Project Title	Does rosuvastatin delay progression of atherosclerosis in people with HIV infection at moderate cardiovascular risk? A multicentre, randomized, double blind, placebo-controlled trial

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1 Signature Form

I, the undersigned, have reviewed this Protocol, including Appendices. I will conduct the clinical study as described and I will adhere to GCP/ICH and all the local ethical and regulatory requirements.

Principal Investigator Melbourne (AUS) **Signature** **Date**

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Site main investigator ***Signature*** ***Date***

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2 List of abbreviations

ACCF	American College of Cardiology Federation
AE	Adverse Events
AHA	American Heart Association
AIDS	Acquired immunodeficiency syndrome
Alb	Albumin
ALP	Alkaline phosphatase
ALT	Alanine aminotransferase
AMI	Acute Myocardial Infarction
ART	Antiretroviral Therapy
ARV	Antiretroviral
BMI	Body Mass Index
Ca	Calcium
cART	Combination Antiretroviral Therapy
CD4+ cells	CD4+ T-cell count
CHD	Coronary Heart Disease
cIMT	Carotid artery Intima Media Thickness
Cl	Chloride
CMV	Cytomegalovirus
CPK	Creatinine phosphokinase
cPWV	Carotid-femoral pulse wave velocity
Cr	Creatinine
CrCl	Creatinine Clearance
CRF	Case Report Form
CVA	Cerebrovascular accident
CVD	Cardiovascular disease
CVE	Cardiovascular events
D.A.D –RS	D.A.D risk score
D.A.D.	Data collection on Adverse events of anti-HIV Drugs
DBP	Diastolic Blood Pressure
DSMB	Data Safety and Monitoring Board
ECG	Electrocardiograph
eGFR	estimated glomerular filtration rate
ESC	European Society of Cardiology
FBE	Full Blood Examination
FRS	Framingham Risk Score
GGT	Gamma- glutamyl transpeptidase
HaCH	HIV and Cardiovascular Health
Hb	Haemoglobin
HCO_3	Bicarbonate
HDL-C	High-density lipoprotein cholesterol
HIV	Human Immunodeficiency Virus
HMG Co-A	3-hydroxy-3-methylglutaryl coenzyme A
HUG	Geneva University Hospitals
hsCRP	High sensitivity C-reactive protein
K+	Potassium
LDL-C	Low-density lipoprotein cholesterol
LFT	Liver Function Tests

LPS	Lipopolysaccharide
Lymp	Lymphocyte Count
MAC	Mycobacterium avian complex
MDRD	Modification of Diet in Renal Disease
Na	Sodium
Neut	Neutrophil Count
PBMC	Peripheral blood mononuclear cells
PBS	Pharmaceutical Benefits Scheme
PCP	Pneumocystis jirovecii pneumonia
Plt	Platelets
PML	Progressive multifocal leucoencephalopathy
PO_4	Phosphate
PVD	Peripheral vascular disease
RNA	Ribonucleic acid
SAE	Serious Adverse Events
SBP	Systolic Blood Pressure
SHCS	Swiss HIV Cohort Study
SLE	Systemic Lupus Erythematosus
Statin	HMG Co-A reductase inhibitor
TC	Total Cholesterol
TG	Triglycerides
TIA	Transient ischaemic attack
TP	Total Protein
UEC	Urea, Electrolytes and Creatinine
ULN	Upper limit of normal
Ur	Urea
VAS	Visual Analogue Scale
VIDRL	Victorian Infectious Diseases Reference Laboratory
WCC	Total White Cell Count
WHF	World Health Federation
β-HCG	Beta-human chorionic gonadotropin

3 Definition of Terms

Study medication	the medication under investigation (rosuvastatin) or the corresponding placebo product administered for blinding

4 Protocol Synopsis

Protocol title: Does rosuvastatin delay progression of atherosclerosis in people with HIV infection at moderate cardiovascular risk? A randomized, placebo-controlled trial

Primary Objective: The primary objective is to determine the effect of rosuvastatin on atherosclerosis progression in individuals with HIV infection who are at moderate cardiovascular risk.

Study Design: This study will be a randomized, double blinded, placebo controlled, multicentre trial comparing the effect of rosuvastatin 20mg daily versus placebo over 96 weeks in people with HIV infection who are at moderate cardiovascular risk (as estimated by a Framingham Risk Score (FRS) between 10 – 15%).Participants will be randomised 1:1 to active rosuvastatin 20mg once daily or matching placebo. Participants on a protease inhibitor will receive dose reduced rosuvastatin (10 mg).

Planned sample size: 102 HIV positive participants (72 participants in Melbourne and 30 in Switzerland)

Inclusion Criteria

1. Provision of written, informed consent
2. Age >30 years
3. Moderate coronary heart Disease (CHD) risk, defined as FRS of 10-15%[1]
4. HIV positive
5. Stable ARV regimen > 3 months (i.e. no recent drug change [changes in dosages are accepted])
6. Plasma HIV viral load <200copies/ml for ≥ 6 months

Exclusion criteria

1. Recommended use of lipid lowering drug therapy according to Australian Guidelines (National heart foundation 2012)[2]
2. Family History of myocardial infarction or stroke
3. Type 2 Diabetes
4. Familial hypercholesterolemia
5. Aboriginal or Torres Strait Islander people with LDL-C >2.5 mmol/L
6. Blood pressure ≥ 180/110
7. Documented history of:
    a. Ischemic stroke or transient ischemic attack (TIA)
    b. Peripheral arterial disease
    c. Congestive heart failure
    d. Coronary artery disease or ECG findings consistent with prior MI
8. Carotid artery stenosis or >50% occlusion of the carotid artery
9. Total Cholesterol > 7.5 mmol/L
10. Triglyceride level >4.0 mmol/L
11. HDL-c <1 and Total cholesterol > 6.5 mmol/L
12. Current or prior (last 6 months) statin, ezetimibe, fibrate or niacin therapy

13. Contraindication to statin use
    a. Pregnancy or lactation
    b. Hypersensitivity to statins
    c. Known myopathy or baseline CK > 3x ULN
    d. Contraindicated concurrent medication
    e. Current cyclosporine, fusidic acid or oral corticosteroid use
14. Concomitant antiplatelet drug
15. Unable to complete study procedures
16. Any active, clinically significant disease
17. Concomitant renal or hepatic disease, defined as the presence of the following:
    a. Creatinine Clearance <50ml/min
    b. Transaminase (ALT, AST) above 3 times upper normal limit
    c. Acute hepatic failure
    d. Compensated cirrhosis Child Class B or C

Study procedures

Carotid intima media thickness (cIMT), carotid-femoral pulse wave velocity (cPWV) and biomarkers of immune activation and inflammation will be measured at baseline and compared to values obtained after 48 and 96 weeks of treatment with the study medication. Other procedures will include assessments of safety, fasting lipid and glucose analysis and storage of plasma and peripheral blood mononuclear cells (PBMCs) for future research.

5 Flow Chart

Assessment	Screen	Baseline	Post randomization				
Week	**-4**	**0**	**12**	**24**	**48**	**72**	**96**
Written Informed consent	**X**						
Inclusion / exclusion criteria	**X**						
Demographic questionnaire[a]	**X**						
Physical examination [b]	**X**	**X**			X		**X**
Compliance assessment[c]					**X**		**X**
Weight & Height measurement[d]	**X**				**X**		**X**
Adverse event assessment[e]		**X**	**X**	**X**	**X**	**X**	**X**
Risk Score Calculation[f]	**X**						
Laboratory Assessments							
T Cells	**X**		**X**	**X**	**X**	**X**	**X**
HIV RNA viral load	**X**		**X**	**X**	**X**	**X**	**X**
FBE[g]	**X**	**X**	**X**	**X**	**X**	**X**	**X**
Biochemistry[h]	**X**	**X**	**X**	**X**	**X**	**X**	**X**
Fasting Lipids/glucose[i]	**X**	**X**		**X**	**X**		**X**
hsCRP		**X**	**X**				**X**
Research Blood samples [j]		**X**	**X**		**X**		**X**
Structural assessments							
Carotid IMT[k]	**X**				**X**		**X**
Pulse Wave Velocity[l]	**X**				**X**		**X**

[a] Demographic data, medical history and medication questionnaire (will be performed with a trained interpreter if required)
[b] Includes blood pressure measurement, cardiovascular examination; electrocardiogram (ECG) at screening visit only
[c] See appendix17.2: Compliance self-assessment questionnaire and visual analogue scale
[d] Height will only be measured at screening visit. Body Mass Index (BMI) will be calculated at screening and 12 and 24 month post randomisation
[e] Unscheduled visits may be performed for safety/tolerability concerns
[f] Framingham (FRS) and Data Collection on Adverse Events of Anti-HIV Drugs (D.A.D) risk scores calculated
[g] Full Blood Examination: Haemoglobin, White cell count, Lymphocyte count, Neutrophil count, Platelet count
[h] Including sodium, potassium, bicarbonate, chloride, calcium, phosphate, urea, creatinine; Liver function tests (LFTs): alanine aminotransferase (ALT), alkaline phosphatase (ALP), total protein, albumin; creatinine phosphokinase (CPK), pregnancy screen in women with child bearing potential
[i] Participants will fast overnight and have bloods taken in the morning for total cholesterol (TC), low-density lipoprotein cholesterol (LDL), high-density lipoprotein cholesterol (HDL), triglycerides (TG) and glucose
[j] Blood for markers of innate immunity and inflammation; see Section11.2 for full description of testing to be performed and stored bloods for future projects
[k] Carotid intima media thickness (cIMT) will be performed on the left and right common carotid arteries, 12 consecutive measurements will be made 1-3cm proximal to the carotid bulb in areas identified as being without plague.
[l] Carotid-femoral Pulse Wave Velocity (cPWV) will be determined by using simultaneous applanation tonometry of the carotid and femoral arteries. Only for Australian site.

6 Background

6.1 Relationship between HIV infection and CVD

HIV positive patients have a two-fold increased risk of CVD
cART has dramatically reduced HIV-related morbidity and mortality resulting in a rapidly growing population of older patients living with HIV[3,4]. The major burden of illness, health care utilization and premature death in people with HIV is now due to diseases of ageing, particularly CVD, which occurs not only at higher rates (2 fold increased relative risk)[5] but also at a younger age than in the general population[6]. In a case-control study performed at the Alfred Hospital (AH) in 2010, the incidence of cardiovascular events (CVE) in HIV positive people was 8.5 cases per 1000 person years[7], twice the rate reported rates in HIV negative males of similar age (3.9 per 1000 person years)[8]. HIV may promote atherogenesis by a reduction in high-density lipoprotein cholesterol (HDL-C) and reverse cholesterol transport[9], immune activation and inflammation, increases in thrombosis and fibrinolysis and endothelial dysfunction[10,11].

Cardiovascular risk is likely to be underestimated in people with HIV**.** The contributing effect of HIV-associated immune activation and cART on CVD risk in HIV positive people is not considered in traditional CVD risk scores (such as the FRS[1]). In a cohort study conducted by our group at the AH, the FRS correlated only moderately with carotid intima media thickness (cIMT), a well validated surrogate marker of CVE. 11% of HIV positive patients with low (<10%) FRS had a cIMT >0.7 mm (*HIV and cardiovascular health* (*HaCH) study pilot data)*. Whilst others have also shown the true CVD risk is likely to be underestimated by FRS in people with HIV[12], correlation between FRS and risk of CVD in HIV patients remains uncertain.

CVD is associated with immune activation and inflammation in people with HIV.
The increased risk of CVD in HIV positive people is thought to be due to a combination of the effects of HIV infection, toxicity from ART and conventional CVD risk factors. The Data collection on Adverse Effects of Anti-HIV Drugs (D:A:D) study, (including data from the AH HIV cohort) provided the first evidence of increased incidence of myocardial infarction with longer duration of cART (26% increased rate of AMI per year of ART use)[13], in addition to different relative risks according to class of ART used and specific ART drugs[14,15]. HIV infection is associated with chronic immune activation and inflammation that persists despite virologic suppression[16]. The increased risk of CVD decreases with successful ART, but does not return to that of the general population[17]. It is also known that increased levels of T cell activation in HIV positive participants predicts subclinical carotid artery disease[18].

The pathogenesis of atherosclerosis is complex but inflammation is a key driving force. Inflammation drives oxidation of plasma low-density lipoprotein (LDL-C) and activates endothelial cells allowing monocytes to attach to them via their CD11b receptor and then migrate into the forming atherosclerotic plaque within the vessel wall. Bacterial endotoxin or lipopolysaccharide (LPS) is a potent inducer of inflammation; chronic endotoxemia and high plasma soluble CD14 (sCD14, released from monocytes and macrophages) are found in most HIV positive people. This is secondary to HIV-induced CD4+ T-cell depletion in the gut and loss of mucosal integrity allowing translocation of microbial products (e.g. LPS) across the gut[19]. LPS binds to monocytes via CD14, signalling cellular activation and pro-inflammatory

cytokine (e.g. IL-6) production that is critical for the initiation of CVD. Production of CRP in the liver is primarily driven by IL-6, which activates further IL-6 production by monocytes[20].

6.2 Surrogate markers of cardiovascular outcomes

Given the large number of patients that have been required to perform clinical outcome studies in CVD it is neither feasible nor practical to design such a study in the HIV population. . Thus surrogate markers of CVD endpoints are necessary to allow to effects of therapeutic interventions on CVD risk to be assessed in this population. In this study we will be utilising two well validated surrogate markers of CVD; cIMT and cPWV.

Carotid intima media thickness

cIMT has been validated as an independent predictor of CVD outcomes in the general population after adjustment for other risk factors[21]. cIMT has been used as an endpoint in clinical trials evaluating the effect of statins on CVD outcomes with a correlation between treatment induced reductions in cIMT and AMI[22]. Several cross-sectional studies have shown HIV+ people have greater cIMT than age and sex matched controls[23-25], and significantly higher progression rates than historical reports in HIV negative populations.

Pulse Wave Velocity

cPWV is a surrogate measure of arterial stiffness and is considered a marker of atherosclerosis. It has been shown to be an independent predictor of CVD events in prospective studies[26]. Increased arterial stiffness has been reported in HIV infection compared with HIV negative controls[25,27,28]. Rosuvastatin has been shown to improve aortic arterial stiffness with changes strongly correlated with reduction in LDL[29]. cPWV will not be performed at Swiss sites.

6.3 Statin therapy

Statins are HMG-CoA reductase inhibitors that lower total cholesterol, improve endothelial function, and halt progression of atherosclerosis[30]. Randomized trials of rosuvastatin in the general population have shown a reduction in major CVD events and in the inflammatory biomarker high sensitivity C-reactive protein (hsCRP) in healthy adults with normal LDL levels (the JUPITER trial)[31]. High levels of baseline hsCRP were an independent predictor of CVD in this cohort[32]. The absolute CVD event reduction with rosuvastatin was greatest in those with highest baseline hsCRP levels and in those who achieve low hsCRP levels regardless of LDL level achieved[33,34]. The cIMT effect size seen with statin therapy correlates with reduction in LDL and baseline cIMT[30]. As previously shown HIV positive people have, on average, greater cIMT and faster cIMT progression rates, thus it is likely that the magnitude of effect seen with statin therapy may be greater.

Furthermore, statins are immune modulators, and inhibit inflammation in part by reducing chemokine and pro-inflammatory cytokine synthesis by monocytes, inhibiting monocyte adhesion to the blood vessel wall as well as improving the function of other cells involved in atherogenesis (smooth muscle cells, platelets, endothelial cells)[35-37]. Rosuvastatin is predicted to alter the plasma levels of inflammatory markers and monocyte phenotype by week 12. Atorvastatin decreased CRP, IL-6 and CCL2 levels in 4 -6 weeks in HIV negative participants[38,39]. Rosuvastatin has been shown to induce a 16% reduction in hsCRP in stable ART-treated HIV positive participants over 45 days[40]. High dose atorvastatin over 8 weeks in ART naive HIV positive participants resulted in significant decreases in immune activation (CD4+ HLA-DR+, CD8+ HLA-DR+ and CD8+ CD38+ T cells)[41]. These effects may provide

additional benefit in HIV positive participants given high baseline levels of immune activation and inflammation and the association between these markers and CVD outcomes.

6.4 Selection of doses

The Jupiter study, using a rosuvastatin dose of 20 mg daily, demonstrated reductions in LDL cholesterol by 50% and hsCRP by 37%; resulting in a 50% reduction in vascular events[31]. The METEOR study reported a significant reduction in cIMT progression after 12 months of rosuvastatin therapy with the divergence continuing to increase with further follow-up out to 24 months[22]. Most rosuvastatin (90%) is excreted unchanged, while 10% undergoes limited metabolism by cytochrome P450 2C9. Pharmacokinetic studies of drug-drug interactions in healthy volunteers have shown that protease inhibitors (PI) in current use caused a 2.4-4.7 fold increase in Cmax and 1.5-3 fold increase in AUC for rosuvastatin[42,43]. For the participants receiving a non-PI based cART regimen, a dose of 20 mg rosuvastatin (1 x20 mg tablet) will be used. Participants on any PI-based cART regimen will receive 1 X 10 mg rosuvastatin (effective exposure 20 mg daily).

6.5 Rationale for performing study

The key questions regarding CVD in HIV positive people is the extent to which the pathogenesis of CVD differs between HIV positive people and the general population, and whether treatment thresholds established in the general population for the initiation of conventional CVD interventions (such as statin therapy) apply to HIV positive people. Given the role of inflammation in atherosclerosis, strong evidence of higher cIMT and greater progression rates of cIMT in HIV infection it is plausible that HIV positive people may experience a clinical benefit from the earlier initiation of statin therapy.

This study will prospectively collect validated surrogate CVD endpoint data and extensive biomarker investigations in HIV positive participants, enabling controlled comparisons of these endpoints between the two treatment arms. It is likely that HIV positive patients at moderate FRS (who would not normally qualify for stain therapy on current guidelines) will experience quantifiable benefits from administration of rosuvastatin due either to higher baseline levels of atherosclerosis not reflected in FRS or due to differential immunological effects in the unique milieu of immune activation seen in HIV positive people.

6.6 Sample size

The METEOR study of rosuvastatin in HIV negative participants with low to intermediate CVD risk found a mean Common Carotid Artery cIMT progression rate of 0.0088 mm/2 years in the placebo arm and 0.0004mm/2 years in the rosuvastatin arm[22], giving an effect size of 0.0084 mm/2 years (95% relative reduction) with a standard deviation (SD) of 0.033 mm/year. A pilot study in HIV positive patients at the AH (n=10) found that in participants treated with non-nucleoside reverse transcriptase inhibitors (the most common cART regimen), the mean cIMT progression rate was 0.04 mm/year with a SD of 0.0782 mm (personal communication Dmitri Sviridov, Baker IDI), similar to estimated values proposed for cIMT progression in HIV positive participants at low to intermediate CVD risk (mean 0.045 mm/year, SD 0.08 mm; 62).

Conservatively assuming a cIMT progression rate of 0.080 mm with a SD of 0.09 mm over 2 years and near stabilisation of cIMT (95% relative reduction) with rosuvastatin, we can assume an effect size of 0.076 mm with a SD of 0.09 mm. Sample size was calculated using an independent groups t-test with an alpha threshold of 1% and a power of 90%. Based on these hypotheses, with 44 participants in each group this study will be able to detect an effect

size of 0.076 mm with a SD of 0.09 mm over 2 years between the 2 groups. With an estimated 15% total drop-out rate over 96 weeks, we estimate that a total study population of 102 will be required.

6.7 Hypothesis

That treatment with rosuvastatin 20mg daily will delay progression of atherosclerosis and reduce biomarkers of activation and inflammation in HIV positive people with intermediate FRS.

7 Study objectives

7.1 Primary Objective

The primary objective is to determine the effect of rosuvastatin on atherosclerosis progression in individuals with HIV infection who are at moderate cardiovascular risk.

The primary outcome measure will be the difference in cIMT progression (measured as a change from baseline) between the rosuvastatin and placebo arms.

7.2 Secondary Objectives

Secondary objectives are to determine in HIV positive patients:

1. The safety profile of rosuvastatin
2. The effect of rosuvastatin on vessel wall function and biomarkers of atherosclerosis and innate immune activation
3. The effect of rosuvastatin on fasting lipids and glucose
4. Whether baseline measures of immune activation and inflammation predicts cIMT or progression of cIMT
5. Whether a change in measures of immune activation and inflammation from baseline after three months of rosuvastatin therapy predicts progression of cIMT

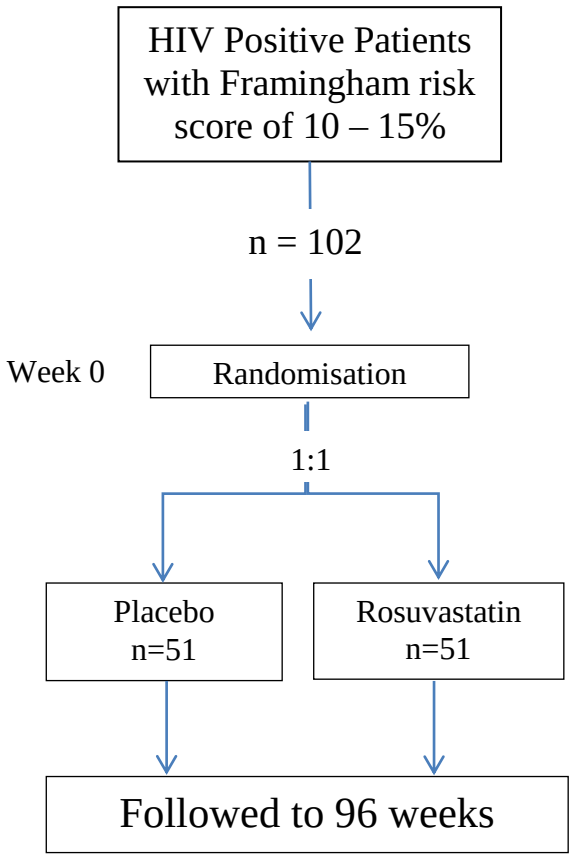
Secondary outcome measures include:

1. The rate of adverse effects (symptomatic and biochemical) between the two treatment arms
2. The effect of rosuvastatin on cIMT and cPWV
3. The effect of rosuvastatin on immunological and inflammatory markers (including sCD14, sCD163, neopterin, S-VCAM-1, adiponectin, CCL2, inflammatory (CD16+) monocyte expression of CD38, CX3CR1 and CD11b)
4. The effect of rosuvastatin on fasting total cholesterol, LDL, HDL, TG and glucose levels after 6, 12 and 24 months of therapy
5. The relationship between baseline measures ofsCD14, sCD163, and neopterin and baseline cIMT
6. The relationship between baseline measures of sCD14, sCD163, and neopterin and rate of progression of cIMT
7. The relationship between change from baseline to 3 months in markers of immune activation and inflammation (sCD14, CCL2, and inflammatory (CD16+) monocyte phenotypic expression of CD38, CD11b) and progression of cIMT at 12 and 24 months.

8 Study Design

8.1 Design

The study will be a randomized, double blinded, placebo controlled, multicentre trial comparing the effect of rosuvastatin 20 mg daily versus placebo over 96 weeks in people with HIV infection at moderate cardiovascular risk.



Individuals (n=102) with moderate CVD risk, as estimated by the FRS (10-15% 10 year risk of CVD), who do not qualify for statin therapy under Australian guidelines[2], will be randomized 1:1 to active rosuvastatin 20mg once daily or matching placebo.

Placebo and rosuvastatin capsules identical in shape and colour will be used to help preserve blinding. Participants on a protease inhibitor based cART regimen will receive 10 mg rosuvastatin or matching placebo.

Randomisation
A computerized random number generator will be used to assign treatment arms. Block Randomisation will be stratified by country.

There will be seven study visits over the 96 week duration of the study.

cIMT, cPWV and biomarkers of immune activation and inflammation will be measured at screening visit and compared to values obtained after 48 and 96 weeks of treatment with the study medication.

cIMT and cPWV measurements will be performed in duplicate, by the same operator at the AH Heart Centre or the Swiss site, who will remain blinded to participant randomization, throughout the study.

All samples will be processed on site at the AH or the Swiss site. Standard laboratory assessments (i.e. biochemistry, full blood examination (FBE), fasting lipids, hsCRP) will be processed by AH pathology department or the Swiss sites' local laboratories. Markers of innate immunity and inflammation will be performed in the Burnet laboratories. Plasma and PBMCs will be separated from research bloods samples, frozen to -140^{0}C and stored onsite in the Burnet laboratory for possible further analysis in the future.
For Switzerland: Plasma samples for testing of inflammation markers will be stored on site at minus 80° and shipped to central biobank (sérothèque) HUG for analysis at the HUG cardiology laboratory.

8.2 Duration

Ninety-six (96) weeks per patient
Expected duration for entire project – 5 years

8.3 Study centres

Patients will be recruited and followed at the Alfred Hospital (Victorian HIV service) Infectious Diseases Clinic.
Switzerland: Patients will be recruited within the HIV Cohort Network, at the following hospitals following regulatory approval: University Hospitals in Geneva, Lausanne, Berne, Zurich and Basel and the Cantonal Hospitals of St Gallen and Lugano, providing that these centers and affiliated Ethics Committee do accept to enrol patients in the present study. The patients will be recruited during their routine visits to the sites by the local investigators. The use of recruitment advertisements or flyers is not intended.

9 Study Population

9.1 Inclusion Criteria

1. Provision of written, informed consent
2. Age >30 years
3. Moderate coronary heart Disease (CHD) risk, defined as FRS of 10-15%[1]
4. HIV positive
5. Stable ARV regimen > 3 months (i.e. no recent drug change [changes in dosages are accepted])
6. Plasma HIV viral load <200copies/ml for ≥ 6 months

9.2 Exclusion criteria

1. Recommended use of lipid lowering drug therapy according to Australian Guidelines (National heart foundation 2012)[2]
2. Family History of myocardial infarction or stroke in a male first degree relative before 55 years of age, or a female first degree relative before 65 years of age
3. Type 2 Diabetes
4. Familial hypercholesterolemia
5. Aboriginal or Torres Strait Islander people with LDL-C >2.5 mmol/L
6. Blood pressure ≥ 180/110
7. Documented history of:
    a. Ischemic stroke or transient ischemic attack (TIA)
    b. Peripheral arterial disease (regardless of severity)
    c. Congestive heart failure
    d. Coronary artery disease or ECG findings consistent with prior MI
8. Carotid artery stenosis or >50% occlusion of the carotid artery known previously or discovered during screening procedures
9. Total Cholesterol > 7.5 mmol/L
10. Triglyceride level >4.0 mmol/L
11. HDL-c <1 and Total cholesterol > 6.5mmol/L
12. Current or prior (last 6 months) statin therapy

13. Current or prior (last 6 months) use of ezetimibe
14. Current or prior (last 6 months) use of fibrates or niacin
15. Contraindication to statin use
    a. Pregnancy or lactation
    b. Hypersensitivity to statins
    c. Known myopathy or baseline CK > 3x ULN
    d. Contraindicated concurrent medication
    e. Current cyclosporine, fusidic acid or oral corticosteroid use
16. Concomitant antiplatelet drug (Aspirin, Abciximab, Anagrelide, Cilostazol, Clopidogrel, Dipyridamole, Eptifibatide, Ticagrelor, Ticlopidine, Tirofiban, Terutroban)
17. Unable to complete study procedures (i.e. attendance at AH for cIMT and cPWV testing or cIMT images not accepted for analysis despite redo examination)
18. Any active, clinically significant disease (including but not limited to; pancreatitis, significant psychiatric disorders, acquired immunodeficiency syndrome (AIDS) defining illnesses) which may impact on the results of the study, increase the risk of serious adverse events (SAE) or limit participants life expectancy to < 24 months
19. Concomitant renal or hepatic disease, defined as the presence of the following:
    a. Creatinine clearance <50 ml/min (calculated using the Cockroft-Gault equation)[45]
    b. Transaminase (ALT, AST) above 3 times upper normal limit
    c. Acute hepatic failure
    d. Compensated cirrhosis Child Class B or C

9.3 Prohibitions

Concurrent participation in non-related clinical trials is allowed as long as there is no impact on the objectives of this trial.

9.4 Removal of participants from therapy/assessment

Participants will be withdrawn from the trial if:

1. A SAE occurs which is thought to be related to involvement in the study
2. The subject withdraws consent
3. The subject becomes pregnant
4. The subject is diagnosed with clinical cardiovascular disease
    a. Cardiovascular
        i. Acute myocardial infarction (AMI)
        ii. Development of angina
        iii. New ECG changes consistent with cardiovascular disease
    b. Cerebrovascular
        i. Stroke or Transient Ischaemic Attack (TIA)
    c. Peripheral vascular disease
        i. Symptomatic claudication
5. The subject is diagnosed with an acute serious medical illness that would be a contraindication to statin therapy i.e.
    a. Acute viral hepatitis (A, B or C)
6. CK or transaminase elevation (> 3 times)

7. Subject is judged by the investigator to be at significant risk of failing to comply with the provisions of the protocol so as to cause harm to self or seriously interfere with the validity of the study result.

9.5 Pregnancy

Women of child-bearing potential will be screened for pregnancy on admission to the study. Due to a lack of study data relating to the effects of statins on pregnant woman and/or the foetus those who are found to be pregnant will be excluded from study participation and referred to an appropriate medical service[46].
Female participants will be advised to avoid pregnancy while participating in the study. Women who become pregnant after randomisation will be withdrawn from the trial but will continue to be monitored for the development of adverse events (AE) or serious adverse events (SAE).
For Switzerland: Women of childbearing potential must use two reliable contraceptive methods during the entire trial, from day 1 to one month after the end of the trial. Accepted methods are hormonal methods such as the birth control pill associated with a barrier method such as the preservative.

10 Study Medication

Participants will be randomly assigned in a 1:1 ratio to receive rosuvastatin or matched placebo.

10.1 Rosuvastatin

Rosuvastatin is a hypolipidaemic agent and member of the drug class of statins used to treat high cholesterol and related conditions. Rosuvastatin is licensed by the Australian Therapeutic Goods Administration (TGA) for the prevention of major cardiovascular events and in patients with hypercholesterolemia (including familial hypercholesterolemia). Rosuvastatin should be used as an adjunct to dietary modification.

Rosuvastatin capsules of 10mg and 20mg dosages will be purchased from the manufacturer - Astra Zeneca.

10.2 Placebo

A placebo identical in appearance to rosuvastatin will be produced by Pharmaceutical Packaging Professionals (PPP)in Thebarton South Australia. Stability tests will be performed by PPP and lot numbers and expiry dates provided to the sites.

10.3 Packaging and Labelling

Packaging and labelling will be in accordance with the applicable local regulatory requirements.

The study medication will be packed into bottles by Pharmaceutical Packaging Professionals (PPP) and shipped to the sites.

Labels will contain the following information: “for clinical trial use only”; study name and number; lot number, expiry date or re-testing date; patient ID or randomization number; “keep out of reach of children”; storage condition; name of PI and Institution.

The study medication will be distributed to the patient by the local research investigator or study nurse.

10.4 Timing of dosing

Rosuvastatin is taken once daily and can be taken with or without food. Participants will be encouraged to take it at the same time every day with a glass of water. Catch up doses should NOT be taken in the setting of a missed/forgotten dose.

10.5 Storage

The study medication should be stored in its provided packaging at room temperature (<30°C) away from heat and moisture.

10.6 Drug Accountability

The Investigator is responsible for ensuring accountability for the study medication, including reconciliation of drugs and maintenance of drug records.

Drug accountability documentation will be performed according to the local regulatory requirements and will include confirmation of the study medication received at the site; the study medication distributed to the patient and returned by the patient; lost or destroyed study medication; corresponding dates, quantities, batch numbers, expiry dates, as well as subject identification numbers.

The investigator should maintain records that adequately document:
- That the subjects were provided the doses specified by the protocol/amendment(s)
- That all study medication provided to the site was fully reconciled.

10.7 Compliance assessment

Compliance to the study medication (rosuvastatin and placebo) will be assessed by self-reported questionnaire using a modified Medication Adherence Self-Report Inventory and visual analogue scale (VAS) [47].

If it appears that a participant is not taking the study medication according to protocol they will be counselled by the investigator in an attempt to improve compliance.

10.8 Warnings and precautions

Musculoskeletal reported side effects

HMG-CoA reductase inhibitors (statins) have been associated with rare cases of severe myopathy and rhabdomyolysis, accompanied by increases in creatine kinase (>10x upper normal limit), myoglobinuria, proteinuria, and renal failure, mainly observed in 40mg daily dosage. Concomitant use with gemfibrozil (fibric acid derivatives), niacin, cyclosporine, erythromycin (macrolides) or azole antifungals may increase the incidence and severity of musculoskeletal side effects. Milder forms of myotoxicity (i.e., myalgia) are commonly reported and occur in approximately 5% to 7% of patients taking a statin drug.

Other reported side effects

frequent (≥1/100, <1/10):
- Myalgia
- Diabetes (JUPITER study 2,8% in the rosuvastatin arm versus 2,3% in the placebo arm)
- Headache, dizziness

- Abdominal pain, constipation, nausea
- Asthenia

Occasional (≥100/10, <1/10):

- Pruritis, rash

Rare (≥1/10'000, <1/1000) side effets include:

- Myopathy, arthralgia
- Hepatic transaminases elevations
- Hypersensitivity reactions
- Pancreatitis

Very rare (<1/10'000) side effects:

- Jaundice, hepatitis
- Hematuria
- Polyneuropathy

Frequency unknown:

- Cough, dyspnea
- Diarrhea
- Steven-Johnson syndrome
- Necrotic myopathy
- Gynecomastia
- Oedema

10.9 Concomitant medications

Participants are not to commence any new medication without notifying the study coordinators to allow an assessment for potential interactions with the study medication.

10.9.1 Contraindications

The use of rosuvastatin is contraindicated in combination with the following medications. A patient requiring commencement of these medications following enrolment will be withdrawn from the study.

- Cyclosporine
  - Combined uses significantly increases rosuvastatin exposure.
- Gemfibrozil and other fibrates
  - Combined use increases the risk of adverse skeletal muscle effects and should only be used with caution
- Niacin
  - Combined use increases the risk of adverse skeletal muscle effects and should only be used with caution
- Fusidic acid
  - Combined use increased rosuvastatin levels and the risk of adverse skeletal muscle effects

10.9.2 Warfarin

Combined use of coumarin anticoagulants with rosuvastatin is not contraindicated but will lead to prolonged INR. Patients should have a stable INR prior to starting rosuvastatin. INR monitoring should occur at increased frequency upon initiation or alteration of rosuvastatin dose.

10.9.3 Antiretrovirals

Participants must be on a stable ARV regimen for > 3 months (with HIV viral load <200 for >6 months) to be eligible for acceptance into the study. ARV regimens will remain at the

discretion of the patients treating physician who will be blinded to study medication but not involvement in the study.

Participants on any PI-based cART regimen will receive 1 x 10 mg rosuvastatin (effective exposure 20 mg daily).

Participants who require a change in antiretroviral regimen following randomisation on the basis of treatment failure or intolerability (that could not be attributed to the study medication) may remain within the study.

- Patients who switch from a PI containing regimen to a non-PI containing regimen will have the dose of rosuvastatin (or placebo) increased to 20mg daily
- Patients who switch from a non-PI containing regimen to a PI containing regimen will have the dose of rosuvastatin (or placebo) reduced to 10mg daily
- Switches within classes of ARV require no change in study medication dose

10.10 Drug interactions list[m]

Table below: Influence of concomitantly administered drugs on exposure to rosuvastatin (AUC, Cmax in descending order of effect size) based on published clinical trials. Source: Swiss Compendium (www.compendium.ch)

Interacting Drug, dosage and treatment period	**Rosuvastatin-dosage and treatment period**	**Effect on rosuvastatin AUC**	**Effect on rosuvastatin-C_{max}**
Ciclosporin 75 mg b.i.d. up to 200 mg b.i.d., 6 Months	10 mg q.d., 10 days	7,1 fold ↑	11 fold ↑
Atazanavir 300 mg/Ritonavir 100 mg q.d., 8 days	10 mg, single dose	3,1 fold ↑	7 fold ↑
Lopinavir 400 mg/Ritonavir 100 mg B.I.D., 17 days	20 mg q.d., 7 days	2,1 fold ↑	5 fold ↑
Gemfibrozil 600 mg b.i.d., 7 days	80 mg, single dose	1,9 fold ↑	2,2 fold ↑
Eltromobopag 75 mg q.d. , 10 days	10 mg, single dose	1,6 fold ↑	2 fold ↑
Darunavir 600 mg/Ritonavir 100 mg b.i.d., 7 days	10 mg q.d., 7 days	1,5 fold ↑	2,4 fold ↑
Tipranavir 500 mg/Ritonavir 200 mg b.i.d., 11 days	10 mg, single dose	1,4 fold ↑	2,2 fold ↑
Dronedaron 400 mg b.i.d.	No data	1,4 fold ↑	No data
Itraconazol 200 mg q.d. , 5 days	10 mg or 80 mg, single dose	1,4 fold ↑	1,4 fold ↑
Ezetimibe 10 mg q.d. , 14 days	10 mg q.d. , 14 days	1,2 fold ↑	1,2 fold ↑
Fosamprenavir 700 mg/ Ritonavir 100 mg b.i.d., 8 days	10 mg, single dose	↑ 8%	1,5 fold ↑
Aleglitazar 0,3 mg, 7 days	40 mg, 7 Days	↔	1,1 fold ↑
Silymarin 140 mg t.i.d., 5 days	10 mg, single dose	↔	↔
Fenofibrat 67 mg t.i.d., 7 days	10 mg, 7 Days	↑ 7%	1,2 fold ↑

[m] Source: Swiss Compendium and translated into the English by the Swiss site : www.compendium .ch

Interacting Drug, dosage and treatment period	Rosuvastatin-dosage and treatment period	Effect on rosuvastatin AUC	Effect on rosuvastatin-C_{max}
Rifampicin 450 mg q.d. , 7 days	20 mg, single dose	↔	↔
Ketoconazol 200 mg b.i.d., 7 days	80 mg, single dose	↑ 2%	↔
Fluconazol 200 mg q.d. , 11 days	80 mg, single dose	↑ 14%	↔
Erythromycin 500 mg q.i.d., 7 days	80 mg, single dose	28% ↓	31% ↓
Baicalin 50 mg t.i.d., 14 Days	20 mg, Single dose	47% ↓	19% ↓

«↑»: Increase.
«↔»: No change (defined as <20% change of rosuvastatin -AUC, C-max).
«↓»: Decrease.

10.11 Blinding and Emergency Unblinding

The personnel involved in the conduct of the trial as well as the study participants will remain blinded to the assigned study medication, throughout the trial.

Unblinding: The study physician may decide to break the randomization code of the participant for security reasons only. Emergency code breaking instructions will be provided to the sites. In Switzerland: the coordinating centre must be informed immediately if a code has been broken.

11 Assessments

All assessments including screening and unplanned study visits will be recorded on the case report form (CRF) – See Appendix 22.1

Demographic data, medical history and medication questionnaire

Patients will be questioned on details necessary for determining eligibility for entry into the trial and important study variables. Topics to be covered include, age, gender, race, presence of CVD risk factors (smoking status, family history of CVD etc.), past medical history, current medications and the presence of any allergies.
The questionnaire will be completed by a study investigator at the screening visit. At all subsequent visits patients will be asked:

1. If they have developed or been diagnosed with any new medical illnesses since the last review
2. If they have started or stopped any non-study medications
3. Their current smoking status.

Compliance assessment

1. Compliance with the study medication will be performed at two time points (Weeks 48 and 96) to estimate compliance throughout the study. A self-assessment question sheet and VAS will be used asking participants to estimate compliance over the last fortnight and month. (See appendix 22.2)

Physical examination

Consists of:

1. Complete physical examination

2. Blood pressure measurement with patient sitting
3. Recording presence of bilateral lower limb peripheral pulses of the posterior tibial and the dorsalis pedis arteries
4. Anthropometry
    a. Weight will be measured in kilograms (kg) with patient clothed; footwear removed
    b. Height will be measured in metres (m) with footwear removed
    c. Waist circumference (adapted from the International Diabetes Federation guidelines on the diagnosis and management of the metabolic syndrome)[48]
        i. Subject should be standing erect dressed in underwear; all outer clothing should be removed.
        ii. Make sure the tape does not compress the tissues during the measurement.
        iii. Record the measurement after the subject has exhaled with the tape measure in a horizontal plane, midway between the inferior margin of the ribs and the superior border of the iliac crest.

Electrocardiogram (ECG)
ECG will be performed by trained study investigators at screening visit.
All ECGs will be read by a blinded study doctor; all important abnormalities on the ECG will be reported. Specifically the presence of findings consistent with prior myocardial infarction (as defined by the 2007 Joint European Society of Cardiology/American College of Cardiology Federation/American Heart Association/World Health Federation (ESC/ACCF/AHA/WHF) Task Force[49];

- Any Q-wave in leads V_2-$V_3 \geq 0.02$s or QS complex in leads V_2 and V_3
- Q-wave ≥ 0.03s and ≥ 0.1mV deep or QS complex in leads I, II, aVL, aVF or V_4-V_6, in any two leads of a contiguous lead grouping (I, aVL, V_6; V_4-V_6; II, III, aVF)
- R-wave ≥ 0.04s in V_1-V_2 and R/S ≥ 1 with a concordant positive T-wave in the absence of a conduction defect

Adverse event assessment
See sections 13 and 14 for details on AE and SAE reporting and assessment
At each study visit patients will be asked to report any untoward medical occurrences and will also be specifically questioned regarding the presence of:

- Myopathic symptoms (weakness, muscle pain)
- Gastrointestinal disturbance (diarrhoea, nausea, vomiting, abdominal pain)
- Jaundice

11.1 Calculations

Framingham Risk Score
Ten-year risk of developing "hard" coronary heart disease endpoints (myocardial infarction and coronary death) will be calculated based on the Framingham Risk Score using an online calculator available at www.old.mdcalc.com/framingham-coronary-heart-disease-risk-score-si-units/

D.A.D Risk Score
The D.A.D equation is a cardiovascular risk assessment model that is tailored for use in HIV positive participants, taking into account exposure to specific PIs, family history of CHD and

previous, as well as current smoking status[50]. A D.A.D. risk score will be calculated on all participants at baseline to allow for a comparison with the FRS and to compare each measure with cIMT. The calculation will be performed using an online tool available at: http://www.cphiv.dk/tools/dadriskequations/tabid/437/default.aspx

Body Mass Index (BMI)
A BMI will be calculated at screening visit and at the forty-eight (48) and ninety-six (96) week visits. Height will only be measured at screening and assumed to remain stable through the study period
BMI = Weight (kg) / height^2 (m)

Creatinine clearance
An estimated creatinine clearance will be calculated at screening visit to determine eligibility for entry into the trial using the Cockroft-Gault equation[45]

For men $Cl = \frac{1.23 \times \text{weight (kg)} \times (140 - age(years))}{\text{Creatinine (µmol/L)}}$

For women $Cl = \frac{1.03 \times \text{weight (kg)} \times (140 - age(years))}{\text{Creatinine (µmol/L)}}$

11.2 Laboratory Assessments

Handling of Biological samples
All biological samples (excluding those for storage and testing of innate immunity) will be processed at the Alfred Hospital laboratory or the Swiss site; local laboratory reference ranges will apply (see appendix 22.3 and 22.4).

Biological samples for testing of innate immunity will be handled at the Burnet Institute. Plasma will be separated and frozen (-80ºC). Plasma markers will be analysed on batched frozen samples by ELISA.
Swiss sites will store plasma samples (6mls per visit) at -80°C and ship to the HUG cardiology laboratory for testing of plasma markers. Innate immunity markers (PBMC) will not be performed at Swiss sites.
A separate laboratory SOP will be provided to all the Swiss sites.

HIV specific testing
HIV monitoring (CD4+ T-cell count and HIV viral load) will be performed at screening, baseline and weeks 12, 48, 72 and 96

Laboratory assessments for safety
Routine laboratory assessments for safety and tolerability will be performed including:

- Full Blood Examination (FBE)
  - Consisting of; Haemoglobin (Hb), total White Cell Count (WCC), Lymphocyte Count (Lymp), Neutrophil Count (Neut) and Platelet count (Plt)
- Biochemistry
  - Consisting of; Sodium (Na), Potassium (K+), Chloride (Cl), Bicarbonate (HCO_3), Calcium (Ca), Phosphate (PO_4), Urea (Ur), Creatinine (Cr) and creatinine phosphokinase (CPK)

- An estimated glomerular filtration rate (eGFR) based on the Modification of Diet in Renal Disease (MDRD)[51] equation is calculated electronically by the AH laboratory and will be recorded
- Liver Function Tests: Total Protein (TP), Albumin (Alb), Bilirubin (Bil), Alanine aminotransferase (ALT), Alkaline phosphatase (ALP) and Gamma-glutamyl transpeptidase (GGT)
- Pregnancy screen in women with child bearing potential (at screening visit); Beta Human chorionic gonadotrophin (β-HCG)

Fasting metabolic parameters
Patients will be requested to attend the study visit having fasted overnight (for 12 hours). Definition of fasting: no food, caffeine or caloric drinks; free water is allowed and encouraged. Samples will be sent for TC, HDL, LDL, TG and glucose.
Study participants and site investigators will be blinded to the results of metabolic testing until the completion of the study. This is to prevent self-modification of lifestyle or diet in an attempt to normalise out-of-range results

Markers of Innate immunity and inflammation
Markers of Innate immunity and inflammation will be measured at baseline, and weeks 12, 48, and 96.
For participants recruited in Melbourne only: A panel of innate immune markers selected from HaCH including monocyte markers (CD14, CD16) of activation (CD38), of expression linked to migration, adhesion and progression of atherosclerotic plaque (CD11b, CX3CR1) will be performed.
In participants from both sites in plasma, markers of inflammation (IL6, sCD163) and monocyte activation / chemokine ligands (sCD14, neopterin, CCL2), S-VCAM-1 and adinopectin will be measured.

High sensitivity C-reactive protein (hsCRP) will be performed by the AH laboratory according to standard protocols

Stored Samples
4ml of plasma will be stored indefinitely for possible future testing and research for participants that give their consent. Storage samples will be collected at baseline and weeks 12, 48 and 96.
Samples will be stored at -80^{0}C in the Burnet research laboratory and -80°C at the Swiss sites. Swiss sites will transfer the samples to the HUG central "sérothèque" for storage. Participants recruited from the Alfred Hospital will also have PBMC's stored at -140 in the Burnet research laboratory.

11.3 Carotid IMT

The bilateral carotid artery will be assessed for cIMT by B Mode ultrasound using a Philips iE33 with 11 MHz linear transducer (Melbourne). The Swiss sites will be using the ultrasound machine tested and accepted by the core lab in Montréal following the Standard Operating Procedures for cIMT. The cIMT measurement is a painless and harmless non-invasive ultrasound procedure performed on patients' left and right common carotid arteries. The procedure takes 20 minutes to perform. The cIMT defined as the distance between lumen-intima interface and media-adventia interface is measured from the 2D high resolution digital images obtained using an automated border-detection algorithm. cIMT will be

determined on areas identified as without plaque by 12 consecutive measurements made 1-3 cm proximal to the carotid bulb, but the presence of plaques will be noted. All measurements will be performed in duplicate, by the same operator at the AH Heart Centre or the Swiss site, who will remain blinded to participant randomization, throughout the study.

Investigators and patients will not receive results from cIMT (or cPWV – see below) until the end of the study, unless a significant carotid plaque warranting further investigation and management is identified. Patients who are identified as having a significant plaque will be withdrawn from the study and referred to a cardiologist at the AH or the Swiss site for further assessment and management as necessary.

11.4 Pulse Wave Velocity

Australian site only: cPWV will be determined using simultaneous applanation tonometry of the carotid and femoral arteries. PWV will be calculated as manubrium sternum-to-femoral artery distance minus carotid artery-to-manubrium sternum distance divided by the time interval between the carotid and femoral pulses calculated from the upstroke of the systolic waveform (maximum of the second derivative). The cPWV will be reported as the average of pulse waves recorded over a 10 second period. It is a painless and harmless procedure that takes 20 min to perform by trained operators. The co-efficient of variation for this measurement is 5%.

12 Visit Schedule

12.1 Screening

The screening procedures will be completed in one visit at the study site.
Participants will present to the study site, having fasted from overnight for at least 12 hours (no food, caffeine or caloric drink; free water is encouraged).

Written informed consent will be obtained at screening visit by trained research staff (see Appendix 22.5 and 22.6). Participants will be informed in written and orally prior to the screening visit and given sufficient time for reflexion before signing the consent form.

Assessments

1. Demographic data, medical history and medication questionnaire to be completed
2. Full physical examination including:
    a. Height and weight
    b. Assessment of peripheral pulses
    c. Blood pressure
    d. ECG
3. Laboratory assessments
    a. FBE and biochemistry
    b. Beta HCG for all women of child bearing potential
    c. Fasting metabolic assessment
    d. HIV viral load and CD4+ T cell count (and percentage)
4. Structural assessments
    a. cIMT
    b. cPWV (*Melbourne Participants only)
5. Calculations
    a. BMI

b. Creatinine clearance
c. FRS
d. D.A.D. risk score

12.1.1 Eligibility

Clinical eligibility will be recorded based on the inclusion (1-6) and exclusion criteria (7-26) listed below.

12.2 Inclusion Criteria

1. Provision of written, informed consent
2. Age >30 years
3. Moderate coronary heart Disease (CHD) risk, defined as FRS of 10-15%[1]
4. HIV positive
5. Stable ARV regimen > 3 months (i.e. no recent drug change [changes in dosages are accepted])
6. Plasma HIV viral load <200copies/ml for ≥ 6 months

12.3 Exclusion criteria

7. Recommended use of lipid lowering drug therapy according to Australian Guidelines (National heart foundation 2012)[2]
8. Family History of myocardial infarction or stroke in a male first degree relative before 55 years of age, or a female first degree relative before 65 years of age
9. Type 2 Diabetes
10. Familial hypercholesterolemia
11. Aboriginal or Torres Strait Islander people with LDL-C >2.5 mmol/L
12. Blood pressure ≥ 180/110
13. Documented history of:
    a) Ischemic stroke or transient ischemic attack (TIA)
    b) Peripheral arterial disease (regardless of severity)
    c) Congestive heart failure
    d) Coronary artery disease or ECG findings consistent with prior MI
14. Carotid artery stenosis or >50% occlusion of the carotid artery known previously or discovered during screening procedures
15. Total Cholesterol > 7.5 mmol/L
16. Triglyceride level >4.0 mmol/L
17. HDL-c <1 and Total cholesterol > 6.5mmol/L
18. Current or prior (last 6 months) statin therapy
19. Current or prior (last 6 months) use of ezetimibe
20. Current or prior (last 6 months) use of fibrates or niacin
21. Contraindication to statin use
    f. Pregnancy or lactation
    g. Hypersensitivity to statins
    h. Known myopathy or baseline CK > 3x ULN
    i. Contraindicated concurrent medication
    j. Current cyclosporine, fusidic acid or oral corticosteroid use

22. Concomitant antiplatelet drug (Aspirin, Abciximab, Anagrelide, Cilostazol, Clopidogrel, Dipyridamole, Eptifibatide, Ticagrelor, Ticlopidine, Tirofiban, Terutroban)
23. Unable to complete study procedures (i.e. attendance at AH for cIMT and cPWV testing or cIMT images not accepted for analysis despite redo examination)
24. Any active, clinically significant disease (including but not limited to; pancreatitis, significant psychiatric disorders, acquired immunodeficiency syndrome (AIDS) defining illnesses) which may impact on the results of the study, increase the risk of serious adverse events (SAE) or limit participants life expectancy to < 24 months,
25. Any active, clinically significant disease (including but not limited to; pancreatitis, significant psychiatric disorders, acquired immunodeficiency syndrome (AIDS) defining illnesses) which may impact on the results of the study, increase the risk of serious adverse events (SAE) or limit participants life expectancy to < 24 months
26. Concomitant renal or hepatic disease, defined as the presence of the following:
    a. Creatinine clearance <50 ml/min (calculated using the Cockroft-Gault equation)[45]
    b. Transaminase (ALT, AST) above 3 times upper normal limit
    c. Acute hepatic failure
    d. Compensated cirrhosis Child Class B or C

If the patient fulfils all eligibility criteria (1-26 above) then a baseline visit will be booked. CRFs from participants assessed but found to be ineligible for inclusion in the study will be entered into the database recording the reason for ineligibility.

12.4 Randomisation

Patients will be block randomised in a 1:1 ratio to receive rosuvastatin or placebo. Randomisation will be stratified by centre.

12.5 Baseline visit

Participants will be required to present to the study site having fasted overnight for at least 12 hours (no food, caffeine or caloric drinks; free water is encouraged)

Assessments performed:

1. Targeted physical examination and updated history, assessment for new concomitant medications
2. Adverse event assessment
3. Laboratory assessments
    a. Biochemistry
    b. Fasting metabolic assessment
    c. hsCRP
    d. Markers of innate immunity and inflammation
    e. Storage of plasma and PBMCs (*Melbourne participants only) for possible further analysis in the future

Patients will be provided with a three (3) month supply of the study medication and educated regarding possible clinical signs of potential adverse events (muscle ache, fever, abdominal pain, jaundice, rash); regardless of randomisation. Patients will also be provided with contact details for study co-ordinators in case of adverse event.

12.6 Week 12 visit

Participants will be required to present to the study site having fasted overnight for at least 12 hours (no food, caffeine or caloric drinks; free water is encouraged)

Assessments performed:

1. Assessment for adverse events
2. Laboratory assessment for:
    a. FBE
    b. Biochemistry
    c. hsCRP
    d. Markers of innate immunity and inflammation
    e. HIV Viral load and CD4+ T-cell count (and percentage)
3. Storage of plasma and PBMCs (*Melbourne participants only) for possible future analysis

Patients provided with a further three (3) month supply of the study medication.

12.7 Week 24 visit

Participants will be required to present having fasted overnight for at least 12 hours (no food, caffeine or caloric drinks; free water is encouraged)

Assessments performed:

1. Assessment for adverse events
2. Laboratory assessment for:
    a. Biochemistry
    b. Fasting metabolic assessment
    c. HIV Viral load and CD4+ T-cell count (and percentage)

Patients will be provided with a six (6) month supply of the study medication

12.8 Week 48 visit

Participants will be required to present having fasted overnight for at least 12 hours (no food, caffeine or caloric drinks; free water is encouraged).

Assessments performed:

1. Targeted physical examination and updated history, assessment for new concomitant medications
2. Weight recorded
3. Compliance assessment
    a. Self-assessment questionnaire and VAS
4. Adverse event assessment
5. Laboratory assessments
    a. Biochemistry
    b. Fasting metabolic assessment
    c. HIV Viral load and CD4+ T-cell count (and percentage)
    d. Markers of innate immunity and inflammation
    e. Storage of plasma and PBMCs (*Melbourne participants only) for possible further analysis in the future
6. Calculations

   a. Creatinine clearance
   b. BMI
7. Structural assessments
   a. cIMT
   b. cPWV (*Melbourne participants only)

Patients will be provided with a six (6) month supply of the study medication

12.9 Week 72 visit

Fasting NOT required for this visit

Assessments performed:

1. Assessment for adverse events
2. Laboratory assessment for:
   a. Biochemistry
   b. HIV Viral load and CD4+ T-cell count (and percentage)

Patients will be provided with a six (6) month supply of the study medication

12.10 Week 96 visit

Participants will be required to present to the AH having fasted overnight for at least 12 hours (no food, caffeine or caloric drinks; free water is encouraged).

Assessments performed:

1. Targeted physical examination and updated history, assessment for new concomitant medications
2. Weight recorded
3. Compliance assessment
   a. Self-assessment questionnaire and VAS
4. Adverse event assessment
5. Laboratory assessments
   a. FBE
   b. Biochemistry
   c. Fasting metabolic assessment
   d. hsCRP
   e. HIV Viral load and CD4+ T-cell count (and percentage)
   f. Markers of innate immunity and inflammation
   g. Storage of plasma and PBMCs (*Melbourne participants only) for possible further analysis in the future
6. Calculations
   a. Creatinine clearance
   b. BMI
7. Structural assessments
   a. cIMT
   b. cPWV (*Melbourne participants only)

Patients will be advised to cease study medication. Statin will be prescribed according to phycisian's assessment.

12.11 Unscheduled visits

Unscheduled visits may be initiated by study co-ordinators and doctors, participants or treating physicians. All assessments made during unscheduled visits will be recorded on the CRF.
This visit may involve, but is not limited to, the following assessments; targeted medical review and physical examination, additional laboratory examination for safety reasons. SAE or AE visits may occur as unscheduled visits.

12.1 Withdrawal visit

For participants that fulfil any of the withdrawal criteria above a withdrawal visit is performed if the participant agrees. All assessments made during the withdrawal visit can be recorded on the CRF (unscheduled visit). This visit will include, but is not limited to, a targeted medical review and physical examination, laboratory examination for safety reasons (chemistry and haematology), pregnancy test for women and study drug return. Tests performed can vary according to the judgement of the study physician.

Clinical or biological abnormalities perceived at the withdrawal visit will be followed at an interval decided by the study physician, until they are resolved or baseline values obtained.

Participants that withdraw from the study may be contacted by telephone at study end for vital status, unless they refuse and this is documented.

In Australia: In the event of withdrawal of consent by the participant, the Form for withdrawal of participants is completed.

12.2 Time windows

The baseline visit will occur within four (4) weeks of screening to allow for laboratory assessments to be completed and FRS to be calculated confirming eligibility
Study visits at weeks 12 and 24 have a visit window of +/- 14 days (to allow for scheduling of structural assessments and subject convenience). Study visits at weeks 48, 72 and 96 have a visit window of +/- 6 weeks.

13 Adverse Events

An AE is defined as follows:
Any untoward medical occurrence in a clinical investigation subject administered a medicinal product and which does not necessarily have a causal relationship with this treatment. An AE can therefore be any unfavourable and unintended sign, symptom, or disease temporally associated with the use of a medicinal product, whether or not considered related to the medicinal product.
Pre-existing or recurrent conditions that occur during the study should not be considered as AEs unless they change in frequency or severity.
All AEs that occur from the time the subject consents to participate in the study and throughout the duration of the study shall be recorded as an AE in the individuals CRF.
At the final study visit (week 96) any ongoing adverse events deemed related to study drug will be followed up for a minimum of 30 days and until resolution.

In case a treatment interruption is needed during the treatment period in the event of a suspected toxicity, the subject will not automatically be withdrawn from the trial, as long as treatment interruption does not exceed 4 weeks.

AEs and SAEs will be categorised and recorded as per the modified Division of AIDS table for grading the Severity of Adverse Events (see Appendix 22.6). Causal relationship of AEs and SAEs to the trial and the study medication will also be assessed.

14 Serious Adverse Events

A serious adverse event (SAE) is defined as follows:
Any adverse drug experience occurring at any dose that results in any of the following outcomes:

- Death
- Life-threatening situation (subject is at immediate risk of death)
- In-patient hospitalisation or prolongation of existing hospitalisation
- Persistent or significant disability/incapacity
- Congenital anomaly/birth defect in the offspring of a subject who received the study drug
- Other medically significant events that may not be immediately life-threatening or result in death or hospitalization, but based upon appropriate medical and scientific judgement, may jeopardize the subject or may require medical or surgical intervention to prevent one of the outcomes listed above.

14.1 Serious Adverse Event Reporting Requirements

The Principal Investigator and/or the project coordinator (coordinating center for Swiss sites) must be notified immediately (within 24 hrs of awareness of the event) regarding the occurrence of any SAEs.
The Principal Investigator and/or the study monitor (coordinating center for Switzerland) will report any SAE that fulfils the criteria for expedited reporting (unexpected and drug related events) to the appropriate regulatory authorities within the required reporting time frame.
SAEs must also be reported to the approving ethics committee(s) as required by the ethics committee reporting procedures.
SAEs must be reported during a subject's participation in the study (whether receiving study medication or not) or within 30 days of receiving the last dose of study agent, whichever is longer.

Any SAE that is ongoing at the final study visit (week 96) will be followed until resolution or stabilisation (for those events that will not resolve).

For Switzerland: Safety reporting will be performed according to regulatory requirements detailed in the Overview of safety reporting procedures that is published on the Swissethics (Swiss association of Ethics Committees for clinical trials) website: http://www.swissethics.ch/doc/templates/Overview_safety_AGEK_dec11_final.pdf.
The coordinating centre Geneva must be reported to immediately by the study site in case of an SAE or SUSAR. The coordinating centre Geneva will report all drug related events (Adverse Drug Reactions) to Swissmedic in an annual update safety report. All SUSARS/SUSADRs (Suspected, unexpected Serious Adverse Drug Reaction) will be reported

to Swissmedic within 7 days for fatal and/or life threatening ADRs, 15 days for all other reportable ADRs.

15 Data safety and monitoring board

An independent Data safety and monitoring board (DSMB) will be set up to monitor the safety of and efficacy in the participants enrolled in the trial. The DSMB will be chaired by A. Carr. Members will include one cardiologist from Switzerland (Proposition: R Lerch), one methodologist (Proposition: Prof Perneger), and one statistician from Australia (Proposition: T Spelman).

Data will be sent to the DSMB every 24 weeks. A summary of SAEs, grade 3/4 AEs and laboratory toxicities, and AEs leading to discontinuation will be provided on a monthly basis.

There will be a single, un-blinded, interim safety and efficacy analysis and review meeting after the last participants has completed 48 weeks of follow-up. The following data will be reviewed:

Safety data:

- Participant recruitment, accrual, retention, and withdrawal information
- Adverse events (AEs) and serious adverse events (SAEs)
- Clinical test results and laboratory values
- Vital signs and physical exam outcomes
- Participant questionnaires
- Study drug dose information
- Any other safety-supporting data requested by the DSMB

Efficacy data

- cIMT data (primary endpoint measure)

Primary outcome measures (cIMT) and the first secondary outcome measure (adverse effects) will be analysed. Based on these analyses, the DSMB will make recommendations regarding the continuation, modification or termination of the trial.

Stopping rules:
The DSMB may recommend stopping of the trial for the following reasons:

- The data show a significantly increased risk of serious adverse effects in one of the treatment groups.
- On the basis of a positive efficacy result only when the data are truly compelling and the risk of a false positive conclusion is acceptably low. The trial will only be stopped for positive efficacy if a strong statistically and clinically significant difference in cIMT is seen between treatment arms.
- If interim data suggest that the product under study is of no benefit (no trend indicating superiority of the product), or that accrual rates are too low and/or that noncompliance is too great to provide adequate power for identifying the specified benefit, the DSMB may consider whether continuation of the study is futile and may recommend termination on this basis.

- It becomes clear that successful completion of the study is not feasible (e.g. there is an excess of patient dropout, missing data, lack of recruitment etc).

The DSMB may recommend modifications to individual stopping rules if additional safety concerns arise during from their continuing reviews of the study data.

16 Trial or site discontinuation

The trial leaders (Principal Investigator in Melbourne and Geneva) reserve the right to discontinue the trial at any time for the following reasons:

- Emergence of safety of other information that could significantly affect the continuation of the trial;
- Failure to meet expected enrolment goals overall or at a particular trial site;
- Violation of GCP or the agreement of the investigator to conduct the trial appropriately.

17 Statistical Analysis

Baseline characteristics will be summarized using median (interquartile range) for quantitative variables and frequency and percentage for qualitative variables.

1. **Analysis of the primary endpoint:**

To study rosuvastatin effect from baseline to week 96 on mean and / or of left and right maximal IMT progression, multi-levels, repeated measures, linear mixed-effects models adjusted for demographics and/or traditional CVD risk factors and centre (Melbourne, Geneva, Lausanne, Berne, Zurich, Basel, St. Gallen, Lugano) will be used. Levels used for the data will be patient and carotid artery locations (CCA, ICA, BIF and ECA) within patients; the repeated measure will be time (baseline, week 48 and week 96).

A comparison across arms (placebo/rosuvastatin) of missing IMT measurements (0, 1, 2 or 3 missing per IMT location) will be performed using a Chi-Square Test with a threshold of 1%.

2. **Analysis of the secondary endpoints:**

To study rosuvastatin effect from baseline to week 48 on mean and / or of left and right maximal IMT progression, multi-levels, repeated measures, linear mixed-effects models adjusted for demographics and/or traditional CVD risk factors and centre will be used. Levels used for the data will be patient and carotid artery locations (CCA, ICA, BIF and ECA) within patients; the repeated measure will be time (baseline and week 48).

Repeated measures linear mixed-effects models adjusted for demographics and/or traditional CVD risk factors and centre will be used to assess the association between the arms (placebo/rosuvastatin) and each of the following parameters at week 0, 12, 24, 48, 72 and 96. We will test the interaction term between the arms and time (Month 0, 6, 12 and 24) to determine whether the rate of progression of the following parameters differed between arms (rosuvastatin versus placebo): Fasting Total Cholesterol, low-density lipoprotein (LDL)-cholesterol, high-density lipoprotein (HDL)-cholesterol, triglycerides and glucose.

Biomarkers of inflammatory process (sCD14, sCD163, neopterin, S-VCAM-1, adiponectin, CCL2, inflammatory (CD16+) monocyte expression of CD38, CX3CR1 and CD11b) will be

analysed using the same kind of regression with the same adjustments as described above including (LDL)-cholesterol and (HDL)-cholesterol.

The rate of adverse effects (symptomatic and biochemical) from the safety report will be summarized using frequency and percentage.

All efficacy analyses will compare the randomised treatment groups on an intention to treat basis regardless of treatments received during the study, including all patients with data at randomisation and at least one follow-up visit. Primary endpoint analyses will use a last value-carried forward approach for any patients permanently lost to follow-up. Secondary endpoints analyses will only include available data.

Statistical analysis will be performed using STATA Release 12.0 or updated version (Stata Statistical Software: Release 12.0, Stata Corporation, and College Station, USA).

We plan to recruit 102 patients. Drop outs will not be replaced unless the number surpasses the attrition rate of 15%.

An interim analysis will be performed at 48 weeks. The final analysis at 96 weeks will be conducted when all patients will have completed the follow-up visits or have been permanently lost to follow-up, and the study database is signed off as checked and complete.

18 Insurance and Finances

Insurance for the Melbourne site is set up by AH and applies only to the one site.
Insurance for Swiss sites is set up by the University Hospitals of Geneva (HUG) to cover the damages that may occur within this trial. The insurance applies to all Swiss participating study sites.

Swiss sites: Costs for the local laboratory tests (haematology, biochemistry, virology) that are not included in the routine HIV patient care will be covered by the patient care payments made to the sites by the leading site, Geneva.

19 Quality Control and quality assurance

19.1 Source documents

Considered source documents are the patient's medical records including, but not limited to written electronic, magnetic and optical records and scans, x-rays, IMT images and electrocardiograms.

The following data will be considered source data:

- CRF: Compliance assessment, physical examination including measurements, smoking status, self-reported pregnancy or breast-feeding status
- Study medication distribution and return details.

19.2 Retention of essential documents

Essential documents as defined by ICH GCP include the signed protocol and any amendment(s), copies of the completed CRFs, signed Informed Consent Forms from all subjects who consented, hospital records, diary cards and other source documents, IRB/IEC

approvals and all related correspondence including approved documents, drug accountability records, trial correspondence and a list of the subject's names and addresses.

The Investigator must maintain all essential study documentation, and take measures to prevent accidental or premature destruction of these documents. The Investigator must retain the study documentation until at least ten years after completion or discontinuation of the study. After that period of time, the documents may be destroyed according local regulations.

19.3 Data protection

Intima carotid ultrasound images will be coded with the subject's ID numbers and transferred for analysis to the cIMT Core Facility, Department of Medicine, **Montreal** Heart Institute, Université de Montréal, **Montreal**, Quebec, Canada **Responsible**: Pr Jean-Claude Tardif. Transfer of this data will be performed strictly anonymously (without personal identifiers), maintaining confidentiality and in line with both the Australian Privacy Law and the Swiss Federal Law on data protection that correspond to applicable laws of the province of Quebec, Canada.

Plasma samples will be coded with the subject's ID number and stored at the Burnet Institute 85 Commercial Rd, Melbourne, Victoria 3004 Australia or at the "sérothèque" (biobank) HUG in Switzerland. Swiss sites will ship the plasma samples to the central biobank ("sérothèque") of the HUG, 4, rue Gabrielle-Perret-Gentil 4, Geneva University Hospitals, Switzerland.

Samples may need to be transferred from Melbourne to Geneva or vice versa for analysis purposes. Shipment of plasma samples between the AH between AH (Burnet Institute, 85 Commercial Rd, Melbourne, Victoria 3004 Australia) and the HUG (Cardiology Laboratory, Hôpitaux Universitaires de Genève, Rue Gabrielle-Perret-Gentil 4, 1211 Geneva, Switzerland) for storage and testing of inflammatory markers will be performed strictly anonymously and in compliance with the Swiss Federal Law on data protection, which corresponds to applicable privacy laws of Australia and the state of Victoria, Melbourne.

19.4 Monitoring, audits and inspections

Independent monitoring of the Swiss sites will be performed to ensure the strict implementation of the protocol and guidelines as well as to check consistency between the source data and the CRF in at least 50 percent of the number of enrolled subjects.

In case of audits or inspections by regulatory authorities or the ethics committee, the investigator will provide direct access to the original data, study documents and the sites facilities as well as to the site's personnel involved directly or indirectly in the trial.

20 Publications and presentations

The final data will be presented at one or more scientific meetings. No patient data will be presented that could permit identification of any individual study participant. Publication of data derived from this protocol will be supervised by the Principal Investigator in Melbourne and Geneva in conjunction with all study investigators. No other publication will be made before the primary manuscript has been agreed upon and accepted for publication and without prior approval of the principal investigator in Melbourne.

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22 Appendix

22.1 Case Record Forms

22.1.1 Screening Visit

Screening Visit – Rosuvastatin Trial		
Screening Number		
Date	_____/_____/_____	
Informed Consent Signed	☐ **Yes** ☐ **No**	
Age (years – round number)		
Gender	☐ **Male** ☐ **Female**	
Ethnicity	☐ **Caucasian**	
	☐ **Asian**	
	☐ **African**	
	☐ **Aboriginal/Torres Strait Islander**	
Date first diagnosed with HIV	_____/_____/_____	
Prior AIDS defining illnesses	☐ **Yes** ☐ **No**	
List any previous AIDS defining illness	**1.**	
	2.	
	3.	
	4.	
	5.	
	6.	
	7.	
Currently taking antiretrovirals	☐ **Yes** ☐ **No**	
Change in antiretroviral in last six (6)	☐ **Yes** ☐ **No**	
Total cumulative years on Indinavir		
Total cumulative years on lopinavir		
HIV Viral load been <200 copies/ml for	☐ **Yes** ☐ **No**	
CD4+ T-cell Nadir		
List all past medical history (Tick box if currently active/being treated)	**1.**	☐
	2.	☐
	3.	☐
	4.	☐
	5.	☐
	6.	☐
	7.	☐
	8.	☐
	9.	☐

	10.	☐
	11.	☐
	12.	☐
Specifically ever diagnosed with:		
a. Coronary Heart Disease/AMI	☐ **Yes** ☐ **No**	
b. Angina	☐ **Yes** ☐ **No**	
c. Diabetes	☐ **Yes** ☐ **No**	
d. Stroke	☐ **Yes** ☐ **No**	
e. Transient Ischaemic attack	☐ **Yes** ☐ **No**	
f. Peripheral vascular disease	☐ **Yes** ☐ **No**	
g. Hypertension	☐ **Yes** ☐ **No**	
h. Hypercholesterolemia	☐ **Yes** ☐ **No**	
i. Familial Hypercholesterolemia	☐ **Yes** ☐ **No**	
j. Myopathy	☐ **Yes** ☐ **No**	
Exposure to the following drugs in last		
a. Statins	☐ **Yes** ☐ **No**	
b. Ezetimibe	☐ **Yes** ☐ **No**	
c. Fibrates	☐ **Yes** ☐ **No**	
d. Niacin	☐ **Yes** ☐ **No**	
e. Anti-hypertensives	☐ **Yes** ☐ **No**	
f. Anti-platelets	☐ **Yes** ☐ **No**	
Pregnant?	☐ **Yes** ☐ **No**	
Breast Feeding?	☐ **Yes** ☐ **No**	
Smoking status	☐ **Never Smoked**	
	☐ **Ex-smoker**	
	☐ **Current smoker**	
IF ex-smoker:		
Time since quitting		
Estimated quantity/day when was smoking		
Duration of smoking history (years)		
IF current smoker		
Estimated quantity/day		
Duration of smoking history (years)		
Family history of heart disease	☐ **Yes** ☐ **No**	
Age of Diagnosis in male 1st degree relative		
Age of Diagnosis in female 1st degree		

Current Antiretroviral Medications			
Trade Name	**Generic Name**	**Daily Dose**	**Start Date**
1.			
2.			
3.			
4.			
5.			
6.			
Concomitant Medications / Supplements			
Trade Name	**Generic Name**	**Daily Dose**	**Start Date**
1.			
2.			
3.			
4.			
5.			
6.			
7.			
8.			
9.			
10.			
11.			
12.			
13.			
14.			
15.			
16.			

Medication Allergies	
Name of Medication	**Description of allergy**
1.	
2.	
3.	
4.	
5.	

Examination	
Height (m)	
Weight (kg)	
Waist circumference (cm)	
Peripheral pulses	☐ **present** ☐ **absent**
Systolic Blood Pressure	
Diastolic Blood Pressure	
Physical examination (Document any relevant abnormalities)	
Date ECG performed	
Date cIMT performed	
Date cPWV performed	
Date bloods taken	
Once Results available:	
Creatinine clearance	
Framingham Risk score	
Is patient eligible for enrolment	☐ **Yes** ☐ **No**
If No, please document why	
If yes, Randomisation number	

Inclusion /Exclusion Checklist

INCLUSION CRITERIA			
Signed consent form		☐ **YES**	☐ **NO**
Age ≥ 30 years		☐ **YES**	☐ **NO**
Framingham Risk Score of 10-15% [FRS =_____]		☐ **YES**	☐ **NO**
HIV positive		☐ **YES**	☐ **NO**
Stable cART regimen for ≥ 6 months		☐ **YES**	☐ **NO**
HIV viral load <200copies/ml for ≥ 6 months		☐ **YES**	☐ **NO**
EXCLUSION CRITERIA			
Coronary heart disease (CHD), stroke or PVD		☐ **YES**	☐ **NO**
Family history of CHD < 55 in a male <u>first</u> degree relative		☐ **YES**	☐ **NO**
Family history of CHD <65 in a female <u>first</u> degree relative		☐ **YES**	☐ **NO**
Type 2 Diabetes		☐ **YES**	☐ **NO**
Familial hypercholesterolaemia		☐ **YES**	☐ **NO**
Aboriginal or Torres Strait Islander people with LDL-C >2.5 mmol/L		☐ **YES**	☐ **NO**
Blood pressure ≥ 180/110		☐ **YES**	☐ **NO**
HDL-C < 1 mmol/L and total cholesterol > 6.5 mmol/L		☐ **YES**	☐ **NO**
Documented history of:			
Ischemic stroke or transient ischemic attack (TIA)		☐ **YES**	☐ **NO**
Peripheral arterial disease (regardless of severity)		☐ **YES**	☐ **NO**
Congestive heart failure		☐ **YES**	☐ **NO**
Coronary artery disease or ECG findings consistent with prior MI		☐ **YES**	☐ **NO**
Carotid artery stenosis or >50% occlusion of carotid artery known previously or discovered during screening procedures		☐ **YES**	☐ **NO**
Total cholesterol >7.5 mmol/L		☐ **YES**	☐ **NO**

Triglyceride level > 4 mmol/L		☐ **YES**	☐ **NO**
HDL-c <1mmol/l and total cholesterol >6.5mmol/l		☐ **YES**	☐ **NO**
Current or prior (last 6 months) statin therapy		☐ **YES**	☐ **NO**
Current or prior (last 6 months) use of ezetimibe		☐ **YES**	☐ **NO**
Current or prior (last 6 months) use of fibrates or niacin		☐ **YES**	☐ **NO**
Pregnancy or lactation		☐ **YES**	☐ **NO**
Hypersensitivity to statins		☐ **YES**	☐ **NO**
Known myopathy or baseline CK > 3x ULN		☐ **YES**	☐ **NO**
Contraindicated concurrent medication (to statin use)		☐ **YES**	☐ **NO**
Current cyclosporine, fusidic acid or oral corticosteroid use		☐ **YES**	☐ **NO**
Concomitant antiplatelet drug		☐ **YES**	☐ **NO**
Unable to complete study procedures (i.e. attendance at AH for cIMT and cPWV testing or cIMT images not accepted for analysis despite redo examination)		☐ **YES**	☐ **NO**
Conocmitant renal or hepatic disease, defind as the presence of the following:		☐ **YES**	☐ **NO**
Creatinine clearance <30 ml/min [CCL = _____]		☐ **YES**	☐ **NO**
Transaminases (ALT, AST) >3x the upper limit of normal		☐ **YES**	☐ **NO**
Acute hepatic failure		☐ **YES**	☐ **NO**
Compensated cirrhosis Child Class B or C		☐ **YES**	☐ **NO**

Other active significant disease ☐ **YES** ☐ **NO**

- **Describe**

  _____

Eligible for Trial? ☐ **YES** ☐ **NO**

Completed by: _____

Signed _____ Date / /

22.1.2 Baseline Visit

Study number			
Date of Visit	_____/_____/_____		
Any new medical diagnosis since screening?	☐ **Yes** ☐ **No**		
If yes, list:	**1.**		
	2.		
	3.		
	4.		
Any new medications since last visit?	☐ **Yes** ☐ **No**		
If yes please detail below			
Trade Name	**Generic Name**	**Daily Dose**	**Start Date**
1.			
2.			
3.			
Any medications ceased since last visit? If yes please detail below	☐ **Yes** ☐ **No**		
Trade Name	**Generic Name**	**Daily Dose**	**Stop Date**
1.			
2.			
3.			
Smoking status	☐ **Non-smoker**		
	☐ **Ex- Smoker**		
	☐ **Current smoker**		
Has an adverse event occurred?	☐ **Yes** ☐ **No**		
If yes please complete adverse event			
Any new abnormalities on	☐ **Yes** ☐ **No**		
If yes list:	**1.**		
	2.		
	3.		
Weight (kg)			
Blood Pressure			
Provided with 3/12 supply of	☐ **Yes** ☐ **No**		
Bloods taken?	☐ **Yes** ☐ **No**		

Completed by: _____Signed _____

22.1.3 Week 12 Visit

Study number			
Date of Visit	_____/_____/_____		
Any new medical diagnosis since screening? **If yes, list:**	☐ **Yes** ☐ **No**		
	1.		
	2.		
	3.		
	4.		
Any new medications since last visit? **If yes please detail below**	☐ **Yes** ☐ **No**		
Trade Name	**Generic Name**	**Daily Dose**	**Start Date**
1.			
2.			
3.			
Any medications ceased since last visit? If yes please detail below	☐ **Yes** ☐ **No**		
Trade Name	**Generic Name**	**Daily Dose**	**Stop Date**
1.			
2.			
3.			
Smoking status	☐ **Non-smoker**		
	☐ **Ex- Smoker**		
	☐ **Current smoker**		
Has an adverse event occurred?	☐ **Yes** ☐ **No**		
Myopathic symptoms	☐ **Yes** ☐ **No**		
Gastrointestinal disturbance	☐ **Yes** ☐ **No**		
Jaundice	☐ **Yes** ☐ **No**		
If yes please complete adverse event			
Any new abnormalities on	☐ **Yes** ☐ **No**		
If yes list:	**1.**		
	2.		
	3.		
Weight (kg)			
Blood Pressure			
Bloods taken?	☐ **Yes** ☐ **No**		

Completed by: _____Signed _____

22.1.4 Week 24 Visit

Study number	
Date of Visit	_____/_____/_____
Any new medical diagnosis since screening?	☐ **Yes** ☐ **No**
If yes, list:	**1.**
	2.
	3.
	4.
Any new medications since last visit?	☐ **Yes** ☐ **No**
If yes please detail below	

Trade Name	Generic Name	Daily Dose	Start Date
1.			
2.			
3.			

Any medications ceased since last visit? If yes please detail below	☐ **Yes** ☐ **No**

Trade Name	Generic Name	Daily Dose	Stop Date
1.			
2.			
3.			

Smoking status	☐ **Non-smoker**
	☐ **Ex- Smoker**
	☐ **Current smoker**
Has an adverse event occurred?	☐ **Yes** ☐ **No**
Myopathic symptoms	☐ **Yes** ☐ **No**
Gastrointestinal disturbance	☐ **Yes** ☐ **No**
Jaundice	☐ **Yes** ☐ **No**
If yes please complete adverse event	
Any new abnormalities on	☐ **Yes** ☐ **No**
If yes list:	**1.**
	2.
	3.
Weight (kg)	
Blood Pressure	
Bloods taken?	☐ **Yes** ☐ **No**

Completed by: _____Signed _____

22.1.5 Week 48 Visit

Study number	
Date of Visit	_____/_____/_____
Any new medical diagnosis since screening?	☐ **Yes** ☐ **No**
If yes, list:	**1.**
	2.
	3.
	4.
Any new medications since last visit?	☐ **Yes** ☐ **No**
If yes please detail below	

Trade Name	Generic Name	Daily Dose	Start Date
1.			
2.			
3.			

Any medications ceased since last visit? If yes please detail below	☐ **Yes** ☐ **No**

Trade Name	Generic Name	Daily Dose	Stop Date
1.			
2.			
3.			

Smoking status	☐ **Non-smoker**
	☐ **Ex- Smoker**
	☐ **Current smoker**
Has an adverse event occurred?	☐ **Yes** ☐ **No**
Myopathic symptoms	☐ **Yes** ☐ **No**
Gastrointestinal disturbance	☐ **Yes** ☐ **No**
Jaundice	☐ **Yes** ☐ **No**
If yes please complete adverse event	
Any new abnormalities on	☐ **Yes** ☐ **No**
If yes list:	**1.**
	2.
	3.
Weight (kg)	
Blood Pressure	
Compliance assessment performed	☐ **Yes** ☐ **No**
Bloods taken?	
Date cIMT/PWV performed /booked	

Completed by: _____Signed _____

Compliance Assessment Week 48 study Visit

Study Number_____
Date _____/_____/_____

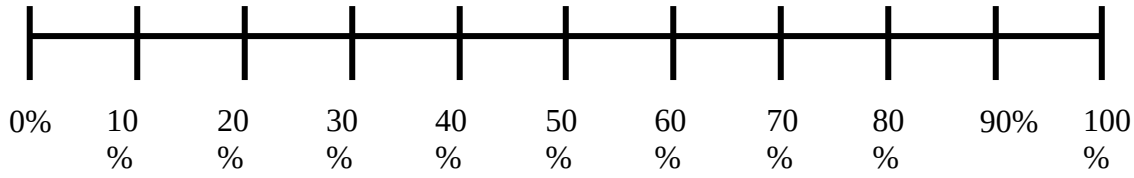
We understand that many people on medications find it very difficult to take them regularly, and often miss doses. It is important for us to know how many doses of the study medication you've missed.

<u>This questionnaire is completely confidential</u>. Your answers will not be shown to your doctor or others involved in your care

How many doses (tablets) have you missed in the last **seven (7)** days?	
How many doses (tablets) have you missed in the last **twenty-eight (28)** days?	

Put an X on the line below at the point showing ***<u>your best guess</u>*** about how much of the study medication you have taken ***during the past 28 days.***

For example, 0% means you haven't taken any dose of the medication above, 50% means you have taken half of the prescribed doses of the medication above and 100% means you have taken every single dose of the medication above



22.1.6 Week 72 Visit

Study number	
Date of Visit	_____/_____/_____
Any new medical diagnosis since screening?	☐ **Yes** ☐ **No**
If yes, list:	**1.**
	2.
	3.
	4.
Any new medications since last visit?	☐ **Yes** ☐ **No**
If yes please detail below	

Trade Name	Generic Name	Daily Dose	Start Date
1.			
2.			
3.			

Any medications ceased since last visit? If yes please detail below	☐ **Yes** ☐ **No**

Trade Name	Generic Name	Daily Dose	Stop Date
1.			
2.			
3.			

Smoking status	☐ **Non-smoker**
	☐ **Ex- Smoker**
	☐ **Current smoker**
Has an adverse event occurred?	☐ **Yes** ☐ **No**
Myopathic symptoms	☐ **Yes** ☐ **No**
Gastrointestinal disturbance	☐ **Yes** ☐ **No**
Jaundice	☐ **Yes** ☐ **No**
If yes please complete adverse event	
Any new abnormalities on	☐ **Yes** ☐ **No**
If yes list:	**1.**
	2.
	3.
Weight (kg)	
Blood Pressure	
Bloods taken?	☐ **Yes** ☐ **No**

Completed by: _____Signed _____

22.1.7 Week 96 Visit

Study number	
Date of Visit	_____/_____/_____
Any new medical diagnosis since screening?	☐ **Yes** ☐ **No**
If yes, list:	**1.**
	2.
	3.
	4.
Any new medications since last visit?	☐ **Yes** ☐ **No**
If yes please detail below	

Trade Name	Generic Name	Daily Dose	Start Date
1.			
2.			
3.			

Any medications ceased since last visit? If yes please detail below	☐ **Yes** ☐ **No**

Trade Name	Generic Name	Daily Dose	Stop Date
1.			
2.			
3.			

Smoking status (circle whichever is appropriate)	**Non-smoker**
	Ex- Smoker
	Current smoker
Has an adverse event occurred?	☐ **Yes** ☐ **No**
Myopathic symptoms	☐ **Yes** ☐ **No**
Gastrointestinal disturbance	☐ **Yes** ☐ **No**
Jaundice	☐ **Yes** ☐ **No**
If yes please complete adverse event	
Any new abnormalities on	☐ **Yes** ☐ **No**
If yes list:	**1.**
	2.
	3.
Weight (kg)	
Blood Pressure	
Compliance assessment performed	☐ **Yes** ☐ **No**
Bloods taken?	
Date cIMT/PWV performed /booked	

Completed by: _____Signed _____

Compliance Assessment Week 96 study Visit

Study Number _____
Date_____/_____/_____

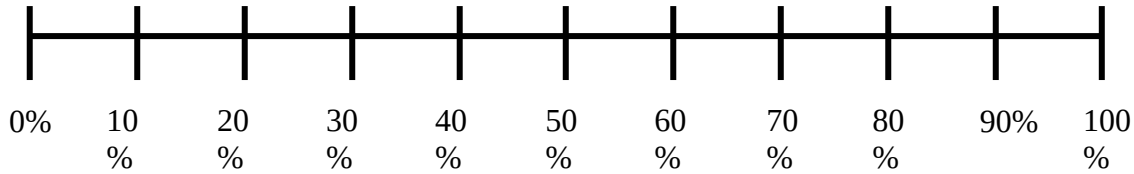
We understand that many people on medications find it very difficult to take them regularly, and often miss doses. It is important for us to know how many doses of the study medication you've missed.

<u>This questionnaire is completely confidential</u>. Your answers will not be shown to your doctor or others involved in your care

How many doses (tablets) have you missed in the last **seven (7)** days?	
How many doses (tablets) have you missed in the last **twenty-eight (28)** days?	

Put an X on the line below at the point showing ***<u>your best guess</u>*** about how much of the study medication you have taken ***during the past 28 days.***

For example, 0% means you haven't taken any dose of the medication above, 50% means you have taken half of the prescribed doses of the medication above and 100% means you have taken every single dose of the medication above



22.1.8 Unscheduled Visits

Study Number	
Date of Visit	**_____/_____/_____ Time: ____:_____hr**
Person initiating unscheduled visit	
Reason for unscheduled visit	
Adverse Event Assessment	
Onset date of Adverse Event	
Time of Onset (if Known)	
Description of Adverse event:	
Adverse Event Severity Grade (refer to Division of AIDS Table for grading of severity)	☐ **Mild (Grade 1)**
	☐ **Moderate (Grade 2)**
	☐ **Severe (grade 3-4)**
Is this a Serious Adverse Event	☐ **Yes** ☐ **No** **(If YES, please fill in the**
Treatment for AE required? (If yes describe in detail)	☐ **Yes** ☐ **No**
Related to the study drug?	☐ **Confirmed**
	☐ **Probable**
	☐ **Possible**
	☐ **Excluded**
	☐ **Non -assessable**
Study medication stopped	☐ **Yes** ☐ **No**
Withdrawn from the study	☐ **Yes** ☐ **No**
Outcome of Adverse Event	☐ **Ongoing**
	☐ **Resolved**
	☐ **Unknown**
Date of resolution of adverse event	**_____/_____/_____ (If not ongoing)**
Date subject will be next reviewed	

Completed by: _____Signed _____

22.2 Serious Adverse Event (SAE) Form

Study Number	
Date of Awareness	**_____/_____/_____ TIME: _____:_____h**
Onset Date of Event	**_____/_____/_____ TIME: _____:_____h**
Stop Date of Event	**_____/_____/_____ TIME: _____:_____h**
Type of Report	**☐ Initial ☐ Follow-up ☐ Final**
Description of SAE:	
Category of SAE	**☐ Death Date of Death _____/_____/_____**
	☐ Life Threatening
	☐ Caused or prolonged hospitalization
	☐ Resulted in significant disability or
	☐ Other important medical condition
Related to the study drug?	**☐ Confirmed**
	☐ Probable
	☐ Possible
	☐ Excluded
	☐ Non -assessable
If Adverse Drug reaction please list:	
- **Generic name**	
- **Lot Number**	
- **Dosage**	
- **Route of administration**	
- **Start date**	**_____/_____/_____**
- **Indication**	
Study medication stopped?	**☐ Yes ☐ No**
If yes did the AE resolve after	**☐ Yes ☐ No**
Was the code broken?	**☐ Yes ☐ No**
If YES, what was the allocation?	
Treatment for SAE required? (If yes describe in detail)	**☐ Yes ☐ No**

Completed by: _____Signed _____ Date _____/_____/_____

22.3 Units of measurement and reference ranges

Investigation	Abbreviation	Units	Reference Range
HIV specific tests			
CD4+ T-cell count	-	cells/µL	410 - 1,545
HIV Viral Load	-	copies/ml	< 20
Full Blood Examination (FBE)			
Haemoglobin	Hb	g/L	128 - 175
Total White Cell count	WCC	cells $x10^9$/L	3.9 – 12.70
Lymphocytes	Lymp	cells $x10^9$/L	0.9 – 3.30
Neutrophils	Neut	cells $x10^9$/L	1.9 – 8.0
Platelets	Plt	cells $x10^9$/L	150 - 396
Biochemistry			
Sodium	Na	mmol/L	135 – 143
Potassium	K+	mmol/L	3.5 – 5.0
Chloride	Cl	mmol/L	99 - 107
Bicarbonate	HCO_3	mmol/L	20 - 32
Calcium	Ca	mmol/L	2.14 – 2.50
Phosphate	PO_4	mmol/L	0.6 – 1.30
Urea	Ur	mmol/L	4.0 – 9.0
Creatinine	Cr	µmol/L	60 - 105
Estimated glomerular filtration rate	eGFR	ml/min	> 90
Beta Human chorionic gonadotrophin	β HCG	U/L	< 3
High sensitivity C- reactive protein	hsCRP	mg/L	< 5.0
Creatinine phosphokinase	CPK	U/L	60 - 285
Liver Function Tests (LFT)			
Total Protein	TP	g/L	60 - 80

Albumin	Alb	g/L	33 - 46
Bilirubin	Bil	µmol/L	< 23
Alanine Aminotransferase	ALT	U/L	12-52
Alkaline Phosphatase	ALP	U/L	42 - 125
Gamma- glutamyl transpeptidase	GGT	U/L	< 62
Fasting Metabolic Assessments			
Total Cholesterol	TC	mmol/L	< 5.5
High Density Lipoprotein Cholesterol	HDL-C	mmol/L	> 1.0
Low Density Lipoprotein Cholesterol	LDL-C	mmol/L	< 3.5
Triglycerides	TG	mmol/L	< 2.0
Glucose	-	mmol/L	3.8 – 7.7
Structural / Physical Assessments			
Carotid intima media thickness	cIMT	mm	n/a
Carotid-femoral pulse wave velocity	cPWV	m/s	n/a
Height	-	Meters (m)	n/a
Weight	-	Kilograms (Kg)	n/a
Calculations			
Body Mass Index	BMI	kg/m^2	< 18.5 Underweight 18.5 – 24.9 Healthy 25.0 – 29.9 Overweight 30.0 – 34.9 Obesity I 35.0 – 39.9 Obesity II > 40 Obesity III
Framingham Risk Score	FRS	% 10 year risk	< 10 % Low Risk 10 -15 % Moderate Risk > 15 % High risk
D.A.D. Risk Score	DRS	% 5 year risk	< 1% Low Risk 1 – 5% Moderate Risk 5 – 10% High Risk > 10% Very High Risk
Estimated creatinine clearance	CrCl	ml/min	> 90

22.4 Units of measurement and reference ranges for Swiss sites

Investigation	Abbreviation	Units	Reference Range
HIV specific tests			
CD4+ T-cell count	-	cells/µl	600 – 1'950
HIV Viral Load	-	copies/ml	< 20
Full Blood Examination (FBE)			
Haemoglobin	Hb	g/L	M: 140-180 F: 120-160
Total White Cell count	WCC	G/L	4.0 – 11.0
Lymphocytes	Lymp	G/L	1.00 - 4.50
Neutrophils	Neut	G/L	1.50-8.00
Platelets	Plt	G/L	150-350
Biochemistry			
Sodium	Na	mmol/L	136-144
Potassium	K+	mmol/L	3.6 – 4.6
Chloride	Cl	mmol/L	96 - 107
Bicarbonate	HCO_3	mmol/L	23.0-30.0
Calcium	Ca	mmol/L	2.20– 2.52
Phosphate	PO_4	mmol/L	0.8-1.5
Urea	Ur	mmol/L	2.8-7.1
Creatinine	Cr	µmol/L	M: 62-106 F: 35-88
Estimated glomerular filtration rate	eGFR	ml/min	> 90
Beta Human chorionic gonadotrophin	β HCG	U/L	
Creatinine phosphokinase	CPK	U/L	M: 47-222 F:33-187
Liver Function Tests (LFT)			
Total Protein	TP	g/L	61-79
Albumin	Alb	g/L	35-48

Bilirubin	Bil	µmol/L	6.8-25
Alanine Aminotransferase	ALT	U/L	M: 12 - 50 F: 9 - 42
Alkaline Phosphatase	ALP	U/L	30 - 125
Gamma- glutamyl transpeptidase	GGT	U/L	M: 9 - 40 F: 9 - 35
Fasting Metabolic Assessments			
Total Cholesterol	TC	mmol/L	< 6.5
High Density Lipoprotein Cholesterol	HDL-C	mmol/L	M: >0.90 F: > 1.00
Low Density Lipoprotein Cholesterol	LDL-C	mmol/L	< 4.0
Triglycerides	TG	mmol/L	< 2.00
Glucose	-	mmol/L	4.1 – 6.0

22.5 Patient Informed Consent Form

Participant Information Sheet/Consent Form
Interventional Study - *Adult providing own consent*

The Alfred Hospital

Title	Does Rosuvastatin delay progression of atherosclerosis in people with HIV infection? A multicentre randomized, double blind placebo-controlled trial
Coordinating Principal Investigator/ Principal Investigator	Dr Janine Trevillyan Prof Jennifer Hoy
Associate Investigator(s)	Professor Suzanne Crowe Dr Julian Elliott A. Professor Anthony Jaworowski Dr James Shaw Professor Anthony Dart
Location	The Alfred Hospital

Part 1 What does my participation involve?

1 Introduction

You are invited to take part in this research project. This is because you have human immunodeficiency virus (HIV) infection, are currently on anti-HIV medications and are thought to have a moderate risk of developing heart disease. The research project is testing a new treatment to prevent heart disease in HIV positive people. The new treatment is called Rosuvastatin, a cholesterol lowering medication.

This Participant Information Sheet/Consent Form tells you about the research project. It explains the tests and treatments involved. Knowing what is involved will help you decide if you want to take part in the research.

Please read this information carefully. Ask questions about anything that you don't understand or want to know more about. Before deciding whether or not to take part, you might want to talk about it with a relative, friend or your local doctor.

Participation in this research is voluntary. If you don't wish to take part, you don't have to. You will receive the best possible care whether or not you take part.

If you decide you want to take part in the research project, you will be asked to sign the consent section. By signing it you are telling us that you:
• Understand what you have read
• Consent to take part in the research project

• Consent to have the tests and treatments that are described
• Consent to the use of your personal and health information as described.

You will be given a copy of this Participant Information and Consent Form to keep.

2 What is the purpose of this research?

Since people started taking anti-HIV medications, illness from AIDS has decreased, but other serious diseases like heart disease (heart attacks) and other diseases of blood vessels (such as strokes) have increased. HIV causes inflammation (irritation) inside the body that cannot be felt but can be measured by certain blood tests. Inflammation may contribute to diseases (such as heart attacks) by damaging blood vessels. HIV therapy can partially lower inflammation, however the levels of inflammation in people who have HIV may remain high even when they are on anti-HIV medications compared with those found in people who do not have HIV.

The main goal of this study is to see if taking rosuvastatin (a cholesterol lowering medication that also decreases inflammation) will slow down the development of blood vessel damage (a sign of future heart attacks) in people infected with HIV who are at moderate risk of heart disease and so are not currently eligible for rosuvastatin.

In addition to observing the effects of rosuvastatin on the level of inflammation measured in the blood, this study will see if rosuvastatin is safe for people with HIV who are also taking medication for HIV.

Medications, drugs and devices have to be approved for use by the Australian Federal Government. Rosuvastatin is approved in Australia to treat high cholesterol levels in the blood and to prevent heart attacks in people at high risk or who have already had a heart attack. However it has not been approved for use in patients who are at moderate risk. Therefore, it is an experimental treatment. This means that it must be tested to see if it is an effective therapy to prevent heart disease in people at moderate risk. Rosuvastatin has been able to lower the level of inflammation in certain other diseases but has not been studied for this purpose in people who have HIV.

The results of this research will be used by the study doctor, Dr Janine Trevillyan to obtain a PhD degree.

This research has been initiated by the study doctor, Professor Jennifer Hoy and is funded through Monash University.

3 What does participation in this research involve?

If you choose to participate in this project you will be asked to sign this consent form prior to any study assessments being performed. If you would like an interpreter to be present at any time we will arrange one for you.

You will be participating in a randomised controlled research project. Sometimes we do not know whether a medication is going to prevent a particular condition. To find out we need to compare the treatment to having no treatment at all. We do this by putting people into groups and giving one group the treatment (Rosuvastatin) and one group a placebo. The results from each group are compared to see if one is better. A placebo is a medication with no active ingredients or any medical benefit. It looks like the real thing but is not. To try to make sure the groups are the same, each participant is put into a group by chance (random). You will have a 50/50 (equal) chance of being in either group.

You will need to take one capsule a day which will contain either the placebo or 20mg of rosuvastatin. Some HIV medications (in particular those from the group of drugs known as protease inhibitors) can cause the level of rosuvastatin to rise. If you are on one of these medications you will be given 10mg of rosuvastatin (or placebo) instead.

You will be participating in a double-blind study. This means that neither you nor your study doctor will know which treatment you are receiving. However, in certain circumstances your study doctor can find out which treatment you are receiving.

This research project has been designed to make sure the researchers interpret the results in a fair and appropriate way and avoids study doctors or participants jumping to conclusions.

Evaluations performed during the study

If you decide to take part in the research project you will be asked some questions about your medical history, the medications you take and any risk factors you have that might predispose you to developing heart disease. We will check how well your liver is functioning and your cholesterol levels. This will let us know if you are eligible to take part. Completing the screening visit will take approximately 15- 30 minutes.

The study visits will occur at the same time as your routine HIV visits with your primary care doctor as far as is possible, and will take between 30 – 45 minutes depending on how many tests need to be performed. At the first visit and four times during the study you will be asked not to eat or drink anything (other than your required medications and normal amounts of plain water) for at least 8 hours (preferably 12 hours) before you come in for blood tests.

At the study visits you will be asked about your health and any medicines you have taken. You will be weighed and have your blood pressure checked and will be asked how often you have taken your medications over the few days and weeks prior to the visit.

At each study visit you will have blood tests taken to check for side effects of the medication and to monitor your liver function. Every six months there will also be blood taken to test for signs of inflammation, cholesterol levels, CD4 (T cell) counts and HIV viral loads.

Prior to starting the rosuvastatin or placebo and at 12 months and 24 months, (the end of the study), you will have an ultrasound of your carotid arteries (the large arteries in your neck) to measure the thickness of the artery wall (which allows us to estimate your chance of developing heart disease). This is a painless procedure that takes about 20 minutes. On the same day we will also measure the speed your blood flows to the carotid artery (in your neck) and the femoral artery (at the top of your thigh). This is done with a machine very similar to an ultrasound and is also painless. It takes about 10 minutes. Both of these tests are performed onsite at the Alfred Hospital.

If at any time during the study you develop a side effect from the medication you may need to come in for an extra visit to check on your safety. You will be assessed by the study doctor and advised whether you should stop the study medication and whether you require any other treatment or investigation.

You will be involved in this study for ninety-six (96) weeks, approximately 2 years. The study will run for five years in total and will be monitored by an independent review board.

There are no additional costs associated with participating in this research project, nor will you be paid. All medication, tests and medical care required as part of the research project will be provided to you free of charge.

You will have to pay for your usual medicines (including HIV medications) like you normally would.

4 What do I have to do?

You do not need to change your diet or level of exercise to participate in this study.

You should keep taking your usual medications (including your HIV medications) throughout the study which will be guided by your usual HIV doctor. If you are taking warfarin your INR level will need to be monitored more often than usual when you first start taking the study drug.

You should not start any of the medications listed below while you're in this study because they may increase your chance of developing a side effect.

- Cholesterol lowering medications including niacin, fibrates or 'statins'
- Fusidic acid (an antibiotic)
- Cyclosporine

Please tell the study team if you need to start any new medications so that they can check if it will be safe to take while taking rosuvastatin.

You can still donate blood while in this study if you wish.

People who have had side effects from cholesterol lowering medications before or have significant problems with their liver or muscles cannot take part in this study. If you are pregnant or planning on becoming pregnant in the next two years you cannot take part in this study.

To be part of the study you need to commit to taking the study medication every day.

5 Other relevant information about the research project

102 people will be taking part in the project. Half (51 participants) will receive rosuvastatin (the cholesterol lowering medication) and the other half (51 participants) will receive a placebo capsule. Participants will be recruited into the trial from two sites; here at the Alfred Hospital in Melbourne Australia and also from the University Hospital of Geneva in Switzerland. It is anticipated that 72 participants will be from Melbourne with the remaining 30 participants from Switzerland.

This project is a collaboration between the Infectious Diseases and Cardiology departments of the Alfred Hospital and the Infectious Diseases Department of the University Hospital of Geneva

6 Do I have to take part in this research project?

Participation in any research project is voluntary. If you do not wish to take part, you do not have to. If you decide to take part and later change your mind, you are free to withdraw from the project at any stage.

Your decision whether to take part or not to take part, or to take part and then withdraw, will not affect your routine treatment, your relationship with those treating you or your relationship with the Alfred

7 What are the alternatives to participation?

The use of rosuvastatin in people with normal cholesterol levels who are not at high risk for heart disease is experimental, and there is no standard clinical treatment which is similar or equal to this. Your alternative is to not join the study and continue to receive standard HIV care from your doctor.

8 What are the possible benefits of taking part?

We cannot guarantee or promise that you will receive any benefits from your participation in this research. However the results from this research may help improve the management of people who are infected with HIV.

By participating in this study the health of your arteries and risk for heart problems will be assessed very thoroughly, in some instances this may allow us to detect serious treatable health issues before you have symptoms**.**

9 What are the possible risks and disadvantages of taking part?

Medical treatments often cause side effects. You may have none, some or all of the effects listed below, and they may be mild, moderate or severe. If you have any of these side effects, or are worried about them, talk with your study doctor. Your study doctor will also be looking out for side effects.

There may be side effects that the researchers do not expect or do not know about and that may be serious. Tell your study doctor immediately about any new or unusual symptoms that you get.

Many side effects go away shortly after treatment ends. However, sometimes side effects can be serious, long lasting or permanent. If a severe side effect or reaction occurs, your study doctor may need to stop your treatment. Your study doctor will discuss the best way of managing any side effects with you.

Rosuvastatin is in general a safe medication that has been taken by many patients worldwide. Some side effects that can be caused by rosuvastatin include

- Muscle problems. Rosuvastatin can very occasionally (less than 1 per 1000 patients) cause serious muscle problems that can lead to kidney problems, including kidney failure and rarely, death.
- Liver problems. Rosuvastatin can occasionally cause liver problems that may rarely be serious or cause death. Your study nurse or doctor will do blood tests to check your liver before you start taking rosuvastatin, and while you take it.

Be sure to let your doctor or study nurse know immediately if you have possible signs of one of these problems, including:

- Muscle problems like weakness, tenderness, or pain that happen without a good reason, especially if you also have a fever or feel more tired than usual.
- Nausea and vomiting.

- Passing brown or dark-colored urine.
- Feeling more tired than usual.
- Noticing the skin and whites of your eyes become yellow.
- Having stomach pain.

Other problems that have been caused by rosuvastatin include headaches, rash, severe allergic reaction or swelling, constipation, gas, diarrhea, tendon rupture, dizziness, memory impairment, and depression. All these problems are uncommon to rare (occurring in less than 1 in 100 people who take rosuvastatin).

Having a blood sample taken may cause some discomfort, bruising, minor infection or bleeding. If this happens, it can be easily treated.

If, during the course of the study we uncover a medical condition that you did not know about the study doctor will explain the condition and arrange for you to have any further investigations or treatment that is necessary.

If you develop any condition (such as high cholesterol) which means that you should be taking rosuvastatin you will not be able to continue in the study and will be advised to stop taking the study medication and to take treatment as recommended by your usual doctor.

Study information that is not critical to your health care will not be given to you or others. This means that no one (not you, your family, your GP, your insurance company or your employer) will have access to this information during the study. At the end of the study you and your GP will be provided with a summary of the results of the study and your personal results including cholesterol levels and estimated risk of developing heart disease in the future.

Risks related to conception, pregnancy and breast feeding

Rosuvastatin is unsafe for unborn babies. Because of this, it is important that research project participants are not pregnant or breast-feeding and do not become pregnant during the course of the research project. You must not participate in the research if you are pregnant or trying to become pregnant, or breast-feeding. If you are female and child-bearing is a possibility, you will be required to undergo a pregnancy test prior to commencing the research project. If you are male, you should not father a child or donate sperm for at least one month after the last dose of study medication.

Both male and female participants are strongly advised to use effective contraception during the course of the research and for one month after completion of the research project. You should discuss methods of effective contraception with your study doctor.

If you do become pregnant whilst participating in the research project, you should advise your study doctor immediately. Your study doctor will withdraw you from the research project and advise on further medical attention should this be necessary. You must not continue in the research if you become pregnant.

You should advise your study doctor if you father a child while participating in the research project. Your study doctor will advise on medical attention for your partner should this be necessary.

If you become upset or distressed as a result of your participation in the research, the study doctor will be able to arrange for counselling or other appropriate support. Any counselling or

support will be provided by qualified staff who are not members of the research project team. This counselling will be provided free of charge.

10 What will happen to my test samples?

By signing the consent form you are consenting to the collection of your blood for the research project.

The samples that you provide will not be used for any purpose other than what has been described in this document. Samples that are part of routine care will be tested at the Alfred Hospital and are destroyed as per hospital policy.

If you consent a small sample of blood will be stored for possible use in other research into the causes and prevention of heart disease in HIV and the actions of “statins”. This may include (but is not limited to) testing for newly discovered markers of inflammation or performing special cholesterol studies. These samples would only be used for future research that has been approved by The Alfred Hospital Ethics Committee.

Your stored blood samples and the information collected about you during the study will be assigned a unique identifying code (that is not your name or birth date). This code will mean that results will be able to be re-identified and linked to individual study participants if needed. A small portion of your sample may be sent to Geneva for specialised testing. This sample will not have your name or date of birth on it and will be labelled only with the study code described above. There will be no need to take any extra blood samples and only samples from participants who have consented to having blood stored for future research will be included. If this does occur any blood remaining after testing is complete in Geneva will be destroyed.

The images taken with the ultrasound machine of the arteries in your neck will be stored on a CD and sent to Montreal, Canada where a specialist will review them, This CD will be labelled with the study code assigned to you and, as with your blood samples, will not contain your name or date of birth. At the completion of the trial the CD will be destroyed and your images will only be retained on file at the Alfred Hospital.

11 What if new information arises during this research project?

Sometimes during the course of a research project, new information becomes available about the treatment that is being studied. If this happens, your study doctor will tell you about it and discuss with you whether you want to continue in the research project. If you decide to withdraw, your study doctor will make arrangements for your regular health care to continue. If you decide to continue in the research project you will be asked to sign an updated consent form.

Also, on receiving new information, your study doctor might consider it to be in your best interests to withdraw you from the research project. If this happens, he/ she will explain the reasons and arrange for your regular health care to continue.

12 Can I have other treatments during this research project?

It is important to tell your study doctor and the study staff about any treatments or medications you may be taking, including over-the-counter medications, vitamins or herbal remedies, acupuncture or other alternative treatments. You should also tell your study doctor about any changes to these during your participation in the research project.

13 What if I withdraw from this research project?

If you decide to withdraw from the project, please notify a member of the research team before you withdraw. This notice will allow that person or the research supervisor to discuss any health risks or special requirements linked to withdrawing.

If you do withdraw your consent during the research project, the study doctor and relevant study staff will not collect additional personal information from you, although personal information already collected will be retained to ensure that the results of the research project can be measured properly and to comply with law. You should be aware that data collected up to the time you withdraw will form part of the research project results, unless you specifically request otherwise.

14 Could this research project be stopped unexpectedly?

It is not anticipated that this project will be stopped unexpectedly. However, this research project may be stopped early if unacceptable side effects were detected.

15 What happens when the research project ends?

After you have completed all the study visits you will stop taking the study medication.

You and your GP will be sent a letter summarising your personal results including cholesterol levels and estimated risk of developing heart disease in the future. Once the whole study is finished you will receive a short report summarising the main findings of the study.

Part 2 How is the research project being conducted?

16 What will happen to information about me?

By signing the consent form you consent to the study doctor and relevant research staff collecting and using personal information about you for the research project. Any information obtained in connection with this research project that can identify you will remain confidential. Information and samples will not be labelled with your name but will instead be assigned a code that will enable them to be re-identified and linked to individual study participants. This will be essential to perform the required study analyses and to monitor for potential side effects. Your information will only be used for the purpose of this research project and it will only be disclosed with your permission, except as required by law.

Information about you may be obtained from your health records held at The Alfred Hospital for the purpose of this research. By signing the consent form you agree to the study team accessing health records if they are relevant to your participation in this research project.

All research records will be kept in locked files located within locked rooms to which only study staff have access. Computer files will be stored on secure password protected computers

Only study staff, members of The Alfred Hospital Ethics Committee and regulatory authorities will have access to study data and participant information. The data and samples will not be used for commercial purposes. Written information will be retained indefinitely according to Alfred Health policy unless you ask for data to be destroyed.

It is anticipated that the results of this research project will be published and presented in a variety of forums. In any publication or presentation, information will be provided in such a way that you cannot be identified, except with your permission.

Information about your participation in this research project may be recorded in your health records.

In accordance with relevant Australian and Victorian privacy and other relevant laws, you have the right to request access to your information collected and stored by the research team. You also have the right to request that any information with which you disagree be corrected. Please contact the study team member named at the end of this document if you would like to access your information.

17 Complaints and compensation

If you suffer any injuries or complications as a result of this research project, you should contact the study team as soon as possible and you will be assisted with arranging appropriate medical treatment. If you are eligible for Medicare, you can receive any medical treatment required to treat the injury or complication, free of charge, as a public patient in any Australian public hospital.

18 Who is organising and funding the research?

This research project is being conducted by Professor Jennifer Hoy

You will not benefit financially from your involvement in this research project even if, for example, your samples (or knowledge acquired from analysis of your samples) prove to be of commercial value to The Alfred Hospital.

No member of the research team will receive a personal financial benefit from your involvement in this research project (other than their ordinary wages).

19 Who has reviewed the research project?

All research in Australia involving humans is reviewed by an independent group of people called a Human Research Ethics Committee (HREC). The ethical aspects of this research project have been approved by the HREC of The Alfred Hospital Ethics Committee and the ethics committee the University Hospital of Geneva

This project will be carried out according to the *National Statement on Ethical Conduct in Human Research (2007)*. This statement has been developed to protect the interests of people who agree to participate in human research studies.

20 Further information and who to contact

The person you may need to contact will depend on the nature of your query.

If you want any further information concerning this project or if you have any medical problems which may be related to your involvement in the project (for example, any side effects), you can contact the principal study doctor on 90762000 or any of the following people:

Clinical contact person

Name	Dr Janine Trevillyan
Position	Study co-ordinator and principal researcher
Telephone	03 90762000 via Alfred Switchboard (24 hours a day)
Email	j.trevillyan@alfred.org.au

Name	Sally Price
Position	Study co-ordinator
Telephone	03 9076 6908
Email	clinresearch@alfred.org.au

If you have any complaints about any aspect of the project, the way it is being conducted or any questions about being a research participant in general, then you may contact:

Complaints contact person

Name	Ms Rowan Frew
Position	Ethics Manager
Telephone	90763848
Email	r.frew@alfred.org.au

Consent Form

Title	Does Rosuvastatin delay progression of atherosclerosis in people with HIV infection? A multicentre randomized, double blind placebo-controlled trial
Coordinating Principal Investigator/ Principal Investigator	Dr Janine Trevillyan Prof Jennifer Hoy
Associate Investigator(s)	Professor Suzanne Crowe Dr Julian Elliott A. Professor Anthony Jaworowski Dr James Shaw Professor Anthony Dart
Location	The Alfred Hospital

Declaration by Participant

I have read the Participant Information Sheet or someone has read it to me in a language that I understand.

I understand the purposes, procedures and risks of the research described in the project.

I give permission for my doctors, other health professionals, hospitals or laboratories outside this hospital to release information to The Alfred Hospital concerning my disease and treatment for the purposes of this project. I understand that such information will remain confidential.

I have had an opportunity to ask questions and I am satisfied with the answers I have received.

I freely agree to participate in this research project as described and understand that I am free to withdraw at any time during the study without affecting my future health care.

I understand that I will be given a signed copy of this document to keep.

Name of Participant (please _____

Signature _____ Date _____

Name of Witness* to Participant's Signature (please print) _____

Signature _____ Date _____

* Witness is not to be the investigator, a member of the study team or their delegate. In the event that an interpreter is used, the interpreter may not act as a witness to the consent process. Witness must be 18 years or older.

Declaration by Study Doctor/Senior Researcher†

I have given a verbal explanation of the research project, its procedures and risks and I believe that the participant has understood that explanation.

Name of Study Doctor/ Senior Researcher† (please print) _____

Signature _____ Date _____

† A senior member of the research team must provide the explanation of, and information concerning, the research project.

Note: All parties signing the consent section must date their own signature.

Consent for storage and use of blood samples

Please indicate your choice by checking (ticking) ONE of the options below:

☐ I consent to the use of my blood samples for tests related to this research project ***and*** for a sample to be stored for future research as described in the relevant section of the Participant information sheet

OR

☐ I consent to the use of blood samples taken from me for use in this project as described in the relevant section of the Participant Information Sheet but ***do not*** authorize their future use in any other research.

Name of Participant (please _____

Signature _____ Date _____

Name of Witness* to Participant's Signature (please print) _____

Signature _____ Date _____

* Witness is not to be the investigator, a member of the study team or their delegate. In the event that an interpreter is used, the interpreter may not act as a witness to the consent process. Witness must be 18 years or older.

Name of Study Doctor/ Senior Researcher† (please print) _____

Signature _____ Date _____

† A senior member of the research team must provide the explanation of and information concerning the research project.
Note: All parties signing the consent section must date their own signature

Form for Withdrawal of Participation - *Adult providing own consent*

Title	Does Rosuvastatin delay progression of atherosclerosis in people with HIV infection? A multicentre randomized, double blind placebo-controlled trial
Coordinating Principal Investigator/ Principal Investigator	Dr Janine Trevillyan Prof Jennifer Hoy
Associate Investigator(s)	Professor Suzanne Crowe Dr Julian Elliott A. Professor Anthony Jaworowski Dr James Shaw Professor Anthony Dart
Location	The Alfred Hospital

Declaration by Participant

I wish to withdraw from participation in the above research project and understand that such withdrawal will not affect my routine treatment, my relationship with those treating me or my relationship with The Alfred Hospital

Name of Participant (please _____

Signature _____ Date _____

In the event that the participant's decision to withdraw is communicated verbally, the Study Doctor/Senior Researcher will need to provide a description of the circumstances below.

Declaration by Study Doctor/Senior Researcher†

I have given a verbal explanation of the implications of withdrawal from the research project and I believe that the participant has understood that explanation.

Name of Study Doctor/ Senior Researcher† (please print) _____

Signature _____ Date _____

† A senior member of the research team must provide the explanation of and information concerning withdrawal from the research project. Note: All parties signing the consent section must date their own signature.

22.6 Patient Informed Consent Form (Geneva)

HUG
Hôpitaux Universitaires de Genève

Consultation des maladies infectieuses / Unité VIH
Version 2 Genève du 28/11/2013

Information à l'intention des participants de l'étude

Titre anglais: « Does Rosuvastatin delay progression of atherosclerosis in people with HIV infection at moderate cardiovascular risk? A multicentre, randomized, double blind placebo-controlled trial"

Titre français : « La rosuvastatine retarde-t-elle la progression de l'athérosclérose chez les personnes infectées par le VIH avec un risque cardiovasculaire modéré ? Un essai multicentrique, randomisé, en double aveugle, contrôlé contre placebo.

Représentant du promoteur en Suisse et investigateur principale Geneve :
Dre A. Calmy
Consultation des maladies infectieuses, Hôpitaux Universitaires de Genève, 4, rue Gabrielle-Perret-Gentil, 1211 Genève 14, Suisse, Tel : 0041 22 372 98 12

Partenaire et investigateur principal en Australie :
Prof Jennifer Hoy
Director, HIV Medicine, Infectious Diseases Unit, The Alfred Hospital, 55 Commercial Road, Melbourne Victoria 3004, Australie

Résumé

Que teste-t-on ? La rosuvastatine (Crestor®) est un médicament qui diminue le taux de cholestérol dans le sang et a également un effet sur l'inflammation. Cette étude a pour but de mesurer l'effet de la rosuvastatine sur la progression de l'athérosclérose, sur les paramètres inflammatoires mesurés dans le sang et d'évaluer la tolérance de la rosuvastatine chez les personnes vivant avec le VIH traitées par des antirétroviraux (médicaments anti-VIH).
L'effet de la rosuvastatine sur l'athérosclérose sera mesuré de façon indirecte par échographie au niveau du cou (mesure de l'épaisseur de la paroi carotidienne) à trois reprises au cours de l'étude lors des visites médicales. Le cholestérol et d'autres marqueurs du risque cardiovasculaires seront mesurés à partir d'échantillons sanguins.

Qui peut participer ? Les personnes infectées par le VIH qui sont à risque modéré de maladie cardiovasculaire et qui n'ont donc pas actuellement une indication à la prise de rosuvastatine, ayant un traitement anti-VIH stable et une virémie intérieure à 200 copies/ml depuis au moins 6 mois.

Que compare-t-on exactement ? Les sujets seront répartis entre 2 groupes : l'inclusion dans l'un ou l'autre des groupes se fera par tirage au sort.

- Le groupe 1 recevra 1 comprimé de rosuvastatine (dose maximale 20mg par jour)
- Le groupe 2 recevra un placebo de rosuvastatine (c'est à dire un comprimé ressemblant à rosuvastatine, mais ne comprenant aucune substance active).

Ni vous ni votre médecin ne saurez quel comprimé vous recevrez.

La durée de l'étude est de 2 ans en collaboration avec une équipe en Australie (Melbourne) et 6 autres centres en Suisse. Au total, 102 participants sont prévus, dont environ 5-10 à Genève.

Quel est le médicament testé ?
La rosuvastatine a une autorisation de mise sur le marché en Suisse (Crestor®), en Europe et aux Etats Unis, avec l'indication suivante : faire baisser le cholestérol dans le sang et prévenir les évènements cardiovasculaires graves chez les personnes à risque accru ou qui ont déjà eu un événement cardio-vasculaire (crise cardiaque). Toutefois, il reste peu étudié dans une population qui n'a pas une indication formelle aux statines sans une maladie cardiovasculaire accrue. La rosuvastatine a montré un effet sur l'inflammation dans d'autres maladies, mais n'a pas été étudiée à cette fin chez les personnes infectées par le VIH.

Que sont les risques ? La rosuvastatine est un médicament sûr qui a été pris par de nombreux patients à travers le monde. Toutefois, il existe des effets secondaires, comme par exemple des troubles musculaires et des troubles de foie. Les effets secondaires sont détaillés dans le chapitre 9 de ce document. Toute apparition de symptômes ou troubles doit être signalée au médecin-investigateur ou à l'infirmière de recherche.

Concrètement, qu'impliquerait votre participation ? La durée de la participation est de 96 semaines (environ 2 ans) comprenant **7 visites**.
Durant les visites de l'étude, vous devrez répondre à quelques questions concernant vos antécédents médicaux, la prise des médicaments et votre observance au médicament de l'étude ainsi que vos facteurs de risque cardiovasculaire.
Les visites de l'étude comprennent également des examens sanguins pour contrôler l'état de votre foie, le taux de cholestérol ainsi que les paramètres de l'infection par le VIH (cellules CD4 et charge virale VIH).
Avant de commencer la rosuvastatine ou le placebo et à 12 mois et 24 mois, (la fin de l'étude), vous aurez une **échographie des artères carotidiennes** (les grosses artères dans le cou) pour mesurer l'épaisseur de la paroi de l'artère (qui nous permet d'estimer vos risques de développer une maladie cardiaque).

Le déroulement est détaillé dans le chapitre 5 ainsi qu'un tableau récapitulatif.

Si j'entre dans l'étude, et change d'avis plus tard, puis-je arrêter ? Vous êtes libre de participer ou pas à cette étude et vous pouvez vous retirer de cette étude à tout moment, sans avoir à vous justifier. Le fait de sortir de l'étude n'aura aucune conséquence sur votre suivi médical. Au cours de l'étude, l'investigateur peut prendre la décision de vous exclure, par exemple, si vous ne répondez plus aux critères exigés par le protocole.

Est-ce que c'est gratuit ? Les médicaments de l'étude seront fournis gratuitement par l'investigateur. Les consultations médicales et examen additionnels occasionnés par cotre participation à l'étude seront également pris en charge par l'investigateur.

Pour une compréhension plus approfondie, veuillez lire attentivement l'information au patient et le consentement éclairé, et en discuter avec votre médecin.

Dre Alexandra Calmy

Madame, Monsieur,

Vous êtes invité(e) à participer à une étude de recherche clinique. Ce document vous informe sur le projet de recherche et explique les examens effectués et le traitement de l'étude ; veuillez le lire attentivement. Les informations vous aideront à décider si vous souhaitez participer à cette recherche. N'hésitez pas à poser des questions à votre médecin traitant avant de vous décider.

1 Sélection des participants à l'essai clinique

Vous avez été sélectionné(e) pour participer à cet essai clinique, parce que vous êtes porteur du virus de l'immunodéficience humaine (VIH), vous êtes actuellement sous traitement anti-VIH efficace et votre risque de développer une maladie cardio-vasculaire est estimé à 10-15% dans les 10 ans. Le projet de recherche teste un nouveau traitement pour prévenir les maladies cardio-vasculaires chez les personnes séropositives pour le VIH. Le traitement s'appelle rosuvastatine, un médicament qui baisse le taux de cholestérol dans le sang.

2 Objet de l'essai

Depuis l'utilisation de la trithérapie anti-VIH, les maladies liées au VIH ont diminué, mais d'autres maladies graves comme les maladies cardio-vasculaires (infarctus du myocarde) et d'autres maladies des vaisseaux sanguins (tels que les accidents vasculaires cérébraux) ont augmenté. Le VIH provoque une inflammation (irritation) qui peut être mesurée par certains tests sanguins. L'inflammation peut endommager les vaisseaux sanguins et ainsi contribuer à des maladies telles que les crises cardiaques. Le traitement anti-VIH peut réduire partiellement l'inflammation, mais le niveau de l'inflammation chez les personnes séropositives peut rester élevé, et ce malgré les médicaments anti-VIH efficace, par rapport au niveau d'inflammation chez les personnes non infectés par le VIH.

L'objectif principal de cette étude est d'évaluer si la prise de Crestor® (substance active = rosuvastatine, un médicament abaissant le cholestérol, et qui diminue également l'inflammation) va ralentir le développement des lésions des vaisseaux sanguins chez les personnes infectées par le VIH et qui n'ont pas actuellement une indication à la prise de rosuvastatine.

Cette étude permettra non seulement d'observer les effets de rosuvastatine au niveau de l'inflammation mesurée dans le sang, mais aussi d'évaluer la tolérance de rosuvastatine chez les personnes vivant avec le VIH qui prennent en même temps des médicaments anti-VIH.

Les résultats de cette recherche seront utilisés par les médecins-investigateurs de l'étude en Australie et à Genève. Cette recherche a été initiée par le médecin-investigateur en Australie, la professeure Jennifer Hoy et est menée conjointement avec la Dre Alexandra Calmy en Suisse. Elle est financée par l'Université Monash de Melbourne, le Fonds National Suisse et le Centre de Recherche Clinique des Hôpitaux Universitaires de Genève.

3 Informations générales sur l'essai clinique

La rosuvastatine est commercialisé en Suisse (Crestor®), en Europe et aux Etats Unis pour traiter les niveaux élevés de cholestérol dans le sang et prévenir les évènements cardiovasculaires graves chez les personnes à risque accru ou qui ont déjà eu un événement cardio-vasculaire (crise cardiaque). Toutefois, il reste peu étudié dans une

population qui n'a pas une indication formelle aux statines sans une maladie cardiovasculaire accrue. La rosuvastatine a montré un effet sur l'inflammation dans d'autres maladies, mais n'a pas été étudiée à cette fin chez les personnes infectées par le VIH.

Vous participerez à un projet de recherche randomisée. Pour savoir si l'effet du médicament n'est pas seulement dû au hasard, nous devons comparer le traitement avec l'absence du traitement en mettant les participants en 2 groupes : un groupe recevra le traitement (rosuvastatine) et l'autre groupe le placebo. Les résultats de chaque groupe seront comparés pour voir si l'un est plus efficace que l'autre. Un placebo est un médicament qui ressemble au vrai médicament mais sans principe actif thérapeutique. Les participants sont assignés à un groupe par hasard (« randomisé ») pour s'assurer que les groupes sont comparables. La probabilité qu'un participant soit traité avec le médicament actif est de 50%.

Si vous participez à l'étude vous prendrez une capsule par jour qui contiendra soit le placebo, soit de la rosuvastatine (10mg ou 20 mg selon le traitement antirétroviral que vous recevez et qui ne sera pas modifé). Certains médicaments anti-VIH (en particulier ceux du groupe de médicaments appelés inhibiteurs de la protéase) peuvent en effet augmenter le niveau de rosuvastatine dans le sang. Si vous prenez un de ces médicaments anti-VIH vous prendrez 10 mg de rosuvastatine (ou le placebo équivalent). La dose recommandée en Suisse ce situe entre 5 et 20 mg une fois/jour.

Vous allez participer à une étude en double-aveugle. C'est-à-dire que ni vous ni le médecin-investigateur ne sauront quel traitement est administré (rosuvastatine ou placebo) pour ne pas influencer l'effet du traitement. Le code de répartition peut être décodé à tout moment Cette étude est réalisée conformément à la législation suisse et aux directives reconnues au niveau international. Elle a par ailleurs été approuvée par la Commission d'éthique de la recherche sur l'être humain des HUG (Hôpitaux universitaires de Genève) et Swissmedic.

en cas d'urgence.

Il s'agit d'une étude internationale multicentrique. Cela signifie qu'elle est menée dans différents centres qui se situent en Australie (Melbourne Alfred Hospital) et en Suisse (Hôpitaux Universitaires de Genève, Lausanne, Berne, Zurich, Bâle et les hôpitaux cantonaux de Saint-Gall et Lugano). 102 participants sont prévus en total et 5-10 participants seront inclus à Genève. L'étude sera menée durant cinq ans.

4 Caractère volontaire de la participation

Votre participation à cet essai est volontaire. Renoncer à y prendre part n'aura aucune incidence sur votre suivi médical ultérieur. Le même principe s'applique en cas de retrait de votre consentement initial. Vous pouvez donc renoncer à tout moment à votre participation. Vous n'êtes tenu(e) de justifier ni la révocation de votre consentement ni un désistement éventuel. En cas de retrait, les données recueillies jusqu'alors continueront toutefois à être utilisées. En revanche, les échantillons de sang prélevés dans le cadre de l'essai clinique ne seront plus utilisés à des fins de recherche. Si vous révoquez votre consentement, vous serez soumis(e) à un examen médical final pour votre propre sécurité.

5 Déroulement de l'essai

Si vous participez à cette étude, vous devriez vous rendre à l'hôpital pour 7 visites (cf. tableau plan de l'étude). La durée de votre participation sera de 96 semaines, environ 2 ans.

Si vous décidez de participer à ce projet de recherche, vous devrez répondre à quelques questions sur vos antécédents médicaux, les médicaments que vous prenez et vos facteurs de risque cardiovasculaires. Vous aurez une prise de sang pour contrôler l'état de votre foie et le taux de cholestérol. Cela nous permettra de savoir si vous êtes éligible pour participer. Un test de grossesse est effectué avant le début de l'étude chez les femmes en âge de procréer (cf. note de bas de page[n]). La visite de sélection durera environ 30 minutes.

Dans la mesure du possible, les visites de l'étude seront combinées avec vos visites de routine de VIH chez votre médecin, et dureront entre 30 à 60 minutes selon le nombre de tests effectués. Lors de la première visite et quatre fois au cours de l'étude, on vous demandera de ne pas manger ou boire (autre que vos médicaments nécessaires et une quantité normale d'eau plate) pendant au moins 8 heures (de préférence 12 heures) avant la prise de sang.

Lors des visites de l'étude, des questions vous seront posées concernant votre état de santé et la prise de médicament. Le médecin ou l'infirmière de recherche vous demandera combien de fois vous avez pris vos médicaments au cours des jours et des semaines précédentes. La prise de poids et la tension artérielle seront également inclues.

A chaque visite de l'étude, vous aurez une prise de sang pour vérifier les éventuels effets secondaires du médicament de l'étude et pour surveiller votre fonction hépatique. Tous les six mois une analyse sanguine sera effectuée pour mesurer les marqueurs d'inflammation, le niveau du cholestérol, les cellules CD4 et la charge virale VIH.

Avant de commencer la rosuvastatine ou le placebo et à 12 mois et 24 mois, (la fin de l'étude), vous aurez une échographie des artères carotidiennes (les grandes artères dans le cou) pour mesurer l'épaisseur de la paroi de l'artère (qui nous permet d'estimer vos risques de développer une maladie cardiaque). C'est une procédure indolore qui prend environ 20 minutes et qui est effectuée de routine aux HUG.

Si à n'importe quel moment au cours de l'étude vous développez un des effets secondaires du médicament testé il se peut que vous deviez venir pour une visite supplémentaire pour des contrôles de sécurité. Vous serez vu(e) par le médecin de l'étude qui évaluera la suite des traitements ou examens supplémentaires.

Lors de toutes vos consultations avec le médecin-investigateur dans le centre d'essai, veuillez ramener les emballages vides, entamés ou pleins du médicament testé.

Tableau: Plan de l'étude

Evaluation/actions	**Sélection**	**Baseline**	**Après randomisation**				
Semaine	**-4**	**0**	**12**	**24**	**48**	**72**	**96**
Visite	**1**	**2**	**3**	**4**	**5**	**6**	**7**
Signature du consentement éclairé et conseil initial	**X**						
Vérification critères d'éligibilité	**X**						
Questions démographiques	**X**						
Examen physique	**X**	**X**			**X**		**X**
Questions concernant la prise du médicament					**X**		**X**
Mesure du poids et taille	**X**				**X**		**X**

Questions concernant des effets secondaires		**X**	**X**	**X**	**X**	**X**	**X**
Calcul du risque cardiovasculaire	**X**						
Analyses laboratoires (♦ = traitement de prise en charge habituelle)							
Cellules CD4	**X♦**		**X**	**X♦**	**X♦**	**X♦**	**X♦**
Charge viral VIH	**X♦**		**X**	**X♦**	**X♦**	**X♦**	**X♦**
Paramètres sanguin : formules sanguin (globules rouge et blanc), Chimie (Analyses du foie)	**X♦**	**X**	**X**	**X♦**	**X♦**	**X♦**	**X♦**
Lipides et glucose **à jeun**	**X**	**X**		**X**	**X**		**X**
Proteine C-réactif de haute sensibilité		**X**	**X**				**X**
Echantillon sanguin de l'étude pour les biomarqueurs et future recherche[o]		**X**	**X**		**X**		**X**
Quantité total du sang prélevé en ml	18	25	25	20	30	13	30
Autres examens							
Echographie (artères carotidiennes)	**X**				**X**		**X**

6 Obligations du participant à l'étude

En tant que participant à l'étude, vous êtes tenu(e) de suivre les instructions médicales de votre médecin-investigateur et de vous conformer au plan de l'étude :

- s'engager à prendre le médicament de l'étude tous les jours. Le médicament est administré oralement une fois par jour avec un peu d'eau (avec ou sans repas) ;
- être à jeun pour les visites 1, 2, 4, 5 et 7;
- informer précisément votre médecin-investigateur de l'évolution de la maladie et lui faire part des éventuels nouveaux symptômes et/ou nouvelles altérations et modifications de votre état ;
- informer votre médecin-investigateur d'un traitement concomitant prescrit par un autre médecin et de la prise de médicaments ; font également partie des médicaments toutes les préparations que vous avez achetées vous-même, disponibles sans ordonnance et/ou rattachées à une médecine alternative ;
- Vous ne devriez pas commencer un des médicaments énumérés ci-dessous lorsque vous participez dans cette étude car ils peuvent augmenter le risque de développer un effet secondaire ;
  - Les médicaments hypocholestérolémiants, y compris la niacine, fibrates ou «statines»
  - L'acide fusidique (antibiotique)
  - Cyclosporine

  Veuillez informer votre médecin-investigateur ou l'infirmière de recherche avant de commencer de prendre un nouveau médicament afin qu'ils puissent vérifier si ce médicament peut être pris en même temps avec la rosuvastatine.
- de continuer à prendre vos médicaments habituels (y compris vos médicaments anti-VIH) tout au long de l'étude selon l'ordonnance de votre médecin traitant VIH ;
- Les personnes ayant eu des effets secondaires des médicaments anti-cholestérol ou des troubles importants musculaires ou du foie dans le passé ne peuvent pas participer à cette étude.

7 Méthodes alternatives de traitement

L'utilisation de rosuvastatine chez les personnes ayant un taux de cholestérol normal sans risque accru d'évènement cardio-vasculaire est expérimentale. Actuellement, le traitement

[o] Echantillon pour futur recherche : uniquement pour personnes ayant donné leur consentement pour la conservation et utilisation de matériel biologique.

standard se base sur une bonne hygiène de vie au niveau de facteurs de risque cardiovasculaire (arrêt du tabac, alimentation saine, activité physique régulière, gestion du stress). L'alternative est de ne pas participer à l'étude et de continuer avec les soins standards du VIH auprès de votre médecin.

8 Avantages pour les participants

Nous ne pouvons garantir ni promettre que participer à cet essai clinique pourra présenter des avantages pour vous. Cependant, votre participation peut permettre à d'autres personnes atteintes de la même pathologie que vous de bénéficier d'une amélioration du traitement.
En participant à cette étude, l'état de vos artères et le risque de maladies cardio-vasculaire seront très soigneusement évalués. Dans certains cas, cela nous permettra de détecter les problèmes de santé graves qui pourront être traitées avant de développer des symptômes.

9 Risques et désagréments

Les traitements médicaux sont souvent la cause d'effets indésirables. En prenant le traitement, il est possible que vous n'en ayez pas, que vous en ayez une partie ou tous les effets énumérés ci-dessous. Ils peuvent être légers, modérés ou sévères. Si vous apercevez un de ces effets, ou si vous êtes inquiet à leur sujet, parlez-en avec votre médecin-investigateur.

On ne peut pas exclure qu'il existe d'autres risques ou effets secondaires encore inconnus à ce jour ; toute apparition de nouveaux symptômes ou troubles doit être signalée au médecin-investigateur.

De nombreux effets secondaires disparaissent peu de temps après l'arrêt du traitement. Cependant, d'autres effets secondaires peuvent être graves, de longue durée ou permanents. Si un effet indésirable grave ou une réaction se produit, il est possible que votre médecin-investigateur vous demande d'interrompre le médicament. Le médecin-investigateur prendra les mesures nécessaires et vous proposera des solutions pour le traitement des effets secondaires.

La rosuvastatine est un médicament sûr qui a été pris par de nombreux patients à travers le monde. La rosuvastatin peut causer des effets secondaires suivants :

- Les problèmes musculaires : La rosuvastatine peut très rarement (moins de 1 pour 1000 patients) entrainer de graves problèmes musculaires qui peuvent conduire à des problèmes rénaux, voir très rarement au décès. .
- Les problèmes de foie : La rosuvastatine peut parfois entrainer des troubles hépatiques qui peuvent rarement être graves, voire mortels. Votre infirmière de l'étude ou le médecin feront des tests sanguins pour contrôler l'état de votre foie avant de commencer à prendre la rosuvastatine, et pendant que vous le prenez.

Toute apparition de symptôme ou trouble ci-dessous doit être signalée **immédiatement** au médecin-investigateur ou à l'infirmière de recherche :

- des problèmes musculaires comme la faiblesse, la sensibilité, ou la douleur qui apparaissent sans une bonne raison, surtout si vous avez de la fièvre ou vous sentez plus fatigué que d'habitude ;
- nausées et vomissements ;
- urines brunes ou de couleur sombre ;
- se sentir plus fatigué que d'habitude ;
- Jaunissement de la peau, ou du blanc des yeux;

- douleurs d'estomac.

D'autres problèmes rapportés pour rosuvastatine comprennent des maux de tête, éruption cutanée, réaction allergique grave ou de gonflement, constipation, gaz, diarrhée, rupture tendineuse, des étourdissements, des troubles de la mémoire et la dépression. Tous ces problèmes sont peu fréquemment à rarement rapportés (survenant chez moins de 1 personne sur 100 qui sont traitées avec la rosuvastatine).

La prise de sang peut provoquer une douleur locale, des ecchymoses, des étourdissements occasionnels, des évanouissements, et très rarement une infection ou des lésions nerveuses au niveau du site du prélèvement de sang. Ces désagréments peuvent facilement être traités.

Si au cours de l'étude, vous présentez une indication (comme le cholestérol élevé) nécessitant un traitement pour baisser le choléstérol, on vous demandera d'arrêter le traitement de l'étude et de sortir de l'étude. Votre médecin traitant vous donnera des conseils concernant un traitement adéquat.

Pour les femmes en âge de procréer

La prise de rosuvastatine peut avoir des effets néfastes sur l'enfant à naître. C'est pourquoi les participantes à l'essai doivent utiliser une double méthode de contraception pendant toute la durée de l'essai, puis encore pendant 1 mois après la fin de l'essai : méthode hormonale (pilule, stérilet) associée à une méthode mécanique, telle que le préservatif ou le diaphragme.

Les participantes qui découvrent qu'elles sont enceintes pendant l'essai clinique doivent informer immédiatement le médecin-investigateur et être exclues de l'étude. Le médecin investigateur discutera avec elles de ce qu'il conviendra de faire. Dans ce cas, elles sont priées de fournir des données sur le déroulement et l'issue de leur grossesse. Les femmes qui allaitent ne peuvent en aucun cas prendre part à une étude clinique.

Pour les hommes

Une altération des spermatozoïdes ne peut être exclue, il convient d'utiliser une méthode contraceptive mécanique pendant et après le traitement (préservatif). Le participant à l'étude doit informer sa/ses partenaire(s) de sa participation à une étude clinique et utiliser un préservatif à chaque rapport sexuel. Quant à sa partenaire, elle doit utiliser en sus une méthode contraceptive efficace (en général hormonale). Si sa partenaire tombe néanmoins enceinte, le participant à l'étude doit, d'entente avec elle, en informer le médecin-investigateur. La partenaire doit par ailleurs être invitée à assister une consultation médicale effectuée dans le cadre de l'étude afin de recevoir certaines informations. Le médecin-investigateur lui demandera en outre son accord pour que des informations sur la grossesse et l'enfant puissent être collectées.

10 Nouvelles découvertes

Le médecin-investigateur vous informera pendant toute la durée de l'étude de toutes les nouvelles découvertes faites, qui pourraient influer sur l'avantage qu'a pour vous l'étude ou sur votre sécurité et, sur votre consentement à y participer. Ces informations vous seront communiquées par oral et par écrit.

En cas de découvertes fortuites qui pourraient contribuer à la prévention, au diagnostic et au traitement de maladies existantes ou peut-être futures, trois choix s'offrent à vous : a) être informé(e) directement de ces résultats b) ne pas en être informé(e), ou c) laisser à votre médecin traitant le soin de décider de ce qu'il convient de faire (cf. Déclaration de consentement).

11 Confidentialité des données

Des données personnelles et médicales vous concernant sont recueillies pendant l'essai clinique. Elles sont toutefois rendues anonymes, c'est-à-dire associées à un code et à votre date de naissance. Cette liste de codes est archivée par le médecin-investigateur. Seules des données anonymisées sont accessibles aux spécialistes à des fins d'évaluation scientifique. Les spécialistes compétents du promoteur (ou de leurs mandataires) peuvent, dans le cadre du contrôle-qualité, contrôler le déroulement de l'étude. Ces spécialistes, de même que les membres des autorités compétentes et des commissions d'éthique peuvent, dans le cadre d'inspections, consulter par l'intermédiaire du médecin-investigateur vos données médicales brutes. En cas de dommages, le représentant de l'assurance peut également consulter, par l'intermédiaire du médecin-investigateur, vos données médicales, mais uniquement dans la mesure où cela est nécessaire pour l'instruction du dossier. Reste que leur confidentialité est strictement garantie pendant toute l'étude et lors des contrôles précités. Votre nom ne pourra donc en aucun cas être publié dans des rapports ou des publications qui découleraient de cette étude.

Dans le cadre de la présente étude, des échantillons de sang sont conservés à la sérologie centrale des hôpitaux universitaires de Genève pour effectuer les analyses des marqueurs de l'étude.

Si vous êtes d'accord, un échantillon de sang (8ml aux visites 2, 3, 5 et 7) sera conservé à la sérologie centrale aux hôpitaux universitaires de Genève indéfiniment pour une utilisation possible dans d'autres recherches concernant les causes et la prévention des maladies cardio-vasculaires chez les patients VIH et les effets des «statines». Ces recherches peuvent concerner, mais ne sont pas limités à des tests sur des marqueurs d'inflammation nouvellement découverts ou des analyses spécifiques du cholestérol. Ces échantillons ne seront utilisés qu'à des fins de recherches futures approuvés par le comité local. Si vous êtes d'accord, il vous sera demandé de signer un consentement supplémentaire concernant la conservation et réutilisation de matériel biologique.

les échantillons pour les biomarqueurs et pour la future recherche sont conservés sous forme anonymisée, avec un code à la sérothèque centrale et au laboratoire de cardiologie des hôpitaux universitaire de Genève. La seule personne à avoir un droit d'accès à ce code est l'investigatrice principale de votre centre de référence, Dre Alexandra Calmy. Vous avez le droit de consulter les données et de demander à ce que les échantillons ne soient plus utilisés. Les échantillons pour les biomarqueurs seront détruits au plus tard 5ans après la fin de l'étude.

Il se peut que les échantillons soient ultérieurement transférés à des fins d'analyse dans une autre biobanque située en Suisse ou à l' « Alfred Hospital » à Melbourne en Australie. Ceux-ci doivent cependant remplir les mêmes standards que la biobanque de la présente étude.

Nous portons à votre attention le fait que les dispositions en vigueur en Suisse concernant la protection des données ne sont pas forcément identiques dans les pays précités. On ne peut donc exclure que le cercle des personnes ayant accès à vos données soit plus large qu'en Suisse. Mais comme seuls des données ou des prélèvements anonymisés peuvent être transmis, cela ne devrait pas vous porter préjudice.

Le promoteur en Suisse, ou le représentant du promoteur étranger en Suisse, répond du respect des dispositions nationales et internationales relatives à la protection des données. Il se porte garant du fait que le pays de destination dispose d'une protection des données équivalente à celle de la Suisse.

12 Frais

Les examens spécifiques à l'essai clinique et médicaments administrés dans le cadre de l'essai clinique, qui sont mentionnés dans le présent document d'information à l'intention des participants, sont gratuits. Ni vous ni votre caisse-maladie n'avez à supporter quelque frais supplémentaire que ce soit qui découlerait de votre participation à cet essai.

13 Dédommagement des participants à l'essai clinique

La participation à cet essai clinique ne vous donne droit à aucun dédommagement.

14 Interruption involontaire de l'essai

Votre participation peut être interrompue par le médecin-investigateur ou par le promoteur de l'étude, et ce en particulier si des effets indésirables non acceptable sont détectés. Dans ce cas, un examen médical final devra être réalisé pour votre propre sécurité. Quant aux médicaments testés non utilisés, ils doivent être rapportés.

15 Réparation des dommages subis

Si pendant ou à l'issue de l'essai clinique, vous deviez souffrir de problèmes de santé ou constater des dommages d'une autre nature, veuillez vous adresser au médecin-investigateur compétente, Dre Alexandra Calmy, qui engagera pour vous la procédure requise.
Les hôpitaux Universitaires de Genève (HUG) ont contracté à cette fin en votre faveur une assurance auprès de la compagnie Axa Winterthur, 1205 Genève.

16 Interlocuteur(s)

En cas d'urgence, d'incertitude ou d'événement inattendu ou indésirable survenant pendant ou après l'essai clinique, vous pouvez vous adresser à tout moment à la personne suivante :

Médecin-investigateur de l'étude :

Dre Alexandra Calmy
Service des maladies infectieuses, 4, rue Gabrielle-Perret-Gentil, CH-1211 Genève 14, Suisse
Tel : 022 372 98 12

Médecin de garde atteignable 24h/24h : 079 200 78 86

Consentement éclairé écrit du patient pour la participation à une étude clinique

- Veuillez lire attentivement ce formulaire.
- N'hésitez pas à poser des questions si certains aspects vous semblent peu clairs ou si vous souhaitez obtenir des précisions.

Numéro de l'essai clinique:	CER-240
Titre de l'essai clinique:	***La rosuvastatine retarde-t-elle la progression de l'athérosclérose chez les personnes infectées par le VIH avec un risque cardiovasculaire modéré ?*** *Un essai multicentrique, randomisé, en double aveugle, contrôlé contre placebo*
Promoteur (adresse complète) :	Hôpitaux universitaires de Genève, Dre A. Calmy, Rue Gabrielle-Perret-Gentil 4, CH - 1211 Genève 14
Lieu de réalisation de l'essai clinique:	Consultation des maladies infectieuses / unité VIH
Médecin-investigateur Nom et prénom :	 Dre Alexandra Calmy
Patient(e) Nom et prénom : Date de naissance :	 ☐ homme ☐ femme

- Je déclare avoir été informé(e), oralement et par écrit, par le médecin signataire des objectifs et du déroulement de l'étude sur rosuvastatine, des effets présumés, des avantages et des inconvénients possibles ainsi que des risques éventuels.
- Je certifie avoir lu et compris l'information écrite aux patients qui m'a été remise sur l'étude précitée, datée du 28.11.2013. J'ai reçu des réponses satisfaisantes aux questions que j'ai posées en relation avec ma participation à cet essai clinique. Je conserve l'information écrite aux patients et reçois une copie de ma déclaration écrite de consentement.
- J'ai été informé(e) de l'existence possible d'autres traitements et thérapies.
- J'ai eu suffisamment de temps pour prendre ma décision.
- Je suis informé(e) qu'une assurance a été souscrite pour couvrir les dommages éventuels découlant de l'étude.
- Je donne mon accord à ce que mon médecin traitant soit informé sur ma participation à l'étude.
- En cas de découvertes fortuites je désire ☐**être informé,** ☐**ne pas être informé,** ☐**je laisse cette décision à mon médecin traitant** (cocher ce qui convient)
- Je sais que mes données personnelles ne seront transmises que sous une forme anonyme à des institutions externes à des fins de recherche. J'accepte que les spécialistes compétents du mandataire de l'étude, des autorités et de la Commission d'éthique cantonale puissent consulter mes données brutes, afin de procéder à des examens et à des contrôles, à condition toutefois que leur confidentialité soit strictement assurée.
- Je consens de participer à cet essai clinique. Je prends part de façon volontaire. Je peux, à tout moment et sans avoir à fournir de justification, révoquer mon consentement à participer à cette étude, sans pour cela en subir quelque inconvénient que ce soit dans mon suivi médical ultérieur. Dans ce cas, je prendrai part à un examen médical final pour ma propre sécurité.
- Je suis conscient(e) du fait que les exigences et les restrictions mentionnées dans l'information aux patients devront être respectées pendant la durée de l'étude. Le médecin-investigateur peut m'exclure à tout moment de l'essai clinique dans l'intérêt de ma santé.

Lieu, date	Signature du patient/de la patiente

Attestation du médecin-investigateur : J'atteste par ma signature avoir expliqué à ce/cette patient/e la nature, l'importance et la portée de l'étude. Je déclare satisfaire à toutes les obligations en relation avec cet essai clinique. Si je devais prendre connaissance, à quelque moment que ce soit durant la réalisation de l'étude, d'informations susceptibles d'influer sur le consentement du/de la patient(e) à participer à l'étude, je m'engage à l'en informer immédiatement.

Lieu, date	Signature du médecin-investigateur

22.7 Informed Consent Form for storage of samples for future research (Geneva version)

Consultation des maladies infectieuses / unité VIH
Version 2 Genève du 28/11.2013

Conservation et réutilisation de matériel biologique et de données à des fins de recherche biomédicale dans l'étude rosuvastatin (dite « ROSICH »)

Titre français complet : La rosuvastatin retarde-t-elle la progression de l'athérosclérose chez les personnes infectées par le VIH avec un risque cardiovasculaire modéré ? Un essai multicentrique, randomisé, en double aveugle, contrôlé contre placebo.

Brochure d'information destinée aux patients/es

Chère patiente, cher patient,

Lors d'un séjour hospitalier, il arrive souvent que des échantillons de fluides (sang, urine ou autre substance corporelle), de cellules ou de tissus soit prélevés et examinés. La plupart du temps, ces échantillons ne sont pas utilisés dans leur totalité à des fins de diagnostic et de traitement. Mais, combinés avec certaines données vous concernant (par ex. âge, sexe, état de santé, etc.), ils représentent des informations précieuses pour la recherche biomédicale. Nous vous prions donc de nous donner votre consentement à la conservation de vos échantillons (4ml de plasma sanguin aux visites 2, 3, 5 et 7) et données et à leur réutilisation à des fins de recherche biomédicale. Votre consentement est libre.

Cette brochure résume les principales informations vous permettant de prendre cette décision et vous informe de vos droits. Pour toute question ou information complémentaire, veuillez vous adresser au médecin responsable qui pourra vous apporter des précisions.

Vous avez des droits
Vos échantillons et données ne peuvent être utilisés pour la recherche **qu'avec votre consentement**. Cela signifie que votre consentement doit être sollicité au préalable. Une fois votre consentement donné, vous êtes libre de le révoquer à tout moment. Toutefois, sans révocation de votre part, votre consentement demeure valable au-delà de votre décès.

Que signifie votre consentement?
Si vous donnez votre consentement, vos échantillons et données pourront être conservés dans une biobanque et **seront ainsi mis à la disposition de la recherche biomédicale.** Les chercheurs pourront utiliser ces échantillons et données pour des projets de recherche biomédicale ayant obtenu - lorsque le droit applicable l'exige - l'autorisation préalable de la commission d'éthique de la recherche compétente.
Votre consentement est également valable pour les projets de recherche ultérieurs. Vous ne serez donc pas informé/e à chaque utilisation future de vos échantillons et

données. Votre consentement ne vous sera, en principe, pas redemandé, sauf dans les cas où la loi ou la commission d'éthique de la recherche compétente exigerait de renouveler votre consentement.
L'accès à vos échantillons et données **sera très strictement réglementé** et uniquement les personnes habilitées pourront consulter les données non codées. De manière générale, **les échantillons et données sont transmis de telle façon que les participants à un projet de recherche ne puissent pas associer un nom à un échantillon. De plus, ils ne peuvent être transmis à d'autres biobanques que si celles-ci observent les mêmes standards que la biobanque d'origine**.

Anonymisation des données
Avant d'être transmis à des chercheurs à l'intérieur ou à l'extérieur de l'hôpital, vos échantillons et données doivent être anonymisés de telle sorte que les participants à la recherche ne puissent pas savoir de qui ils proviennent.
Ce n'est que sous certaines conditions, soumises à l'autorisation de la commission d'éthique de la recherche compétente, que les responsables de la biobanque (et non pas les chercheurs directement impliqués dans le projet) peuvent rechercher votre identité, par exemple en cas de besoin d'échantillons ou de données supplémentaires.

Modes d'anonymisation

Anonymisation réversible (possibilité de réidentifier le donneur)
Les indications susceptibles de vous identifier (comme le nom, la date de naissance, le domicile, le numéro de patient, etc.) sont modifiées à l'aide d'un code, de telle sorte que le chercheur ne puisse établir un lien avec vous en tant que patient/e (par ex. en attribuant un numéro à la personne). Toutefois, la clé de codage est conservée par le médecin de l'étude afin de permettre - sous certaines conditions soumises à l'autorisation de la commission d'éthique de la recherche compétente - la réidentification du/de la patient/e, par ex. en cas de nécessité d'échantillons ou de données supplémentaires.

Résultats de recherche significatifs
La plupart des études ne s'attachent pas à l'analyse d'échantillons isolés, mais à toute une série d'échantillons, ceux-ci intéressant les chercheurs dans leur globalité et non dans leur individualité. En règle générale, vous ne serez donc pas informé/e activement des résultats des projets de recherche individuels dans lesquels vos échantillons ont été utilisés.

Sont exceptés les résultats grâce auxquels des maladies existantes ou éventuelles pourraient être évitées, diagnostiquées et/ou traitées. Vous décidez vous-même de la manière de procéder avec de tels résultats (voir formulaire de consentement).

Le donneur ne peut prétendre à aucun bénéfice commercial
Les résultats de projets de recherche peuvent, le cas échéant, contribuer au développement de produits commerciaux, par exemple de nouveaux médicaments. Votre consentement sous-entend que vous renoncez à toute prétention à des bénéfices commerciaux ou brevets en relation avec vos échantillons et données.

Droit de révocation
Une fois votre consentement révoqué, vos échantillons et données ne peuvent plus être transmis à des chercheurs ou à d'autres biobanques. Le cas échéant, veuillez adresser votre révocation à :

Dre Alexandra Calmy
Consultation des maladies infectieuses
Hôpitaux Universitaires de Genève
Rue Gabrielle Perret-Gentil 4
1211 Genève 14
Téléphone : +41 (0)22 372 98 12

Mais quel est donc le but de la recherche avec des biobanques ?
Ces dernières décennies, la recherche biomédicale a fait d'énormes progrès. Toutefois, dans de nombreux domaines, les causes des maladies doivent encore être explorées et le dépistage et le traitement des maladies être améliorés. Dans ce but, il est donc important que la recherche biomédicale dispose d'échantillons et de données provenant d'un nombre élevé de personnes, qui sont déjà conservés dans une biobanque.

Votre participation est libre
Avant de vous décider, nous récapitulons encore une fois les informations essentielles : vous, et vous seul, pouvez décider de mettre vos échantillons et données à disposition de la recherche biomédicale – ceci tout à fait librement, sans pression et après avoir obtenu toutes les informations nécessaires.
Le fait de donner votre consentement ne donnera lieu à **aucun avantage ni inconvénient** pour vous. Le diagnostic et le traitement de votre maladie ne seront influencés en aucune façon.

Vous souhaitez en savoir d'avantage ?
Pour toute question ou information complémentaire, veuillez vous adresser au médecin responsable qui pourra vous renseigner de manière détaillée.
Chaque biobanque dispose aussi d'un règlement dont tout/e donneur/se a le droit de prendre connaissance.

En mettant à disposition vos échantillons et données dans une biobanque, vous apportez un soutien précieux à la recherche biomédicale. Nous vous en remercions cordialement.

Déclaration de consentement éclairé pour la conservation et la réutilisation de matériel biologique et de données à des fins de recherche biomédicale dans l'étude rosuvastatine (dite « ROSICH »)

Titre français complet : La rosuvastatine retarde-t-elle la progression de l'athérosclérose chez les personnes infectées par le VIH avec un risque cardiovasculaire modéré ? Un essai multicentrique, randomisé, en double aveugle, contrôlé contre placebo.

Chère patiente, cher patient,

Lors d'un séjour hospitalier, il arrive souvent que des échantillons de fluides (sang, urine ou autre substance corporelle), de cellules ou de tissus soient prélevés et examinés. La plupart du temps, ces échantillons ne sont pas utilisés dans leur totalité à des fins de diagnostic et de traitement. Mais, combinés avec certaines données vous concernant (par ex. âge, sexe, état de santé, etc.), ils représentent des informations précieuses pour la recherche biomédicale.

Par le présent formulaire, vous consentez à la conservation de vos échantillons et données et à leur réutilisation à des fins de recherche biomédicale.

Vous trouverez des informations complémentaires concernant la réutilisation d'échantillons et données à des fins de recherche biomédicale dans la brochure d'information aux patients.

Consentement

Par la présente, je consens à ce que

- mes échantillons/données soient conservés jusqu'à un éventuel retrait de mon consentement ;
- mes échantillons/données puissent être utilisés pour des projets de recherche biomédicale actuellement encore indéterminés, et ce, sans que je sois informé du cas concret et sans qu'il soit nécessaire de signer une autre déclaration de consentement, à condition que :
  - le projet de recherche – lorsque le droit applicable l'exige – ait été autorisé par la commission d'éthique de la recherche compétente et que
  - les échantillons/données soient anomymisés avant leur transmission, de sorte que les participants aux différents projets de recherche ignorent de qui ils/elles proviennent ;
- mes échantillons/données puissent être transmis à d'autres biobanques, à condition :
  - que celles-ci garantissent au moins les mêmes standards de conservation, et
  - que leurs responsables se soient engagés à respecter les mêmes conditions lors de leur transmission à d'autres projets de recherche ou biobanques.

Je sais qu'en tant que donneur/se, j'ai le droit d'être informé/e des résultats significatifs du point de vue diagnostique et/ou thérapeutique, dans la mesure où ceux-ci atteignent un certain de degré de certitude et demeurent pertinents hors du cadre de la recherche.
Le médecin responsable est en principe chargé de me transmettre ces résultats et il veillera à ce que je bénéficie de conseils adéquats.
Je peux aussi renoncer au préalable à la possibilité d'être informé/e de ces résultats significatifs, ou laisser le médecin responsable décider s'il veut ou non m'en informer.

- ❑ Je veux, à l'avenir, être informé/e dans tous les cas des résultats significatifs du point de vue diagnostique et/ou thérapeutique par le médecin responsable.
- ❑ Je laisse au médecin responsable le soin de décider si, en l'espèce, je devrais être informé/e des résultats de recherche s'avérant significatifs pour moi du point de vue diagnostique et/ou thérapeutique.
- ❑ Je renonce à mon droit d'information ; je ne veux pas, à l'avenir, être informé/e des résultats de recherche susceptibles d'être significatifs pour moi du point de vue diagnostique et/ou thérapeutique.

Je prends acte que le présent consentement demeure valable au-delà de mon décès.

Consentement
Je confirme que - j'ai été suffisamment informé/e au sujet de la conservation et la réutilisation d'échantillons/données à des fins de recherche biomédicale. - j'ai eu la possibilité de poser des questions et que les réponses obtenues ont été satisfaisantes ; - j'ai été informé que mon consentement est libre et qu'aucun inconvénient ou avantage ne résultera de ma décision quelle qu'elle soit.
Les échantillons (4ml de plasma aux visites 2, 3, 5 et 7) seront conservées à la sérothèque centrale des hôpitaux universitaires de Genève, rue Gabrielle Perret-Gentil 4, 1211 Genève sous la responsabilité de Dr P. Lescuyer, tél : (+41) 22 37 27 361.
Tous les échantillons seront anonymisés au moyen d'un code avec le numéro de l'étude et les initiales du patient, la liste des codes étant conservée par le médecin responsable de l'étude. Les spécialistes qui utiliseront scientifiquement ces échantillons n'auront accès qu'à des données codées. Cela étant, les données personnelles vous concernant resteront codées dans tous les cas. En cas de besoin, il sera possible d'activer la procédure de décodage pour ré-identifier un participant à l'étude.
Consentement
Lieu, date, signature légale[p] Lieu, date, signature du collaborateur qui a procédé à l'information et recueilli le consentement.

[p] Signature du/de la représentant/e légal/e pour les personnes mineures ou interdites. Le/la représentant/e légal/e de la personne mineure capable de discernement ratifie le consentement donné de manière personnelle.

22.8 Severity Grading of Adverse Events

Modified DIVISION OF AIDS TABLE FOR GRADING THE SEVERITY OF ADULT ADVERSE EVENTS

VERSION 1.0, DECEMBER, 2004; CLARIFICATION AUGUST 2009

The Division of AIDS Table for Grading the Severity of Adult and Pediatric Adverse Events ("DAIDS AE Grading Table") is a descriptive terminology which can be utilized for Adverse Event (AE) reporting. A grading (severity) scale is provided for each AE term.

Instructions and Clarifications
In the classification of adverse events, the term "severe" is not the same as "serious." Severity is an indication of the intensity of a specific event (as in mild, moderate, or severe chest pain). The term "serious" relates to a participant/event outcome or action criteria, usually associated with events that pose a threat to a participant's life or functioning.

For any AE where the outcome is death, the severity of the AE is classified as Grade 5.

Determining Severity Grade for Parameters "Between Grades"
If the severity of a clinical AE could fall under either one of two grades (e.g., the severity of an AE could be either Grade 2 or Grade 3), select the higher of the two grades for the AE. If a laboratory value that is graded as a multiple of the ULN or LLN falls between two grades, select the higher of the two grades for the AE. For example, Grade 1 is 2.5 x ULN and Grade 2 is 2.6 x ULN for a parameter. If the lab value is
2.53 x ULN (which is between the two grades), the severity of this AE would be Grade 2, the higher of the two grades.

Values Below Grade 1: Any laboratory value that is between either the LLN or ULN and Grade 1 should not be graded.

Definitions of terms used in the Table:

Basic Self-care Functions	Activities such as bathing, dressing, toileting, transfer/movement, continence, and feeding
LLN	Lower limit of normal
Medical Intervention	Use of pharmacologic or biologic agent(s) for treatment of an AE.
NA	Not Applicable
Operative Intervention	Surgical OR other invasive mechanical procedures
ULN	Upper limit of normal

PARAMETER	GRADE 1 MILD	GRADE 2 MODERATE	GRADE 3 SEVERE	GRADE 4 POTENTIALLY LIFE-THREATENING
ESTIMATING SEVERITY GRADE				
Clinical adverse event NOT identified elsewhere in this DAIDS AE Grading Table	Symptoms causing no or minimal interference with usual social & functional activities	Symptoms causing greater than minimal interference with usual social & functional activities	Symptoms causing inability to perform usual social & functional activities	Symptoms causing inability to perform basic self-care functions OR Medical or operative intervention indicated to prevent permanent impairment, persistent disability, or death
SYSTEMIC				
Acute systemic allergic reaction	Localized urticaria (wheals) with no medical intervention indicated	Localized urticaria with medical intervention indicated OR Mild angioedema with no medical intervention indicated	Generalized urticaria OR Angioedema with medical intervention indicated OR Symptomatic mild bronchospasm	Acute anaphylaxis OR Life-threatening bronchospasm OR laryngeal edema
Chills	Symptoms causing no or minimal interference with usual social & functional activities	Symptoms causing greater than minimal interference with usual social & functional activities	Symptoms causing inability to perform usual social & functional activities	NA
Fatigue Malaise	Symptoms causing no or minimal interference with usual social & functional activities	Symptoms causing greater than minimal interference with usual social & functional activities	Symptoms causing inability to perform usual social & functional activities	Incapacitating fatigue/ malaise symptoms causing inability to perform basic self-care functions
Fever (nonaxillary)	37.7 – 38.6°C	38.7 – 39.3°C	39.4 – 40.5°C	> 40.5°C
Pain (indicate body site) DO NOT use for pain due to injection (See Injection Site Reactions: Injection site pain) See also Headache, Arthralgia, and Myalgia	Pain causing no or minimal interference with usual social & functional activities	Pain causing greater than minimal interference with usual social & functional activities	Pain causing inability to perform usual social & functional activities	Disabling pain causing inability to perform basic self-care functions OR Hospitalization (other than emergency room visit) indicated
Unintentional weight loss	NA	5 – 9% loss in body weight from baseline	10 – 19% loss in body weight from baseline	20% loss in body weight from baseline OR Aggressive intervention indicated [e.g., tube feeding or total parenteral nutrition (TPN)]

PARAMETER	GRADE 1 MILD	GRADE 2 MODERATE	GRADE 3 SEVERE	GRADE 4 POTENTIALLY LIFE-THREATENING
INFECTION				
Infection (any other than HIV infection)	Localized, no systemic antimicrobial treatment indicated AND Symptoms causing no or minimal interference with usual social & functional activities	Systemic antimicrobial treatment indicated OR Symptoms causing greater than minimal interference with usual social & functional activities	Systemic antimicrobial treatment indicated AND Symptoms causing inability to perform usual social & functional activities OR Operative intervention (other than simple incision and drainage) indicated	Life-threatening consequences (e.g., septic shock)
INJECTION SITE REACTIONS				
Injection site pain (pain without touching) Or Tenderness (pain when area is touched)	Pain/tenderness causing no or minimal limitation of use of limb	Pain/tenderness limiting use of limb OR Pain/tenderness causing greater than minimal interference with usual social & functional activities	Pain/tenderness causing inability to perform usual social & functional activities	Pain/tenderness causing inability to perform basic self-care function OR Hospitalization (other than emergency room visit) indicated for management of pain/tenderness
Injection site reaction (localized)	Erythema OR Induration of 5x5 cm – 9x9 cm (or 25 cm^2 – 81cm^2)	Erythema OR Induration OR Edema > 9 cm any diameter (or > 81 cm^2)	Ulceration OR Secondary infection OR Phlebitis OR Sterile abscess OR Drainage	Necrosis (involving dermis and deeper tissue)
Pruritis associated with injection See also Skin: Pruritis (itching - no skin lesions)	Itching localized to injection site AND Relieved spontaneously or with < 48 hours treatment	Itching beyond the injection site but not generalized OR Itching localized to injection site requiring 48 hours treatment	Generalized itching causing inability to perform usual social & functional activities	N/A
SKIN – DERMATOLOGICAL				
Alopecia	Thinning detectable by study participant (or by caregiver for young children and disabled adults)	Alopecia	Thinning detectable by study participant (or by caregiver for young childrer and disabled adults)	Alopecia
Cutaneous reaction (Rash)	Localized macular rash	Diffuse macular, maculopapular, or morbilliform rash OR Target lesions	Diffuse macular, maculopapular, or morbilliform rash with vesicles or limited number of bullae OR Superficial ulcerations of mucous membrane limited to one site	Extensive or generalized bullous lesions OR Stevens-Johnson syndrome OR Ulceration of mucous membrane involving two or more distinct mucosal sites OR Toxic epidermal necrolysis (TEN)
Pruritis (itching – no skin lesions) (See also Injection Site Reactions: Pruritis associated with injection)	Itching causing no or minimal interference with usual social & functional activities	Itching causing greater than minimal interference with usual social & functional activities	Itching causing inability to perform usual social & functional activities	NA

Vasovagal episode (associated with a procedure of any kind)	Present without loss of consciousness	Present with transient loss of consciousness	NA	NA
Ventricular dysfunction (congestive heart failure)	NA	Asymptomatic diagnostic finding AND intervention indicated	New onset with symptoms OR Worsening symptomatic congestive heart failure	Life-threatening congestive heart failure
GASTROINTESTINAL				
Anorexia	Loss of appetite without decreased oral intake	Loss of appetite associated with decreased oral intake without significant weight loss	Loss of appetite associated with significant weight loss	Life-threatening consequences OR Aggressive intervention indicated [e.g., tube feeding or total parenteral nutrition (TPN)]
Ascites	Asymptomatic	Symptomatic AND Intervention indicated (e.g., diuretics or therapeutic paracentesis)	Symptomatic despite intervention	Life-threatening consequences
Cholecystitis	NA	Symptomatic AND Medical intervention indicated	Radiologic, endoscopic,or operative intervention indicated	Life-threatening consequences (e.g., sepsis or perforation)
Constipation	NA	Persistent constipation requiring regular use of dietary modifications, laxatives, or enemas	Obstipation with manual evacuation indicated	Life-threatening consequences (e.g., obstruction)
Diarrhea	Transient or intermittent episodes of unformed stools OR Increase of ≤ 3 stools over baseline per 24-hour period	Persistent episodes of unformed to watery stools OR Increase of 4 – 6 stools over baseline per 24-hour period	Bloody diarrhea OR Increase of ≥7 stools per 24-hour period OR IV fluid replacement indicated	Life-threatening consequences (e.g., hypotensive shock)
Dysphagia-Odynophagia	Symptomatic but able to eat usual diet	Symptoms causing altered dietary intake without medical intervention indicated	Symptoms causing severely altered dietary intake with medical intervention indicated	Life-threatening reduction in oral intake
Mucositis/stomatitis (clinical exam) Indicate site (e.g., larynx, oral) See Genitourinary for Vulvovaginitis	Erythema of the mucosa	Patchy pseudomembranes or ulcerations	Confluent pseudomembranes or diffuse ulcerations OR Mucosal bleeding with minor trauma	Tissue necrosis OR spontaneous mucosal bleeding OR Life-threatening consequences

Nausea	Transient (< 24 hours) or intermittent nausea with no or minimal interference with oral intake	Persistent nausea resulting in decreased oral intake for 24 – 48 hours	Persistent nausea resulting in minimal oral intake for > 48 hours OR Aggressive rehydration indicated (e.g., IV fluids)	Life-threatening consequences (e.g., hypotensive shock)

PARAMETER	**GRADE 1 MILD**	**GRADE 2 MODERATE**	**GRADE 3 SEVERE**	**GRADE 4 POTENTIALLY LIFE-THREATENING**
Pancreatitis	NA	Symptomatic AND Hospitalization not indicated (other than emergency room visit)	Symptomatic AND Hospitalization indicated (other than emergency room visit)	Life-threatening consequences (e.g., circulatory failure, hemorrhage, sepsis)
Proctitis (functional-symptomatic) Also see Mucositis/stomatitis for clinical exam	Rectal discomfort AND No intervention indicated	Symptoms causing greater than minimal interference with usual social & functional activities OR Medical intervention indicated	Symptoms causing inability to perform usual social & functional activities OR Operative intervention indicated	Life-threatening consequences (e.g., perforation)
Vomiting	Transient or intermittent vomiting with no or minimal interference with oral intake	Frequent episodes of vomiting with no or mild dehydration	Persistent vomiting resulting in orthostatic hypotension OR Aggressive rehydration indicated (e.g., IV fluids)	Life-threatening consequences (e.g., hypotensive shock)
NEUROLOGIC				
Alteration in personality-behavior or in mood (e.g., agitation, anxiety, depression, mania, psychosis)	Alteration causing no or minimal interference with usual social & functional activities	Alteration causing greater than minimal interference with usual social & functional activities	Alteration causing inability to perform usual social & functional activities	Behavior potentially harmful to self or others (e.g., suicidal and homicidal ideation or attempt, acute psychosis) OR Causing inability to perform basic self-care functions
Altered Mental Status For Dementia, see Cognitive and behavioral/attentional disturbance (including dementia and attention deficit disorder)	Changes causing no or minimal interference with usual social & functional activities	Mild lethargy or somnolence causing greater than minimal interference with usual social & functional activities	Confusion, memory impairment, lethargy, or somnolence causing inability to perform usual social & functional activities	Delirium OR obtundation, OR coma
Ataxia	Asymptomatic ataxia detectable on exam OR Minimal ataxia causing no or minimal interference with usual social & functional activities	Symptomatic ataxia causing greater than minimal interference with usual social & functional activities	Symptomatic ataxia causing inability to perform usual social & functional activities	Disabling ataxia causing inability to perform basic self-care functions

Cognitive and behavioral/attentional disturbance (including dementia and attention deficit disorder)	Disability causing no or minimal interference with usual social & functional activities OR Specialized resources not indicated	Disability causing greater than minimal interference with usual social & functional activities OR Specialized resources on part-time basis indicated	Disability causing inability to perform usual social & functional activities OR Specialized resources on a full-time basis indicated	Disability causing inability to perform basic self-care functions OR Institutionalization indicated
CNS ischemia (acute)	NA	NA	Transient ischemic attack	Cerebral vascular accident (CVA, stroke) with neurological deficit
Headache	Symptoms causing no or minimal interference with usual social & functional activities	Symptoms causing greater than minimal interference with usual social & functional activities	Symptoms causing inability to perform usual social & functional activities	Symptoms causing inability to perform basic self-care functions OR Hospitalization indicated (other than emergency room visit) OR Headache with significant impairment of alertness or other neurologic function
Insomnia	NA	Difficulty sleeping causing greater than minimal interference with usual social & functional activities	Difficulty sleeping causing inability to perform usual social & functional activities	Disabling insomnia causing inability to perform basic self-care functions
Neuromuscular weakness (including myopathy & neuropathy)	Asymptomatic with decreased strength on exam OR Minimal muscle weakness causing no or minimal interference with usual social & functional activities	Muscle weakness causing greater than minimal interference with usual social & functional activities	Muscle weakness causing inability to perform usual social & functional activities	Disabling muscle weakness causing inability to perform basic self-care functions OR Respiratory muscle weakness impairing ventilation
Neurosensory alteration (including paresthesia and painful neuropathy)	Asymptomatic with sensory alteration on exam or minimal paresthesia causing no or minimal interference with usual social & functional activities	Sensory alteration or paresthesia causing greater than minimal interference with usual social & functional activities	Sensory alteration or paresthesia causing inability to perform usual social & functional activities	Disabling sensory alteration or paresthesia causing inability to perform basic self-care functions
Seizure: (new onset) **– Adult ≥18 years** See also Seizure: (known pre-existing seizure disorder)	NA	1 seizure	2 **–** 4 seizures	Seizures of any kind which are prolonged, repetitive (e.g., status epilepticus), or difficult to control (e.g., refractory epilepsy)

Seizure: (known pre-existing seizure disorder)	NA	Increased frequency of pre-existing seizures (non-repetitive) without change in seizure character OR Infrequent break- through seizures while on stable medication in a previously controlled seizure disorder	Change in seizure character from baseline either in duration or quality (e.g., severity or focality)	Seizures of any kind which are prolonged, repetitive (e.g., status epilepticus), or difficult to control (e.g., refractory epilepsy)
Vertigo	Vertigo causing no or minimal interference with usual social & functional activities	Vertigo causing greater than minimal interference with usual social & functional activities	Vertigo causing inability to perform usual social & functional activities	Disabling vertigo causing inability to perform basic self-care functions

PARAMETER	GRADE 1 MILD	GRADE 2 MODERATE	GRADE 3 SEVERE	GRADE 4 POTENTIALLY LIFE-THREATENING
RESPIRATORY				
Bronchospasm (acute)	FEV1 or peak flow reduced to 70 – 80%	FEV1 or peak flow 50 – 69%	FEV1 or peak flow 25 – 49%	Cyanosis OR FEV1 or peak flow < 25% OR Intubation
Dyspnea or respiratory distress	Dyspnea on exertion with no or minimal interference with usual social & functional activities	Dyspnea on exertion causing greater than minimal interference with usual social & functional activities	Dyspnea at rest causing inability to perform usual social & functional activities	Respiratory failure with ventilatory support indicated
MUSCULOSKELETAL				
Arthralgia See also Arthritis	Joint pain causing no or minimal interference with usual social & functional activities	Joint pain causing greater than minimal interference with usual social & functional activities	Joint pain causing inability to perform usual social & functional activities	Disabling joint pain causing inability to perform basic self-care functions
Arthritis See also Arthralgia	Stiffness or joint swelling causing no or minimal interference with usual social & functional activities	Stiffness or joint swelling causing greater than minimal interference with usual social & functional activities	Stiffness or joint swelling causing inability to perform usual social & functional activities	Disabling joint stiffness or swelling causing inability to perform basic self-care functions
Bone Mineral Loss	BMD t-score -2.5 to -1.0	BMD t-score < -2.5	Pathological fracture (including loss of vertebral height)	Pathologic fracture causing life-threatening consequences
Myalgia (non-injection site)	Muscle pain causing no or minimal interference with usual social & functional activities	Muscle pain causing greater than minimal interference with usual social & functional activities	Muscle pain causing inability to perform usual social & functional activities	Disabling muscle pain causing inability to perform basic self-care functions
Osteonecrosis	NA	Asymptomatic with radiographic findings AND No operative intervention indicated	Symptomatic bone pain with radiographic findings OR Operative intervention indicated	Disabling bone pain with radiographic findings causing inability to perform basic self-care functions

PARAMETER	GRADE 1 MILD	GRADE 2 MODERATE	GRADE 3 SEVERE	GRADE 4 POTENTIALLY LIFE-THREATENING
GENITOURINARY				
Cervicitis (symptoms) (For use in studies evaluating topical study agents)	Symptoms causing or minimal interference with usual social & functional activities	Symptoms causing greater than minimal interference with usual social & functional activities	Symptoms causing inability to perform usual social & functional activities	Symptoms causing inability to perform basic self-care functions
Cervicitis (clinical exam) (For use in studies evaluating topical study agents) For other cervicitis see Infection: Infection (any other than HIV infection)	Minimal cervical abnormalities on examination (erythema, mucopurulent discharge, or friability) OR Epithelial disruption	Moderate cervical abnormalities on examination (erythema, mucopurulent discharge, or friability) OR Epithelial disruption of 25 – 49% total surface	Severe cervical abnormalities on examination (erythema, mucopurulent discharge, or friability) OR Epithelial disruption 50 – 75% total surface	Epithelial disruption > 75% total surface
Inter-menstrual bleeding (IMB)	Spotting observed participant OR Minimal blood observed during clinical or colposcopic examination	Inter-menstrual bleeding not greater in duration or amount than usual menstrual cycle	Inter-menstrual bleeding greater in duration or amount than usual menstrual cycle	Hemorrhage with life-threatening hypotension OR Operative intervention indicated
Urinary tract obstruction (e.g., stone)	N	Signs or symptoms of urinary tract obstruction without hydronephrosis or renal dysfunction	Signs or symptoms of urinary tract obstruction with hydronephrosis or renal dysfunction	Obstruction causing life-threatening consequences
OCULAR/VISUAL				
Uveitis	Asymptomatic but detectable on exam	Symptomatic anterior uveitis OR Medical intervention indicated	Posterior or pan-uveitis OR Operative intervention indicated	Disabling visual loss in affected eye(s)
Visual changes (from baseline)	Visual changes causing no or minimal interference with usual social & functional activities	Visual changes causing greater than minimal interference with usual social & functional activities	Visual changes causing inability to perform usual social & functional activities	Disabling visual loss in affected eye(s)
ENDOCRINE/METABOLIC				
Abnormal fat accumulation (e.g., back of neck, breasts, abdomen)	Detectable by study participant (or by caregiver for young children and disabled adults)	Detectable on physical exam by health care provider	Disfiguring OR Obvious changes on casual visual inspection	NA

Diabetes mellitus	NA	New onset without need to initiate medication OR Modification of current medications to regain glucose control	New onset with initiation of medication indicated OR Diabetes uncontrolled despite treatment modification	Life-threatening consequences (e.g., ketoacidosis, hyperosmolar non-ketotic coma)

PARAMETER	GRADE 1 MILD	GRADE 2 MODERATE	GRADE 3 SEVERE	GRADE 4 POTENTIALLY LIFE-THREATENING
Gynecomastia	Detectable by study participant or caregiver (for young children and disabled adults)	Detectable on physical exam by health care provider	Disfiguring OR Obvious on casual visual inspection	NA
Hyperthyroidism	Asymptomatic	Symptomatic causing greater than minimal interference with usual social & functional activities OR Thyroid suppression therapy indicated	Symptoms causing inability to perform usual social & functional activities OR Uncontrolled despite treatment modification	Life-threatening consequences (e.g., thyroid storm)
Hypothyroidism	Asymptomatic	Symptomatic causing greater than minimal interference with usual social & functional activities OR Thyroid replacement therapy indicated	Symptoms causing inability to perform usual social & functional activities OR Uncontrolled despite treatment modification	Life-threatening consequences (e.g., myxedema coma)
Lipoatrophy (e.g., fat loss from the face, extremities, buttocks)	Detectable by study participant (or by caregiver for young children and disabled adults)	Detectable on physical exam by health care provider	Disfiguring OR Obvious on casual visual inspection	NA

LABORATORY				
PARAMETER	**GRADE 1 MILD**	**GRADE 2 MODERATE**	**GRADE 3 SEVERE**	**GRADE 4 POTENTIALLY LIFE-THREATENING**
HEMATOLOGY	***Standard International Units are listed in italics***			
Absolute neutrophil count (ANC)	*1.000 x 10^9 – 1.300 x 10^9/L*	*0.750 x 10^9 – 0.999 x 10^9/L*	*0.500 x 10^9 – 0.749 x 10^9/L*	*< 0.500 x 10^9/L*
Fibrinogen, decreased	*1.00 – 2.00 g/L* OR 0.75 – 0.99 x LLN	*0.75 – 0.99 g/L* OR 0.50 – 0.74 x LLN	*0.50 – 0.74 g/L* OR 0.25 – 0.49 x LLN	*< 0.50 g/L* OR < 0.25 x LLN OR Associated with gross bleeding

LABORATORY				
PARAMETER	**GRADE 1 MILD**	**GRADE 2 MODERATE**	**GRADE 3 SEVERE**	**GRADE 4 POTENTIALLY LIFE-THREATENING**
Hemoglobin (Hgb)				
HIV POSITIVE ONLY	8.5 – 10.0 g/dL	7.5 – 8.4 g/dL	6.50 – 7.4 g/dL	< 6.5 g/dL
HIV NEGATIVE ONLY	10.0 – 10.9 g/dL OR Any decrease 2.5 – 3.4 g/dL	9.0 – 9.9 g/dL OR Any decrease 3.5 – 4.4 g/dL	7.0 – 8.9 g/dL OR Any decrease ε4.5 g/dL	< 7.0 g/dL
Comment: The decrease is a decrease from baseline				
International Normalized Ratio of prothrombin time (INR)	1.1 – 1.5 x ULN	1.6 – 2.0 x ULN	2.1 – 3.0 x ULN	> 3.0 x ULN
Methemoglobin	5.0 – 10.0%	10.1 – 15.0%	15.1 – 20.0%	> 20.0%
Prothrombin Time (PT)	1.1 – 1.25 x ULN	1.26 – 1.50 x ULN	1.51 – 3.00 x ULN	> 3.00 x ULN
Partial Thromboplastin Time (PTT)	1.1 – 1.66 x ULN	1.67 – 2.33 x ULN	2.34 – 3.00 x ULN	> 3.00 x ULN
Platelets, decreased	*100.000 x 10^9 – 124.999 x 10^9/L*	*50.000 x 10^9 – 99.999 x 10^9/L*	*25.000 x 10^9 – 49.999 x 10^9/L*	*< 25.000 x 10^9/L*
WBC, decreased	*2.000 x 10^9 – 2.500 x 10^9/L*	*1.500 x 10^9 – 1.999 x 10^9/L*	*1.000 x 10^9 – 1.499 x 10^9/L*	*< 1.000 x 10^9/L*
CHEMISTRIES				
Acidosis	NA	pH < normal, but ε7.3	pH < 7.3 without life-threatening consequences	pH < 7.3 with life-threatening consequences
Albumin, serum, low	*30 g/L – < LLN*	*20 – 29 g/L*	*< 20 g/L*	NA
Alkaline Phosphatase	1.25 – 2.5 x ULN†	2.6 – 5.0 x ULN†	5.1 – 10.0 x ULN†	> 10.0 x ULN†
Alkalosis	NA	pH > normal, but δ7.5	pH > 7.5 without life-threatening consequences	pH > 7.5 with life-threatening consequences
ALT (SGPT)	1.25 – 2.5 x ULN	2.6 – 5.0 x ULN	5.1 – 10.0 x ULN	> 10.0 x ULN
AST (SGOT)	1.25 – 2.5 x ULN	2.6 – 5.0 x ULN	5.1 – 10.0 x ULN	> 10.0 x ULN
Bicarbonate, serum, low	*16.0 mmol/L – < LLN*	*11.0 – 15.9 mmol/L*	*8.0 – 10.9 mmol/L*	*< 8.0 mmol/L*
Bilirubin (Total)	1.1 – 1.5 x ULN	1.6 – 2.5 x ULN	2.6 – 5.0 x ULN	> 5.0 x ULN
Calcium, serum, high	*2.65 – 2.88 mmol/L*	*2.89 – 3.13 mmol/L*	*3.14 – 3.38 mmol/L*	*> 3.38 mmol/L*
Calcium, serum, low	*1.95 – 2.10 mmol/L*	*1.75 – 1.94 mmol/L*	*1.53 – 1.74 mmol/L*	*< 1.53 mmol/L*

Cardiac troponin I (cTnI)	NA	NA	NA	Levels consistent with myocardial infarction or unstable angina as defined by the manufacturer
Creatine Kinase	3.0 – 5.9 x ULN†	6.0 – 9.9 x ULN†	10.0 – 19.9 x ULN†	≥ 20.0 x ULN†
Creatinine	1.1 – 1.3 x ULN†	1.4 – 1.8 x ULN†	1.9 – 3.4 x ULN†	≥ 3.5 x ULN†

Lipase	1.1 – 1.5 x ULN	1.6 – 3.0 x ULN	3.1 – 5.0 x ULN	> 5.0 x ULN
Lactate	ULN - < 2.0 x ULN without acidosis	ε2.0 x ULN without acidosis	Increased lactate with pH < 7.3 without life-	Increased lactate with pH < 7.3 with life-
Magnesium, serum, low	*0.60 – 0.70 mmol/L*	*0.45 – 0.59 mmol/L*	*0.30 – 0.44 mmol/L*	*< 0.30 mmol/L*
Pancreatic amylase	1.1 – 1.5 x ULN	1.6 – 2.0 x ULN	2.1 – 5.0 x ULN	> 5.0 x ULN
Phosphate, serum, low	*0.81 mmol/L – < LLN*	*0.65 – 0.80 mmol/L*	*0.32 – 0.64 mmol/L*	*< 0.32 mmol/L*
Potassium, serum, high	*5.6 – 6.0 mmol/L*	*6.1 – 6.5 mmol/L*	*6.6 – 7.0 mmol/L*	*> 7.0 mmol/L*
Potassium, serum, low	*3.0 – 3.4 mmol/L*	*2.5 – 2.9 mmol/L*	*2.0 – 2.4 mmol/L*	*< 2.0 mmol/L*
Sodium, serum, high	*146 – 150 mmol/L*	*151 – 154 mmol/L*	*155 – 159 mmol/L*	ε*160 mmol/L*
Sodium, serum, low	*130 – 135 mmol/L*	*125 – 129 mmol/L*	*121 – 124 mmol/L*	δ*120 mmol/L*
URINALYSIS	***Standard International Units are listed in italics***			
Hematuria (microscopic)	6 – 10 RBC/HPF	> 10 RBC/HPF	Gross, with or without clots OR with RBC casts	Transfusion indicated
Proteinuria, random collection	1 +	2 – 3 +	4 +	NA
Proteinuria, 24 hour collection				
Adult	*0.200 – 0.999 g/d*	*1.000 – 1.999 g/d*	*2.000 – 3.500 g/d*	*> 3.500 g/d*

PARAMETER	**GRADE 1 MILD**	**GRADE 2 MODERATE**	**GRADE 3 SEVERE**	**GRADE 4 POTENTIALLY LIFE-THREATENING**
Glucose, serum, high				
Nonfasting	*6.44 – 8.88 mmol/L*	*8.89 – 13.88 mmol/L*	*13.89 – 27.75 mmol/L*	*> 27.75 mmol/L*
Fasting	*6.11 – 6.94 mmol/L*	*6.95 – 13.88 mmol/L*	*13.89 – 27.75 mmol/L*	*> 27.75 mmol/L*
Glucose, serum, low	*3.05 – 3.55 mmol/L*	*2.22 – 3.06 mmol/L*	*1.67 – 2.23 mmol/L*	*< 1.67 mmol/L*