

Title: A multicenter randomized study to compare the efficacy and safety of lower dose atazanavir/ritonavir (ATV/r 200/100 mg OD) versus standard dose (ATV/r 300/100 mg OD) in combination with 2NRTIs in well virology suppressed HIV-infected adults

การศึกษาแบบสุ่มแบบสหสถาบันเพื่อเปรียบเทียบประสิทธิภาพและความปลอดภัยของยาเอทาคานาเวียร์/ริโทนาเวียร์ขนาดต่ำ (200/100 มิลลิกรัมวันละครั้ง) เปรียบเทียบกับยาเอทาคานาเวียร์/ริโทนาเวียร์ขนาดมาตรฐาน (300/100 มิลลิกรัมวันละครั้ง) ร่วมกับยาเอ็นอาร์ทีไออีก 2 ตัว ในผู้ใหญ่ที่มีเชื้อเอชไอวีที่มีปริมาณไวรัสถูกกดอย่างดี

Protocol version 6.0, dated 1 October 2012

Short title: LASA (Low dose Atazanavir/r vs. Standard dose Atazanavir/r)

Trial number : HIV-NAT 110
Clinicaltrials.gov number : NCT01159223
Investigational Product : Atazanavir/ritonavir
Clinical Phase : IV

Principal Investigator: Kiat Ruxrungtham, MD, M.Sc.; HIV-NAT, The Thai Red Cross AIDS Research Centre (TRCARC), and Faculty of Medicine, Chulalongkorn University, Bangkok, Thailand

Senior project Coordinator: Anchalee Avihingsanon, MD; HIV-NAT, TRCARC, and Faculty of Medicine, Chulalongkorn University, Bangkok, Thailand

Project Coordinator: Torsak Bunupuradah, MD; HIV-NAT, TRCARC

Co-investigators:

Praphan Phanuphak, MD, PhD	HIV-NAT, TRCARC
Jintanat Ananworanich, MD, PhD	SEARCH, HIV-NAT, TRCARC
Ploenchana Chetchotisakd, MD	Khon Kaen University, Khon Kaen
Chureeratana Bowonwattanuwoong, MD	Chonburi Hospital, Chonburi
Patcharee Kantipong, MD	Chiangrai Prachanukroh Hospital, Chiangrai
Virat Klinbuayaem, MD	Sanpatong Hospital, Chiang Mai
Wisit Prasithsirikul, MD	Bamrasnaradura Infectious Disease Institute, Nonthaburi
Sasisopin Kiertiburanakul, MD, MHS	Ramathibodi Hospital, Bangkok
Supunnee Jirajariyavej, MD	Taksin Hospital, Bangkok
Warangkana Munsakul, MD	Faculty of Medicine, University of Bangkok Metropolitan Administration (Vajira Hospital)
Niramon Leerattanapetch, MD	Khon Kaen Hospital
Malee Techapornroong, MD	Prapokklao Hospital
Sireethorn Nimitvilai, MD	Nakhon Phatom Hospital
Sukit Banchongkit, MD	Rayong Hospital

Sripetcharat Mekviwattanawan, MD	Pranangklaio Hospital
Winai Sawasdivorn, MD	The National Health Security Office (NHSO)
Sorakij Bhakeecheep, MD	The National Health Security Office (NHSO)
David Cooper, MD	Kirby Institute for Infection and Immunity in Society, UNSW, Sydney, Australia, HIV-NAT
Sean Emery, MD	Kirby Institute for Infection and Immunity in Society, UNSW, Sydney, Australia

Sponsors: Kirby Institute for Infection and Immunity in Society, UNSW, Sydney, Australia, The National Health Security Office (NHSO) for antiretroviral therapy and some lab testing

Trial Coordinator center : HIV-NAT Thai Red Cross AIDS Research Centre
104 Rajdumri Road, Pathumwan, Bangkok 10330
Thailand, tel: +66 2255 7334-5, fax:+66 2252 5779

PROTOCOL SYNOPSIS

<i>Title</i>	A multicenter randomized study to compare the efficacy and safety of lower dose atazanavir/ritonavir (ATV/r 200/100 mg OD) versus standard dose (ATV/r 300/100 mg OD) in combination with 2NRTIs in well virology suppressed HIV-infected adults
<i>Trial number</i>	HIV-NAT 110
<i>Clinical phase</i>	IV
<i>Sponsor</i>	Kirby Institute, NHSO
<i>Principal Investigator</i>	Kiat Ruxrungtham, MD, M.Sc.; HIV-NAT, The Thai Red Cross AIDS Research Centre, and Faculty of Medicine, Chulalongkorn University, Bangkok, Thailand
<i>Trial Centres</i>	<ol style="list-style-type: none"> 1. HIV-NAT, and King Chulalongkorn Memorial Hospital 2. Srinagarind Hospital, KhonKaen University 3. Chonburi Hospital 4. Chiangrai Prachanukroh Hospital 5. Sanpatong Hospital 6. Bamrasnaradura Infectious Diseases Institute 7. Ramathibodi Hospital 8. Taksin Hospital 9. Faculty of Medicine, University of Bangkok Metropolitan Administration (Vajira Hospital) 10. Khon Kaen Hospital 11. Prapokklao Hospital 12. Nakhon Phatom Hospital 13. Rayong Hospital 14. Pranangklaio Hospital
<i>Objective(s)</i>	<p>1. PRIMARY OBJECTIVE:</p> <p>To demonstrate non-inferiority of treatment with atazanavir/ritonavir (ATV/r) 200/100 mg once daily (OD) compared to the control group (ATV/r 300/100 mg OD) in regards to the proportion of virologic responders (plasma HIV RNA < 200 copies/mL) at 48 weeks</p>

2. SECONDARY OBJECTIVES:

2.1 To compare immunologic change (as measured by CD4 count) in the ATV/r 200/100 group versus that in ATV/r 300/100 OD group over 48 weeks

2.2 to compare additional measures of HIV replication (viral rebound >200 copies/ml) between the ATV/r 200/100 group versus the ATV/r 300/100 OD group over 48 weeks

2.3 To evaluate and compare the tolerability and safety e.g. change the dose or ATV/r or switch the regimen due to clinical jaundice, proportion of elevated ALT or bilirubin grade 3/4 and abnormal lipids of ATV/r 200/100 OD versus ATV/r 300/100 OD

2.4 Comparison of the number of patients with any adverse events (AEs), and the cumulative incidence of AEs associated with cessation of randomly assigned therapy between treatment arms.

2.5 To evaluate the relationship between ATV Ctrough and efficacy and safety of ATV/r 200/100 OD versus the ATV/r 300/100 OD.

2.6 To assess treatment adherence between two treatment groups as measured by the modified Medication Adherence Self Report Inventory (VAS)

2.7 To assess quality of life after switching to ATV/r based regimen

2.8 To assess cardiovascular risk after switching to ATV/r based regimen

2.9 To assess lipodystrophy after switching to ATV/r based regimen

Study design

Trial subjects

Multicentre, open-label, randomized controlled trial

560 HIV-infected adults

Inclusion criteria:

1. HIV infected adults aged ≥ 18 years
2. Received ritonavir boosted PI-based HAART for ≥ 3 months prior screening visit
3. History of all HIV RNA results < 50 copies/ml within 12 months prior to screening visit
4. HIV-RNA < 50 copies/ml at screening visit
5. Signed written informed consent

Exclusion criteria:

1. Active AIDS-defining disease or active opportunistic infection
2. History of virological failure (confirmed plasma HIV-RNA $\geq 1,000$ copies/ml) after 24 weeks of any ritonavir boosted PI-based HAART
3. Pregnancy or lactation at screening visit
4. Relevant history or current conditions or illnesses that might interfere with drug absorption, distribution, metabolism or excretion e.g. chronic diarrhea, malabsorption
5. Use of concomitant medication that may interfere with the pharmacokinetics of the study drugs e.g. rifampicin, proton pump inhibitor
6. History of sensitivity/idiosyncrasy to the atazanavir/ritonavir
7. ALT ≥ 200 IU/L at screening visit
8. Creatinine clearance < 60 c.c. per min by Cockcroft-Gault formula at screening visit

TREATMENTS

Treatments

ATV 200mg OD + RTV 100mg OD or ATV 300mg OD + RTV 100mg OD in combination with 2NRTIs

ASSESSMENTS

Medical history, physical examination, weight, clinical jaundice	Screening, week 0, 12, 24, 36, and 48
Height	Screening
Blood pressure, waist/hip circumference	week 0, 24 and 48
Laboratory safety : ALT	Screening, week 0, 12, 24, 36, and 48
CD4,CBC, Lipid profile	week 0, 24 and 48
HIV RNA	Screening, week 0, 12, 24, and 48
ATV Ctrough	Week 12 and 24 (only 1 time point/visit), ATV Ctrough will be analysed retrospectively. The target minimum concentration (C through or Cmin) of boosted ATV ≥ 0.15 mg/L at pre-dose measurement
Adverse events	week 0, 12, 24, 36, and 48
Adherence questionnaire	week 0, 12, 24, 36, and 48 by visual analogue scale
Quality of life questionnaire	week 0, 12 and 48 by MOS-HIV questionnaire
Acceptability and Gastrointestinal Symptom questionnaire	Acceptability and Gastrointestinal Symptom Rating Scale (GSRS) questionnaire will be used at week 0, 12, and 48
Cardiovascular risk questionnaire	week 0 and 48 by EGAT and Framingham risk equations
Lipodystrophy questionnaire	week 0 and 48

ANALYTICAL AND STATISTICAL METHODS

Bioanalysis

Plasma concentrations of ATV and RTV will be measured in all available samples by means of a validated HPLC method. This will be done for retrospective analysis after the clinical trial has been completed. Prospective measurement of the pharmacokinetics of study medications is not permitted.

Statistical methods

The primary endpoint is the comparison of proportions of participants in each arm whose plasma HIV RNA is < 200 copies/mL after 48 weeks.

Under the assumption that there is no difference in the failure rate in randomized treatment arms, to have 90% power to demonstrate non-inferiority in the ITT analysis using a 10% margin at a 2-sided significance level of 5% will require 256 participants per arm to be randomized, making a total of 512 participants.

To ensure that the PP analysis also has adequate power to demonstrate non-inferiority, the sample size needs to be increased to allow for patients who swap from the 300mg/100mg arm because of clinical jaundice. This is estimated to be no more than 5%, and it is estimated that an additional 5% of study participants may be lost to follow-up. Applying a 10% adjustment for loss to follow up and regimen swaps due to toxicity would bring the sample size in each arm to 280 patients in each arm, or a total of 560 subjects. We will therefore aim to recruit 560 patients to the study. The power of the ITT

analysis in this case is 93%.

Schedule of analyses:

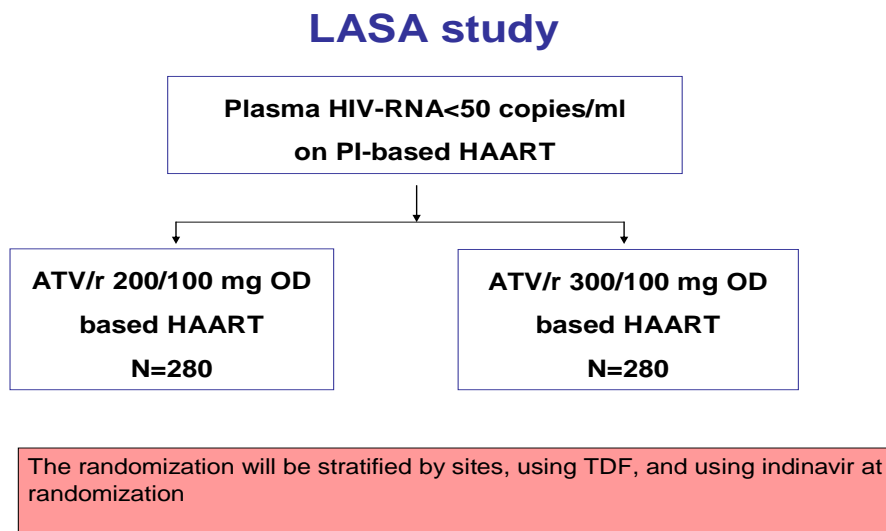
An interim analysis will occur when 50% of randomised subjects (140 subjects in each arm) have had their week 24 study visit, or have discontinued the study. The primary analysis of all study endpoints will occur when all patients have completed their week 48 study week.

The interim analysis will be reviewed by an independent data monitoring and safety board, who will recommend to the protocol steering committee on whether the study should continue unchanged or be amended in the light of observed differences between treatment arms, or aspects of study conduct that warrant modification (e.g. poor recruitment, safety concerns or losses to follow-up). A conservative Peto-Prentice type stopping rule ($p < 0.001$) will be used to judge whether one arm should be ceased for inferiority at the interim analysis.

Time line:

Start of Study:	First enrolment in May 2011
Completed enrolment:	June 2013
Expected end of study follow-up:	June 2014

Figure 1: Study design



LASA (Low dose Atazanavir/r vs. Standard dose Atazanavir/r)

ATV/r: atazanavir/ritonavir, PI: protease inhibitor, HAART: highly active antiretroviral therapy, OD: once daily, TDF: tenofovir

Note: The reason to stratify by TDF and IDV because; TDF can decrease the area under the concentration-time curve for atazanavir/ritonavir[1], either IDV or atazanavir can cause renal toxicity, acute interstitial nephritis and renal stone[2].

Table 1 Flow Chart

Procedure for LASA 6.0	Screening (-6 weeks)	W 0	W 12	W 24	W 36	W 48
Informed consent	X					
Randomization ¹		X				
Medical history, AE, physical examination	X	X	X	X	X	X
Weight (kg)	X	X	X	X	X	X
Height (cm)	X					
Blood pressure and waist/hip circumference		X		X		X
Adherence questionnaire by VAS		X	X	X	X	X
Quality of life questionnaires ²		X	X			X
Acceptability and GSRS questionnaires ³		X	X			X
Lipodystrophy questionnaires		X				X
Cardiovascular risk assessment ⁴		X				X
CBC and CD4 count (7ml)		X		X		X
HIV-1 RNA (7ml)	X	X	X	X		X
ALT (2ml)	X	X ⁵	X	X	X	X
Total/direct bilirubin (2ml) ⁶		X	X	X	X	X
Cr (1ml)	X	X ⁵		X		X
Fasting Glu, chol, TG, HDL (3ml)		X		X		X
ATV Ctrough level (2mL)			X ⁷	X ⁷		
Serum storage (7 ml)		X		X		X
Plasma/PBMC storage (20 ml)		X		X		X
Dry cell pellet storage*				X		
HBs Ag ⁸ , anti HCV ⁸ (2 ml)		X				
Urine analysis		X		X		X
Urine pregnancy test ⁹	X					
Total Maximum Volume of Blood Draw (ml)	10	51	14	51	4	49

Note: the window period for week 12, 24, 36, 48 visits is \pm 6 weeks

* Dry cell pellet will be extracted from the left over sample of CBC and CD4 count, therefore, no additional blood drawn is needed

1 Randomization will be performed before week 0 or at date of week 0

2 MOS-HIV Quality of life questionnaires will be used

3 The modified Gastrointestinal Symptom Rating Scale (GSRS) questionnaire for Protease inhibitor[3]

4 evaluated by EGAT [4, 5] and Framingham risk equations

5 could be skipped at week0 if screening and week0 visit period \leq 14 days

6 Sample will be stored at HIV-NAT lab and performed retrospectively. The results will be blinded to patient and investigator except the patient has clinical hepatitis or elevated ALT (>200 IU/L) during study.

7 Sample will be stored at HIV-NAT lab and performed retrospectively

8 could be skipped if patients already had previous results

9 for women of childbearing potential only

List of abbreviations

AE	Adverse event
ANOVA	Analysis of Variance
AUC	Area under the plasma concentration-time curve
ARV	Antiretrovirals
ATV	Atazanavir
ATV/r	Atazanavir/ritonavir
BD	Twice Daily
BP	Blood Pressure
C _{max}	The maximum plasma drug concentration
C _{min}	The minimal plasma drug concentration
CRF	Case record (or report) form
HAART	Highly active antiretroviral therapy
HIV	Human Immunodeficiency Virus
HIV-NAT	HIV Netherlands Australia Thailand Research Collaboration
HPLC	High Performance Pressure Liquid Chromatography
LLOQ	Lower Limit Of Quantification
NRTI	Nucleoside reverse transcriptase inhibitor
OD	Once daily
PI	Protease inhibitor
PK	Pharmacokinetic
QA	Quality assurance
RTV	Ritonavir
SAE	Serious adverse event
t _½	Elimination half-life associated with the terminal slope of a semilogarithmic concentration-time curve
t _{max}	Time to reach maximum plasma drug concentration
TDF	Tenofovir dispoxil fumarate
TDM	Therapeutic drug monitoring

1. Introduction

1.1. Background

The standard of care for the treatment of human immunodeficiency virus type 1 (HIV-1) infection uses a combination of antiretroviral drugs based on a backbone of two nucleoside or nucleotide reverse transcriptase inhibitors (N(t)RTI) and either a non-nucleoside reverse transcriptase inhibitor (NNRTI) or a protease inhibitor (PI) [6]. Such triple therapy produces durable suppression of viral replication but has been associated with the emergence of metabolic, tolerability, adherence, resistance and drug interaction concerns, particularly with PI-based regimens[6, 7]. Long-term complications with PIs, such as hyperlipidemia, are common. This perturbation of normal metabolism is thought to contribute to the development of cardiovascular disease.

Atazanavir (ATV) is an azapeptide PI compound that is approved for use in combination treatment of HIV-1. ATV is currently used at a fixed dose of either 300 mg in combination with low-dose ritonavir (100 mg) once daily or, less frequently, at 400 mg once daily, both taken with food[6]. Several review articles have already been published that point out the advantages and disadvantages of this PI[8-10]. The major advantages of ATV are its simplicity of once-daily administration, its minimal effect on the lipid profiles compared to other PIs, and its distinct resistance profile with an I50L protease substitution appearing to be the signature mutation[11].

ATV is bound to both α 1acid glycoprotein and albumin to similar extents (89% and 86%, respectively)[12]. The drug is metabolized mainly via hepatic cytochrome P450, primarily the CYP3A4/CYP3A5 isoenzymes[13]. ATV inhibits UDP glucuronyltransferase UGT1A1, CYP3A, and P-glycoprotein transport in vitro[14]. Therefore, the potential for drug-drug interactions is high as with other PIs. Large interpatient and inpatient variabilities in ATV disposition have been previously reported[15], and poor adherence to recommendations regarding food intake or drug interactions may further weaken antiviral coverage, particularly with ATV 400 mg OD[16]. Insufficient concentrations in plasma are clearly associated with HIV RNA rebound and increased risk for the emergence of viral resistance[6].

Several studies from HIV-NAT have demonstrated high nevirapine[17], indinavir[18], saquinavir[19] and lopinavir/r[20] levels in Thais when compared to those reported in Caucasians. We have recently reported that pharmacokinetic parameters of ATV/r 200/100 mg OD plus 2 NRTIs in Thais were comparable to historical Caucasian cohorts using the standard dose of ATV/r 300/100 mg OD[21]. Recent studies have shown that plasma ATV trough concentration is related to hyperbilirubinemia[22]. Patients with an ATV C_{trough} higher than 0.85 mg/L have a threefold higher risk of bilirubin elevation[23]. A trough plasma concentration (C_{trough}) of ATV between 0.15 and 0.85 mg/L has been suggested as the optimal drug concentration interval associated with the highest probability of virological response and the lowest probability of unconjugated-bilirubin increase[23]. In our previous report, 64% and 27% of patients on ATV/r 300/100 and ATV/r 200/100, respectively had atazanavir $C_{\text{trough}} > 0.85 \text{ mg/L}$ [21]. In addition, these Thais who had high ATV levels with the ATV/r 300/100 OD dose regimen and 36% of them had hyperbilirubinemia grade 3/4 (compared to only 8% in Caucasian population). In addition, there was a significant reduction in total bilirubin concentration and proportion of patients with hyperbilirubinemia after dose reduction from ATV/r 300/100 mg to ATV/r 200/100 mg OD. Although hyperbilirubinemia associated with ATV exposure is predominantly a cosmetic concern for patients, such adverse events have been associated with poor adherence to therapy[24]. Chetchotisakd P et al[25] provided further support for a lower dose of ATV/r in Thai patients. In a small cohort of 14 Thai patients who switched from other regimens to atazanavir/r 200/100 mg once daily, all patients maintained their plasma HIV RNA < 50 copies/mL during the median follow-up of 68 weeks (IQR 36 -118; range 12 – 165)[25].

Access to effective antiretroviral therapy in Thailand has increased in the last 5 years, particularly with local production of generic versions of antiretroviral drugs of the NRTI classes. However, ATV is not yet successfully produced as generic drug, and the commercial price of ATV remains expensive and well out of the reach of the majority of people living with HIV/AIDS in Thailand. If ATV/r can be effectively used at 200/100 mg OD, this will provide a significant reduction of one third of the cost. Hence, ATV/r 200/100mg once daily plus appropriate backbone is warranted for a further long term efficacy study in patients of Thai and Asian ethnicity. In addition to an improved toxicity profile, a dose reduction will have a considerable impact on access to medications. In Thailand, an increasing number of patients are in need for PI-based second line treatment. Lopinavir/ritonavir (LPV/r) is widely used for second line treatment in resource limited settings including Thailand. The long term efficacy of LPV/r has been established, although dyslipidemia and insulin resistance are frequent side effects[6]. Since HIV-infected patients are getting older and cardiovascular risk are complicating treatment options, antiretroviral therapy with a lipid friendly profile is advised[6]. SLOAT[26] and SWAN[27] trials have shown that the replacement of LPV/r by ATV provides a significant reduction in total cholesterol and triglycerides, without an increased risk of virological failure. Thus, for patients developing hyperlipidemia, ATV could be a good, but expensive alternative. Reducing the dose would make atazanavir more accessible to those patients.

In view of the preliminary data supporting the efficacy and safety of reduced dose ATV, and the potential cost savings to the National Treatment Programme, we propose investigate the long term efficacy, safety and tolerability of a lower dose (200mg) compared to standard dose (300mg) boosted atazanavir in Thai HIV-infected patients.

Rationale

We are interested in once daily ATV/r 200/100 mg OD because ATV dose reduction may reduce toxicity and cost compared to standard dose ATV/r at 300/100mg OD. There are limited prospective randomized studies evaluating the long term efficacy and safety of lower dose ATV/r OD dose in combination of NRTIs in HIV-1 pretreated patients. We believe that the efficacy of ATV/r given at 200/100mg daily in Thai patients will be equivalent to ATV/r 300/100mg once daily when combined with 2NRTIs, and that the low dose ATV/r will have better safety, tolerability profile, and cost saving while maintaining good CD4 and HIV RNA outcomes.

1.2. Atazanavir

ATV (BMS-232632, ATV) is an azapeptide PI that has demonstrated *in vitro* antiviral potency (EC_{50} 2 - 5 nM) against a variety of HIV isolates. HIV isolates taken from patients not previously exposed to ARV therapy have been shown to be extremely sensitive to ATV. In previously untreated subjects, infrequent ATV resistance is uniformly associated with the appearance of the I50L codon change as a unique signature mutation for this drug that has no defined role in the development of resistance to other PI drugs[12]. ATV has been shown to have a pharmacokinetic (PK) profile that clearly supports once-daily administration as either a single PI or in combination with ritonavir. This profile has been demonstrated in both Phase I studies in healthy individuals and in Phase II/III studies in HIV-infected patients[12, 28].

Review of clinical trial data demonstrates that in treatment naïve patients ATV dosed at 400mg daily is as effective as efavirenz (EFV)[29]. In treatment-experienced patients ATV (300mg once daily in combination with ritonavir 100mg) was as effective as LPV/r[30].

Pharmacokinetics

ATV is rapidly absorbed, with peak plasma concentration (C_{max}) occurring at approximately 2 hours. There are no data on absolute bioavailability of ATV. The relative bioavailability of ATV is 60%[28]. AUC and C_{max} are increased 70% and 57% respectively with light meal and considerably lower on an empty stomach. Plasma protein binding is about 86%. ATV is extensively metabolised in the liver by cytochrome P450 isoenzyme CYP3A with a 79% biliary excretion and 13% urinary elimination. Unchanged drug accounted for 20% in faeces and 7% in urinary excretion. When ATV is administered alone as 400 mg once daily in HIV infected patients, the pharmacokinetic parameters, C_{trough} and AUC are 0.273mg/L, and 14.187mg·h/L, respectively. The PK parameters of ATV, AUC (46.073 mg·h/L) and C_{trough} (0.862 mg/L) are higher with RTV 100 mg boosting (ATV/r 300/100 mg OD)[12].

Adverse Events and Precautions

In clinical trials the most frequent side effects of >grade 1 severity and significantly more frequent than any comparator drug were jaundice, scleral icterus and hyperbilirubinemia. Jaundice that is invariably associated with increases in unconjugated serum bilirubin and is not linked to hepatotoxicity. Very few events in any of these categories required permanent cessation of atazanavir⁷.

2. Trial objectives

2.1 PRIMARY OBJECTIVE :

To demonstrate non-inferiority of treatment with atazanavir/ritonavir (ATV/r) 200/100 mg once daily (OD) compared to the control group (ATV/r 300/100 mg OD) in regards to the proportion of virologic responders (plasma HIV RNA < 200 copies/mL) at 48 weeks with a maximum allowable difference of 10%.

2.2 SECONDARY OBJECTIVES :

- To compare immunologic change (as measured by CD4 count) in the ATV/r 200/100 group versus that in ATV/r 300/100 OD group over 48 weeks
- to compare additional measures of HIV replication (viral rebound >200 copies/ml) between the ATV/r 200/100 group versus the ATV/r 300/100 OD group over 48 weeks
- To evaluate and compare the tolerability and safety e.g. change the dose or ATV/r or switch the regimen due to clinical jaundice, proportion of elevated ALT or bilirubin grade 3/4 and abnormal lipids of ATV/r 200/100 OD versus ATV/r 300/100 OD
- Comparison of the number of patients with any adverse events (AEs), and the cumulative incidence of AEs associated with cessation of randomly assigned therapy between treatment arms.
- To evaluate the relationship between ATV Ctrough and efficacy and safety of ATV/r 200/100 OD versus the ATV/r 300/100 OD.
- To assess treatment adherence between two treatment groups as measured by the modified Medication Adherence Self Report Inventory (VAS)
- To assess quality of life after switching to ATV/r based regimen
- To assess cardiovascular risk after switching to ATV/r based regimen
- To assess lipodystrophy after switching to ATV/r based regimen

3. Trial design

3.1 Overall Trial Design

560 HIV-infected adults using stable doses of LPV/r-based HAART or any PI-based HAART for at least 3 months and suppressed viral load will be randomized to ATV/r 200 mg/100 mg OD +2NRTIs or ATV/r300 mg/100 mg OD +2NRTIs (Figure 1). The trial will consist of a screening period of 6 weeks, and a 48 week treatment period.

Study sites

1. HIV-NAT, and King Chulalongkorn Memorial Hospital
2. Srinagarind Hospital, KhonKaen University
3. Chonburi Hospital
4. Chiangrai Prachanukroh Hospital
5. Sanpatong Hospital
6. Bamrasnaradura Infectious Diseases Institute
7. Ramathibodi Hospital
8. Taksin Hospital
9. Faculty of Medicine, University of Bangkok Metropolitan Administration (Vajira Hospital)
10. Khon Kaen Hospital
11. Prapokklao Hospital
12. Nakhon Phatom Hospital
13. Rayong Hospital
14. Pranangklao Hospital

3.2 Patient Selection

Inclusion criteria:

1. HIV infected adults aged ≥ 18 years
2. Received ritonavir boosted PI-based HAART for ≥ 3 months prior screening visit
3. History of all HIV RNA results < 50 copies/ml within 12 months prior to screening visit
4. HIV-RNA < 50 copies/ml at screening visit
5. Signed written informed consent

Exclusion Criteria:

1. Active AIDS-defining disease or active opportunistic infection
2. History of virological failure (confirmed plasma HIV-RNA $\geq 1,000$ copies/ml) after 24 weeks of any ritonavir boosted PI-based HAART
3. Pregnancy or lactation at screening visit
4. Relevant history or current conditions or illnesses that might interfere with drug absorption, distribution, metabolism or excretion e.g. chronic diarrhea, malabsorption
5. Use of concomitant medication that may interfere with the pharmacokinetics of the study drugs e.g. rifampicin, proton pump inhibitor
6. History of sensitivity/idiosyncrasy to the atazanavir/ritonavir
7. ALT ≥ 200 IU/L at screening visit
8. Creatinine clearance < 60 c.c. per min by Cockcroft-Gault formula at screening visit

3.3 Study procedure

Subjects volunteering to participate, having signed the informed consent form (ICF) and found to be eligible for the trial at screening (week-6), will be randomized in a 1:1 ratio to one of the following treatment arms (Figure 1):

- A. ATV/r 200/100 mg OD
- B. ATV/r 300/100 mg OD

Randomisation will be stratified for recruiting centre, use or not of tenofovir (TDF), use or not of indinavir as a component of the background regimen.

The randomisation visit (week 0 or baseline visit) should be scheduled within 6 weeks after screening visit. ARV treatment (Arm A or B) will be initiated within the next day of week 0. The study drug will take with a meal, preferably breakfast. Along with the randomized study medication (ATV/r 200/100 or ATV/r 300 /100 OD), NRTIs background will remain unchanged if possible. The dosage and regimen of NRTIs background could be modified for some toxicity such as AZT 300 mg BID could be reduced to AZT 200 mg BID in case of anemia[31] or TDF dose reduction to 300 mg alternate day if GFR 30-49 cc/min.

Temporary interruption or switching of any ARVs during the treatment period will be allowed in the event of suspected toxicity, as long as the temporary interruption is associated with and can be linked to an adverse event (AE) or a serious adverse event (SAE). The maximum duration of a single treatment interruption for atazanavir/ritonavir toxicity reasons will be 4 weeks and the maximum cumulative duration of the allowed treatment interruptions for toxicity reasons will be 8 weeks. Additional unscheduled visits may be performed for safety or tolerability reasons. Re-initiation of therapy including the background regimen will only be allowed once the event has resolved or decreased to a grade 2 or below.

Throughout the treatment period, the subjects will have regular visits: randomisation, weeks 12, 24, 36, and 48 (Table 1).

3.4 Removal of Subjects from Therapy or Assessment

A subject may decide to withdraw from the trial at any time. If so, the Investigator must be informed immediately. Early termination of the trial may also be recommended by the Data Safety Monitoring Board or for administrative reasons by the Protocol Steering Committee. Patients who cease randomly assigned study medications for whatever reason should remain in follow-up as specified in the protocol. Losses to follow-up should be kept to an absolute minimum.

3.5 Replacement of Subjects

Subjects who are lost to follow-up or who withdraw consent after randomisation will not be replaced.

3.6 Discontinuation Criteria

Participants who expressly wish to discontinue association with the study and sign the 'Withdrawal of Consent' are considered as to have withdrawn from the study. Patients who discontinue or change study medications permanently or temporarily are NOT withdrawn from the study and should be followed as per the protocol.

3.7 Plan for premature discontinuation

Where possible and before consent is withdrawn participants who withdraw consent due to any reasons should be asked perform the procedures shown in the protocol for the week 48 visit.

3.8 Pregnancy

Sexually active women of childbearing potential must use an effective method of birth control during the course of the study. Women found to be pregnant during follow-up should be managed as the national guideline and will be followed as protocol schedules until study end.

3.9 Rescreening

Subjects with history of all HIV RNA results < 50 copies/ml within 12 months prior to screening visit but had HIV-RNA 50-200 copies/ml at screening visit are allowed to be rescreened in LASA study.

4. Treatment

4.1 Overview All participants will be randomized to take ATV/r 200/100 mg OD or ATV/r 300/100 mg OD. NRTIs background regimens will remain unchanged if possible. NRTIs background may include lamivudine (3TC) plus zidovudine (AZT), 3TC plus stavudine (d4T), 3TC plus didanosine (DDI), DDI plus AZT, TDF plus 3TC, AZT plus TDF, TDF plus emtricitabine (FTC). NRTI backbone could be switched or modified due to toxicity or intolerance. However, TDF + ddl or AZT+d4T, or d4T+ddl should not be used.

4.2 Packaging and Labelling of Trial Medication The trial medication will be dispensed by the hospital pharmacist.

4.3 Selection and Timing of Dosing and Dietary All patients should take the study drug with food (preferably breakfast).

4.4 Prior and Concomitant Therapy Subjects are not allowed to take medications that interfere significantly with the PK of ATV and RTV. Whenever a patient needs

concomitant medication if medically indicated, this will be reviewed by the investigator. The prohibited concomitant drugs are

- All investigational drugs
- All NNRTI
- All medications labelled as having a CYP3A4 inhibitory effect e.g. Calcium Channel Blocker, Proton pump inhibitor, rifampin
- Ergotamine derivative
- Systemic steroid

4.5 Treatment Compliance The Investigator or his/her designee must maintain an adequate record of the receipt and distribution of all trial supplies. These forms must be available for inspection at any time. At each study visit, subjects will be asked about treatment compliance. This will be recorded in the CRF.

5. Adverse Events Adverse event (AE) is defined as any untoward medical occurrence in a patient or clinical investigation subject administered a pharmaceutical product and which does not necessarily have to have a causal relationship with this treatment. Subjects will be monitored for AE at each study visit by the medical and nursing staff of the HIV-NAT. Subjects should voluntarily report any AE or in response to general questioning (e.g. 'How has your health been since the last visit?'). The severity of an adverse event was determined using the US NIH Division of AIDS 2004 toxicity grading table[32]. All clinical adverse events (grade 1-4) and abnormal laboratory grade 3-4 will be reported.

Adverse events that occur between the signing of the Informed Consent and the first intake of trial product will be documented as a pre-treatment symptom (PTS) and will be recorded on the case record form (CRF).

AEs meeting the definition of a serious AE (SAE) must be reported using an SAE form. SAEs occurring within a period of 30 days following the last intake of trial medication will also be handled as such if spontaneously reported to the Investigator. All AEs of subjects who received trial medication will be included in the final report. For each AE the following information will be recorded: start and stop date, severity, relationship to trial medication (ATV/r) and other antiretroviral drugs, action taken, and outcome.

Serious Adverse Event (SAE)

A serious adverse event (experience) or reaction is any untoward medical occurrence that at any dose:

- results in death,
- is life-threatening,
Note: The term "life-threatening" in the definition of "serious" refers to an event in which the patient was at risk of death at the time of the event; it does not refer to an event which hypothetically might have caused death if it were more severe.
- requires inpatient hospitalization or prolongation of existing hospitalization,
- results in persistent or significant disability/incapacity,
- is a congenital anomaly/birth defect, or
- Clinical AE grade 4 or abnormal laboratory grade 4

The Investigator will report SAE events to the appropriate Institutional Review Board/Independent Ethics Committee (IRB/IEC) in accordance with local regulations within seven days, stating a description of the reaction, any required intervention and the outcome.

6. Study Assessments

6.1 Clinical Assessments

Please see Table 1 for scheduled clinical assessments. A symptom-directed physical examination may be performed at other visits, as appropriate and will focus on the patient's specific area(s) of complaint. Patients will be assessed for any current or prior AIDS-defining events and serious non-AIDS events at screening, baseline and all subsequent study visits. The adherence questionnaire, quality of life questionnaire, lipodystrophy questionnaire, acceptability and the modified Gastrointestinal Symptom Rating Scale (GSRS) questionnaire, and cardiovascular risk assessment will be asked to participants as scheduled in Table 1. Adverse events, serious adverse events, adverse events leading to premature discontinuation, and all events resulting in death will be assessed throughout the study.

6.2 Laboratory Assessments

Urine pregnancy test will be performed at screening visit for women of childbearing potential. HIV genotype resistance testing will be performed only in case of virologic failure (plasma HIV-RNA \geq 1,000 copies/ml). Please see Table 1 for scheduled laboratory testing including plasma HIV-1 RNA viral load, CD4+ cell count and hematology, total bilirubin/direct bilirubin and ALT, fasting lipid profile (cholesterol, HDL, and triglycerides) and fasting glucose.

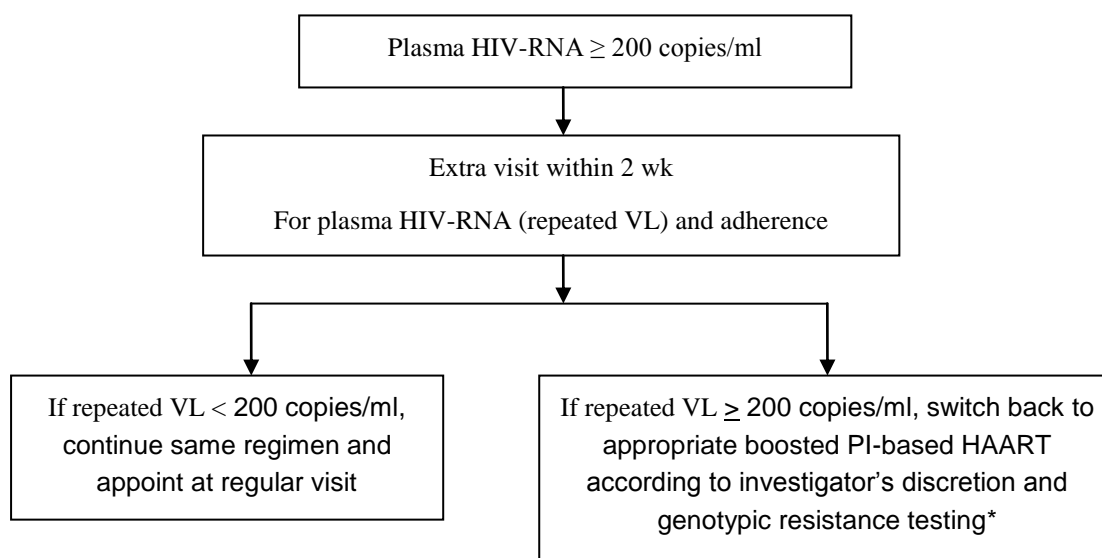
The sample storage including serum storage, plasma/PBMC storage, and dry cell pellet will be stored at HIV-NAT Research Laboratory, Bangkok, Thailand for 10 years after study completion. The stored samples will be used in the future studies e.g. the immunologic response of the white blood cell to HIV or antigen, tested for antiretroviral drug level, and tested to see the evolution of HIV mutation. The dry cell pellet samples at week 24 will be used for pharmacogenetic study to see the correlation of host gene and ATV/r drug level. The stored samples will be used for the tests that have been mentioned in this protocol. The stored samples will not be shipped out of Thailand and not be used for any commercial purposes.

Any new proposed research proposal using stored samples would be submitted for review by the local ethic committees. However, it is up to the research group and the ethic committees to determine if there is a requirement for further informed consent or whether the main study consent adequately covers the future research proposal.

6.3 Plan for subjects with plasma HIV-RNA \geq 200 copies/ml and virologic Failure

Plan for subjects with plasma HIV-RNA \geq 200 copies/ml at any visit

1. Obtain a second sample for HIV-RNA immediately (repeated HIV-RNA) no later than 2 weeks after the site investigator receiving the report of the first HIV RNA \geq 200 copies/ml, and continue the same therapy (Figure 2)
2. The results of the second HIV-RNA should be available within 4 weeks of the first HIV RNA \geq 200 copies/ml
 - If the repeated HIV-RNA is $<$ 200 copies/ml, it indicated a viral blip or transient viremia, therefore, continue the same therapy.
 - If the repeated HIV-RNA is \geq 200 copies/ml, switch back to pre-study (e.g. LPV/r-based) HAART or appropriate regimen according to investigator's discretion and genotypic resistance testing (if HIV RNA \geq 1000).

Figure 2: Plan for subjects with plasma HIV-RNA ≥ 200 copies/ml at any visit

Note: *at any visit, if VL ≥ 1000 copies/ml, the genotypic resistance testing will be performed and adapt ARV regimen accordingly

A virological threshold of 200 copies/mL was chosen because of this viral load threshold is sufficiently sensitive, while avoiding unreliable very low level viral load failures ('blips') that on subsequent measurement are not confirmed[33, 34].

Definition and Procedures for Virologic Failure

Virologic failure is defined as any HIV-RNA $\geq 1,000$ copies/ml at any visit. The HIV genotyping sample will be assayed. Any patient who has virologic failure can be switched to the appropriate regimen selected on the basis of results of genotypic resistance testing, and remain in the study.

6.4 Toxicity Management

Clinical events and clinically significant laboratory abnormalities will be graded according to the DAIDS Common Toxicity Grading Scale[32].

6.4.1 Grade 1 or 2 toxicity

Subjects who develop a Grade 1 or 2 adverse event or toxicity may continue study drugs without modification.

6.4.2 Grade 3

If the investigator has compelling evidence that the adverse event has NOT been caused by the study drug(s), dosing may continue. Subjects who develop a Grade 3 adverse event or toxicity, except for elevated triglycerides, glucose, cholesterol, bilirubin, asymptomatic grade 3 pancreatic amylase elevations in subjects with no history of concomitant disease of pancreatitis, and asymptomatic grade 3 AST/ALT elevation may continue study drugs without modification.

Symptomatic grade 3 AST/ALT elevation should have their antiretroviral study drugs withheld, at the investigator's discretion.

The subject should be re-evaluated weekly until the adverse event returns to Grade ≤ 2 , at which time the study drugs may be reintroduced at the discretion of the investigator or according to standard practice.

If the same Grade 3 adverse event recurs within four weeks, study drug(s) must be permanently discontinued if the investigator, following discussion with the nominated protocol team medical monitor, considers the adverse event related to study drug(s). However, if the same Grade 3 adverse event recurs after four weeks, the management scheme outlined above may be repeated.

6.4.3 Grade 4 adverse events

Subjects who develop a Grade 4 adverse event or toxicity at least possible related to ATV/r or antiretroviral drugs (ART) will have ATV/r or ART temporarily discontinued.

The AEs should be resolved or less than grade 2 before any decision is made to rechallenge the subject with study drugs. Subjects experiencing Grade 4 AEs requiring permanent discontinuation of study drug therapy should be followed weekly until resolution of the adverse event. The patient should remain on study and continue to undergo protocol-specified evaluations and assessments.

Subjects with Grade 4 asymptomatic or non-significant laboratory abnormalities may continue study drug therapy if the investigator has compelling evidence that the toxicity is NOT related to the study drug(s).

6.5 Protocol-specific toxicity management guidelines

6.5.1 Hypertriglyceridaemia/ Hyperlipidaemia

If elevated triglyceride or lipid levels are from a non-fasting blood draw, please repeat the draw after an eight hour fast. Only levels done in a fasting state should be graded for toxicity.

Subjects with asymptomatic Grade ≥ 3 triglyceride, total cholesterol, or LDL elevations may continue study medications at the discretion of the investigator. Appropriate dietary modification and anti-hyperlipidaemic therapy should be considered. The preferred first line treatment is fenofibrate 100-300 mg QD, 30 minutes prior to the evening meals. Fasting triglycerides should be rechecked at fortnightly intervals. For persistent uncontrolled hypertriglyceridaemia and/or hypercholesterolaemia, the addition of HMG-CoA reductase inhibitor may be considered. Several HMG-CoA reductase inhibitors have substantial interactions with PIs. The use of pravastatin or atorvastatin is advised.

6.5.2 Hyperglycaemia

Subjects with Grade ≥ 3 hyperglycaemia may continue study medications at the discretion of the investigator and be managed with oral hypoglycaemic medications or insulin, with referral to endocrinologists as appropriate.

6.5.3 LFT elevations

For asymptomatic grade 3 elevation in AST or ALT, study medications may be continued at the discretion of the site investigator. Careful assessments should be done to rule out the use of alcohol, non-study medication-related drug toxicity, or viral hepatitis as the cause of the Grade 3 elevation. The possibility of lactic acidosis syndrome should also be explored.

For Grade 4 elevations in AST or ALT, all study medications should be withheld until the toxicity grade returns to Grade ≤ 2 .

6.5.4 Management for jaundice

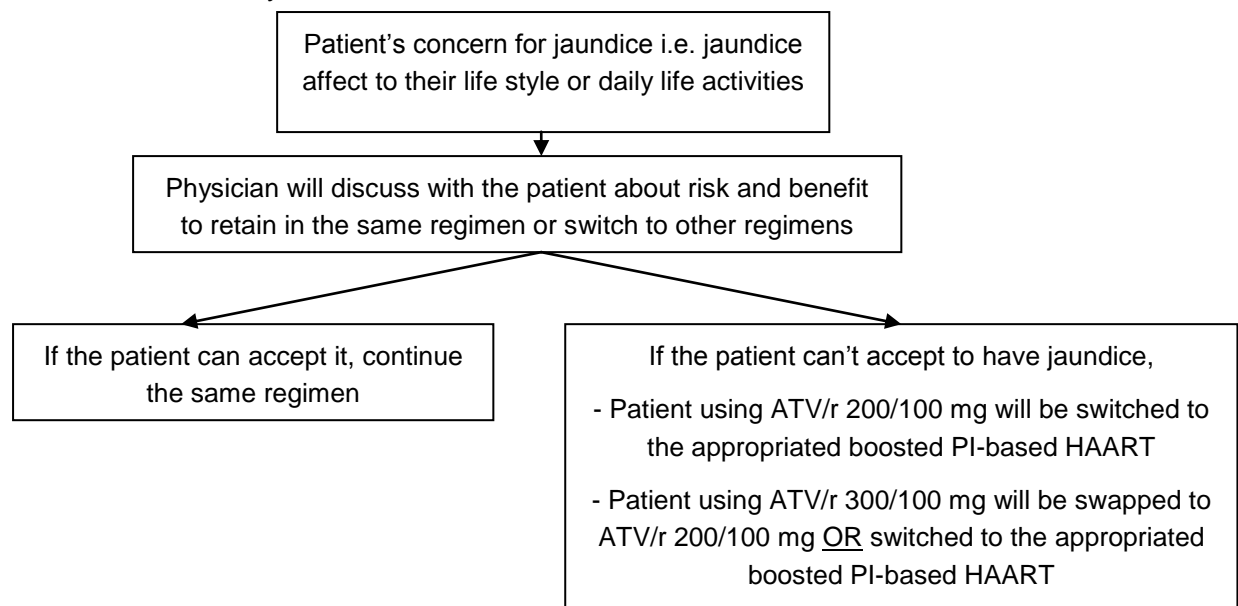
Atazanavir can cause increasing levels of indirect bilirubin in patients who took it but not all patients will have clinical jaundice. High bilirubin levels can be a sign of liver damage but this is not the case for people taking atazanavir. This drug blocks normal removal of bilirubin but without elevated alanine transferase (ALT) or clinical hepatitis. Bilirubin levels will return to normal within a few days in people who stopped taking atazanavir.

During study, if the patient has jaundice, investigator will evaluate for severity. The grading for jaundice was adapted from grading for lipodystrophy[35, 36]

- Grade 0: absent
- Grade 1: mild (noticeable on close inspection)
- Grade 2: moderate (readily noticeable)
- Grade 3: severe (readily noticeable to other observers)

The bilirubin will be performed during study period but all participants and investigators including physicians and study nurses will be blinded for the results of bilirubin to decrease the bias of dose adjustment of the study drug. The management for jaundice without other symptom and sign of hepatitis and ALT<200 IU/L will be based upon patient's concern and investigator's discretion (Figure 3). However, if the patient has sign or symptom of hepatitis or ALT≥200 IU/L during study, the bilirubin level for this case will be un-blinded.

Figure 3: Management for jaundice without other symptom and sign of hepatitis and ALT<200 IU/L at any visit



6.5.5 Lactic acidosis

The relevance of asymptomatic lactic acid elevations is unclear, and lactates are not part of the routine safety evaluations for this study. Routine lactate monitoring is not currently recommended. The syndrome of lactic acidosis that is sometimes fatal and often associated with evidence of hepatic steatosis is a recognized, but uncommon complication of NRTI therapy. This syndrome is felt to be secondary to mitochondrial toxicity induced by the inhibitory effect of NRTIs on DNA polymerase gamma, a key enzyme needed for mitochondrial DNA synthesis. Current knowledge regarding this

syndrome is not complete, although obesity and prolonged NRTI exposure may be risk factors. The clinical features of lactic acidosis frequently involve non-specific symptoms such as fatigue, weakness, and fever, but in the majority of cases also involve symptoms suggestive of hepatic dysfunction such as nausea, vomiting, abdominal or epigastric discomfort, abdominal distension, hepatomegaly, and new onset elevated liver enzymes. A high index of suspicion may be required to diagnose this condition. Alternatively, unwarranted concern may be raised by over interpretation of lactate levels. NRTI toxicity is only one cause of lactic acidosis. Type “B” lactate elevations or those without clinically apparent tissue hypoxia are also seen in the context of diabetes mellitus, uraemia, liver disease, infections, malignancies, alkaloses, and drug and toxin ingestion of such substances as ethanol, methanol, ethylene glycol, and salicylates

6.5.6 Renal toxicity

Routine assessment of renal function is required with derivation of creatinine clearance (CLcr) using the Cockcroft-Gault equation. Dosing with tenofovir should be modified if the estimated CLcr falls to <50mL/min in keeping with the package insert for TDF or Truvada.

Creatinine clearance				Hemodialysis patients
Recommended 300 mg dosing interval	≥50	30-49	10-29	
	Every 24 hours	Every 48 hours	Twice a week	Every 7 days or after a total of approximately 12 hours of dialysis

7. Data analysis

7.1 Sample Size Calculation

The primary endpoint is the comparison of proportions of people in each arm whose plasma HIV RNA is <200 copies/mL, 48 weeks after switching from a LPV/r based or other PI-based regimen. Soriano et al [26] in the SLOAT trial reported on patients who commenced treatment with LPV/r for 24 weeks and then continued on the same therapy or swapped to ATV 400mg QD or ATV/r 300/100mg OD. In 53 patients who were switched to ATV/r, and 7 (13%) had a plasma HIV-RNA > 50 copies/mL at week 48, a virological success rate of 87%.

Non-inferiority will be defined as the lower 95% confidence limit of the difference in proportions with undetectable viral load lying above -10% (i.e. a non-inferiority margin of 10%). Virological response is defined as plasma HIV-RNA (<200 copies/mL).

Sample size calculations rely on the assumption that all patients are virologically suppressed at baseline, and the proportion of patients with virological response in the ATV/r 300/100mg arm will be the same as observed in SLOAT. Under the assumption that there is no difference in the failure rate in randomized treatment arms, to have 90% power to demonstrate non-inferiority in the ITT analysis using a 10% margin at a 2-sided significance level of 5% will require 256 participants per arm to be randomized, making a total of 512 participants.

To ensure that the PP analysis also has adequate power to demonstrate non-inferiority, the sample size needs to be increased to allow for patients who swap from the 300mg/100mg arm because of clinical jaundice. This is estimated to be no more than 5%, and it is estimated that an additional 5% of study participants may be lost to follow-up. Applying a 10% adjustment for loss to follow up and regimen swaps due to toxicity would bring the sample size in each arm to 280 patients in each arm, or a total of 560

subjects. We will therefore aim to recruit 560 patients to the study. The power of the ITT analysis in this case will be 93%.

Supplementary sample size assessments for exploratory analyses

Estimates of variability (standard deviations for changes from baseline) to detect differences in bilirubin measures with an 90% power for pair-wise comparisons between arms I and II were obtained from the study by Avihingsanon et al[21] comparing a low dose of Ritonavir-boosted Atazanavir in HIV infected Thai adults. The incidence of grade 3-4 hyperbilirubinemia (total bilirubin >3.2 mg/dl) was 36% for ATV /r 300/100 and 14% for 200/100 mg. 280 Participants per study arm has 100% power to demonstrate a difference in incidence of Grade 3 – 4 hyperbilirubinaemia of 36% and 14% between study arms.

7.2 Data collection and Data Management All data obtained in the clinical trial described in this protocol will be recorded on CRFs or trial specific entry forms. Data will be clearly documented in the Trial Documentation file which data will be collected as source data only. Laboratory data will be recorded electronically. However, printouts are considered as source and will be signed by the Investigator. There will be a form showing the signatures and handwritten initials of all individuals who are authorized to make or change entries on CRFs or source documents.

Confidentiality of trial documents and patient records

The investigator will assure that subjects' anonymity will be maintained and that their identities are protected from unauthorised parties. On CRFs or other documents submitted to the sponsor, subjects would not be identified by their names, but by an identification code. The investigator would keep a subject enrolment log showing codes, names and addresses. The investigator would maintain documents e.g., subjects' written consent forms, in strict confidence.

7.3 Therapeutic drug monitoring

The Pharmacokinetic assessment and Bioanalysis will be performed at HIV-NAT Research Laboratory, Bangkok, Thailand. The quantitative determination of atazanavir and ritonavir in plasma will be carried out by means of a validated HPLC method. Validation and analysis report(s) will be added to the report. These assays will not be performed in real time.

7.4 Analysis plan

Treatment estimates and 95% confidence intervals will be calculated and used to assess primary and secondary efficacy endpoints between randomised treatment groups.

Binary endpoints will be analysed using chi-square tests or logistic regression. Continuous endpoints will be analysed using ANOVA methods or non-parametric equivalents. Time to event endpoints will be analysed using survival analysis methods. For all endpoints and analysis populations, the primary treatment comparisons will be simple, unadjusted, two group comparisons. If there are important imbalances in baseline characteristics, then adjusted analyses will also be performed and presented in addition to unadjusted analyses.

Data on demographics, treatment compliance, concomitant medication and safety of all included subjects (including drop-outs) will be included in the clinical trial report. Demographics, safety data at randomisation, laboratory safety data and concomitant medication will be listed. Descriptive statistics will be calculated for the subject characteristics. There will be no formal comparisons of randomised treatments for

demographic and baseline characteristics (i.e. no p-values), as any imbalance will by definition have occurred by chance.

7.4.1 The primary study endpoint

ATV/r 200/100mg will be judged to be non-inferior to ATV 300/100mg if the lower limit of the 95% confidence interval for the difference in proportion of patients with virological response between the two groups does not exceed -10%.

The ITT population will be the primary analysis dataset, although an analysis on the PP population will also be performed. If non-inferiority is established for the primary comparison (ITT and secondary PP analyses) further analyses to assess for superiority will be undertaken.

7.4.2 Secondary endpoint analyses

The following secondary endpoints will be analysed using both the ITT and PP datasets.

A secondary efficacy analysis will explore the impact of changing the lower limit of detection of viral load to <50 copies/mL.

Absolute CD4 count changes from randomization will be summarized at each study week, and a formal comparison between study arms will be made on the time weighted average change in CD4 count after 48 weeks of therapy.

All other secondary endpoints will use a per protocol population.

Changes in HDL, LDL, cholesterol, triglycerides and bilirubin from randomization to each study week will be summarized by randomized treatment arms. A formal comparison of change from baseline will be made at week 48.

Serious adverse events will be summarised and listed by randomised treatment arm.

The number of grade 3 and 4 laboratory adverse events will be summarized and compared by treatment arms. The cumulative incidence of AEs associated with cessation of randomly assigned therapy, and the time to switch between treatment arms will be formally compared at week 48.

Population PK curves will be modelled in our population using non-linear mixed models accounting for gender, age, body weight and height, ATV dose, NRTI backbone and concomitant medications. Using these models we will be able to compare parameters derived from people of other ethnicities, and also assess the relationship between safety and efficacy of ATV in our own population.

Mean percentage of self reported adherence to antiretroviral therapy determined by visual analogue scale will be compared at each treatment visit by randomised treatment arm. We will also categorise patients with good or poor adherence using a cut-off of 95% adherence and compare the proportions by randomised treatment group and assess associations with the virologic responders in each arm.

Quality of life questionnaire results will be compared by randomised treatment arm at randomisation, week 24 and week 48. Questionnaire responses are on a Likert Scale. Raw scores from questions in each quality of life domain will be transformed to a 0 to 100 scale according to the following formula: Transformed score = [(actual raw score – lowest possible raw score) / (highest possible raw score – lowest possible raw score)] x 100]. Changes from baseline will be formally compared at week 48.

Cardiovascular risk will be assessed by EGAT[4, 5] and Framingham risk equations at baseline and after 48 weeks of using ATV based treatment. A formal comparison will be made comparing the baseline risk and week 48 risk in each patient, by randomised arm.

7.4.3 The intention to treat (ITT) population

The ITT population is defined as all participants who are randomised receive at least one dose of study medication. Participants will be compared as randomised regardless of the treatment received. The following describes a framework for the analysis of the primary endpoint based on a particular handling of anticipated events that could result in different exposures to ART over the study period:

1. In the event the patient dies or becomes lost to follow-up the patient will be considered to have failed their randomised treatment and will be imputed as a virological failure for the primary endpoint analysis
2. In the event that ART is changed because of plasma HIV RNA ≥ 200 copies/mL on two separate occasions at least 2 weeks apart, the patient will be considered to have failed their randomised treatment. ART changes for any other reason do not constitute failure in the ITT population
3. If the week 48 primary endpoint data are missing, this will be imputed as treatment failure.

This analysis corresponds to a comparison of the randomised treatment strategies, including all changes to ART regimens that occur subsequent to randomisation and will constitute the primary analysis.

7.4.4 The per protocol (PP) population

The PP population is defined as all participants included in the ITT population excluding those who changed randomly assigned ART for any reason other than plasma HIV RNA ≥ 200 copies/mL. Analyses will be based on available data and according to the ART received, and patients will be censored once they cease their randomized treatment. This approach corresponds to a comparison of the effectiveness of the two randomised ART regimens as if participants had adhered to their randomly allocated ART.

7.4.5 Schedule of analyses

There will be 2 analyses. An interim analysis will occur when 50% of randomized subjects (140 patients each arm) have had their week 24 study visit or have discontinued the study. A primary analysis of all study endpoints will occur when all patients have completed their 48 week study visit.

The interim analysis will be reviewed by an independent data monitoring and safety board. The DSMB will get information on study conduct, protocol deviations, primary efficacy endpoint and key safety measures of interest. The aim of the interim analysis is to ensure that there is no evidence of a substantially different performance between regimens in virological suppression. The trial may be stopped if one arm is found to be inferior on the endpoint of percentage of participants with detectable plasma HIV RNA at week 24, using a two-sided significance level of 0.001.

The DSMB will make recommendations to the protocol steering committee on whether the study should continue unchanged or be amended in light of observed differences between treatment arms or aspects of study conduct that warrant modification (e.g. poor recruitment, safety concerns, and/or substantial losses to follow-up). Unblinded datasets

will not be made available for review outside the DSMB and the relevant project statistician.

Primary analysis will occur when the last patient randomised has completed 48 weeks of follow-up. This analysis will be reviewed firstly by the Protocol Steering Committee and then presented publicly with treatment arms identified.

Post trial plan (after week 48 or premature withdrawal)

Currently, atazanavir is restricted drug for NHSO for patients with high risk of coronary artery disease (i.e. diabetes mellitus, hypertension, dyslipidemia) and the low dose of ATV/r 200/100 mg is not standard dose. Therefore, after week 48, the participants using ATV/r 200/100 mg will be switched to standard dose of ATV/r 300/100 mg if indicated or switched to LPV/r-based HAART or other appropriated regimens. Moreover, the participant using standard dose of ATV/r 300/100 mg will continue it if indicated or will be switched to LPV/r-based HAART or other appropriated regimens. The antiretroviral regimen will be adjusted by based on physician's discretion.

References

- [1] Taburet AM, Piketty C, Chazallon C, Vincent I, Gerard L, Calvez V, et al. Interactions between atazanavir-ritonavir and tenofovir in heavily pretreated human immunodeficiency virus-infected patients. *Antimicrobial agents and chemotherapy*. 2004 Jun;48(6):2091-6.
- [2] Rho M, Perazella MA. Nephrotoxicity associated with antiretroviral therapy in HIV-infected patients. *Current drug safety*. 2007 May;2(2):147-54.
- [3] de la Fuente JS, Granja V, Escobar I, de la Fuente EC, Moreno V, Rubio R. Study of the gastrointestinal tolerance of a new tablet formulation of the lopinavir/ritonavir antiretroviral in HIV-infected patients. *Journal of acquired immune deficiency syndromes (1999)*. 2009 Mar 1;50(3):294-8.
- [4] Barzi F, Patel A, Gu D, Sritara P, Lam TH, Rodgers A, et al. Cardiovascular risk prediction tools for populations in Asia. *J Epidemiol Community Health*. 2007 Feb;61(2):115-21.
- [5] Pattanaprichakul S JS, Yamwong S, Laothammatas J, Sritara P. RAMA-EGAT Risk Score for Predicting Coronary Artery Disease Evaluated ASEAN Heart Journal. 2007;15(1):18-22.
- [6] DHHS. Guidelines for the use of antiretroviral agents in HIV-1 infected adults and adolescents. . Department of Health And Human Services November 3, 2008.:access online at www.aidsinfo.nih.gov Feb 13, 2009
- [7] Hammer SM, Eron JJ, Jr., Reiss P, Schooley RT, Thompson MA, Walmsley S, et al. Antiretroviral treatment of adult HIV infection: 2008 recommendations of the International AIDS Society-USA panel. *JAMA*. 2008 Aug 6;300(5):555-70.
- [8] Goldsmith DR, Perry CM. Atazanavir. *Drugs*. 2003;63(16):1679-93; discussion 94-5.
- [9] Havlir DV, O'Marro SD. Atazanavir: new option for treatment of HIV infection. *Clin Infect Dis*. 2004 Jun 1;38(11):1599-604.
- [10] Swainston Harrison T, Scott LJ. Atazanavir: a review of its use in the management of HIV infection. *Drugs*. 2005;65(16):2309-36.
- [11] Colonna R, Rose R, McLaren C, Thiry A, Parkin N, Friborg J. Identification of I50L as the signature atazanavir (ATV)-resistance mutation in treatment-naïve HIV-1-infected patients receiving ATV-containing regimens. *J Infect Dis*. 2004 May 15;189(10):1802-10.
- [12] Le Tiec C, Barrail A, Goujard C, Taburet AM. Clinical pharmacokinetics and summary of efficacy and tolerability of atazanavir. *Clin Pharmacokinet*. 2005;44(10):1035-50.
- [13] Perloff ES, Duan SX, Skolnik PR, Greenblatt DJ, von Moltke LL. Atazanavir: effects on P-glycoprotein transport and CYP3A metabolism in vitro. *Drug Metab Dispos*. 2005 Jun;33(6):764-70.
- [14] Zhang D, Chando TJ, Everett DW, Patten CJ, Dehal SS, Humphreys WG. In vitro inhibition of UDP glucuronosyltransferases by atazanavir and other HIV protease inhibitors and the relationship of this property to in vivo bilirubin glucuronidation. *Drug Metab Dispos*. 2005 Nov;33(11):1729-39.
- [15] Winston A, Bloch M, Carr A, Amin J, Mallon PW, Ray J, et al. Atazanavir trough plasma concentration monitoring in a cohort of HIV-1-positive individuals receiving highly active antiretroviral therapy. *J Antimicrob Chemother*. 2005 Aug;56(2):380-7.
- [16] Colombo S, Buclin T, Franc C, Guignard N, Khonkarly M, Tarr PE, et al. Ritonavir-boosted atazanavir-lopinavir combination: a pharmacokinetic interaction study of total, unbound plasma and cellular exposures. *Antivir Ther*. 2006;11(1):53-62.
- [17] Avihingsanon A MW, Kantipong P, et al. . Pharmacokinetics and 48 weeks Efficacy of Nevirapine 400 mg versus 600 mg per day in HIV Infected Patients with active Tuberculosis Receiving Rifampin *Antivir Ther*. 2008;13:529-36.
- [18] Boyd M, Mootsikapun P, Burger D, Chuenyam T, Ubolyam S, Mahanontharit A, et al. Pharmacokinetics of reduced-dose indinavir/ritonavir 400/100 mg twice daily in HIV-1-infected Thai patients. *Antivir Ther*. 2005;10(2):301-7.

- [19] Autar RS, Boffito M, Hassink E, Wit FW, Ananworanich J, Siangphoe U, et al. Interindividual variability of once-daily ritonavir boosted saquinavir pharmacokinetics in Thai and UK patients. *J Antimicrob Chemother.* 2005 Nov;56(5):908-13.
- [20] van der Lugt J, Autar RS, Ubolyam S, Garcia EF, Sankote J, Avihingson A, et al. Pharmacokinetics and short-term efficacy of a double-boosted protease inhibitor regimen in treatment-naïve HIV-1-infected adults. *J Antimicrob Chemother.* 2008 May;61(5):1145-53.
- [21] Avihingsanon A, van der Lugt J, Kerr SJ, Gorowara M, Chanmano S, Ohata P, et al. A low dose of ritonavir-boosted atazanavir provides adequate pharmacokinetic parameters in HIV-1-infected Thai adults. *Clinical pharmacology and therapeutics.* 2009 Apr;85(4):402-8.
- [22] Smith DE, Jeganathan S, Ray J. Atazanavir plasma concentrations vary significantly between patients and correlate with increased serum bilirubin concentrations. *HIV Clin Trials.* 2006 Jan-Feb;7(1):34-8.
- [23] Colombo S, Buclin T, Cavassini M, Decosterd LA, Telenti A, Biollaz J, et al. Population pharmacokinetics of atazanavir in patients with human immunodeficiency virus infection. *Antimicrob Agents Chemother.* 2006 Nov;50(11):3801-8.
- [24] Mills EJ, Nachega JB, Buchan I, Orbinski J, Attaran A, Singh S, et al. Adherence to antiretroviral therapy in sub-Saharan Africa and North America: a meta-analysis. *JAMA.* 2006 Aug 9;296(6):679-90.
- [25] Chetchotisakd P AS. Low-dose, once-daily atazanavir/ritonavir (200/100): an effective treatment for HIV-infected patients in Thailand. *J Acquir Immune Defic Syndr.* 2009;49(2):230-1.
- [26] Soriano V, Garcia-Gasco P, Vispo E, Ruiz-Sancho A, Blanco F, Martin-Carbonero L, et al. Efficacy and safety of replacing lopinavir with atazanavir in HIV-infected patients with undetectable plasma viraemia: final results of the SLOAT trial. *J Antimicrob Chemother.* 2008 Jan;61(1):200-5.
- [27] Gatell J, Salmon-Ceron D, Lazzarin A, Van Wijngaerden E, Antunes F, Leen C, et al. Efficacy and safety of atazanavir-based highly active antiretroviral therapy in patients with virologic suppression switched from a stable, boosted or unboosted protease inhibitor treatment regimen: the SWAN Study (AI424-097) 48-week results. *Clin Infect Dis.* 2007 Jun 1;44(11):1484-92.
- [28] Goldsmith DR, Perry CM. Atazanavir. *Drugs.* 2003;63(16):1679-93; discussion 94-5.
- [29] Squires K, Lazzarin A, Gatell JM, Powderly WG, Pokrovskiy V, Delfraissy JF, et al. Comparison of once-daily atazanavir with efavirenz, each in combination with fixed-dose zidovudine and lamivudine, as initial therapy for patients infected with HIV. *J Acquir Immune Defic Syndr.* 2004 Aug 15;36(5):1011-9.
- [30] Cohen C, Nieto-Cisneros L, Zala C, Fessel WJ, Gonzalez-Garcia J, Gladysz A, et al. Comparison of atazanavir with lopinavir/ritonavir in patients with prior protease inhibitor failure: a randomized multinational trial. *Curr Med Res Opin.* 2005 Oct;21(10):1683-92.
- [31] Duncombe C, Kerr SJ, Liddy J, Avihingsanon A, Ruxrungtham K, Phanuphak P. Efficacy and tolerability of zidovudine 200 mg twice a day as part of combination antiretroviral therapy for 96 weeks. *Journal of acquired immune deficiency syndromes (1999).* 2010 Aug 15;54(5):e19-20.
- [32] National Institute of Allergy and Infectious Disease. Division of AIDS Table for Grading the Severity of Adult and Pediatric Adverse Events. http://www3.niaid.nih.gov/research/resources/DAIDSclinRsrch/PDF/Safety/DAIDSAEG_radingTable.pdf 2004 (Clarification August 2009).
- [33] Ribaud H, Lennox J, Currier J, et al., Virological Failure Endpoint Definition in Clinical Trials Is using HIV-1 RNA Threshold <200 copies/mL Better than <50 Copies/mL? An Analysis of ACTG Studies. Program and abstracts of the 16th Conference on Retroviruses and Opportunistic Infections, February 8-11, 2009, Montreal, Canada, abstract 580.
- [34] Puls RL, Srasuebku P, Petoumenos K, Boesecke C, Duncombe C, Belloso WH, et al. Efavirenz versus Boosted Atazanavir or Zidovudine and Abacavir in Antiretroviral

Treatment-Naive, HIV-Infected Subjects: Week 48 Data from the Altair Study. *Clin Infect Dis.* 2010 Oct 1;51(7):855-64.

[35] Antiretroviral therapy, fat redistribution and hyperlipidaemia in HIV-infected children in Europe. *AIDS (London, England).* 2004 Jul 2;18(10):1443-51.

[36] Aarpibul L, Puthanakit T, Lee B, Mangklabruks A, Sirisanthana T, Sirisanthana V. Lipodystrophy and metabolic changes in HIV-infected children on non-nucleoside reverse transcriptase inhibitor-based antiretroviral therapy. *Antivir Ther.* 2007;12(8):1247-54.