Impact of Rosuvastatin on Atherosclerotic Progression in People with HIV at Moderate Cardiovascular risk; a multinational, randomized, double blind, placebo-controlled trial

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Conflicts of Interest

- I have received honoraria from Gilead Health Sciences for speaker responsibilities unrelated to this project

- Prof Hoy's institution received reimbursement for her participation in Advisory Boards for Gilead Sciences, ViiV Healthcare and MSD.

- Prof Calmy's institution received unrestricted educational grants from Gilead Health Sciences, ViiV, AbbVie and MSD.

Background

- People with HIV are at increased risk for cardiovascular disease
- Risk scores designed to predict myocardial infarctions lack sensitivity and specificity in people with HIV
- Current guidelines based on these scores may underestimate the need for statins for primary preventative therapy
- It's not yet known if people with HIV should start primary preventative therapy at different thresholds, or for different indications, to those recommended in the general population

Aims

- This study aimed to determine the effect of 96 weeks of rosuvastatin on atherosclerotic progression (as estimated by change in carotid intima media thickness, cIMT) in people with HIV at moderate cardiovascular risk who did not fulfil criteria for the recommendation of statin therapy.

- Secondary Aim: To determine the safety profile of rosuvastatin in people with HIV on antiretroviral therapy

Methods

- A randomized, double blinded, placebo controlled, multinational trial
- Participants were randomized 1:1 (stratified by site) to rosuvastatin 20mg daily or matched placebo for 96 weeks
- Participants on a boosted-protease inhibitor or cobicistat received reduced dose (10mg) rosuvastatin

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Inclusion Criteria

- HIV positive
- Age >30 years
- Moderate coronary heart disease risk, defined as Framingham Risk Score 10-15%[1]
- Stable ARV regimen > 3 months
- Plasma HIV viral load <200 copies/ml for ≥ 6 months

[1]www.old.mdcalc.com/framingham-coronary-heart-disease-risk-score-si-units/.

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Exclusion Criteria

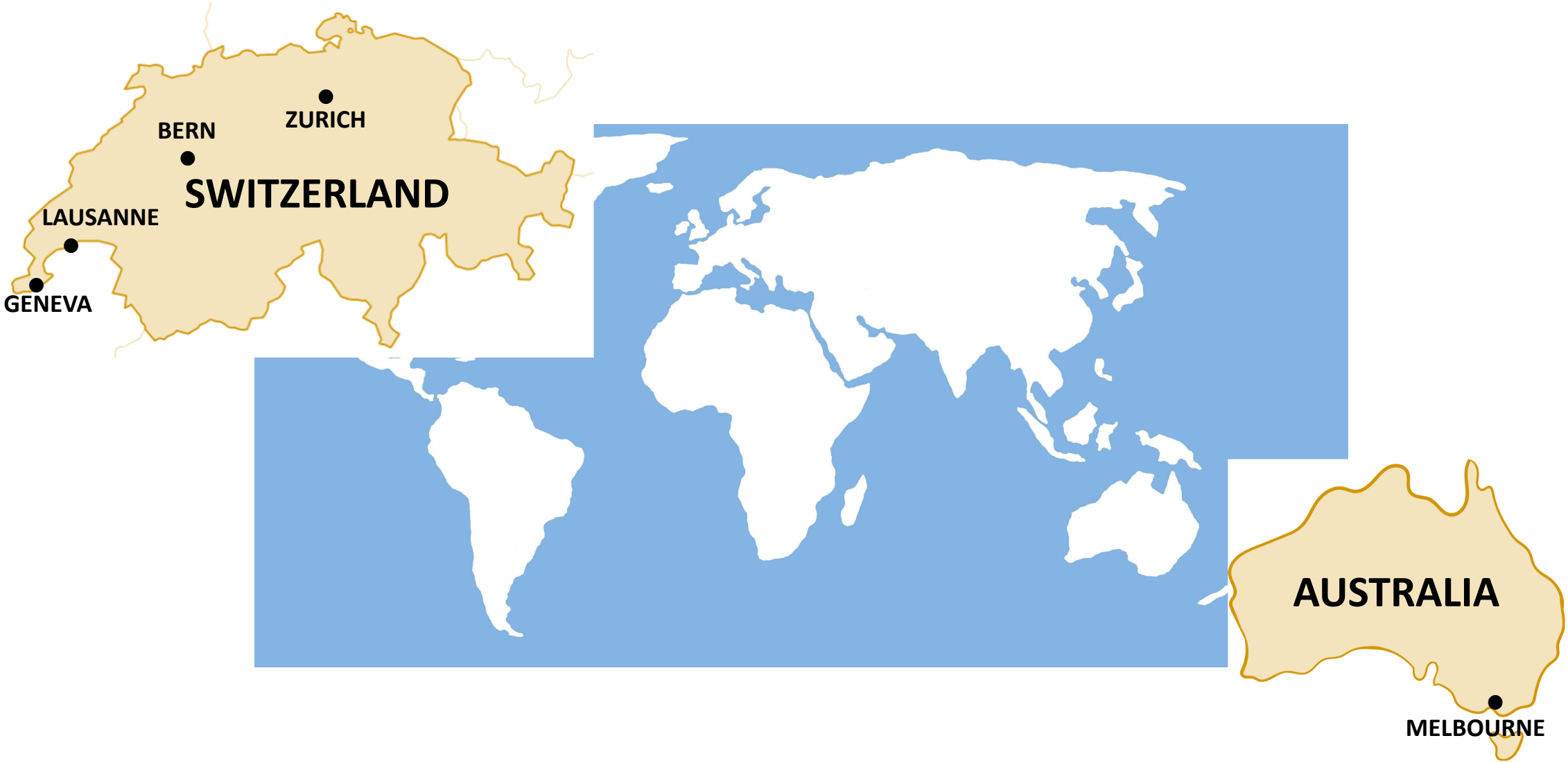
- Recommended use of lipid lowering drug therapy according to Australian Guidelines[1]
  - History of cardiovascular disease
  - Type 2 Diabetes
  - Familial hypercholesterolemia
  - Blood pressure ≥ 180/110
  - Total Cholesterol > 7.5 mmol/L
  - Triglyceride level >4.0 mmol/L
  - HDL-c <1 and total cholesterol > 6.5 mmol/L

[1]Guidelines for the management of absolute cardiovascular disease risk. Accessed at www.heartfoundation.com.au

Exclusion Criteria cont.

- Carotid artery stenosis or >50% occlusion of the carotid artery
- Current or prior (last 6 months) statin, ezetimibe, fibrate or niacin therapy
- Contraindication to statin use
- Creatinine clearance <50ml/min
- Moderate Hepatic Dysfunction

Study sites



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Timeline of Assessments

	Screening	Baseline	Week 12	Week 24	Week 48	Week 72	Week 96
Fasting Bloods	X	X		X	X		X
cIMT*	X				X		X
Physical Examination	X	X			X		X
Compliance Assessment					X		X

*cIMT images were all read by a central ultrasound team, blinded to treatment allocation

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Statistical Methods

- All primary analyses were based on the intention-to-treat population
- Analyses were then repeated on the per-protocol population (participants who remained on randomized treatment and completed the full 96 week assessments)
- Analysis of the primary endpoint was performed using restricted maximum likelihood methods to account for the measurement of the primary endpoint at sequential time points (Baseline, 48 and 96 weeks) and to account for any potential variance by site.

Statistical Methods continued..

- **The primary endpoint:** change from baseline to week 96 in mean common carotid artery IMT
- Lipid, immunological and inflammatory markers were analysed using linear mixed models
- Values are described as means (standard deviations) for longitudinal variables and number (%) for categorical ones
- No adjustment for multiple comparisons has been made

Sample Size

- A sample size of 102 was initially targeted ($p<0.01$ and power 95%) but this was reduced to n=84 with support of the DSMB in August 2016 due to slow recruitment.

- With 84 participants (15% LTFU) the study has 90% power to detect a difference of 0.06mm between treatment arms at week 96 ($p<0.05$)

[1]Bots ML, et al. J Intern Med (2009) 265:698-707.

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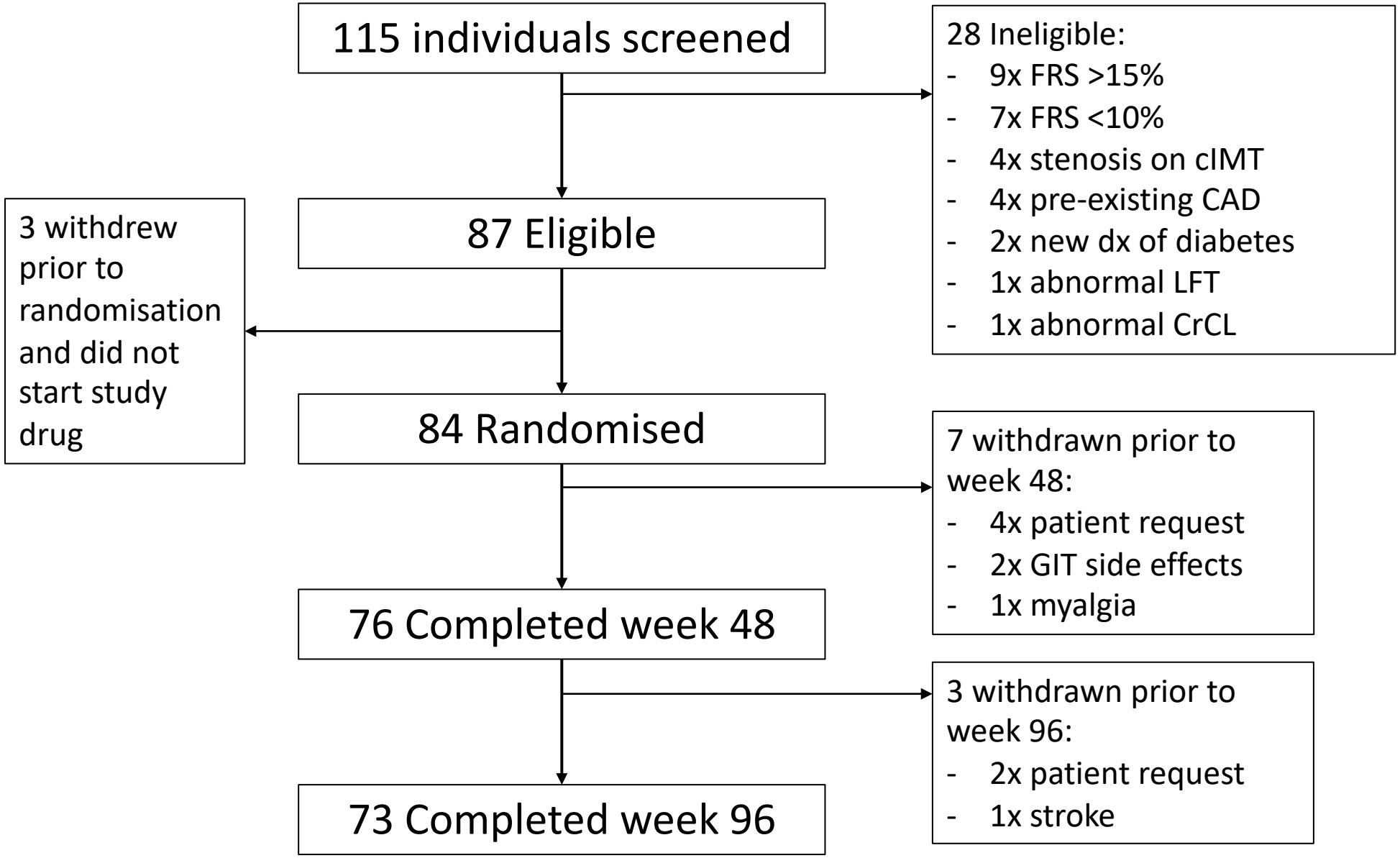

Flow chart of participant recruitment

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Baseline Demographics

mean (SD) or n (%)	Rosuvastatin (n=44)	Placebo (n=40)
Age (years)	53.8 (5.8)	54.3 (6.3)
Male	42 (95%)	40 (100%)
Race		
Caucasian/White	40 (90%)	34 (85%)
Asian	2 (6%)	1 (2%)
Black	1 (2%)	5 (12%)
Framingham risk score (%)	11 (1)	11 (1)
Current smoker	16 (36%)	12 (30%)
Family History of myocardial infarction	14 (31%)	12 (30%)
Body Mass Index (kg/m^2)	26.3 (3.6)	26.4 (3.3)
Systolic Blood Pressure (mmHg)	128 (13)	128 (14)

Baseline HIV Demographics

mean (SD) or n (%)	Rosuvastatin (n=44)	Placebo (n=40)
Duration HIV infection (years)	17.2 (8.1)	13.6 (7.6)
Current CD4 cell count (cells/ul)	699 (257)	550 (254)
Nadir CD4 cell count (cells/ul)	218 (173)	159 (137)
Undetectable viral load	44 (100%)	40 (100%)
Previous AIDS defining illness	11 (25%)	13 (32%)
Current Antiretroviral therapy		
Protease inhibitor	18 (43%)	18 (45%)
NNRTI	17 (41%)	21 (52%)
Integrase inhibitor	12 (29%)	13 (32%)
Abacavir	10 (24%)	10 (25%)
Tenofovir	26 (63%)	25 (62%)

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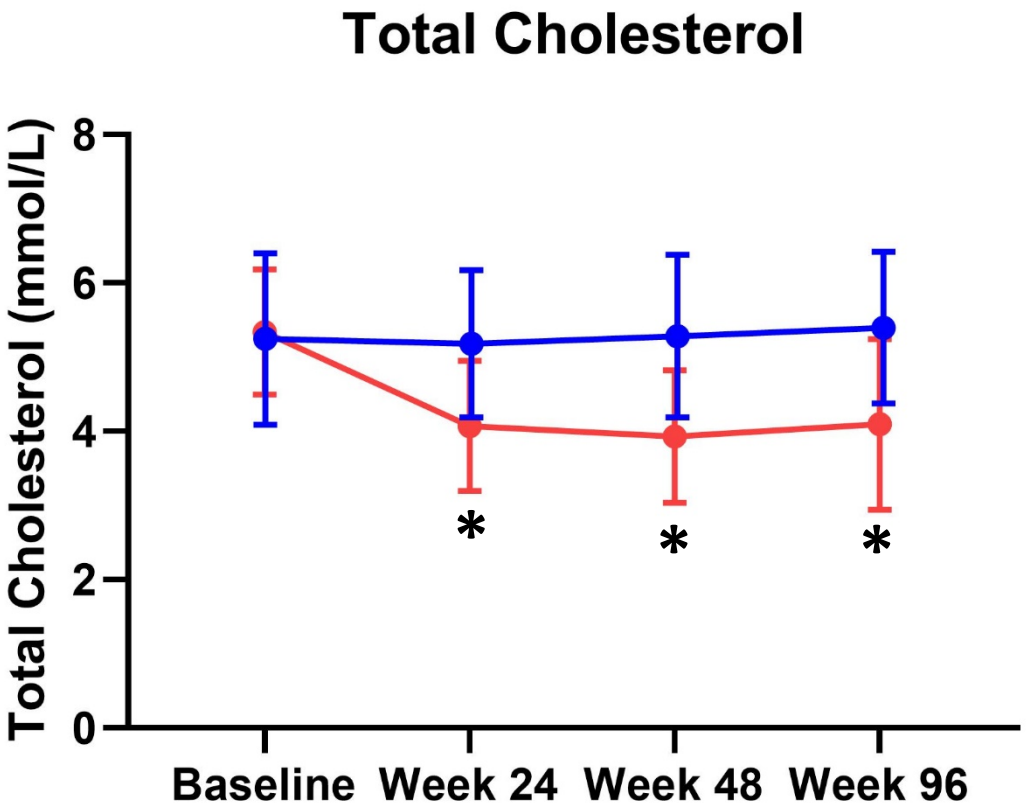
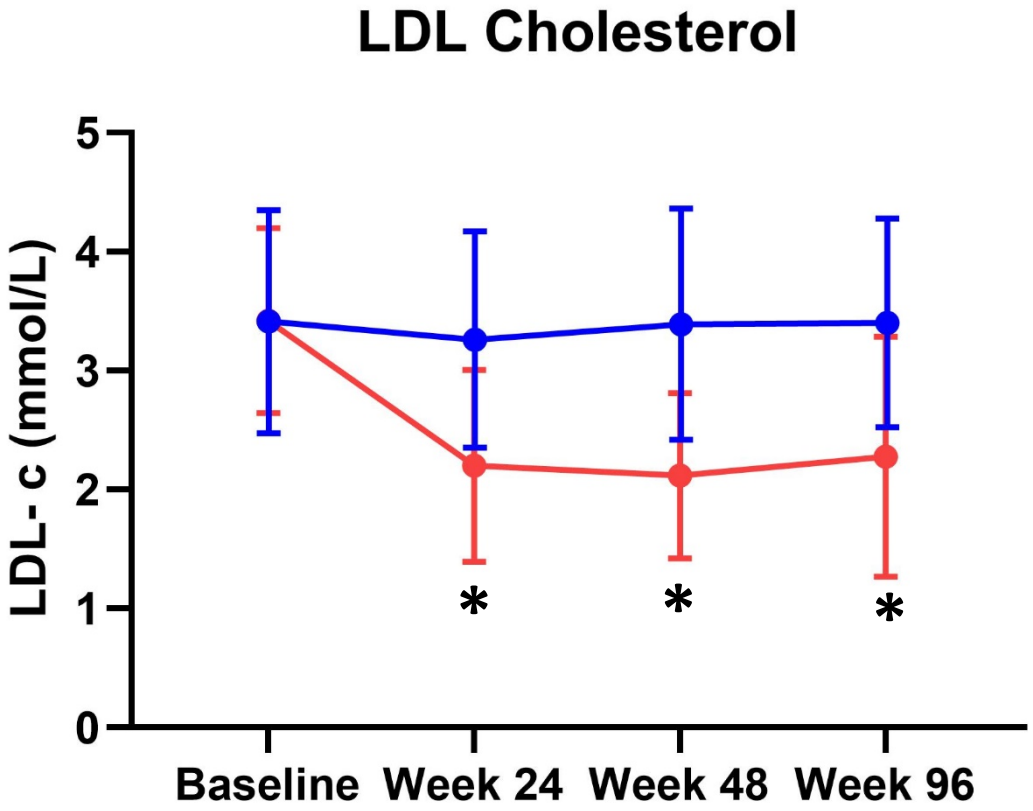
Rosuvastatin lead to predictable changes in total and LDL-cholesterol





* p-value for the difference between arms <0.001
Circular symbols = means; error bars = standard deviation

● Placebo
● Rosuvastatin

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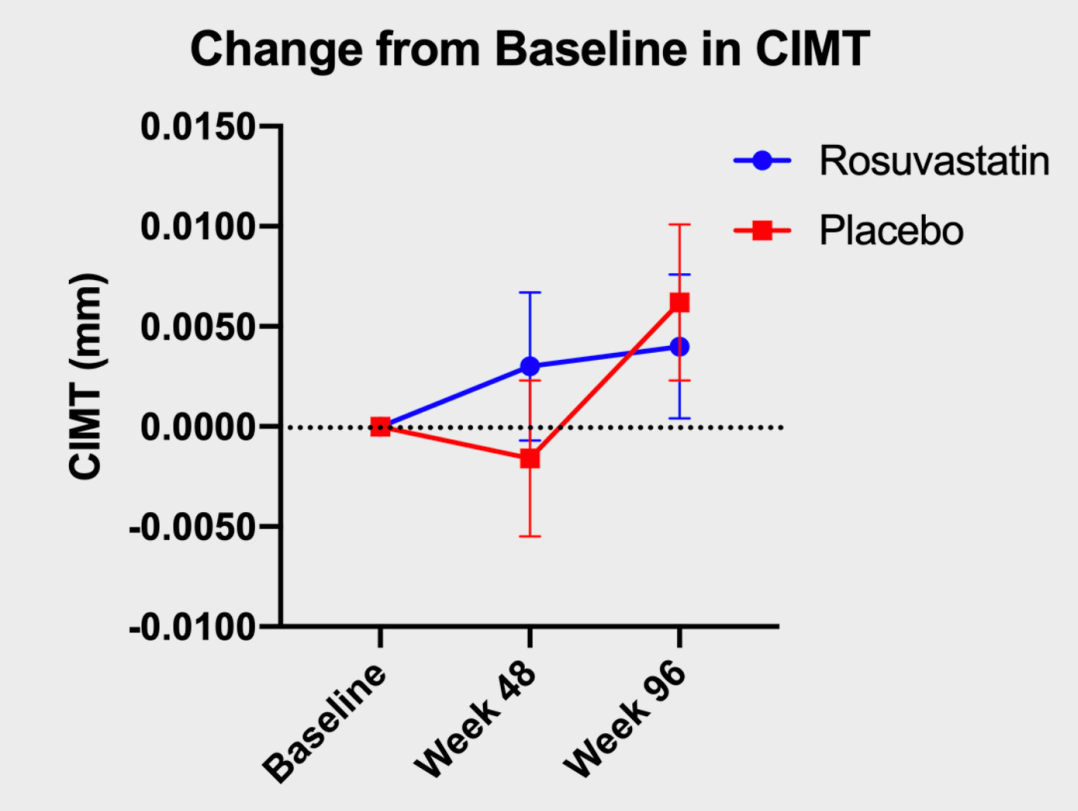
No difference in CIMT progression between rosuvastatin and placebo arms



Mean CIMT by arm at each time point

	Baseline	48 weeks	96 weeks	P-value[a]
Rosuvastatin	0.722 (0.032)	0.726 (0.032)	0.726 (0.032)	0.319
Placebo	0.772 (0.033)	0.771 (0.033)	0.779 (0.033)	0.115
P-value[b]	0.115	0.158	0.097	

*mean (standard deviation)
[a]p-value for within arm change from baseline to 96 weeks
[b]p-value for difference between arms at each time point

*Intention to treat population

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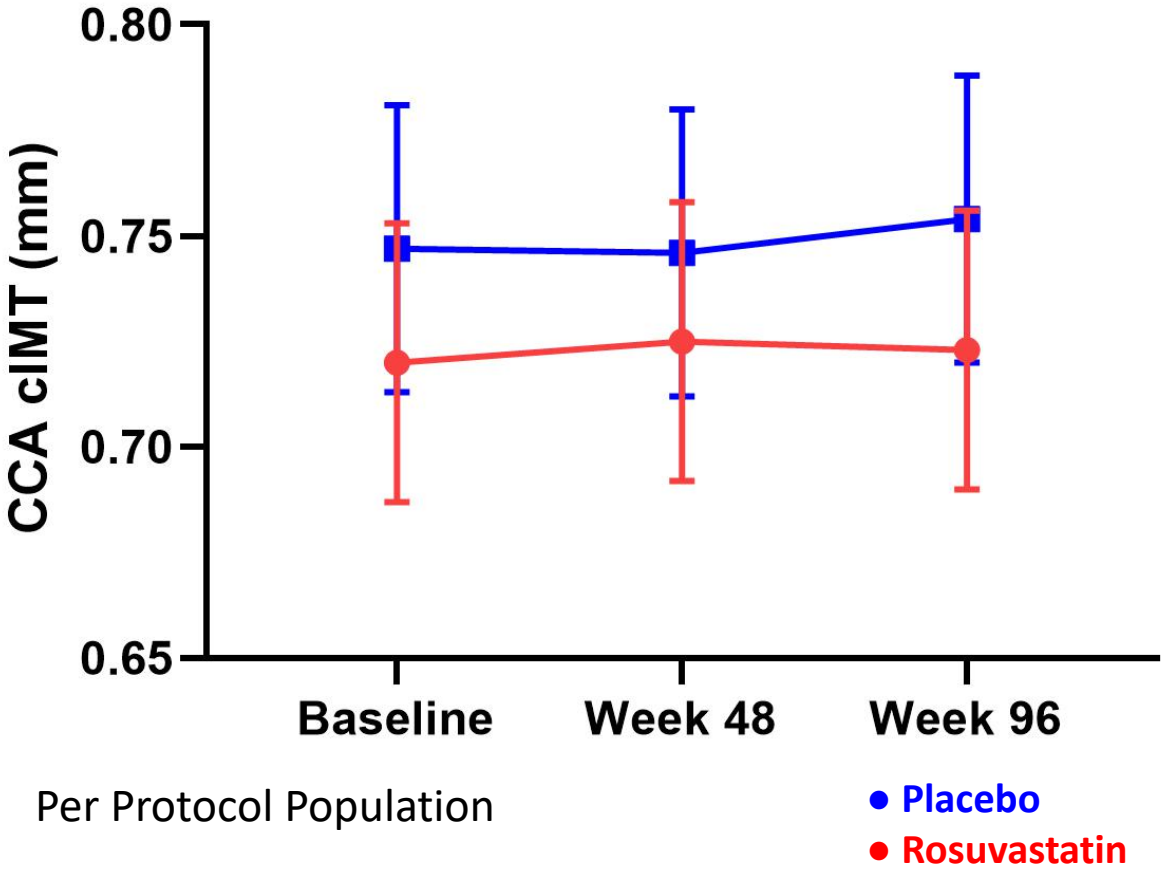
Results were also similar when restricted to the per-protocol participant population



Per Protocol Population

	Baseline	48 weeks	96 weeks	P-value[a]
Rosuvastatin	0.720 (0.033)	0.725 (0.033)	0.723 (0.033)	0.428
Placebo	0.747 (0.034)	0.746 (0.034)	0.754 (0.034)	0.113
P-value[b]	0.394	0.493	0.337	

*mean (standard deviation)

[a]p-value for within arm change from baseline to 96 weeks

[b]p-value for difference between arms at each time point

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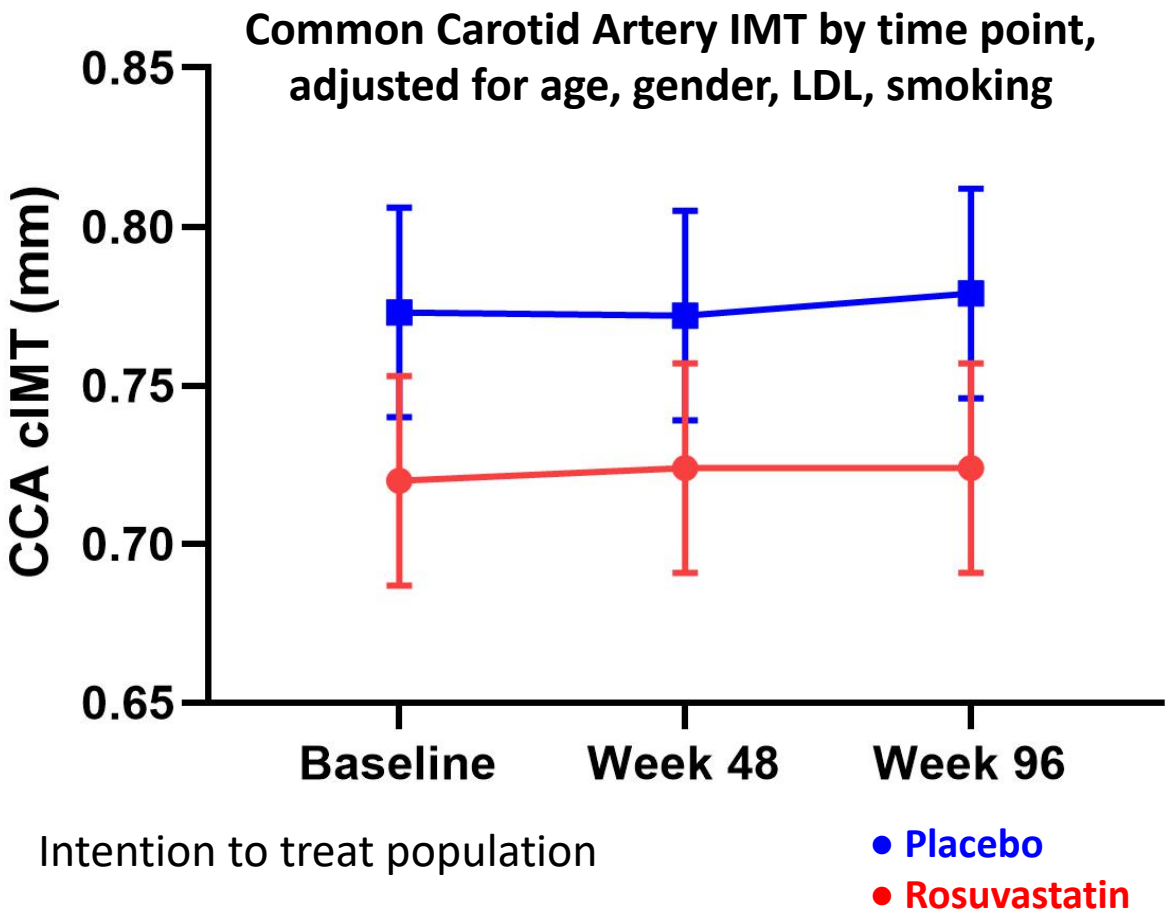
This result was not altered following adjustment for age, gender and baseline cardiovascular risk



Intention to treat population

	Baseline	48 weeks	96 weeks	P-value[a]
Rosuvastatin	0.72 (0.033)	0.724 (0.033)	0.724 (0.033)	0.319
Placebo	0.773 (0.033)	0.772 (0.033)	0.779 (0.033)	0.119
P-value[b]	0.092	0.129	0.078	

*mean (standard deviation)

[a]p-value for within arm change from baseline to 96 weeks

[b]p-value for difference between arms at each time point

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Change in cIMT from baseline at different sites

	Change from baseline to week 48			Change from baseline to week 96		
	Rosuvastatin	Placebo	P-value	Rosuvastatin	Placebo	P-value
Right CCA	0 (0.008)	0.004 (0.008)	0.600	-0.001 (0.008)	-0.003(0.008)	0.406
Left CCA	0 (0.008)	-0.002 (0.008)	0.811	-0.011 (0.008)	-0.006(0.009)	0.664
Right ICA	-0.004 (0.009)	-0.007 (0.011)	0.514	0 (0.009)	-0.01 (0.011)	0.783
Left ICA	-0.018 (0.009)	-0.002 (0.012)	0.865	-0.016 (0.009)	-0.008 (0.011)	0.621
Right Bulb	-0.008 (0.01)	0.018 (0.01)	0.076	0.004 (0.01)	0.005 (0.01)	0.189
Left Bulb	0.01 (0.01)	-0.004 (0.01)	0.703	0.006 (0.01)	-0.02 (0.01)	0.111

*mean (standard deviation)

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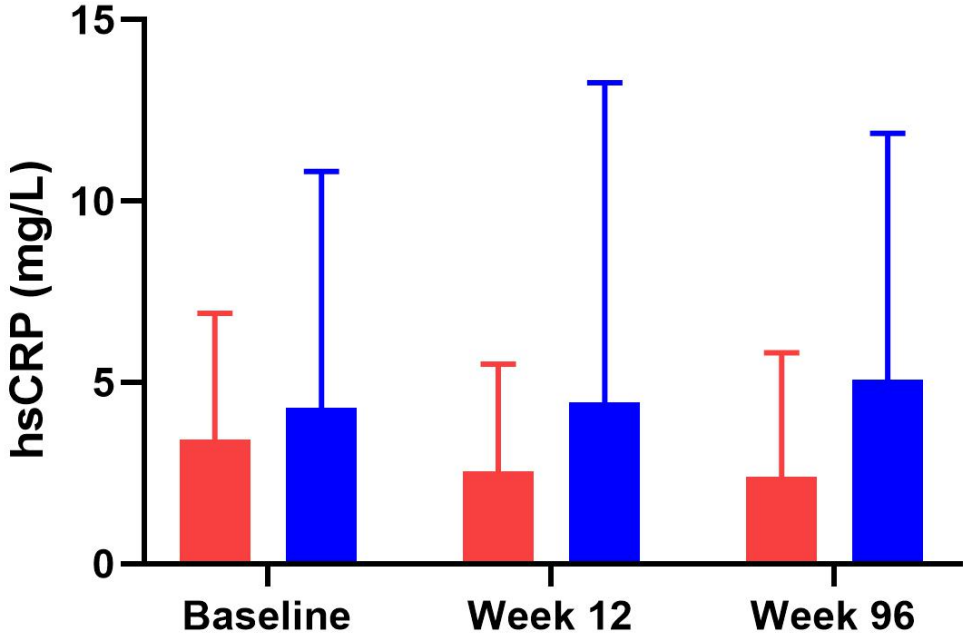
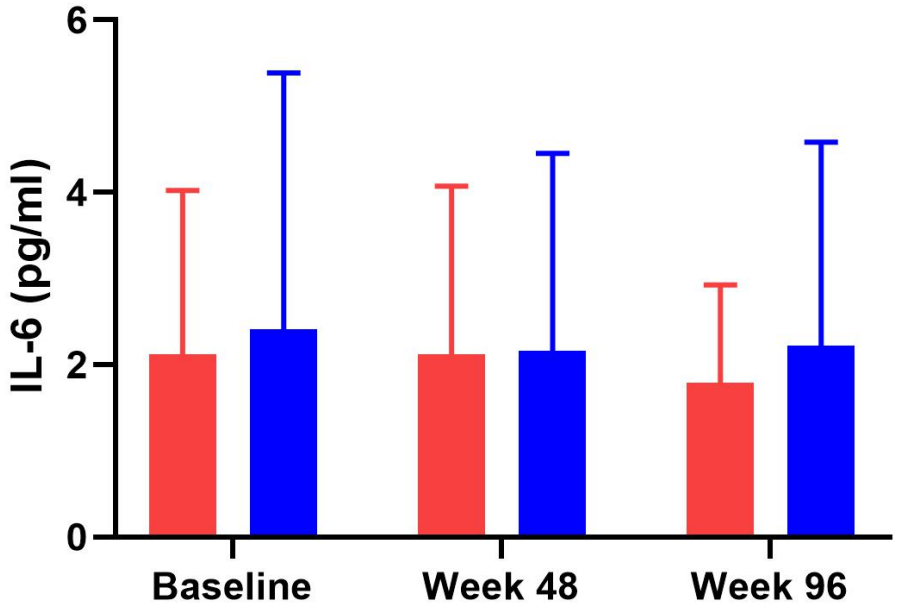
Slightly lower hsCRP with rosuvastatin, but no change in interleukin-6

hsCRP



(p = 0.751) (p = 0.347) (p = 0.053)

IL-6



(p = 0.427) (p = 0.531) (p = 0.901)

- Placebo
- Rosuvastatin

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Adverse Events

	Rosuvastatin (n=44)	Placebo (n=40)
Overall* – n (%)	33 (75%)	11 (27%)
Grade 4	2 (4%)	0 (0%)
- Stroke		
- Asympt. CK 9,100U/L		
Grade 3	5 (11%)	0 (0%)
- 2x AMI		
- 2 x new T2DM		
- Heart Failure		
Grade 2	12 (27%)	0 (0%)
Grade 1	49 (111%)	14 (35%)

* Individuals with at least one adverse event

Summary of Grade 1 & 2 events

	Total (n=84)	Rosuvastatin (n=44)	Placebo (n=40)
Myalgia	12 (14%)	2 (4%)	10 (25%)
Musculoskeletal	10 (11%)	10 (22%)	--
Abdominal Bloating	8 (9%)	8 (18%)	--
Respiratory (cough/SOB)	7 (8%)	7 (16%)	--
Rash/Itch	7 (8%)	7 (16%)	--
Infections	7 (8%)	7 (16%)	--
CK elevations >4x ULN	5 (6%)	2 (4%)	3 (7%)
ALT elevations >4x ULN	3 (3%)	2 (4%)	1 (2%)

*n (%)

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Limitations

- Small sample size
- Homogeneous participant population with a significant lack of women
- Surrogate endpoint may not represent true effect of rosuvastatin on clinical endpoints
- cIMT progression in the placebo arm was well below anticipated

Conclusions

- Despite predictable effects on total and LDL-cholesterol 96 weeks of rosuvastatin in PWHIV at moderate cardiovascular risk did not alter progression of atherosclerosis (as estimated by cIMT) compared with placebo
- Rosuvastatin was however associated with increased incidence of side effects
- Thus the benefits of statin therapy in PWHIV at low-moderate risk may not justify the potential harms
- Need to await the currently running REPREIVE trial before different thresholds for the institution of primary preventative therapy in people with HIV can be recommended

Acknowledgments

The **participants** without whom this project could not have been completed

Cath Downes, Janine Roney, Kerrie Watson, Anne Mak, Donatienne Cordier, Sabine Bavamian, Rachel Spycher-Elbes, Yoana Dimitrova, Thanh Lecompte, Baris Gencer, Fabrizio Montecucco, Laura Ciaffi, Patricia Vasquez, Victoria Rollason, and The Swiss HIV Cohort Study Network.

Funders (Swiss Sites): Swiss Foundation of Cardiology, Swiss National Foundation FNRS#32003B_135745, Reuter Foundation No 519, Boninchi Foundation, Foundation Gerbex-Bourget, Clinical Research Center, University Hospital and Faculty of Medicine, Geneva

Funders (Australian Sites): National Health and Medical Research Council (APP1111626); Faculty of Medicine Monash University, Alfred Health Department of Cardiology

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