Rosuvastatin versus Protease Inhibitor Switching for Hypercholesterolaemia in HIV-infected Adults

INVESTIGATORS (Sydney)
Professor Andrew Carr (Principal investigator)
Dr. Frederick J. Lee
Professor Bruce Brew
Associate Professor Debbie Marriott
Associate Professor Tony Kelleher
Dr. Gail Matthews
Dr. Sarah Pett
Robyn Richardson, RN
Nicola Mackenzie, RN
St. Vincent's Hospital, AMR-CRP
University of New South Wales

Dr. Mark Bloch
Holdsworth House Medical Practice

Dr. David Baker
East Sydney Doctors

Dr. Robert Finlayson
Taylor Square Private Clinic

INVESTIGATORS (Melbourne)
Professor Jennifer Hoy
Alfred Hospital and Monash University

Dr. Norman Roth
Prahran Market Clinic

Dr. Richard Moore
Northside Clinic

Dr. Ban Kiem Tee
Centre Clinic

INVESTIGATORS (Spain)
Associate Professor Esteban Martínez
University of Barcelona

Protocol Version: 5.0
Date of Protocol: October 22, 2012
NCT Number: NCT01935674

TABLE OF CONTENTS

Investigator Agreement and Signature Page

We accept responsibility for the conduct of the research detailed in the proposal including all protocol-specific assessments, and we agree to abide by all decisions made by our Ethics Committee.

We agree to the above which, in conjunction with the NHMRC Statement on Ethical Conduct in Research Involving Humans, will serve as the basis for co-operation in this study.

Responsible Investigator

Professor Andrew Carr (signature and date)		

Co-Investigators

Dr. Sarah Pett (signature and date)		
Professor Bruce Brew (signature and date)		
A/Professor Debbie Marriott (signature and date)		
A/Professor Tony Kelleher (signature and date)		
Dr. Gail Matthews (signature and date)		
Dr. Frederick J. Lee (signature and date)		
Robyn Richardson, RN (signature and date)		
Nicola Mackenzie, RN (signature and date)		
Dr. Mark Bloch (signature and date)		
Dr. David Baker (signature and date)		
Dr. Robert Finlayson (signature and date)		
Professor Jenny Hoy (signature and date)		
Dr. Norman Roth (signature and date)		
Dr. Richard Moore (signature and date)		

Dr. Ban Kiem Tee (signature and date)		

A/Professor Esteban Martínez (signature and date)		

CONTACT DETAILS

Sponsor Project Team

Co-ordinating Investigator	Professor Andrew Carr
Project Manager/Co-investigator	Dr. Frederick J. Lee
Co-investigator	Robyn Richardson, RN
Study Co-ordinator/Co-investigator	Nicola Mackenzie, RN

Address:
Centre for Applied Medical Research
Clinical Research Program and
HIV, Immunology and Infectious Diseases Unit
Level 4 Xavier Building
St Vincent's Hospital
390 Victoria Street
Darlinghurst NSW 2010

External Site Principal Investigators

Professor Jenny Hoy
Infectious Diseases Unit
Level 2, Burnet Institute
The Alfred Hospital
85 Commercial Road
Melbourne VIC 3004

Dr. Mark Bloch
Holdsworth House Medical Practice
32a Oxford Street
Darlinghurst NSW 2010

Dr. David Baker
East Sydney Doctors
102 Burton St
East Sydney NSW 2010

Dr. Robert Finlayson
Taylor Square Private Clinic
393 Bourke St
Darlinghurst NSW 2010

Dr. Norman Roth
Prahran Market Clinic
Prahran Central, Mezzanine Level
Corner Commercial Road & Chapel Street
Prahran VIC 3181

Dr. Richard Moore
Northside Clinic
370 St Georges Rd
Fitzroy North VIC 3068

Dr. Ban Kiem Tee
Centre Clinic
The rear 77 Fitzroy St
St Kilda, VIC 3182

A/Professor Esteban Martínez
Infectious Diseases Unit
Hospital Clinic
University of Barcelona
08036 Barcelona
Spain European Union

PROTOCOL SYNOPSIS

Protocol title: Rosuvastatin versus Protease Inhibitor Switching for Hypercholesterolaemia in HIV-infected Adults.

Primary Objective: To compare the effect of rosuvastatin to protease inhibitor switching on fasting total cholesterol over 12 weeks.

Study design: The study is an open-label, randomised, 12-week trial. Sixty (60) eligible participants will be randomly allocated 1:1 to:

a. switch their existing ritonavir-boosted protease inhibitor to another potent antiretroviral therapy (ART) drug with lesser effects on serum cholesterol selected by the investigator. Potential switch drugs include:
- for patients receiving a ritonavir-boosted protease inhibitor (PI) with 2 nucleoside analogue reverse transcriptase inhibitors (NRTIs): raltegravir, nevirapine, rilpivirine and unboosted atazanavir
- for patients receiving a ritonavir-boosted PI plus 1 or more other drugs (e.g. raltegravir, efavirenz) but not a NRTI - additional switch options include tenofovir, lamivudine and emtricitabine, such that the patient is receiving at least 3 potent drugs after the switch)

OR

b. continue ritonavir-boosted PI-based ART and commence rosuvastatin 10 mg daily (5 mg daily in Asian participants).

Planned sample size: Sixty (60) eligible participants

Inclusion criteria:
1. HIV-positive status
2. Adults (≥18 years of age)
3. Stable and well-tolerated combination ART including a ritonavir-boosted PI for the previous 6 months
4. HIV RNA <50 copies/mL for at least the preceding 3 months
5. Fasting total cholesterol ≥5.5 mmol/L (>213 mg/dL)
6. Framingham risk score ≥8% at 10 years **OR** diabetes mellitus **OR** a family history of premature coronary artery disease in a first-degree relative
7. Provision of written, informed consent

Exclusion criteria:
8. Any statin in the previous 12 weeks
9. Previous statin-induced myopathy or hepatitis
10. History of coronary artery disease, stroke or any other indication for the use of statin therapy (hyperlipidaemia: genetic, secondary or idiopathic)
11. Concurrent use of:
    - oral corticosteroids use other than for replacement therapy (ie. prednisolone 5-7.5 mg, hydrocortisone 20-30 mg, cortisone acetate 25-37.5 mg daily)
    - other immunosuppressive or immunomodulating drugs

12. Contra-indication to rosuvastatin therapy:
    - liver transaminases >5 times the upper normal limit
    - creatinine clearance <30 mL/min
    - known myopathy
    - current fibrate therapy
    - known resistance to one or more “backbone” ART drugs
13. No potent switch ART drug available to replace the current ritonavir-boosted PI
14. Known intolerance to rosuvastatin or the proposed switch ART drug
15. Women attempting or likely to become pregnant, or who are pregnant or breast-feeding
16. A patient with a history or current evidence of any condition, therapy, or laboratory abnormality, or other circumstance that might confound the results of the study, or interfere with the patient’s participation for the full duration of the study
17. Unable to complete study procedures

Study procedures:
There will be 4 study visits over the 14-week study period. Procedures will include assessments of safety, HIV viral load, and fasting lipid and glycaemic levels.
All participants will receive standardised dietary and exercise education at each visit.
Patients and physicians will be blinded to lipid results until week 12.

Flow chart of assessments

Time of Visit	**Screen**	**Baseline**		
Week	**-2**	**0**	**4**	**12**
Clinical				
Informed consent	x			
Inclusion / exclusion criteria	x			
Demographic data	x			
Full physical examination / history	x			
Targeted physical examination		x	x	x
Concomitant medication	x	x	x	x
Adverse events		x	x	x
Select drug to replace current boosted PI	x			
Randomization*	x			
Framingham and DAD scores	x			x
Vital signs (pulse, blood pressure, temperature)	x	x	x	x
Height		x		
Weight	x	x	x	x
SF-12 QOL & GIT symptoms questionnaires		x	x	x
Dispense rosuvastatin or change PI		x	x	
Dietary and exercise education		x	x	x
Pathology				
Pregnancy test	x^			
HIV RNA viral load	x^		x^	x^
Biochemistry[1]	x^	x^	x^	x^
Full blood count		x^	x^	x^
CD4+ lymphocyte count and percentage		x^	x^	x^
Fasting total cholesterol	x^			
Complete fasting lipid profile[2]	x^	x	x	x
LDL particle size (fasting)		x	x	x
Glucose / insulin (fasting)		x^		x^
D-dimer[3]		x	x	x
Plasma and serum storage[4]		x	x	x

* Randomization to take place at Day -2 or -1, after all eligibility criteria confirmed

1 *Biochemistry:* urea, electrolytes (including calcium, magnesium and phosphate), creatinine, liver function tests (alanine aminotransferase [ALT], aspartate aminotransferase [AST], albumin, total protein, alkaline phosphatase [ALP], gamma glutamyltransferase [GGT], bilirubin), creatine kinase

^ Requested as standard-of-care pathology

2 *Complete fasting lipid profile:* Triglycerides, total cholesterol, HDL and LDL cholesterol, and calculated VLDL cholesterol. Measured VLDL cholesterol, if required, is available for participants from Sydney sites only. Blood samples collected after a 9- to 12-hour overnight fast (usual intake of water recommended)

3 Collected as plasma storage samples; D-dimer will be analysed at the end of study from stored samples

4 4 x 1 mL plasma and 3 x 1 mL serum aliquots to be stored

Unscheduled visits would include: targeted medical review, safety bloods, and study co-ordinator assessment

1. BACKGROUND

1.1. Management of dyslipidaemia in HIV-infected adults receiving a protease inhibitor

Dyslipidaemia, and in particular elevated plasma levels of total and low-density lipoprotein (LDL) cholesterol, is common in HIV-infected adults. Dyslipidaemia is associated with protease inhibitor (PI) -based anti-retroviral therapy (ART) and an increased risk of myocardial infarction [(1)].

Dyslipidaemia has proven to be a common reason for switching from PI-based therapy, particularly from lopinavir-ritonavir, initially to atazanavir, and more recently to raltegravir. The effects of ritonavir-boosted darunavir and fosamprenavir are very similar to those of lopinavir-ritonavir – switching from ritonavir-boosted darunavir as likely to become more common as more patients commence darunavir as first-line ART.

The two proven strategies to lower total and LDL cholesterol levels in HIV-infected adults receiving a PI and who have hypercholesterolaemia are statin therapy and PI-switching to an alternative ART [(2-6)]. The preferred strategy is unknown.

The preferred statin in this population may be rosuvastatin 10 mg daily, as it had greater lipid-lowering activity than and similar tolerability to pravastatin 40 mg daily [(6)].

Potential switch drugs for patients receiving a ritonavir-boosted PI with 2 nucleoside analogues are raltegravir, nevirapine, rilpivirine and unboosted atazanavir, all of which have little if any effect on lipid metabolism (although not all drugs may be suitable for virological or other reasons). For patients receiving a ritonavir-boosted PI plus other drugs (e.g. raltegravir, efavirenz) but not a nucleoside analogue, additional switch options without lipid effects are include tenofovir, abacavir, lamivudine and emtricitabine. Statin therapy and PI switching both have potential advantages and disadvantages:

- Statin therapy - potential advantages
    - proven efficacy in reducing cardiovascular risk in the general population both as primary and secondary prevention
    - generally well-tolerated. Indeed, simvastatin is available over-the-counter in some countries without a prescription
    - several statins (pravastatin, atorvastatin or rosuvastatin) can be used safely with PI therapy, although smaller than usual doses of atorvastatin and rosuvastatin are often used as both drugs can attain higher levels in patients receiving a PI because of pharmacokinetic interactions
    - statins may have anti-inflammatory effects independent of their lipid-lowering effects [(7)] that have been hypothesised to incur additional cardiovascular benefit
    - minimal risk of virological failure
- Statin therapy - potential disadvantages
    - potential side effects (hepatitis and myopathy/rhabdomyolysis)
    - means using a drug to treat another drug toxicity
    - increases pill burden and treatment costs, both undesirable in a disease in which pill burden associates with ART efficacy and in a disease that is lifelong

- PI switching - potential advantages
    - removes cause of the hypercholesterolaemia
    - less likely to increase pill burden or costs
- PI switching - potential disadvantages
    - PI therapy may not be the cause of dyslipidaemia in many patients - other causes include genetics, diet and obesity
    - virological failure; e.g. in the SWITCHMRK study, switching from a protease inhibitor to raltegravir resulted in significantly greater virological failure, which was evident within 12 weeks of switching [8]
    - drug toxicity from the new antiretroviral drug
    - reduces available ART choices, which is increasingly important given the greatly diminishing HIV drug pipeline

Only one study has compared the statin and switch strategies [2]. In this trial, statin therapy appeared similar to PI switching at lowering total and LDL cholesterol over 24 weeks. However, this study has numerous limitations and uncertainties:

- one of the switch drugs was efavirenz, which is also known to occasionally induce very similar lipid changes as protease inhibitor therapy
- the PI drugs evaluated are now rarely prescribed (indinavir, saquinavir, nelfinavir)
- the maximum effect on cholesterol levels was observed at 24 weeks, which is substantially later than the 4 to 6 weeks stated in statin product labels [9,10]
- the statin used was pravastatin 40 mg nocte, which has subsequently been found to be less potent than rosuvastatin 10 mg daily [6].

Intervening for hypercholesterolaemia will only be clinically meaningful if patients have elevated underlying cardiovascular risk that, for the purposes of this study, is defined as a Framingham score of at least 8% at 10 years (a score of at least 10% would be reasonable in HIV-negative patients, but HIV-infected adults appear to have a rate of myocardial infarction higher than expected for any given Framingham score), or a diagnosis of diabetes mellitus, or a family history of premature coronary artery disease.

We propose a randomised, open-label, 12-week trial in which eligible participants will be randomised 1:1 to either:

A. Switch of existing ritonavir-boosted protease inhibitor to another potent antiretroviral drug without effects on serum cholesterol selected by the investigator. Potential switch drugs:

- for patients receiving a ritonavir-boosted PI with 2 nucleoside analogues - raltegravir, nevirapine, rilpivirine, and unboosted atazanavir.
- for patients receiving a ritonavir-boosted PI plus 1 or more other drugs (e.g. raltegravir, efavirenz) but not a nucleoside analogue - additional switch options include tenofovir, abacavir, lamivudine and emtricitabine, such that the patient is receiving at least 3 potent drugs after the switch.

OR

B. Continue ritonavir-boosted protease inhibitor-based ART and commence rosuvastatin 10 mg daily (5 mg daily in Asian participants).

1.2. Rationale for Performing the Study

Intervening for hypercholesterolaemia will only be of clinical significance if patients have an elevated underlying cardiovascular risk profile. For the purposes of this study, this is defined as any of the following: a Framingham score of ≥8% at 10 years in an HIV-infected person OR a diagnosis of diabetes mellitus OR a family history of premature coronary artery disease in a first-degree relative. In persons who are HIV-negative, a Framingham score of 10% would be not unreasonable, but HIV-infected adults have a trend of higher rates of myocardial infarction for any given Framingham score.

Presently, the two proven and accepted strategies for lowering total and LDL cholesterol levels in HIV-infected adults receiving a ritonavir-boosted PI with hypercholesterolaemia are either:

(1) statin therapy; or

(2) switching the ritonavir-boosted PI to an alternative ART [2-6].

The optimal strategy however, is not known. Therefore, we propose a randomised, open-label, 12-week prospective trial to compare the effect of rosuvastatin to protease inhibitor switching on fasting total serum cholesterol.

1.3. Hypothesis

That rosuvastatin will be more effective than protease inhibitor switching for hypercholesterolaemia in HIV-infected adults receiving a ritonavir-boosted protease inhibitor.

2. STUDY OBJECTIVES

2.1. Primary Objective

To compare the effect of rosuvastatin to protease inhibitor switching on fasting total cholesterol over 12 weeks

2.2. Secondary Objectives

To compare the effects of rosuvastatin to protease inhibitor switching on:

- Total cholesterol through week 12
- Safety parameters (HIV viral load, clinical adverse events, serious adverse events, laboratory adverse events, modifications to antiretroviral therapy)
- Quality of life (SF-12)
- Fasting LDL cholesterol (estimated with Friedwald equation unless triglycerides >400mg/dL, in which case LDL-C would be measured directly), HDL cholesterol, total : HDL cholesterol ratio, LDL particles sizes, triglycerides
- Fasting glucose and insulin
- Framingham cardiovascular risk score (available at: http://hp2010.nhlbihin.net/atpiii/calculator.asp?usertype=prof)
- D:A:D 5-year estimated risk calculator (available at: http://www.cphiv.dk/TOOLS/DADRiskEquations/tabid/437/Default.aspx)

2.3. Key Outcomes Expected

That rosuvastatin therapy will lead to greater reduction in total cholesterol than protease inhibitor switching, with similar safety and no adverse effect on HIV virological control.

3. STUDY DURATION

Twelve (12) weeks

3.1. Number of Centres

This study will be performed at nine sites:

1. St Vincent's Centre for Applied Medical Research (AMR), Clinical Research Program (CRP) St Vincent's Hospital, Sydney
2. Holdsworth House Medical Practice, Sydney
3. East Sydney Doctors, Sydney
4. Taylor Square Private Clinic, Sydney
5. Infectious Diseases Unit, Alfred Hospital, Melbourne
6. Prahran Market Clinic, Melbourne
7. Northside Clinic, Melbourne
8. Centre Clinic, Melbourne
9. Infectious Diseases Department, Hospital Clinic, University of Barcelona

4. SELECTION CRITERIA

4.1. Total Number of patients

Sixty (60) eligible participants

4.2. Inclusion criteria:

1. HIV-positive status
2. Adults (≥18 years of age)
3. Stable and well-tolerated combination ART including a ritonavir-boosted protease inhibitor for the previous 6 months
4. HIV RNA <50 copies/mL for at least the preceding 3 months
5. Fasting total cholesterol ≥5.5 mmol/L (>213 mg/dL)
6. Framingham risk score ≥8% at 10 years **OR** diabetes mellitus **OR** a family history of premature coronary artery disease in a first-degree relative
7. Provision of written, informed consent

4.3. Exclusion criteria:

8. Any statin in the previous 12 weeks
9. Previous statin-induced myopathy or hepatitis
10. History of coronary artery disease, stroke or any other indication for the use of statin therapy (hyperlipidaemia: genetic, secondary or idiopathic)
11. Concurrent use of:
    - oral corticosteroids use other than for replacement therapy (i.e. prednisolone 5-7.5 mg, hydrocortisone 20-30 mg, cortisone acetate 25-37.5 mg daily)
    - other immunosuppressive or immunodulating drugs
12. Contraindication to rosuvastatin therapy:
    - liver transaminases >5 times the upper normal limit
    - creatinine clearance <30 mL/min
    - known myopathy
    - current fibrate therapy
    - known resistance to one or more "backbone" ART drugs

13. No potent switch ART drug available to replace the current ritonavir-boosted protease inhibitor
14. Known intolerance to rosuvastatin or the proposed switch ART drug
15. Women attempting or likely to become pregnant, or who are pregnant or breast-feeding
16. A patient with a history or current evidence of any condition, therapy, or laboratory abnormality, or other circumstance that might confound the results of the study, or interfere with the patient's participation for the full duration of the study
17. Unable to complete study procedures

5. STUDY DESIGN

5.1. Design

This is a randomized, open-label, 12-week prospective trial. Sixty (60) eligible subjects will be randomly allocated 1:1 to either:

(A) switch their existing ritonavir-boosted PI to another potent ART drug with lesser effects on serum cholesterol selected by the investigator; **OR**

(B) continue ritonavir-boosted PI-based ART and commence rosuvastatin 10 mg daily (5 mg daily in Asian participants).

For patients in the switch arm, potential switch drugs that are recommended are shown in the table below:

Lipid switch or statin study – Switch options

Current regimen	Switch options for rPI (per DHHS guidelines)[1]	New regimen	Considerations (apart from prior resistance)
TDF-FTC-rPI	NNRTI	TDF-FTC-NNRTI	• Nevirapine and rilpivirine preferred[3]
	Raltegravir	TDF-FTC-RAL	•
ABC-3TC-rPI	NNRTI	ABC-3TC-NNRTI	• Nevirapine and rilpivirine preferred[3]
	Raltegravir	ABC-3TC-RAL	•
	Unboosted atazanavir[2]	ABC-3TC-AZV	•
NNRTI-rPI	TDF-FTC	TDF-FTC-NNRTI	•
	ABC-3TC	ABC-3TC-NNRTI	•
RAL-rPI	TDF-FTC	RAL-TDF-FTC	•
	ABC-3TC	RAL-ABC-3TC	•

Footnotes:

1. rPI switch to etravirine is not permitted until etravirine switching is approved by the Therapeutic Good

Administration and ASHM (Australia) or by the European Medicines Agency and EACS (Spain). rPI switch to maraviroc is not permitted until maraviroc switching using the DNA tropism assay is approved by the Therapeutic Good Administration and ASHM (Australia) or by the European Medicines Agency and EACS (Spain).

2. Unboosted atazanavir should NOT be used with tenofovir.
3. Efavirenz as a switch NNRTI is acceptable, but not preferred.

Randomisation will be stratified by baseline protease inhibitor type and by baseline total cholesterol (>7.0 mmol/L or ≤7.0 mmol/L [275 mg/dL]). Randomisation (blocks of six) within each stratum will be performed by Centre for Applied Medical Research (CAMR) staff otherwise not involved in the study. A computerized random number generator with a blocking factor of 3 will be used to produce a random number list.

There will be 4 study visits over the 14-week study period. Procedures will include assessments of safety, HIV viral load, and fasting lipid and glycaemic levels.

All participants will receive standardised dietary and exercise education at each visit.

LDL particle size testing will be performed at one central laboratory (LipoScience Global Research Services, North Carolina, USA). All other study pathology will be performed locally for each of the participating study sites.

New interventions (new pharmacological or antiretroviral drug change, depending on randomised study arm) will be discouraged. Patients and physicians will be blinded to lipid results until week 12. However, if the total cholesterol rises during the study by ≥2.0 mmol/L from Baseline (Week 0), then this result will be unblended and notified to the respective principal investigators at the corresponding sites for review, follow-up and monitoring. Crossover between study arms will not be permitted. Modifications after week 12 will be based on local practice.

5.2. Interventions and Assessments

All study procedures will be performed at the individual study sites over 12 weeks.

Dietary and exercise education: Standardised dietary and exercise education will be provided to study patients at baseline, and followed up at week 4 and week 12 visits.

Anthropometry: Weight (at all visits) and height (at baseline only) will be measured. Body Mass Index (BMI) will be calculated by dividing weight by height squared (kg/m^2).

Fasting metabolic parameters: After arrival and a 10 minute rest, fasting samples will be taken for triglycerides, total cholesterol, HDL and LDL cholesterol. LDL particle size, glucose and insulin. VLDL cholesterol will be calculated, but if a measured value is required, this is only available for participants from Sydney sites. D-dimer will be measured at the end of study from a sodium citrate tube (light blue top) collected as part of plasma storage.

Study participants and study staff will be blinded to the results of these tests until completion of the study at week 12. This is to prevent self-modification of lifestyle or diet in an attempt to normalise out-of-range results.

Quality of Life Questionnaire SF-12: Study participants will be asked to complete the SF-12 (standard, 4 week) quality of life questionnaire at baseline, weeks 4 and 12. (see appendix 2).

GIT symptoms questionnaire: At baseline, week 4 and week 12, specific questions will be asked regarding presence of nausea and diarrhoea and severity if applicable (see appendix 3).

Blood for storage: Some plasma will be stored for possible subsequent testing of as-yet undecided plasma proteins. These proteins might include one or more lipid, glycaemic, cardiovascular or inflammatory plasma proteins that are potentially related to cardiovascular disease in HIV-infected adults and/or in the general population. Storage samples will be collected at visits baseline, week 4 and week 12.

6. STUDY MEDICATION

Participants will be randomly allocated 1:1 to switch their existing ritonavir-boosted protease inhibitor to another potent antiretroviral or continue ritonavir-boosted protease inhibitor-based ART and commence rosuvastatin 10mg daily (5 mg daily in Asian participants).

6.1. Rosuvastatin

Rosuvastatin is a hypolipidaemic agent and member of the drug class of statins (HMG-CoA reductase inhibitors) 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 hypercholesterolaemia (including familial hypercholesterolaemia). Rosuvastatin should be used as an adjunct to dietary modification.

In the ROSUVASTATIN [6] study, treatment with rosuvastatin 10 mg daily resulted in a 28% reduction in total cholesterol (SD=18%) and 35% reduction in LDL cholesterol (SD=17%). Rosuvastatin 10mg daily had similar tolerability and greater lipid-lowering effect in that study than pravastatin 40 mg daily. Therefore, rosuvastatin is the statin to be used in the present study.

Patients randomised to the rosuvastatin treatment arm will continue their ritonavir-boosted protease inhibitor-based ART and commence rosuvastatin 10 mg daily (5 mg daily for Asian participants, as the risk of myopathy during rosuvastatin therapy may be increased in Asians). Please refer to the rosuvastatin product label and prescribing information for further information on the side-effect profile.

6.2. ART Switch Options

The switch drug will be selected by the site investigator at the screening visit and prior to randomisation.

Potential preferred switch drugs for patients receiving a ritonavir-boosted PI with 2 nucleoside analogues include: raltegravir, nevirapine, rilpivirine, and unboosted atazanavir.

Potential switch drugs for patients receiving a ritonavir-boosted PI plus 1 or more other drugs (e.g. raltegravir, efavirenz) but not a nucleoside analogue include: tenofovir, lamivudine, abacavir and emtricitabine, such that the patient is receiving at least 3 potent drugs after the switch.

6.3. Provision of Antiretroviral drugs and Rosuvastatin at Study Completion

Once the final study visit has occurred (week 12 visit) all ART will be obtained by prescription from the study participant's treating doctor. If at the end of the study

rosuvastatin is shown to be safe and effective, the study participant's treating doctor will continue to prescribe rosuvastatin.

7. VISIT SCHEDULE

Eligibility Screening Form

An eligibility screening form should be completed at the screening visit. Participant details will be entered on the study participant identification log including whether or not the participant was included, and if excluded, the reason why.

Eligibility of participants

Prior to screening, participants must be on stable and well-tolerated ART including a ritonavir-boosted protease inhibitor for at least 6 months prior to randomisation.

Informed consent should be obtained and forms signed and dated by the participant prior to any study-related procedures being performed.

7.1. Screening Visit (days -14 to -1)

The screening procedures will be completed in one visit.
Participants will present to the study site, having fasted from overnight for the previous 9 to 12 hours (no food, caffeine or caloric drink; free water intake encouraged to maintain adequate hydration) for at least 12 hours.

Assessments (results to be recorded in the CRF)

Clinical eligibility will be measured by inclusion criteria numbers 1-7 and exclusion criteria numbers 8-17 as listed below.

7.2. Inclusion criteria:

1. HIV-positive status
2. Adults (≥18 years of age)
3. Stable and well-tolerated combination ART including a ritonavir-boosted PI for the previous 6 months
4. HIV RNA <50 copies/mL for at least the preceding 3 months
5. Fasting total cholesterol ≥5.5 mmol/L (>213 mg/dL)
6. Framingham risk score ≥8% at 10 years **OR** diabetes mellitus **OR** a family history of premature coronary artery disease in a first-degree relative
7. Provision of written, informed consent

7.3. Exclusion criteria:

8. Any statin in the previous 12 weeks
9. Previous statin-induced myopathy or hepatitis
10. History of coronary artery disease, stroke or any other indication for the use of statin therapy (hyperlipidaemia: genetic, secondary or idiopathic)
11. Concurrent use of:
    - oral corticosteroids use other than for replacement therapy (ie. prednisolone 5-7.5 mg, hydrocortisone 20-30 mg, cortisone acetate 25-37.5 mg daily)
    - other immunosuppressive or immunomodulating drugs
12. Contra-indication to rosuvastatin therapy:
    - liver transaminases >5 times the upper normal limit
    - creatinine clearance <30mL/min
    - known myopathy
    - current fibrate therapy
    - known resistance to one or more “backbone” ART drugs
13. No potent switch ART drug available to replace the current ritonavir-boosted protease inhibitor
14. Known intolerance to rosuvastatin or the proposed switch ART drug
15. Women attempting or likely to become pregnant, or who are pregnant or breast-feeding
16. A patient with a history or current evidence of any condition, therapy, or laboratory abnormality, or other circumstance that might confound the results of the study, or interfere with the patient’s participation for the full duration of the study
17. Unable to complete study procedures

Other screening assessments

- Demographic data: date of birth, age, gender, race, smoking status (nil ever, years since stopped, current per day), alcohol intake (drinks per week)
- Framingham and D:A:D score and components
  - number of years on indinavir, lopinavir
  - myocardial infarction or stroke in a first degree relative (mother, father or sibling) and age of relative at time of incident
  - use of medication to treat blood pressure
  - has the patient been diagnosed with diabetes
- Full physical examination, medical history concomitant medications information and selection of drug to replace current boosted PI will be obtained by the study doctor
- Pulse and blood pressure will be recorded with the patient sitting for at least 10 minutes
- Weight
- Quality of life and GIT symptoms questionnaires

After 10 minutes of rest, blood samples will be taken for <u>Pathology</u>

Safety

- For potentially child-bearing female participants a blood test will be done to exclude pregnancy.
- HIV antibodies/Western blot/proviral DNA (if report not available prior to study entry)
- HIV RNA viral load
- Biochemistry – urea, electrolytes (sodium, potassium, chloride, bicarbonate, calcium, magnesium and phosphate), creatinine, liver function tests (alanine aminotransferase [ALT], aspartate aminotransferase [AST], albumin, total protein, alkaline phosphatase [ALP], gamma glutamyltransferase [GGT], bilirubin, creatine kinase

Fasting metabolic parameters

- total cholesterol, triglycerides, HDL/LDL cholesterol and calculated VLDL cholesterol. Measured VLDL cholesterol is available for subjects from Sydney sites only.
- D-dimer will be measured at the end of study from a sodium citrate tube (light blue top) collected as part of the plasma storage sample.

Pathology results are to be attached behind the pathology collection page of the screening CRF.

7.4. Eligibility of participants

Screened participants will have their switch ART (to replace current boosted PI) by an investigator during the screening visit, prior to randomisation. If the participant meets all the eligibility criteria (1 to 17) then a Baseline (Week 0) Visit will be booked.

7.5. Randomisation

Eligible subjects will be randomly allocated 1:1 to switch their existing ritonavir-boosted PI to another potent antiretroviral drug without effects on serum cholesterol selected by the investigator **OR** continue ritonavir-boosted PI-based ART and commence rosuvastatin 10 mg daily (5 mg daily in Asian participants).

Participant randomisation to one of the two arms should occur as soon as screening pathology results are available, but in any case not less than one (1) working day prior to baseline visit to allow for medication arrangement and coordination of Baseline Visit.

Central randomisation will be performed by a staff member of the Clinical Research Program, St Vincent's Hospital, NSW, Australia who is uninvolved in the conduct of the trial. A computerized random number generator with a blocking factor of 3 will be used to produce a random number list.

Following randomisation, a prescription for the switch ART or rosuvastatin will be written by the study doctor. The hospital pharmacy will prepare the script prior to the Baseline Visit in preparation for the participants scheduled Baseline Visit.

7.6. Baseline Visit (week 0)

Participants will present to the study site having fasted from overnight for the previous 9 to 12 hours (no food or drink with calories; but free water intake encouraged to maintain adequate hydration).

Baseline assessments will be recorded in the CRF: vital signs (blood pressure and pulse rate), height and weight, targeted physical examination, new concomitant medications, and adverse events and SF-12 quality of life and GIT Symptoms questionnaires.

After 10 minutes of rest, blood samples will be taken for full blood count, biochemistry – urea, electrolytes (sodium, potassium, chloride, bicarbonate, calcium, magnesium and phosphate), creatinine, liver function tests (alanine aminotransferase [ALT], aspartate aminotransferase [AST], albumin, total protein, alkaline phosphatase [ALP], gamma glutamyltransferase [GGT], bilirubin), creatine kinase, CD4+ lymphocyte count, total cholesterol, triglycerides, HDL and LDL cholesterol, LDL particle size, glucose, insulin and plasma and serum for storage. VLDL cholesterol will be calculated, but if a measured value is required, this is only available for participants from Sydney sites. D-dimer will be measured at the end of study from a sodium citrate tube (light blue top) collected as part of the plasma storage sample.

Dietary and exercise advice will be provided (Dietary and exercise advice for HIV-positive persons with high cholesterol, Master Version 1.0, June 30, 2012).

Study participants will be provided with one (1) month's supply of study medication, sufficient to cover 4 weeks, including the allowable study window (±2 days).

7.7. Week 4

Participants will present to the study site having fasted from overnight for the previous 9 to 12 hours (no food or drink with calories; but free water intake encouraged maintain adequate hydration).

Week 4 assessments will be recorded in the CRF: vital signs (blood pressure and pulse rate), weight, targeted physical examination, new concomitant medications, and adverse events and SF-12 quality of life and GIT Symptoms questionnaires.

After 10 minutes of rest, blood samples will be taken for full blood count, biochemistry – urea, electrolytes (sodium, potassium, chloride, bicarbonate, calcium, magnesium and phosphate), creatinine, liver function tests (alanine aminotransferase [ALT], aspartate aminotransferase [AST], albumin, total protein, alkaline phosphatase [ALP], gamma glutamyltransferase [GGT], bilirubin), creatine kinase, CD4+ lymphocyte count, total cholesterol, triglycerides, HDL and LDL cholesterol, LDL particle size, glucose, insulin and plasma and serum for storage. VLDL cholesterol will be calculated, but if a measured value is required, this is only available for participants from Sydney sites. D-dimer will be measured at the end of study from a sodium citrate tube (light blue top) collected as part of the plasma storage sample.

Dietary and exercise advice will be provided (Dietary and exercise advice for HIV-positive persons with high cholesterol, Master Version 1.0, June 30, 2012).

At Week 4, study participants will be provided with study medication for two (2) months plus an additional two (2) weeks supply to allow for the allowable study window (±7 days). The additional supply is dispensed at this visit, and not baseline, to ensure tolerability.

7.8. Week 12

Participants will present to the study site having fasted from overnight for the previous 9 to 12 hours (no food or drink with calories; but free water intake encouraged to maintain adequate hydration).

Week 12 assessments will be recorded in the CRF: vital signs (blood pressure and pulse rate), weight, targeted physical examination, new concomitant medications, and adverse events and SF-12 quality of life and GIT Symptoms questionnaires.

After 10 minutes of rest, blood samples will be taken for full blood count, biochemistry – urea, electrolytes (sodium, potassium, chloride, bicarbonate, calcium, magnesium and phosphate), creatinine, liver function tests (alanine aminotransferase [ALT], aspartate aminotransferase [AST], albumin, total protein, alkaline phosphatase [ALP], gamma glutamyltransferase [GGT], bilirubin, creatine kinase, CD4+ lymphocyte count, total cholesterol, triglycerides, HDL and LDL cholesterol, LDL particle size, glucose, insulin and plasma and serum for storage. VLDL cholesterol will be calculated, but if a measured value is required, this is only available for participants from Sydney sites. D-dimer will be measured at the end of study from a sodium citrate tube (light blue top) collected as part of plasma storage.

Dietary and exercise advice will be provided (Dietary and exercise advice for HIV-positive persons with high cholesterol, Master Version 1.0, June 30, 2012).

Calculation of the Framingham and D:A:D Risk Scores. Lipid results for all study visits will be made available (unblinded) at this time point.

7.9. Study Visit Windows

- Baseline and Week 4 visits have a visit window of ±2 days.
- Week 12 visit has a visit window of ±7 days.

8. UNSCHEDULED VISIT

Unscheduled visit assessments will be recorded in the CRF including the reason(s) for the visit. This visit would include, but is not limited to, the following study assessments: targeted medical review, blood pressure, pulse rate, physical examination, safety bloods and study doctor and or study coordinator assessment.

This visit could also include Serious Adverse Event (SAE) or Adverse Event (AE) assessment/follow up.

9. PREGNANCY

Because of the unknown effects of the study drugs, women should avoid becoming pregnant during the course of this trial. If a participant becomes pregnant, she will be required to withdraw from the trial but will continue to be monitored. These precautions are

necessary because the information on the effects on the unborn or newborn baby of both study drugs is still very limited.

10. PATHOLOGY SPECIMEN MANAGEMENT

Safety parameters will be assessed by the local laboratory at each site. Local laboratory pathology reference ranges will apply. Safety parameter blood samples will be transported according to the local laboratory requirements for measurement of: urea, electrolytes (including calcium, magnesium and phosphate), creatinine, liver function tests - alanine aminotransferase (ALT), aspartate aminotransferase (AST), albumin, total protein, alkaline phosphatase (ALP), gamma glutamyltransferase (GGT), bilirubin and creatine kinase.

Fasting metabolic parameters will be assessed by the local laboratory at each site and LDL particle size testing will be performed at a central laboratory LipoScience Global Research Services, North Carolina, USA). Local laboratory and LipoScience Global Research Services laboratory reference ranges will apply. Fasting metabolic blood samples will be transported according to the local laboratory and LipoScience Global Research Services laboratory requirements for measurement of: triglycerides, total cholesterol, HDL, LDL, VLDL cholesterol, glucose, insulin, and LDL particle size.

HIV parameters will be assessed by the central laboratories for each area (Sydney, Melbourne and Barcelona). Local laboratory pathology reference ranges will apply. HIV parameter blood samples will be transported to according to the local laboratory requirements for measurement of: full blood count, CD4+ lymphocyte count and percentage and HIV viral load.

11. ADVERSE EVENTS

An adverse event (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 should be recorded as an AE in the individuals CRF.

At the final study visit (week 12) any ongoing adverse events deemed related to study drug will be followed up for 30 days and until resolution. Phone contact with the patient is acceptable unless pathology tests are required.

12. 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.

12.1. Serious Adverse Event Reporting Requirements

The Co-ordinating Principal Investigator and/or the project coordinator must be notified immediately regarding the occurrence of any serious adverse events (SAEs).

The Coordinating Principal Investigator and/or the study monitor 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. The study monitor will be responsible for reporting all SAEs to pharmaceutical companies as/if necessary.

Any SAE that is ongoing at the final study visit (week 12) must be followed until resolution or until the event stabilises (for those events that will not resolve).

13. Data Safety and Monitoring Board

The independent Data Safety and Monitoring Board (DSMB) will be composed of members with expertise in HIV management, cardiovascular risk and statistical and trial design. Members will elect a chairperson. The first meeting will occur after 20 patients have been enrolled, at which time terms of reference will be ratified and frequency of meetings decided upon.

All reported SAEs and adverse events that are unexpected and drug related events will be summarised (by the project coordinator) on a regular basis and reviewed by the study team at weekly project meetings. HIV RNA data on each participant will be included.
All SAEs and any patterns of repeated adverse events will be communicated to the DSMB Chairperson and may lead to consideration by other DSMB members and/or full interim safety data review as is thought appropriate. Based on formal review of data the DSMB may recommend one of the following courses of action:

i) continue the study without modification,
ii) continue the study with modifications to the protocol
iii) suspend enrolment pending either resolution of specific issues or amendment of the protocol as specified
iv) terminate the study

The DSMB Chairperson will be responsible for providing a written report of findings and recommendations to the coordinating investigator in a timely manner. The coordinating investigator and project coordinator will be responsible for informing the HREC, study sites and appropriate regulatory authorities of any DSMB recommendation relating to conduct of the study.

14. Sample size and Statistical analysis

14.1. Statistical analysis

All analyses will be performed after all participants have completed the study, permanently withdrawn or been lost to follow-up. The primary outcome is percentage change from baseline in total cholesterol at 12 weeks by intent-to-treat analysis.

Descriptive statistics will be used for continuous and ordinal variables. For continuous data, mean change from baseline to weeks 4, and 12 will be calculated for participants with baseline and at least 1 follow-up visit. We will conduct intention-to-treat and on-treatment analyses and use T tests to compare groups (Wilcoxon's test if data are not normally distributed). To assess differences in proportions, we will use Fisher's exact test and calculate exact CIs. Hazard ratios for comparison of event rates, adjusted for duration of randomized therapy, will be assessed using Cox regression. All analyses will use a 2-sided α of 0.05. No adjustment will be made for multiple comparisons. Analyses will be primarily by intent-to-treat. As this study is designed to evaluate the biological effects of an intervention, a per-protocol analysis will also be performed.

14.2. Sample size

In published cholesterol-lowering treatment studies in HIV-infected adults, the following reductions in total or LDL cholesterol were reported:

- ROSUVASTATIN [6]: Rosuvastatin 10mg daily, caused a 28% reduction in total cholesterol (SD 18%), 35% reduction in LDL cholesterol (SD 17%)
- SWITCHMRK [8]: Switching lopinavir/ritonavir to raltegravir caused a 12% relative reduction (13% absolute; SD not reported) in total cholesterol, 4% reduction in LDL cholesterol (SD not reported)
- SPIRAL [11]: Switching one of various ritonavir-boosted protease inhibitors to raltegravir caused a 14% relative reduction (6% absolute; SD not reported) in total cholesterol, 17% for those switching from lopinavir/ritonavir, 3% for those switching from atazanavir/ritonavir, 9% relative reduction (6% absolute; SD not reported) in LDL cholesterol.

These data suggest a difference in total cholesterol between rosuvastatin and lopinavir/r switching of about 15%.

With a 1:1 randomisation, to be able to reject the null hypothesis that the population means of the experimental and control groups are equal with a Type-1 error probability of 0.05, 80% power and assuming a 10% drop-out, the sample size is:
If all participants are on lopinavir/r at baseline (estimated 15% difference for total cholesterol), the sample size is 27 per group if the SD is 18%. If 50% of participants are on lopinavir/r and 50% on atazanavir/r at baseline, the between-group difference for total cholesterol would be expected to be larger (about 20%), the sample size is 16 per group if the SD is 20%.

The effects of ritonavir-boosted darunavir and ritonavir-boosted fosamprenavir on cholesterol levels are similar to those of ritonavir-boosted lopinavir, so the sample size is similar if any of these drugs is being used. Therefore, we propose to recruit 30 patients per group.

Patient retention on assigned therapy >90% is highly likely. Loss to follow-up in previous trials led by the investigators was <5% per year. Rosuvastatin was well tolerated in the one trial in HIV+ adults. Failure or intolerance of new antiretroviral therapy over 12 weeks is likely to be no more than 5%. With a sample size of 30 per arm, the study would also have 99.7% power to demonstrate an anticipated 24% difference in LDL cholesterol between groups, assuming 18% SD, with a Type-1 error of 0.05.

15. Recording and transfer of study data

15.1. Data recording

Each study site will be provided with CRF folders for the input of study data. These should be completed according to the printed set of instructions accompanying these folders. Participants will not be identified by name on any CRFs, but rather by a site-specific ‘Study Identifier’ and ‘Name Code’.

Details of the Study Identifier and Name Code are included in the ‘SoS Study Manual of Operations’ (Version 1, July 16, 2012) to be supplied to each of the sites.

It is a requirement of the study protocol that all forms must be fully completed prior to their returning to the Study Sponsor (St. Vincent’s Clinical Research Program).

15.2. Data transfer to Study Sponsor

The completed study CRFs should be transferred to the Study Sponsor via fax, and addressed to the Project Manager (Dr. Frederick Lee).

Any standard-of-care pathology results being transferred, also by fax, to the Study Sponsor should be de-identified of participants' full names. Only the site-specific Study Identifier and Name Code should be used on pathology reports.

All CRF pages and relevant standard-of-care pathology reports should be sent to the Project Manager as soon as scheduled visits are completed and pathology results are available. This should happen no later than seven (7) working days after the final study visit at Week 12.

Any data queries generated will be addressed in consultation with site study co-ordinators and study monitors.

16. 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 study participant. Publication of data derived from this protocol will be supervised by Co-ordinating Investigator, Professor Andrew Carr 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.

17. REFERENCES

1. DAD Study Group. Class of antiretroviral drug and the risk of myocardial infarction. N Engl J Med 2007; 356: 1723-35.
2. Calza L, Manfredi R, Colangeli V, et al. Substitution of nevirapine or efavirenz for protease inhibitor versus lipid-lowering therapy for the management of dyslipidaemia. AIDS 2005; 19: 1051-58.
3. Mallon PWG, Miller J, Kovacic JC, et al. Effects of pravastatin on body composition and markers of cardiovascular disease in HIV-infected men: a randomised, placebo-controlled study. AIDS 2006; 20: 1003-10.
4. Martínez E, Arnaiz JA, Podzamczer D, et al. Substitution of nevirapine, efavirenz, or abacavir for protease inhibitors in patients with human immunodeficiency virus infection. N Engl J Med 2003; 349: 1036-46.
5. Carr A, Hudson J, Chuah J, et al. HIV protease inhibitor substitution in patients with lipodystrophy: a randomised, multicentre, open-label study. AIDS 2001; 15: 1811-22.
6. Aslangul E, Assoumou L, Bittar R, et al. Rosuvastatin versus pravastatin in dyslipidemic HIV-1-infected patients receiving protease inhibitors: a randomized trial. AIDS 2010; 24: 77-83.
7. Ganesan A, Crum-Cianflone N, Higgins J, et al. High dose atorvastatin decreases cellular markers of immune activation without affecting HIV-1 RNA levels: results of a double-blind randomized placebo controlled clinical trial. J Infect Dis 2011; 203: 756-64.
8. Eron JJ, Young B, Cooper DA, et al. Switch to a raltegravir-based regimen versus continuation of a lopinavir-ritonavir-based regimen in stable HIV-infected patients with suppressed viraemia (SWITCHMRK 1 and 2): two multicentre, double-blind, randomised controlled trials. Lancet 2010; 375: 396-407.
9. Food and Drug Administration. Rosuvastatin product label. Available at: http://www.accessdata.fda.gov/drugsatfda_docs/label/2010/021366s021lbl.pdf (Accessed May 21, 2011).
10. Food and Drug Administration. Pravastatin product label. Available at: http://www.accessdata.fda.gov/drugsatfda_docs/label/2007/019898s060lbl.pdf (Accessed May 21, 2011).
11. Martínez E, Larrousse M, Llibre JM, et al. Substitution of raltegravir for ritonavir-boosted protease inhibitors in HIV-infected patients: the SPIRAL study. AIDS 2010; 24: 1697-707..

18. Appendix 1 – Ethics Reference

- The 2007 revised National Statement on Ethical Conduct in Human Research was tabled in parliament on the 28th of March 2007.
- Australian Code for the Responsible Conduct of Research. Guides institutions and researchers in responsible research practices.
- World Medical Association Declaration of Helsinki: Recommendations Guiding Medical Doctors in Biomedical Research Involving Human Subjects, October, 2000 version.
- The International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use (ICH).

19. Appendix 2 – SF-12

Your Health and Well-Being

This questionnaire asks for your views about your health. This information will help keep track of how you feel and how well you are able to do your usual activities. ***Thank you for completing this survey!***

For each of the following questions, please mark an ☒ in the one box that best describes your answer.

1. **In general, would you say your health is:**

Excellent	Very good	Good	Fair	Poor
☐ 1	☐ 2	☐ 3	☐ 4	☐ 5

2. **The following questions are about activities you might do during a typical day. Does <u>your health now limit you</u> in these activities? If so, how much?**

	Yes, limited a lot	Yes, limited a little	No, not limited at all
a. <u>Moderate activities</u>, such as moving a table, pushing a vacuum cleaner, bowling, or playing golf	☐ 1	☐ 2	☐ 3
b. Climbing <u>several</u> flights of stairs	☐ 1	☐ 2	☐ 3

SF-12v2™ Health Survey © 1994, 2003 Health Assessment Lab, Medical Outcomes Trust and QualityMetric Incorporated. All rights reserved.
SF-12® is a registered trademark of Medical Outcomes Trust.
(IQOLA SF-12v2 Standard, Australia (English))

3. During the past 4 weeks, how much of the time have you had any of the following problems with your work or other regular daily activities as a result of your physical health?

	All of the time	Most of the time	Some of the time	A little of the time	None of the time
a. Accomplished less than you would like	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
b. Were limited in the kind of work or other activities	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5

4. During the past 4 weeks, how much of the time have you had any of the following problems with your work or other regular daily activities as a result of any emotional problems (such as feeling depressed or anxious)?

	All of the time	Most of the time	Some of the time	A little of the time	None of the time
a. Accomplished less than you would like	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
b. Did work or other activities less carefully than usual	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5

5. During the past 4 weeks, how much did pain interfere with your normal work (including both work outside the home and housework)?

Not at all	A little bit	Moderately	Quite a bit	Extremely
☐ 1	☐ 2	☐ 3	☐ 4	☐ 5

SF-12v2™ Health Survey © 1994, 2003 Health Assessment Lab, Medical Outcomes Trust and QualityMetric Incorporated. All rights reserved.
SF-12® is a registered trademark of Medical Outcomes Trust.
(IQOLA SF-12v2 Standard, Australia (English))

6. **These questions are about how you feel and how things have been with you during the past 4 weeks. For each question, please give the one answer that comes closest to the way you have been feeling. How much of the time during the past 4 weeks…**

	All of the time	Most of the time	Some of the time	A little of the time	None of the time
a. Have you felt calm and peaceful?	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
b. Did you have a lot of energy?	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
c. Have you felt downhearted and depressed?	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5

7. **During the past 4 weeks, how much of the time has your physical health or emotional problems interfered with your social activities (like visiting with friends, relatives, etc.)?**

All of the time	Most of the time	Some of the time	A little of the time	None of the time
☐ 1	☐ 2	☐ 3	☐ 4	☐ 5

Thank you for completing these questions!

SF-12v2™ Health Survey © 1994, 2003 Health Assessment Lab, Medical Outcomes Trust and QualityMetric Incorporated. All rights reserved.
SF-12® is a registered trademark of Medical Outcomes Trust.
(IQOLA SF-12v2 Standard, Australia (English))

20. Appendix 3 – GIT symptoms questionnaire

1. Have you experienced any nausea since the last study visit?

   Yes ☐
   No ☐

   If '**Yes**', how would you grade it?

   Mild ☐
   Moderate ☐
   Severe ☐

2. Have you experienced any diarrhea since the last study visit?

   Yes ☐
   No ☐

   If '**Yes'**, how would you grade it?

   Mild ☐
   Moderate ☐
   Severe ☐

21. Appendix 4 – drugs@FDA links for information re contra-indicated (absolute and relative) medications in patients receiving: rosuvastatin, raltegravir, etravirine, tenofovir, atazanavir, nevirapine, lamivudine and emtricitabine

Rosuvastatin
http://www.accessdata.fda.gov/drugsatfda_docs/label/2010/021366s021lbl.pdf

Raltegravir
http://www.accessdata.fda.gov/drugsatfda_docs/label/2011/022145s018lbl.pdf

Etravirine
http://www.accessdata.fda.gov/drugsatfda_docs/label/2011/022187s008lbl.pdf

Tenofovir
http://www.accessdata.fda.gov/drugsatfda_docs/label/2011/021356s037lbl.pdf

Atazanavir
http://www.accessdata.fda.gov/drugsatfda_docs/label/2011/021567s026lbl.pdf

Nevirapine
http://www.accessdata.fda.gov/drugsatfda_docs/label/2011/020933s028,020636s037lbl.pdf

Lamivudine
http://www.accessdata.fda.gov/drugsatfda_docs/label/2008/020564s028lbl.pdf

Emtricitabine
http://www.accessdata.fda.gov/drugsatfda_docs/label/2008/021500s010,021896s004lbl.pdf