of assessment (baseline, 48, 96 weeks), the carotid artery site and body side and their two-way and three-way interactions, along with random effects for study site. These were repeated following adjustment for baseline characteristics were summarized using means [standard deviations (SD)] for continuous variables and number (%) for categorical variables. No adjustment was made for multiple comparisons. Participants with missing data were treated as missing at random and all observed data was considered for analysis with the mixed-effects models assuming noninformative dropout. Statistical significance: \( P \leq 0.05 \). All analyses were performed using SAS software, version 9.4 (SAS Institute, Cary, North Carolina, USA). Figures were drawn using Prism, version 8.2.1 (GraphPad Software Inc., San Diego, California, USA) Clinicaltrials.gov (NCT01813357).

**Results**

Recruitment occurred from July 2013 to August 2016; follow-up was completed in May 2018. See supplementary Figure 1, http://links.lww.com/QAD/B916: Participant flowchart.

| Table 1. Baseline demographics. |
|--------------------------------|
| Rosuvastatin | Placebo |   |
| (n = 44)     | (n = 40) |   |
| Age (years)  | 53.9 (5.9) | 54.4 (6.4) |
| Male         | 42 (95.3%) | 40 (100%)  |
| Recruitment site |   |   |
| Melbourne    | 28 (63.6%) | 27 (67.5%) |
| Geneva       | 4 (9.1%)  | 7 (17.5%)  |
| Zurich       | 8 (18.2%) | 4 (10%)    |
| Berne        | 3 (6.8%)  | 1 (2.5%)   |
| Lausanne     | 1 (2.3%)  | 1 (2.5%)   |
| Race         |   |   |
| Caucasian    | 40 (90.9%) | 35 (81.4%) |
| Asian        | 3 (6.8%)  | 2 (4.5%)   |
| African      | 1 (2.2%)  | 6 (13.9%)  |
| FRS, %       | 10 (1.9)  | 10 (2.0)   |
| Current smoker | 16 (36.4%) | 12 (30%)  |
| Ex-smoker    | 15 (34.1%) | 14 (35%)   |
| Family history of AMI | 14 (31.8%) | 12 (30%) |
| BMI (kg/m²)  | 26.4 (3.6) | 26.4 (3.3) |
| SBP (mmHg)   | 128 (13)  | 128 (14)   |
| DBP (mmHg)   | 85 (13)   | 83 (9)     |
| IL-6 (pg/ml) | 2.1 (1.8) | 2.4 (2.9)  |
| Total cholesterol (mmol/l) | 5.4 (0.8) | 5.3 (1.1) |
| LDL-cholesterol (mmol/l) | 3.5 (0.7) | 3.5 (0.9) |
| HDL-cholesterol (mmol/l) | 1.1 (0.3) | 1.2 (0.3) |
| Triglycerides (mmol/l) | 1.9 (0.9) | 1.5 (0.7) |
| Glucose (mmol/l) | 5.2 (0.5) | 5.0 (0.5) |
| Time from HIV diagnosis (years) | 17.2 (8.5) | 13.6 (7.6) |
| Current CD4+ cell count (cells/µl) | 653 (259) | 550 (254) |
| Nadir CD4+ cell count (cells/µl) | 217 (169) | 159 (137) |
| Undetectable viral load | 44 (100%) | 40 (100%) |
| Current antiretroviral therapy |   |   |
| Protease inhibitor | 18 (41.9%) | 18 (45%) |
| NNRTI | 19 (44.2%) | 21 (52.5%) |
| Integrase inhibitor | 12 (27.9%) | 13 (32.5%) |
| Abacavir | 10 (23.3%) | 10 (25%) |
| Tenofovir | 28 (65.1%) | 25 (62.5%) |

Mean (standard deviation) or n (%) as appropriate. AMI, acute myocardial infarction; FRS, Framingham risk score; hsCRP, high-sensitivity C-reactive protein; HDL, high-density lipoprotein; IL-6, interleukin-6; LDL, low-density lipoprotein; NNRTI, nonnucleoside reverse transcriptase inhibitors.

*Defined as a history of AMI in a male first-degree relative before 55 years of age, or a female first-degree relative before 65 years of age.

*Defined as less than 200 copies/ml.

*All tenofovir disoproxil fumerate except for two tenofovir alafenamide (one in each arm).

Participants were predominantly men (97.6%), 54.1 years (range 42–68) and Caucasian (88.1%) (Table 1).

There was no difference in the change in CIMT between the rosuvastatin (0.004 mm; SE 0.0036) and placebo (0.0062 mm; SE 0.0039) arms \( (P = 0.684) \) at 96 weeks, leading to no difference in CIMT levels between groups \( (P = 0.749) \) (see supplementary Figure 2, http://links.lww.com/QAD/B917). This result remained consistent following adjustment for age, sex, smoking status, and LDL cholesterol [delta CIMT from baseline to week 96 rosuvastatin 0.004 mm (SE 0.0036); placebo 0.0061 mm (SE 0.0039), \( P = 0.694 \)]. No difference was
detected when the results were restricted to the per-protocol population; delta CIMT baseline to week 96; rosuvastatin 0.0037 mm (SE 0.004); placebo 0.0066 mm (SE 0.0042), P = 0.616. No participant had new plaque development in either arm. There was no difference in progression when individual sites of CIMT were compared (see Supplementary Table 1, http://links.lww.com/QAD/B918).

Rosuvastatin led to predictable reductions in total and LDL-cholesterol by week 24, which was sustained to week 96. At week 96, mean total cholesterol; rosuvastatin 4.13 mmol/l (SE 0.163), P < 0.001; LDL-cholesterol; rosuvastatin 2.29 mmol/l (SE 0.137), P < 0.001. There was no change in HDL cholesterol in either arm from baseline to week 96 [rosuvastatin 1.18 mmol/l (SE 0.043), placebo 1.23 mmol/l (SE 0.045), P = 0.424]. Neither the baseline total or LDL-cholesterol levels, nor the change from baseline to week 96 in total or LDL-cholesterol, predicted change in CIMT.

There was no change in interleukin-6 (IL-6) levels in either arm [mean change rosuvastatin −0.25 pg/ml (SD 2.0), placebo 0.03 pg/ml (SD 1.5), P = 0.925]. Rosuvastatin was associated with decreased hsCRP [mean change rosuvastatin −0.75 mg/l (SD 3.8), placebo 1.3 mg/l (SD 6.6), P = 0.008].

Fifty-seven (67%) participants experienced 146 adverse events. Most mild, grade 1 or 2 [131 (89.7)] (Table 2). These were more common with rosuvastatin [108 (73.9%)]. Participants were more likely to cease study medication because of an adverse event on rosuvastatin [7 (15.9%) versus 2 (5.0%)]. There was one death (rosuvastatin arm) from a haemorrhagic cerebrovascular infarct, unrelated to study participation.

**Discussion**

This study demonstrated no effect of rosuvastatin on the progression of CIMT in PLHIV at moderate cardiovascular risk but rosuvastatin was poorly tolerated, with over 15% of participants interrupting study treatment. This is contrary to previous reports of rosuvastatin being associated with 0.019 mm less progression of CIMT over 96 weeks [5]. These discordant findings may be explained by baseline differences in the enrolled participants, with that study requiring participants to have elevated inflammatory markers at baseline, whereas our population had low-normal inflammatory marker levels. This would be consistent with the findings from the JUPITER trial, which demonstrated a significant reduction in major cardiovascular events in individuals without dyslipidaemia (or HIV) but with an elevated hsCRP [6]. This suggests that perhaps utilization of markers of inflammation, rather than a cardiovascular risk score, may more accurately identify individuals who will benefit from statins.

The CIMT progression of 0.006 mm in our placebo arm was lower than anticipated. This suggests that, despite attempting to enrich our study population with those most likely to benefit from therapy, participants were generally quite healthy, perhaps reflecting global trends of reducing CVD in settings in which PLHIV have access to

**Table 2. Summary of adverse events.**

|                      | Rosuvastatin (n = 44) | Placebo (n = 40) |
|----------------------|-----------------------|-----------------|
| Any adverse event    | 35 (79.5) (108 events) | 22 (55.0) (38 events) |
| Grade 3 or 4 adverse event* | 2 (4.5) | 1 (2.5) |
| Myocardial infarction | 2 (4.5) | 0 (0.0) |
| Diabetes             | 1 (2.2) | 1 (2.5) |
| Elevated ALT at least 5 × ULN | 1 (2.2) | 0 (0.0) |
| Elevated creatine kinase at least 10 × ULN | 3 (6.8) | 1 (2.5) |
| Study drug-related serious adverse event* | 7 (15.9) | 2 (5) |
| Adverse event leading to study drug discontinuation* | 13 (29.5) | 4 (10) |
| Elevated liver enzymes | 1 (2.2) | 7 (17.5) |
| Myopathic symptoms*  | 4 (9.0) | 3 (7.5) |
| Hypertension         | 13 (29.5) | 11 (27.5) |
| Gastrointestinal symptoms | 5 (11.3) | 4 (10) |

Data are expressed as n (%). ALT, alanine aminotransferase; ULN, upper limit of normal.

*Additionally, in the rosuvastatin arm, there was one incident each of heart failure, hypertension (SBP ≥180 mmHg) and cerebrovascular disease. In the placebo arm, there was one incident each of acute mesenteric ischemia, oesophageal malignancy, lumbar vertebral disc herniation, and haemoptysis.

*Probable or possible.

*Four participants in the rosuvastatin arm stopped study medication as it was recommended they commence open label statin for new-onset cardiovascular disease (acute myocardial infarction or cerebrovascular event) or type 2 diabetes. In the rosuvastatin arm, gastrointestinal intolerances, musculoskeletal pain, and elevated creatinine kinase in one instance each led to study drug cessation. In the placebo arm, one participant ceased study medication because of ALT rise more than 5× upper limit of normal, and one for mild gastrointestinal symptoms.

*Including myalgia and perceived muscle weakness.
minimally toxic antiretrovirals and durable viral suppression is the norm [7]. Previous observational studies have demonstrated CIMT progression rates of 0.074 mm (SD 0.13 mm) over 1 year in PLHIV, which is significantly greater than that seen in the HIV-negative controls [8]. Our observed rates are closer to what is described in the general population [9].

CIMT is a well validated surrogate marker of atherosclerosis and a strong predictor of future vascular events [9]. Multiple trials of lipid lowering and antihypertensive interventions have previously used it as an endpoint [10]. Although recent meta-analyses found that increased CIMT was associated with future cardiovascular events [11], there have been conflicting results as to whether change in CIMT accurately reflects change in cardiovascular risk.

We had hypothesized that statins, through their pleiotropic anti-inflammatory and immune-modulatory effects [12], may be more effective in PLHIV as HIV is associated with an elevated inflammatory state, which persists despite long-term viral suppression [13]. Our findings that statin therapy did not lead to significant differences in CIMT and had only minimal effects on inflammatory markers are supported by findings from other groups of minimal effects of statins on biomarkers of HIV persistence, immune activation, and inflammation in PLHIV [14]. This raises the possibility that statin's anti-inflammatory effects are in pathways less affected by HIV.

An important finding was the high rate of adverse events in those receiving rosuvastatin. Although the difference in the mild adverse events is unlikely to be clinically meaningful, the four treatment-related serious adverse events (two new diagnoses of diabetes and a case each of significant elevations in liver function tests and creatinine kinase) are important when considering starting a statin in a PLHIV in whom the benefit is not yet clear. There are a number of drug interactions between antiretrovirals and statins, which can lead to elevated side effect risk. To minimize this, participants receiving ritonavir or cobicistat were prescribed dose-reduced (10 mg) rosuvastatin. As such we do not believe that drug interactions are responsible for the high rates of side effects observed.

This study has a number of limitations, notably its small sample size and homogenous participant population. It is, however, strengthened by its multinational recruitment and robust randomized placebo-controlled design. Although CIMT is a well validated surrogate endpoint for cardiovascular events [15], it may not truly reflect the impact of rosuvastatin on hard coronary endpoints and perhaps the choice of an alternate surrogate endpoint may have resulted in a different outcome. We thus await with interest the results of the Randomized Trial to Prevent Vascular Events in HIV (REPRIEVE) Trial [16], a prospective, randomized placebo-controlled trial of pitavastatin for the primary prevention of major adverse cardiovascular events in PLHIV.

Conclusions

In PLHIV at moderate risk, rosuvastatin did not alter the progression of atherosclerosis but was associated with increased side effects.

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Authors’ contributions: J.M.T. wrote study protocol, recruited and monitored Australian participants, co-ordinated trial completion, assisted with collation and analysis of data, wrote manuscript.

A.D. provided expert cardiology advice on the study design and interpretation of the results. E.P. conducted development of the statistical analysis plan and the analysis of the results. M.C. co-ordinated the trial in Lausanne. J.F. co-ordinated the trial in Zurich. C.S. co-ordinated the trial in Berne. E.M.D. developed the CIMT standard operating procedure and performed scanning in Australia. J.F.H. conceived the study idea, and contributed to the protocol development, supervised co-ordination of the trial in Australia, and contributed to the analysis of the results and drafting of the manuscript. A.C. supervised co-ordination of the trial in Switzerland, and contributed to protocol development and the drafting of the manuscript.

Conflicts of interest

J.M.T. has received honoraria from Gilead Health Sciences for speaker responsibilities unrelated to this project. J.F.H.’s institution has received reimbursement for her participation in Advisory Boards for Gilead Sciences, ViiV Healthcare, and MSD. A.C.’s institution has received unrestricted educational grants from Gilead Health Sciences, ViiV, AbbVie, and MSD.
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