A5290

A Randomized, Phase 2b Study of a Double-Dose Lopinavir/Ritonavir-Based Antiretroviral Regimen with Rifampin-Based Tuberculosis Treatment versus a Standard-Dose Lopinavir/Ritonavir-Based Antiretroviral Regimen with Rifabutin-Based Tuberculosis Treatment with or without Raltegravir in HIV-1-Infected Persons Requiring Treatment for Active TB and HIV

A Multicenter Trial of the AIDS Clinical Trials Group (ACTG)

DAIDS ES # 11703

This file contains the current ACTG A5290 protocol, which includes the following documents, presented in reverse chronological order:

- Clarification Memorandum #1, dated 18 April 2013
- Protocol Version 1.0, dated 31 January 2012

Clarification Memorandum #1 for:

ACTG A5290
A Randomized, Phase 2b Study of a Double-Dose Lopinavir/Ritonavir-Based Antiretroviral Regimen with Rifampin-Based Tuberculosis Treatment versus a Standard-Dose Lopinavir/Ritonavir-Based Antiretroviral Regimen with Rifabutin-Based Tuberculosis Treatment with or without Raltegravir in HIV-1-Infected Persons Requiring Treatment for Active TB and HIV

A Multicenter Trial of the AIDS Clinical Trials Group (ACTG)

DAIDS ES # 11703

Clarification Memo Date: 18 April 2013

This clarification memo is being issued primarily to allow the study to open as quickly as possible (ie, before requiring that 4-5 sites are ready to implement the study) (see item #4 below). This change is being made to ensure the feasibility of the current plan for shipment and testing of samples and the near real-time reporting of results (see protocol section 6.3.11). Implementation of this plan at a slightly slower pace than would be expected if 4-5 sites began enrolling at the same time will allow for rapid correction of any issues that arise.

In addition, this memo includes clarifications related to the requirement for rifampin resistance testing (item #1) and to the window for reporting use of certain prescription drugs (item #2), and to remove mention of the FDA in several instances where it is not required (item #3).

The following are the specific clarifications to individual sections of protocol A5290, Version 1.0, 02/17/12:

1. Note A in section 4.2.3 should be understood to read as shown below:

   NOTE A: **All specimens available at entry should be tested for RIF resistance.** ~~Participants~~ **Candidates who meet entry criterion 4.1.3** may be enrolled **even if no specimens are available or** pending the results of RIF drug susceptibility testing ~~if~~ **by** a rapid HAIN GenoType MTBDR Plus line probe assay, GeneXpert® MTB/RIF assay, or other rapid MTB RIF drug resistance assay ~~result is not yet available~~. However, ~~if RIF drug susceptibility test results are not available within 60 days after study entry or~~ if any drug susceptibility testing subsequently demonstrates RIF resistance, participants will be discontinued from the study and referred to their primary clinician/clinical facility or TB and ART program and treated with the best available TB and ART according to local standards of care.

2. In section 6.3.4, the timeframe for reporting 'Prescription drugs for treatment of opportunistic infections' should be '**Within 30 days prior to study entry'** in the Medication History table (5th row below headers, 2nd column). The current 'Complete history' should be deleted.

3. In sections 8.3 (final bullet), 11.3.2, 12.2, and 12.3, references to the US Food and Drug Administration (or FDA) are no longer applicable because A5290 is a non-IND study. Sites may also remove mention of the FDA from the informed consents' sections on confidentiality.

4. In section 9.4.3, Overall accrual, the first paragraph should be understood to read as shown below:

   Accrual period 1 will open **as soon as the first registered site is ready to enroll participants. O**nce ~~at least~~ 4-5 sites ~~have all regulatory approvals completed and~~ are ~~ready to~~ enroll**ing** participants**,** ~~immediately. The team estimates that these 4-5 sites should be able to accrue~~ approximately ~~4-6~~ **3-5** participants **should be enrolled** per month per site**, and** ~~. As other sites begin accrual period 1, the team anticipates that~~ **full enrollment for** accrual period 1 (n=60) should be completed within approximately ~~2-~~4 months.

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A Randomized, Phase 2b Study of a Double-Dose Lopinavir/Ritonavir-Based Antiretroviral Regimen with Rifampin-Based Tuberculosis Treatment versus a Standard-Dose Lopinavir/Ritonavir-Based Antiretroviral Regimen with Rifabutin-Based Tuberculosis Treatment with or without Raltegravir in HIV-1-Infected Persons Requiring Treatment for Active TB and HIV

A Multicenter Trial of the AIDS Clinical Trials Group (ACTG)

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IND #

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FINAL Version 1.0
January 31, 2012

ACTG
AIDS CLINICAL TRIALS GROUP

CONTENTS

Page

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At least one research nurse responsible for the conduct of the study at each participating site must complete the "PK Tutorial: Pharmacology Study Conduct – Its Impact on PK-PD Analyses." The tutorial is accessible from the Frontier Science and Technology Research Foundation web site at www.fstrf.org (either via the "ACTG Data Management" portal or the "Clinical Pharmacology Quality Assurance Program" portal).

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STUDY MANAGEMENT

All questions concerning this protocol should be sent to actg.teamA5290@fstrf.org via e-mail. The appropriate team member will respond with a "cc" to actg.teamA5290@fstrf.org. A response should generally be received within 24 hours (Monday-Friday).

Protocol E-mail Group
Sites registering to this study must contact the Computer Support Group at the Data Management Center (DMC) to have the relevant personnel at the site added to the actg.protA5290 email group. Include the protocol number in the e-mail subject line.

- Send an e-mail message to actg.user.support@fstrf.org.

Clinical Management
For questions concerning entry criteria, toxicity management, concomitant medications, and coenrollment, contact the protocol co-chairs. Send an e-mail message to actg.coreA5290@fstrf.org (ATTN: Constance Benson and Umesh Lalloo). Include the protocol number, patient identification number (PID), and a brief relevant history.

Laboratory
For questions specifically related to virologic or pharmacologic laboratory tests, contact the protocol virologist or pharmacologist. Send an e-mail message to actg.coreA5290@fstrf.org (ATTN: Carole Wallis or Courtney Fletcher).

Data Management
For nonclinical questions about transfers, inclusion/exclusion criteria, case report forms (CRF), the CRF schedule of events (SOE), randomization, delinquencies, and other data management issues, contact the data manager.

- For transfers, reference the Patient Transfer from Site to Site SOP 119, and contact Susan Owens directly.
- For other questions, send an e-mail message to actg.coreA5290@fstrf.org (ATTN: Susan Owens).
- Include the protocol number, PID, and a detailed question.

Randomization
For randomization questions or problems and study identification number SID lists.

- Send an e-mail message to rando.support@fstrf.org. Call the Statistical and Data Analysis Center (SDAC)/DMC Randomization Desk at (716) 898-7301.

Computer and Screen Problems
Contact the SDAC/DMC programmers.

- Send an e-mail message to actg.support@fstrf.org or call (716) 834-0900 x7302.

Protocol Document Questions
For questions concerning the protocol document, contact the clinical trials specialist. Send an e-mail message to actg.teamA5290@fstrf.org (ATTN: Katharine Bergstrom).

Copies of the Protocol
To request hard copies of the protocol, send a message to ACTGOpsCenter@s-3.com (ATTN: Diane Delgado) via e-mail. Electronic copies can be downloaded from the ACTG Web site (https://www.actgnetwork.org).

Product Package Inserts or Investigator Brochures
To request copies of product package inserts or investigator brochures, contact the DAIDS Regulatory Support Center (RSC) at RIC@tech-res.com or call (301) 897-1708.

Protocol Registration
For protocol registration questions:
- Send an e-mail message to Protocol@tech-res.com or call (301) 897-1707.

Study Drug
For questions or problems regarding study drug, dose, supplies, records, and returns, call Ruth Ebiasah, protocol pharmacist, at (301) 496-8213.

IND (Investigational New Drug) Number or Questions
Contact the DAIDS RSC at Regulatory@tech-res.com or call (301) 897-1706.

Study Drug Orders
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Expedited Adverse Event (EAE) Reporting/Questions
Contact DAIDS through the RSC Safety Office at DAIDSRSCSafetyOffice@tech-res.com or call 1-800-537-9979 or (301) 897-1709; or fax 1-800-275-7619 or (301) 897-1710.

Phone Calls
Sites are responsible for documenting any phone calls made to protocol team members. Send an e-mail to actg.teamA5290@fstrf.org.

Protocol-Specific Web Page
Additional information concerning study management of ACTG studies can be found on the ACTG Web page.

GLOSSARY OF TERMS

AFB	acid fast bacilli
ALT	alanine aminotransferase
ANC	absolute neutrophil count
AST	aspartate aminotransferase
ATV	atazanavir
AUC	area under the concentration curve
BID	twice daily
BLQ	below the limit of quantitation
BMI	body mass index
C_{12h}	12-hour post dose plasma concentration
C_{24h}	24-hour post dose plasma concentration
CI	confidence interval
CL/F	apparent oral clearance
C_{max}	maximum plasma concentration
C_{min}	minimum plasma concentration
CSF	cerebrospinal fluid
CT	computed tomography
DOT	directly observed therapy
EFV	efavirenz
EMB	ethambutol
GMR	geometric mean ratio
t½	half life
INH	isoniazid
IRIS	immune reconstitution inflammatory syndrome
LPV	lopinavir
LPV/r	lopinavir/ritonavir
MDR TB	multidrug-resistant tuberculosis (TB), defined as TB with demonstrated resistance to rifampin (RIF) and isoniazid (INH)
MIC	minimum inhibitory concentration
MTB	Mycobacterium tuberculosis
NVP	nevirapine
OI	opportunistic infection
PBMC	peripheral blood mononuclear cells
PZA	pyrazinamide
q12h	every 12 hours
RAL	raltegravir
RBT	rifabutin
RIF	rifampin

RNA	ribonucleic acid
RTV	ritonavir
TB	tuberculosis
TIW	three times weekly
T_{max}	time to maximum plasma concentration
UGT1A1	UDP-glucuronosyltransferase 1A1
ULN	upper limit of normal
XDR	extensively drug resistant TB, defined as TB with demonstrated resistance to RIF, INH, plus resistance to fluroroquinolones, and to at least one second-line injectable anti-TB drug (e.g., amikacin, kanamysin, or capreomycin)

SCHEMA

A5290
A Randomized, Phase 2b Study of a Double-Dose Lopinavir/Ritonavir Based Antiretroviral Regimen with Rifampin-Based Tuberculosis Treatment versus a Standard-Dose Lopinavir/Ritonavir Based Antiretroviral Regimen with Rifabutin-Based Tuberculosis Treatment with or without Raltegravir in HIV-1-Infected Persons Requiring Treatment for Active TB and HIV

DESIGN

A5290 is a prospective, randomized (1:1:1), open-label, phase 2b study comparing three lopinavir/ritonavir (LPV/r)-based antiretroviral (ARV) regimens among participants in high tuberculosis (TB) endemic resource-constrained settings undergoing treatment for confirmed or probable TB and requiring protease inhibitor (PI)-based antiretroviral therapy (ART). A two accrual period design will be used, including a full pharmacokinetic (PK) and safety evaluation to be conducted when 54-60 participants enrolled during the accrual period 1 have completed 28 days of ARV treatment and day 12 ± 2 (after initiation of ART) drug levels are available (an early interim PK and safety evaluation will also be completed when 10-12 participants per arm have completed 28 days of ARV treatment and day 12 ± 2 drug levels are available).

DURATION

Each participant will be followed until week 72.

SAMPLE SIZE

471 participants.

POPULATION

HIV-infected persons (male or female) at least 18 years of age with documented HIV infection, a clinical diagnosis of probable or confirmed active TB (including extrapulmonary TB) with susceptibility to rifampin (RIF), and who require a PI-based ARV regimen.

REGIMENS

Study-provided drugs include lopinavir/ritonavir (LPV/r), ritonavir (RTV), raltegravir (RAL), and rifabutin (RBT).

Arm A

- ART: LPV 400 mg/RTV 100 mg twice daily (BID) + two NRTIs.
- Anti-TB therapy: Isoniazid (INH) 300 mg daily, RBT 300 mg daily, then 150 mg daily upon initiation of ART, ethambutol (EMB) (weight-based dose) daily, pyrazinamide (PZA) (weight-based dose) daily, and pyridoxine 25 mg daily. EMB and PZA will be discontinued after 8 weeks of treatment (after completion of the intensive TB treatment phase); INH, RBT 150 mg daily (or the adjusted dose determined by PK testing), and pyridoxine will continue through week 24 for a minimum total duration of 24 weeks, and may continue beyond 24 weeks to a maximum of 48 weeks at the discretion of the primary clinician; the protocol core team must be notified (actg.corea5290@fstrf.org) if TB treatment is continued beyond 24 weeks.

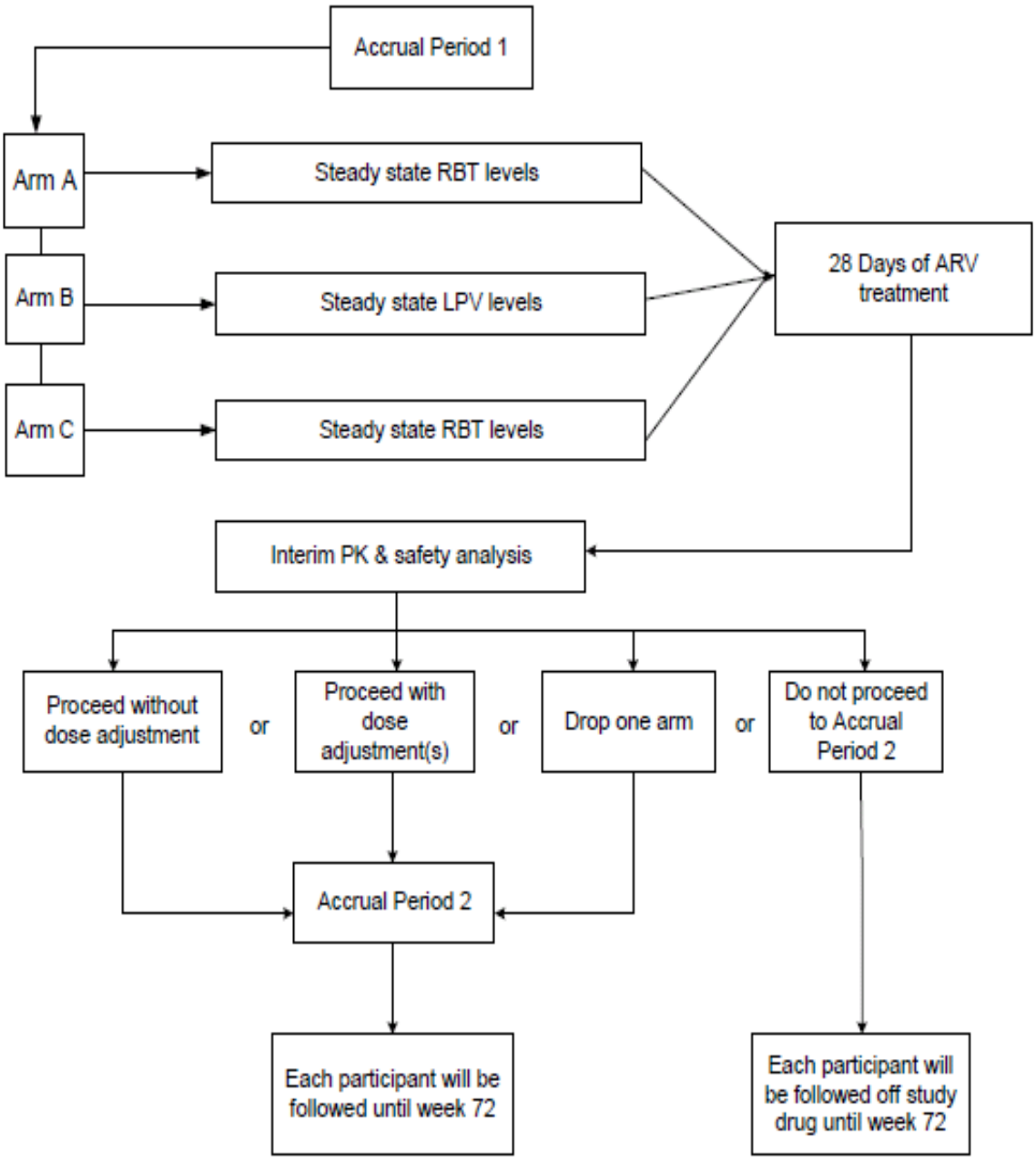
- After completion of TB treatment, LPV/r + two NRTIs will be continued with LPV/r at standard dosing (400mg/100mg BID) through week 72.

Arm B
- ART: LPV 800 mg/RTV 200 mg BID + two NRTIs.
- Anti-TB therapy: INH 300 mg daily, rifampin (RIF) (weight-based dose) daily, EMB (weight-based dose) daily, PZA (weight-based dose) daily, and pyridoxine 25 mg daily. EMB and PZA will be discontinued after 8 weeks of treatment (after completion of the intensive TB treatment phase); INH, RIF, and pyridoxine will continue through week 24 for a minimum total duration of 24 weeks, and may be continued beyond 24 weeks to a maximum of 48 weeks at the discretion of the primary clinician; the protocol core team must be notified (actg.corea5290@fstrf.org) if TB treatment is continued beyond 24 weeks.
- After completion of TB treatment, LPV/r + two NRTIs will be continued with LPV/r at standard dosing (400mg/100mg BID) through week 72.

Arm C
- ART: LPV 400 mg/RTV 100 mg BID + two NRTIs + RAL 400 mg BID.
- Anti-TB therapy: INH 300 mg daily, RBT 300 mg daily, then 150 mg daily upon initiation of ART, EMB (weight-based dose) daily, PZA (weight-based dose) daily, and pyridoxine 25 mg daily. EMB and PZA will be discontinued after 8 weeks of treatment (after completion of the intensive TB treatment phase); INH, RBT 150 mg daily (or the adjusted dose determined by PK), and pyridoxine will be continued through week 24 for a minimum total duration of 24 weeks, and may be continued beyond 24 weeks to a maximum of 48 weeks at the discretion of the primary clinician; the protocol core team must be notified (actg.corea5290@fstrf.org) if TB treatment is continued beyond 24 weeks.
- After completion of TB treatment, LPV/r + two NRTIs + RAL will be continued with LPV/r at standard dosing (400mg/100mg) through week 72.

If LPV/r is prematurely discontinued at any time during TB treatment for Arms A and C, the team must be notified, and the RBT dose should be increased to 300 mg daily pending further instructions from the team.

Figure 1. Study Schema



1.0 HYPOTHESIS AND STUDY OBJECTIVES

1.1 Hypothesis

For HIV-1-infected participants with active tuberculosis (TB) who require protease inhibitor (PI)-based antiretroviral therapy (ART), a standard dose lopinavir/ritonavir (LPV/r) regimen, with or without raltegravir (RAL), coupled with rifabutin (RBT)-based TB treatment is superior to a double dose LPV/r regimen coupled with rifampin (RIF)-based TB treatment.

1.2 Primary Objective

To compare rates of virologic suppression to < 400 copies/mL at 48 weeks for the two standard dose LPV/r and RBT arms versus the double-dose LPV/r and RIF arm.

1.3 Secondary Objectives

1.3.1 To evaluate TB treatment outcomes (as measured by week 8 mycobacterial culture conversion, treatment failure at or after week 24, TB relapse/recurrence by week 72) between RBT-containing arms and the RIF-containing arm, to include the association between RBT or RIF exposure as well as other factors potentially associated with outcomes of TB treatment.

NOTE: TB treatment outcome measurements for participants who enroll with probable TB for whom week 8 mycobacterial culture conversion rates cannot be assessed will include either week 8 AFB smear conversion rate coupled with resolution of signs, symptoms, and radiographic abnormalities on which the diagnosis of probable TB was based or solely resolution of signs, symptoms, and radiographic abnormalities for participants with negative AFB smears or AFB smears that are not available at baseline; in addition, TB treatment failure at or after week 24, and TB relapse/recurrence by week 72 will be captured as TB outcome measures.

1.3.2 To compare rates of virologic suppression to < 50 copies/mL at 48 weeks for the two standard dose LPV/r and RBT arms versus the double-dose LPV/r and RIF arm.

1.3.3 To compare rates of virologic suppression to < 50 copies/mL and < 400 copies/mL at 48 weeks for standard dose LPV/r and RBT versus standard dose LPV/r, RBT, and RAL.

1.3.4 To compare safety and tolerability during TB treatment of double-dose LPV/r and RIF between the three treatment arms.

1.3.5 To compare the proportion of participants with virologic failure and time to virologic failure between the three treatment arms.

1.3.6 To compare the emergence of HIV-1 drug resistance mutations in gag, protease, reverse transcriptase (RT), and integrase in participants with virologic failure between the three treatment arms.

1.3.7 To compare the proportion of participants with TB drug-resistance among cases of TB treatment failure and relapse/recurrence of TB between the three treatment arms.

1.3.8 To characterize TB immune reconstitution inflammatory syndrome (IRIS) events.

1.3.9 To compare changes in CD4+ T-cell count, and proportion of participants who experience new AIDS-defining illness, HIV disease progression (defined as new AIDS-defining illness or death), or death between the three treatment arms.

1.3.10 To evaluate LPV pharmacokinetic (PK) characteristics (area under the curve [AUC], maximum concentration [C_{max}], minimum concentration [C_{min}]) in participants enrolled in Arms A, B, and C, accrual periods 1 and 2.

1.3.11 To evaluate the RBT PK characteristics (AUC, C_{max}, C_{min}) in participants enrolled in Arms A and C, accrual periods 1 and 2.

1.3.12 To evaluate RAL PK characteristics (AUC, C_{max}, C_{min}) in participants enrolled in Arm C, accrual period 2.

1.3.13 To evaluate the cost-benefit analysis of the addition of RAL.

1.4 Tertiary Objective

1.4.1 To submit sputum, serum, and urine specimens at specified time points to the Consortium for TB Biobank for analysis of biomarkers associated with TB treatment response.

2.0 INTRODUCTION

2.1 Background

TB is the most common opportunistic infection (OI) among patients living with HIV disease globally, most importantly in high TB endemic resource-constrained settings. There is an increased risk of HIV disease progression (new AIDS-related OIs or death) among ART-naïve HIV-1-infected patients presenting with active TB[1]. The provision of cotrimoxazole[2,3] and ART during TB treatment markedly decreases the risk of HIV disease progression[4,5,6,7]. For example, in a large cohort of participants with HIV-related TB in Thailand, the risk of death was decreased 83% among those who received ART[6]. Three large randomized controlled trials as well as other cohort studies have also demonstrated that early initiation of ART during TB treatment is associated with reduced mortality in HIV-infected participants, particularly those with advanced immunosuppression as defined by a CD4+ T-cell count of < 50 cells/µL[4,8,9.10,11].

Therefore, patients with HIV-related TB should be a high priority group for evaluation and initiation of ART. This issue has been recently addressed in revised World Health Organization (WHO) treatment guidelines, which recommend initiation of ART as soon as is feasible in all HIV-infected persons with active TB regardless of CD4+ T-cell count[12].

The standard cotreatment regimen for HIV-related TB and the need for alternatives

The preferred cotreatment regimen for HIV-related TB in resource-constrained settings is RIF-based anti-TB therapy with efavirenz (EFV)-based ART (EFV + 2 nucleoside analogue reverse transcriptase inhibitors [NRTIs])[13]. Nevirapine (NVP) is substituted for EFV in some settings when patients cannot take or do not have access to EFV, although data from clinical trials in the setting of active TB are less robust in terms of virologic and TB outcomes, and NVP cannot be safely used for persons with higher CD4+ T-cell counts. Outcomes of EFV-based ART are generally comparable among patients with or without concomitant active TB[14], although viral suppression rates < 400 copies/mL at 48 weeks of ART may differ according to when ART is initiated during TB treatment[8, 9,10]. In the SAPiT trial, among participants with active TB starting ART within the first 8 weeks of TB treatment initiation, overall viral suppression rates were higher than for those for whom ART was delayed until after the completion of TB treatment (although by 6 months after completion of TB treatment, viral suppression rates were similar)[8]. However, in both the CAMELIA trial and the A5221/STRIDE trial of early vs. deferred ART in persons initiating TB treatment, viral suppression rates were comparable when ART was started within the first 2 versus 8-12 weeks of TB treatment, despite differences in mortality and IRIS rates[9, 10]. In each of these studies, EFV + 2 NRTIs was the ART regimen used, and in general, viral suppression rates were similar to those reported among HIV-infected persons initiating ART in the setting of advanced immunosuppression but without active TB. However, not all patients with HIV-related TB can be treated with this preferred cotreatment regimen. Some patients cannot tolerate the neuropsychiatric side effects of EFV or develop other significant treatment-limiting toxicities due to EFV or NVP, such as hypersensitivity reactions. Moreover, EFV is teratogenic, and, therefore, cannot be used early in pregnancy (the safety of EFV in the latter part of pregnancy is currently being evaluated). Children generally cannot be treated with EFV as there is no approved formulation of EFV for young children, and the correct dosing of EFV in older children is uncertain[15].

Combination EFV- or NVP-based ART has been very successful as initial treatment in high HIV-burden settings[16,17]. Nevertheless, virologic failure of initial ARV regimens occurs, and such patients often have HIV with high-level resistance to non-NRTIs (NNRTIs) and NRTIs commonly available in such settings. In several large cohorts in Africa, the rate of virologic failure of initial NNRTI-based ART was approximately 2% per year[16,17]. Cohorts in middle-income countries with more mature ART programs report rates of approximately 4% per year. In addition, women who have received single dose NVP for the prevention of mother to child transmission of HIV have high virologic failure rates associated with initial NVP-based ART, and HIV with high level resistance to NVP and EFV has been detected either at baseline or at the time of subsequent virologic failure in these women[18]. While the initial virologic failure rates in many of these studies were low with careful follow-up and monitoring, these studies may underestimate the failure rate in areas where treatment default rates are high, and the number of patients

who will need second-line ART is large because of the very success of the ARV roll-out in high-burden countries. Furthermore, patients who have failed an initial regimen often have advanced immunodeficiency, and, therefore, are at higher risk of developing TB. A recent estimate is that there will be 392,000 to 902,000 patients with TB while on second-line ART over the next 7 years (Stop TB/HIV Working Group, WHO, 2009). Therefore, there is a rapidly growing need to identify cotreatment regimens for HIV-related TB that can be used among patients in resource-constrained settings who have resistance to EFV and NRTIs or who require second-line ART with a protease inhibitor (PI)-based regimen.

Managing the interaction between rifamycins and PI-based ART regimens

At present, there is no satisfactory cotreatment regimen for HIV-related TB among patients who have failed initial NNRTI-based ART or require the use of a PI-based regimen because they are unable to take or tolerate NNRTIs or for other reasons. The basis of second-line ART in many high-burden countries is the HIV-1 PI class of medications. RIF markedly decreases the plasma concentrations of all of the available PIs, particularly atazanavir/ritonavir (ATV/RTV) and LPV/r, the two recommended PI agents in high-burden countries. With the addition of relatively high doses of RTV (up to 200-400 mg twice-daily), the effect of RIF on selected PIs (notably LPV and saquinavir) can be largely overcome[19,20], and this approach has been termed “super-boosted” PI therapy (or double-dose PI therapy when fixed-dose combinations are used). This approach has not been tested with other PIs.

While it is pharmacologically possible to overcome the effect of RIF on PIs, the problem of the strategy of double-dose or super-boosted PI therapy is tolerability. The combination of higher dose RTV, a second PI, and RIF has been poorly tolerated in studies of healthy adult volunteers, with high rates of gastrointestinal symptoms (nausea and vomiting) and drug-induced liver injury[21,22,23]. There is limited published experience with double-dose or super-boosted PI therapy among patients with HIV-related TB on RIF-based treatment[19,21,24,25]. In healthy volunteer studies, LPV/r 800 mg/200 mg administered twice daily (BID) (double-dose) appears to be better tolerated than a regimen utilizing a 400 mg LPV and 400 mg RTV BID dose (super-boosted), although the PK variability may be greater for the double-dose regimen, perhaps owing to the fact that a 400 mg dose of RTV BID is better able to overcome the RIF drug interaction.

There appear to be substantial differences in response to double-dose or super-boosted PI regimens in children compared to adults. Among children, the combination of super-boosted PI and RIF-based TB treatment was relatively well-tolerated and effective in the short term. In a cohort study from Soweto, South Africa, young children treated with RIF-based TB treatment and super-boosted LPV/r-based ART had similar clinical and virologic outcomes as children without TB treated with standard-dose LPV/r-based therapy[23]. In a study of adults with HIV-related TB, super-boosted saquinavir-based ART with RIF-based TB treatment had good virologic outcomes among those who remained on ART, but only 10 of 20 participants tolerated this cotreatment regimen[19]. Side effects resulting in discontinuation of HIV-TB cotreatment were nausea, vomiting, and drug-induced liver injury. Thus, in adults, double-dose LPV/r may provide reasonable trough concentrations, albeit with perhaps greater variability than super-boosted doses, while super-boosted doses are poorly tolerated. In children, super-boosted LPV is better

tolerated and is associated with better trough concentrations and virologic outcomes than double-dose LPV/r. Despite the limitations of published data on the efficacy of double-dose or super-boosted PI therapy with RIF-based TB treatment, particularly in adults, these combinations continue to be used in high-burden resource-constrained settings because of the lack of good alternatives.

There are also issues related to the better tolerability and reduced toxicity in healthy volunteers associated with dosing the PI first, followed by the addition of RIF, as demonstrated in ACTG A5213. This issue will be difficult to overcome, however, in the setting of active TB, as there is an imperative to initiate TB treatment as soon as possible once TB is diagnosed, and for the most part, patients must be started on anti-TB treatment before they are started on ART. Those who need to make a switch in ART because they require anti-TB treatment will also likely not be able to start PI-based ART first.

Use of an 800 mg/200 mg BID dose of LPV/r may also be easier to administer in resource-constrained settings because this dose takes advantage of the better tolerated and more stably stored Meltrex co-formulated tablets that do not require a separate prescription for extra doses of the additional RTV. This trial will evaluate the strategy of double-dose LPV/r in combination with RIF-based TB therapy using the now standard heat-stable Meltrex formulation of LPV/r. This regimen of double-dose LPV/r (800 mg/200 mg BID) is currently being used as standard of care in South Africa and other resource-constrained settings for patients being treated for active TB with a RIF-based regimen and who require ART containing a PI. A recent small PK study among stable participants on LPV/r-based ART showed that serum concentrations of LPV/r were dramatically decreased after the addition of RIF, but that doubling the dose of LPV/r restored trough concentrations of LPV/r[26]. Two participants in the study had increased liver transaminases following the addition of RIF to LPV/r-based ART, but both participants did well with discontinuation of RIF. This strategy has not been evaluated in controlled clinical trial settings that evaluate both virologic and TB treatment outcomes, and there are very limited data about its tolerability and efficacy for patients with HIV-related TB.

Some of these PK and dosing issues associated with double-dose LPV/r and RIF were addressed in a small PK study conducted in South Africa in HIV-infected adults virologically suppressed on a LPV/r regimen[27]. All study participants had CD4+ T-cell counts > 400 cells/µL, viral loads < 400 copies/mL, and none had active TB. Steady state PK of LPV/r was evaluated at baseline, one week after initiation of RIF, and one week after gradual dose escalation of LPV/r to 1.5 and then 2x the standard dose (i.e., double-dose). A total of 21 participants were enrolled. Median LPV 12-hour post dose concentration was 3.7 mg/L (IQR 1.2-7.7) with double-dose LPV/r, and there were no significant differences in LPV AUC_{0-12}, C_0, C_{12}, C_{max}, or $T_{1/2}$ for the baseline vs. double-dose LPV/r time points after steady state RIF was achieved. The doses were generally well-tolerated with only two participants developing asymptomatic Grade 3 or 4 elevations of liver transaminases. All participants achieved therapeutic C_0 trough concentrations with double-dose LPV/r; 18/20 did so with a dose of 1.5 times standard LPV/r, suggesting this may be effective as a step-down dose for those unable to tolerate a full double dose. The authors caution that these data should not be extrapolated to

treatment of persons with active TB, as these were not included in this study, and safety data were available for only 22 days. However, these data do provide support for the further evaluation of this regimen in HIV-infected adults with active TB.

In summary, RIF, the cornerstone of TB treatment, has very problematic drug-drug interactions with PIs. The use of relatively high doses of RTV appear necessary to overcome this interaction, but it is unclear whether the cotreatment regimen of RIF-based TB treatment and double-dose PI-based ART will be safe and tolerable for patients with HIV-related TB and effective in treating both HIV and TB.

Rifabutin and protease-inhibitors

RBT is a rifamycin antibiotic with potent activity against *Mycobacterium tuberculosis* (MTB), both *in vitro* and in animal models of TB treatment. In three randomized clinical trials, RBT appeared to be as effective as RIF for the treatment of pulmonary TB, but overall numbers of participants treated and the design of the trials have led to the conclusion that further careful study, particularly in HIV-infected participants receiving ART, is needed[28,29,30,31]. Of note for the treatment of HIV-related TB, RBT has limited effect on serum concentrations of HIV-1 PIs than does RIF[32]. In fact, RBT has very little effect on PIs in common use, i.e., LPV/r and ATV[34,35]. In small clinical studies, the cotreatment regimen of RBT-based TB treatment and PI-based ART has been well-tolerated and effective[36], and it is recommended in the United States for patients unable to take EFV-based ART, even though RBT is not licensed for this indication.

However, there are limitations to the use of RBT in PI cotreatment regimens. First, experience using RBT for TB treatment is limited, and as outlined above, a Cochrane Review of the literature recently concluded that there are insufficient data to be assured of RBT's effectiveness in TB treatment[29]. Second, RBT is generally not available in high-burden countries for treatment of HIV-related TB, although this is expected to change over time with the addition of RBT to the WHO Essential Medicines list and the availability of generic formulations of the drug in some countries. Third, although RBT has limited effect on serum concentrations of currently-used PIs, the concentrations of RBT and its primary metabolite are markedly increased by PIs, particularly RTV. The resulting high concentrations of RBT and its metabolite can cause toxicity – uveitis, leucopenia/neutropenia, skin discoloration, and nausea. A recent small PK study of atazanavir/ritonavir with RBT in healthy volunteers who received a RBT dose of 150 mg twice weekly was stopped prematurely due to excess neutropenia. The RBT C_{max} was increased by 149% and the 25-O-desacetyl active metabolite of RBT was increased by 5-10 fold, which probably accounted for the excess neutropenia[33]. Atazanavir C_{max} and AUC were decreased by 25% when compared with historical controls using the twice weekly dosing of RBT. The authors provided modeling simulations based on the drug levels they measured and suggested that RBT should be given in a dose of 150 mg three times weekly (TIW) in persons with active TB when administered with ATV/r; however, they did not actually evaluate this dose regimen in their study, and there was no indication from their models whether the further increase in the RBT and 25-O-desacetyl metabolite that would accompany the increased dosing frequency might further reduce atazanavir C_{max} or AUC. Based on all of the aforementioned considerations, the currently recommended dose of RBT must be decreased when it is

administered with PIs, but data are urgently needed to understand what should be the optimal dose to ensure safe and effective treatment of TB in this setting.

Based primarily on results from studies in healthy volunteers, standard dose reductions of RBT have been recommended when administered with PIs, but there is a critical need to validate those recommendations among participants with HIV-related TB. Notably, the reduced dose of RBT would likely be inadequate for TB treatment if the PI therapy was discontinued. Therefore, the approach of reduced dose RBT relies on adherence to a PI and there may be differences among PIs with regard to the impact on PK/PD. In one small study, 10 HIV-infected participants hospitalized in a TB treatment facility were started on RBT-based TB treatment at a dose of 300 mg TIW without LPV/r, had week 2 RBT concentrations obtained, then added a LPV/r-based ART regimen and reduced their RBT dose to 150 mg TIW, per current recommendations[37]. The C_{max} obtained at week 4 to 5 was ≤ 0.30 µg/mL for 9 of 10 participants while the partially active 25-O-desacetyl metabolite of RBT was increased, as was the AUC_{0-24} and AUC_{0-48}. Most unbound RBT C_{max} values were below the minimum inhibitory concentration (MIC) for drug-susceptible MTB and values for the plasma concentration-time curve were below those that had been associated with TB treatment failure or relapse (i.e., an AUC_{0-24} < 4.5 µg*h/mL) in a previously conducted TB Trials Consortium Study[23,35,38]. Eight of the 10 participants in the study were men with a median weight of 74 kg and a median body mass index (BMI) of 23.1, a heavier population with a different gender proportion than participants likely to be enrolled from some resource-constrained settings. In another report, three participants experienced a relapse of TB with a RIF-resistant isolate after treatment with a RTV-boosted PI-based ART regimen coupled with a RBT-based TB regimen using a 150 mg TIW dose schedule[39]. These studies raise some uncertainty about current dosing recommendations for RBT in the setting of PI-based therapy, although results from a recent PK study conducted in South Africa shed further light on this issue. In this study, the PK of RBT was evaluated in 16 HIV coinfected participants with active TB. These participants were initially treated with a RBT-based anti-TB regimen (using RBT in a dose of 300 mg daily) before starting ART that included standard doses of LPV/r 400/100 mg BID daily[40]. Participants were established on their anti-TB therapy and were then randomized after starting LPV/r to receive RBT 150 mg daily x 4 weeks followed by 150 mg TIW or to the converse dosing strategy. Serial RBT and 25-O-desacetyl RBT concentrations were measured after each 4 week interval. The median AUC_{0-24}, and C_{max} on RBT 300 mg daily, 150 mg TIW, and 150 mg daily, respectively, were 3026 ng/mL.h and 297 ng/mL, 2307 ng/mL.h and 168 ng/mL, and 5010 ng/mL.h and 311 ng/mL. All doses were well tolerated with only one case of uveitis that occurred prior to starting LPV/r and one episode each of Grade 2 transaminitis and neutropenia reported. When coupled with standard doses of LPV/r, the dose of RBT that best approximated the 300 mg dose in the absence of LPV/r, and that achieved a C_{max} concentration of RBT within recommended target ranges for TB treatment of 300-900 ng/mL, was the RBT 150 mg daily dose. These data in aggregate suggest that in the context of PI-based therapy, the current recommended dose of RBT is insufficient. Finally, RBT is not available in fixed-dose combination formulations of TB medications that are commonly used in high-burden settings. Therefore, the use of RBT, rather than RIF, will be associated with higher pill burdens and will be more complex for patients and TB control programs.

In summary, the cotreatment regimen of RBT-based TB treatment and PI-based ART is promising for patients unable to take EFV. However, much more data are needed to evaluate the most appropriate doses, tolerability, anti-TB efficacy, and programmatic aspects of substituting RBT for RIF in this setting.

Ensuring sufficient ARV regimen potency in second-line therapy

In addition to the difficulty of using a PI with RIF, the standard second-line ARV regimen may be unsatisfactory for other reasons. Among patients who have failed an initial NNRTI-based regimen, there is a high risk of substantial resistance not only to NNRTIs but also to the NRTI class. In many resource-constrained settings, viral load monitoring is not routinely available, and decisions about switching to second-line regimens are based on CD4+ T-cell count decline, "clinical failure" as defined by a new or recurrent OI, or a viral load, if available, above a threshold of 5,000 to 10,000 copies/mL in two consecutive measurements. Recent studies have documented that this approach may be associated with prolonged virologic failure and accumulation of NRTI resistance mutations in a substantial proportion of patients. While cross-resistance between NRTIs is not as common as it is between the first generation NNRTIs, it is still substantial, particularly for thymidine analogues. Therefore, an additional problem with a second-line regimen of a PI and two new NRTIs is the risk of virologic failure due to the inadequacy of the NRTI components of the regimen. While data from a small number of studies suggest that LPV/r or ATV/r monotherapy can be effective in the short term in patients who have failed a first-line regimen, no studies of this approach have been done in participants with active TB. When coupled with the drug-drug interactions associated with RIF or RBT, there is the potential for a LPV/r or ATV/r-based regimen combined with a compromised NRTI backbone to be further compromised by the interaction with the rifamycins.

The integrase-inhibitor RAL offers a way to increase the potency of second-line therapy regimens following virologic failure of NNRTI and NRTI regimens. Based on data from clinical trials, the combination of RAL and a PI-boosted with RTV appears to be potent. RAL is metabolized by glucuronidation, an enzymatic process that is upregulated by RIF via induction of UDP-glucuronosyltransferase 1A1 (UGT1A1). As a result, RAL concentrations are decreased by approximately 50% when given with RIF. The US Food and Drug Administration (FDA) has now recommended that the RAL dose be doubled to 800 mg BID if given with RIF because of this interaction, and the package insert has been updated to reflect this change. This increased dose has not been evaluated in patients, so uncertainty remains about the efficacy and tolerability of this dose and schedule.

Data evaluating the interaction between RAL and RBT have recently been reported[41]. In an open-label two-period study in 16 HIV-uninfected healthy adults, the combination of RAL 400 mg every 12 hours (q12h) and RBT 300 mg daily demonstrated no serious adverse events (SAEs) and no clinically important alteration in RAL PK. Based on this lack of effect, the investigators concluded that RBT could be coadministered with RAL without dose adjustment of RBT. No RBT concentrations were evaluated in this study. A5290 will provide an important opportunity to evaluate the RBT PK in a treatment arm in which RAL is combined with LPV/r, and to assess the impact of the PI-adjusted RBT dose on TB treatment outcomes in this important patient population. The results will

have important implications for the use of both RAL and RBT in the treatment of TB in HIV-infected individuals.

Need for PK data in the treatment of HIV-related TB
There has been limited evaluation of the PK of TB drugs among patients with HIV co-infection. There have long been concerns that patients with HIV coinfection malabsorb first-line TB drugs, though the results of previous small studies have been inconclusive (with some studies showing lower drug exposure among patients with HIV-related TB than among HIV-uninfected TB patients, but other studies showing similar drug exposures).

Very few studies have evaluated the pharmacodynamics of TB drugs among participants with HIV-related TB. As above, it appears that low RBT exposure has been associated with TB treatment failure with acquired rifamycin resistance, but the details of this relationship are not clear from the relatively small studies that have been published. This trial is a valuable opportunity to collect sparse PK data from a large group of participants with HIV-TB who will be followed for both HIV and TB treatment outcomes.

2.2 Rationale

There is a rapidly-growing need to identify evidence-based, safe and effective cotreatment regimens for HIV-related TB among patients who require PI-based ART. This trial will compare three alternative co-treatment regimens:

- LPV/r + two NRTIs with RBT-based TB therapy
- Double-dose LPV/r + two NRTIs with RIF-based TB therapy
- LPV/r + two NRTIs + RAL with RBT-based TB therapy

This study is designed to address several urgent and practical questions for endemic TB countries with large HIV-infected populations: 1) What is the best approach to HIV treatment in participants requiring PI-based ART in the setting of TB co-treatment? 2) Is the efficacy of RIF and RBT similar in participants treated with dose-adjusted LPV/r regimens and, as a corollary, what is the optimal dose of RBT in the setting of PI-based ART? 3) Does the addition of an integrase inhibitor improve the virologic outcome of anti-HIV treatment in the setting of drug-drug interactions for participants receiving a dose-adjusted PI-based regimen with a rifamycin during TB treatment? 4) What is the impact of PK dose-adjusted LPV/r coupled with RBT and/or RAL on TB treatment outcomes in HIV-infected persons? The outcome of this trial will have major public health implications for areas of the world with high burdens of HIV-related TB.

3.0 STUDY DESIGN

A5290 is a prospective, randomized (1:1:1), open-label, phase 2b study comparing three LPV/r-based ARV regimens among participants in high TB endemic resource-constrained settings undergoing treatment for confirmed or probable TB and requiring second-line PI-based ART.

Table 3.1. Regimen Rationale

Arm	ART	Anti-TB therapy	After completion of TB treatment	Rationale
A	LPV 400 mg/RTV 100 mg BID + two NRTIs	Isoniazid (INH) 300 mg daily, RBT 300 mg daily, then 150 mg daily upon initiation of ART*, EMB (weight-based dose) daily, pyrazinamide (PZA, weight-based dose) daily, and pyridoxine 25 mg daily. EMB and PZA will be discontinued after 8 weeks of treatment; INH, RBT 150 mg daily (or the adjusted dose determined by PK), and pyridoxine will continue through week 24 for a minimum total duration of 24 weeks. INH, RBT, and pyridoxine may continue beyond 24 weeks to a maximum of 48 weeks at the discretion of the primary clinician; the protocol core team must be notified.	LPV/r + two NRTIs will continue at standard dosing through week 72.	This regimen substitutes dose-adjusted RBT to replace RIF in an attempt to overcome the adverse drug interaction of RIF with standard dose LPV/r.
B	LPV 800 mg/RTV 200 mg BID + two NRTIs	INH 300 mg daily, RIF (weight-based dose) daily, EMB (weight-based dose) daily, PZA (weight-based dose) daily, and pyridoxine 25 mg daily. EMB and PZA will be discontinued after 8 weeks of treatment; INH, RIF, and pyridoxine will continue for a minimum total duration of 24 weeks. INH, RIF, and pyridoxine may continue beyond 24 weeks to a maximum of 48 weeks at the discretion of the primary clinician; the protocol core team must be notified.	LPV/r + two NRTIs will continue at standard dosing through week 72.	This arm allows use of standard RIF doses but with higher doses of LPV/r in an attempt to overcome the adverse drug interaction of RIF with standard dose LPV/r.

Arm	ART	Anti-TB therapy	After completion of TB treatment	Rationale
C	LPV 400 mg/RTV 100 mg tabs BID + two NRTIs + RAL 400 mg BID	INH 300 mg daily, RBT 300 mg daily, then 150 mg daily upon initiation of ART*, EMB (weight-based dose) daily, PZA (weight-based dose) daily, and pyridoxine 25 mg daily. EMB and PZA will be discontinued after 8 weeks of treatment; INH, RBT 150 mg daily (or the adjusted dose determined by PK), and pyridoxine will continue for a minimum total duration of 24 weeks. INH, RBT, and pyridoxine may continue beyond the 24 weeks to a maximum of 48 weeks at the discretion of the primary clinician; the protocol core team must be notified.	LPV/r + two NRTIs + RAL will continue at standard dosing through week 72	This regimen follows the same rationale as for Arm A but adds RAL in an attempt to enhance the antiviral activity of LPV/r when combined with RBT to evaluate whether this approach is associated with a better virologic response than the other two arms.

*NOTE: In Arms A and C, RBT should be administered at a dose of 300 mg daily until the start of antiretroviral therapy at which time the dose should be reduced to the 150 mg daily dose. If LPV/r is stopped prematurely during TB treatment, the RBT dose should be increased to 300 mg daily and the team should be notified. All participants will receive TB treatment according to in-country TB guidelines for daily TB treatment and directly observed therapy (DOT), except that all study participants will receive daily TB treatment 7 days per week, i.e., participants will not use a 5 days per week schedule that may be recommended in some in-country TB programs.

Accrual will take place in two accrual periods. Accrual period 1 will enroll participants who will undergo an initial dose-finding period before continuing regular study follow-up through 72 weeks. Once review of the dose-finding data in accrual period 1 is completed, accrual period 2 will begin.

<u>Accrual Period 1</u>

Sixty participants will be randomized 1:1:1 (20 participants per arm) to one of three treatment arms as detailed above. Anti-TB therapy with study-provided RBT or non-study-provided RIF and non-study-provided INH, EMB, and PZA should be started within 72 hours of randomization. ART should be started as soon as possible after initiating anti-TB therapy, but may be delayed for up to 7-14 days after starting anti-TB therapy to allow participants sufficient time to assess tolerability of TB medications. Participants will then undergo a formal PK and safety evaluation to include:

- Steady-state (day 12 ± 2 after initiation of ART) RBT PK parameters ($C_{min,}$ $C_{max,}$ and 24-hour AUC) for those randomized to Arm A and Arm C.

- Steady-state (day 12 ± 2 after initiation of ART) LPV PK parameters ($C_{min,}$ $C_{max,}$ and 12-hour AUC) for those randomized to Arm B.
- Grade 3 AEs attributed to study-provided drug(s) by 28 days after ART initiation.
- Discontinuations of study-provided drug(s) for treatment-limiting toxicity or intolerance (such that PK assessments within the day 12 ± 2 window cannot be completed).

Interim PK and safety analysis will be conducted when the first 10-12 accrual period 1 participants per treatment arm have completed 28 days of ART and day 12 ± 2 (after initiation of ART) drug concentrations are available and when 54-60 accrual period 1 participants have completed 28 days of ART and day 12 ± 2 (after initiation of ART) drug concentrations are available. Because participants enrolled during accrual period 1 will be undergoing treatment for active TB, they will continue on their randomized therapy pending the results of these interim PK and safety analysis. Sites will be encouraged to organize recruitment in a manner to ensure rapid accrual to accrual period 1 to the extent possible so that participants are not exposed to prolonged treatment in the absence of these PK assessments; however, some participants may require dose adjustments of RBT and/or LPV/r prior to the completion of the interim analyses, as described below.

NOTE: While the intent is to conduct the full accrual period 1 PK and safety interim analysis after 54-60 accrual period 1 participants have completed 28 days of ART, as previously discussed, available drug concentrations and safety data will be assessed weekly by the core team in an unblinded fashion as follows. Sites will be asked to batch PK samples and ship them every two weeks to the ACTG repository, which will immediately re-ship them to the PK laboratory. The PK laboratory will measure drug concentrations as soon as possible after receipt of shipments and will report results to the core team within 2 weeks of receiving the samples. The core team will monitor all available concentrations weekly for those results received to date. An early interim analysis of PK results and safety criteria will be conducted after the first 10-12 participants in each arm complete 28 days of ART and the day 12 ± 2 PK results are available to assess any early trends suggesting lower or higher than expected concentrations of any study drug(s). If early assessments indicate concentrations out of acceptable ranges for more than three participants in a treatment arm or trends related to safety criteria, an early ACTG Study Monitoring Committee (SMC) evaluation will be triggered. Any dose adjustments recommended by the SMC in consultation with the core team after this interim evaluation will be implemented for any new accrual period 1 participants enrolled as soon as possible after the review and for any already enrolled participants who have drug concentrations clearly out of acceptable ranges. However, the decision to revise dose schedules and treatment duration of participants with inadequate drug concentrations would be made based not just on the drug concentrations, but also on all available clinical data regarding TB and HIV endpoints. While true real-time reporting of drug concentrations will not be possible, individual participants identified, either during weekly core team monitoring or during any early SMC monitoring assessments, who have clearly inadequate concentrations of any study-provided drug(s) will be reported to the sites as soon as that determination is made, and individual dose adjustments

may be recommended according to the dose adjustment schedule in Table 5.1. Accrual period 1 participants for whom early dose adjustments are recommended will have drug concentrations repeated 12 ± 2 days after initiating the adjusted dose. If no early PK or safety trends are identified during core team or SMC monitoring, dosing will continue in participants enrolled during accrual period 1 as per assigned treatment arm.

Accrual period 2 will not open until completion of the full accrual period 1 PK and safety analysis and determination of subsequent dosing for LPV/r and RBT for participants enrolled during accrual period 2 is made. Based on this monitoring, if criteria are determined to be unacceptable in any treatment arm before the three cohorts are fully enrolled during the accrual period 1, further accrual to the arm in question may be stopped. If a dose adjustment of LPV/r or RBT is deemed necessary, as described in the note above, accrual period 1 participants identified by the core team with clearly inadequate concentrations will be reassigned to the new adjusted dose, the intensive TB treatment phase will be extended at the new adjusted dose for participants in the relevant treatment arm, and these participants will undergo an additional day 12 ± 2 PK assessment. The core team will communicate recommendations to the sites related to which participants will require dose adjustments as soon as is feasible. In this circumstance, it is possible that a portion of accrual period 1 participants may receive an additional 28-42 days (i.e., up to a total of 16 weeks) of intensive phase TB treatment at the new adjusted dose before beginning the 16-week continuation phase of TB treatment. However, those accrual period 1 participants with drug concentrations deemed adequate on their originally-assigned doses of study-provided medications will not be required to be reassigned to the new adjusted dose (and additional intensive phase TB treatment), but will continue on their originally-assigned dose and proceed to their continuation phase of TB treatment and regular study follow-up through week 72.

NOTE: Any participants determined to have clearly inadequate RBT concentrations during the accrual period 1 PK evaluation should be monitored closely after dose adjustments for TB outcomes throughout the course of their TB treatment.

Refer to Table 5.1 (LPV/r and RBT Dose Adjustment Table) in section 5.1.

<u>Monitoring Prior to Opening Accrual Period 2</u>
The core team, together with the SMC, will review the results of the accrual period 1 interim PK and safety analysis. If the acceptable PK criteria for RBT and LPV are met, and if no more than three participants in each treatment arm report ≥ Grade 3 AEs attributed to study-provided drug(s) by 28 days after ART initiation, and if no more than three participants in each treatment arm discontinue study-provided drug(s) for treatment-limiting toxicity or intolerance (such that PK assessments cannot be completed), then accrual period 2 will open at the planned dose schedules of LPV/r and RBT.

If acceptable PK criteria are not met, or if more than three participants in one or more treatment arms report ≥ Grade 3 AEs attributed to study-provided drug(s) by 28 days after initiation of ART, or if more than three participants in one or more treatment arms discontinue study-provided drug(s) for treatment-limiting toxicity or intolerance (such that

PK assessments cannot be completed), the SMC, in consultation with the core team, may elect to adjust the doses of RBT and/or LPV/r, as described above, for participants in the affected arm identified with inadequate drug concentrations, and repeat steady-state (day 12 ± 2 after dose adjustment) drug concentrations will be obtained for only the study arm participants in which a dose was adjusted (see dose adjustment schedule above). A second accrual period 1 PK and safety interim analysis will be conducted after all accrual period 1 participants undergoing dose adjustment have completed 28 days of dose-adjusted treatment and when day 12 ± 2 post-dose adjustment drug concentrations are available. This second analysis will include all accrual period 1 participants with available data.

The core team and SMC will then review the results of the second accrual period 1 interim PK and safety analysis. If acceptable PK criteria are not met, or if more than three participants in one or more treatment arms report ≥ Grade 3 AEs attributed to study-provided drug(s) by 28 days after initiation of ART, or if more than three participants in one or more treatment arms discontinue study-provided drug(s) for treatment-limiting toxicity or intolerance (such that PK assessments cannot be completed, then a decision will be made about whether to continue, modify (e.g., add additional participants to the accrual period 1 to assure adequate PK assessment are completed), or halt the treatment arm(s) in question, based on analysis of the nature of the AEs and reasons for study-provided drug discontinuation, and the degree of PK criteria failure. At the second interim review, if three or fewer participants report ≥ Grade 3 AEs attributed to study-provided drug(s) in all treatment arms, and if three or fewer participants in all treatment arms discontinue study-provided drug(s) for treatment-limiting toxicity or intolerance (such that PK assessments cannot be completed), and acceptable PK criteria are met for at least two of the treatment arms, the SMC, in consultation with the core team, will determine whether accrual period 2 will open.

If, based on the SMC's determination, unacceptable PK and/or safety criteria are met within two treatment arms, then further enrollment into the study may be stopped, and accrual period 1 participants will be managed according to best available local TB and ARV treatment. These participants will be followed off study-provided drug (LPV/r, RTV, RAL, and/or RBT) for the remainder of study follow-up (up to 72 weeks).

If the SMC determines that accrual period 2 enrollment should proceed, accrual period 2 participants will be randomized 1:1:1 to Arm A, B, or C (or with equal probability to the remaining sample size in the remaining treatment arms) at the doses determined during the dose-finding period in accrual period 1 participants. Samples for LPV/r, RBT, and RAL steady state plasma concentrations will be obtained as outlined in the Schedule of Events. No individual dose adjustments will be made based on drug concentrations for accrual period 2 participants. Anti-TB treatment (INH and RIF or RBT) will continue for a minimum duration of 24 weeks; EMB and PZA will be discontinued after 8 weeks of TB treatment, except as otherwise specified for accrual period 1 participants who had a dose adjustment of RBT and/or LPV/r.

NOTE: As participants may enter the study with severe cavitary or extrapulmonary TB, or with other manifestations or clinical conditions that meet current recommendations for longer duration anti-TB therapy, additional anti-TB therapy

(INH and RIF or RBT) beyond 24 weeks up to a maximum of 48 weeks of TB treatment will be allowed as determined by the primary clinician and the protocol team must be notified. Participants will continue their assigned ARV regimen through week 24 or until the completion of anti-TB treatment, and will then continue on therapy at the currently recommended standard dose of LPV/r + 2 NRTIs with or without RAL through week 72.

All participants will receive TB treatment according to in-country TB guidelines for daily TB treatment and DOT, except that all study participants will receive daily TB treatment 7 days per week, i.e., participants will not use a 5 day per week schedule that may be recommended in some in-country TB programs.

NOTE: Any participants determined to have clearly inadequate RBT concentrations during accrual period 1 evaluation should be monitored closely after dose adjustments for TB outcomes throughout the course of their TB treatment.

4.0 SELECTION AND ENROLLMENT OF PARTICIPANTS

4.1 Inclusion Criteria

4.1.1 HIV-1 infection, documented by any licensed rapid HIV test or HIV enzyme or chemiluminescence immunoassay (E/CIA) test kit at any time prior to study entry and confirmed by a licensed Western blot or a second antibody test by a method other than the initial rapid HIV and/or E/CIA, or by HIV-1 p24 antigen, plasma HIV-1 RNA viral load.

NOTE: The term “licensed” refers to a US FDA-approved kit, which is required for all IND studies, or for sites located in countries other than the US, a kit that has been certified or licensed by an oversight body within that country and validated internally. Non-US sites are encouraged to use US FDA-approved methods for IND studies.

WHO and the US Centers for Disease Control and Prevention (CDC) guidelines mandate that confirmation of the initial test result must use a test that is different from the one used for the initial assessment. A reactive initial rapid test should be confirmed by either another type of rapid assay or an E/CIA that is based on a different antigen preparation and/or different test principle (e.g., indirect versus competitive), or a Western blot, plasma HIV-1 RNA viral load, or an HIV-1 p24 antigen test.

4.1.2 CD4+/CD8+ T-cell count obtained within 30 days prior to study entry at any laboratory that has a CLIA certification or any Division of AIDS (DAIDS) approved laboratory.

4.1.3 Confirmed or probable pulmonary or extrapulmonary TB, as defined below.

Confirmed pulmonary TB is defined as the presence of compatible clinical symptoms (e.g., cough, hemoptysis, shortness of breath, chest pain, weight loss, fever, or night sweats) with or without abnormal chest X-ray, chest computed tomography [CT] scan or other chest imaging (e.g., hilar lymphadenopathy, paratracheal lymphadenopathy, alveolar consolidation, miliary pattern, lung parenchymal breakdown/cavitation, or Ghon focus) and sputum, bronchial alveolar lavage fluid, pleural fluid, pleural tissue, lung tissue, or gastric acid lavage culture positive for MTB, or a nucleic acid amplification test positive for MTB or MTB Complex.

Confirmed extrapulmonary TB is defined as the presence of compatible clinical symptoms as previously described plus clinical features of organs involved, such as sterile pyuria or other renal involvement, pericarditis, ascites, pleural effusion, meningitis, arthritis, orchitis, enteritis, extrathoracic lymphadenitis, or osteitis and positive culture for MTB or nucleic acid amplification test positive for MTB or MTB Complex from fluid or tissue biopsies from any of these organ or tissue sites, including bone marrow, liver, and blood.

Probable Pulmonary TB is based on the clinician's judgment and includes compatible clinical symptoms as previously described, and at least one of the following: 1) positive sputum smear for acid fast bacilli (AFB); or 2) abnormal CXR, chest CT scan or other chest imaging; or 3) evidence of granulomata with organisms positive for AFB or caseating granulomata on lung tissue biopsy; or 4) positive tuberculin skin test (TST) ($\geq$ 5mm) or interferon gamma release assay (IGRA); and without concurrent illness that would explain the findings, but MTB cultures are negative or not available.

Probable Extrapulmonary TB is based on the clinician's judgment and includes compatible clinical symptoms as previously described plus clinical features of organs involved as previously described, or evidence of granulomata with organisms positive for AFB or caseating granulomata on tissue biopsy from relevant site(s); and specific antituberculous therapy initiated or recommended, but MTB cultures are negative or not available.

NOTE: Participants whose qualifying episode of TB was later determined not to be TB will continue to be followed on study but off study drugs for safety and ART endpoints.

4.1.4 Chest x-ray within 30 days prior to study entry.

4.1.5 A PI-based ART regimen is required, as determined by the participant's primary clinician/clinical facility.

NOTE: Enter the reason, in the eligibility checklist, for the PI-based ART regimen from among the following choices:

The PI-based therapy was required:

1) Because the participant failed an NNRTI regimen or;
2) Because the participant had an adverse reaction to an NNRTI regimen or;
3) Because the participant received single dose nevirapine during pregnancy and could have NNRTI resistance mutations archived at the time the participant was starting ART;
4) Other, specify.

4.1.6 Laboratory values obtained within 14 days prior to study entry:

Accrual period 1

- Absolute neutrophil count (ANC) ≥ 750 cells/mm^3
- Hemoglobin ≥ 8.5 g/dL
- Platelet count ≥ 50,000/mm^3
- Alanine aminotransferase (ALT) (SGPT) ≤ 2 x upper limit of normal (ULN)
- Aspartate aminotransferase (AST) (SGOT) ≤ 5 x ULN
- Total bilirubin ≤ 2.5 x ULN

Accrual period 2

- ANC ≥ 500 cells/mm^3
- Hemoglobin ≥ 7.5 g/dL
- Platelet count ≥ 50,000/mm^3
- AST (SGOT) and ALT (SGPT) ≤ 5 x ULN
- Total bilirubin ≤ 5 x ULN

4.1.7 For females of reproductive potential, negative serum or urine pregnancy test within 7 days prior to study entry and 72 hours of starting study medications.

NOTE: Female participants of reproductive potential are defined as women who have reached menarche or who have not been post-menopausal for at least 24 consecutive months (i.e., who have had menses within the preceding 24 months) or have not undergone surgical sterilization (e.g., hysterectomy, or bilateral oophorectomy or salpingectomy).

4.1.8 All participants must agree not to participate in a conception process (e.g., active attempt to become pregnant or to impregnate, donate sperm, or in vitro fertilization).

4.1.9 Female participants who are participating in sexual activity that could lead to pregnancy must agree to use at least two reliable methods of contraception: a barrier method of contraception (condoms or cervical cap) together with another reliable form of contraception (condoms, with a spermicidal agent; a diaphragm or cervical cap with spermicide; an IUD; or hormone-based contraceptive) while receiving RIF, or other rifamycin, and for 6 weeks after stopping these drugs.

- Female participants who are not of reproductive potential, as defined above, or whose male partner(s) have undergone successful vasectomy with documented azoospermia or have documented azoospermia for any other

reason, are eligible without requiring the use of contraceptives. Participant-reported history is acceptable documentation of menopause, hysterectomy, or bilateral oophorectomy or salpingectomy.

4.1.10 Karnofsky performance score > 40 within 14 days prior to study entry, and likelihood of survival, in the opinion of the site investigator, for at least 6 months.

4.1.11 Men and women ≥ 18 years of age, who have attained the minimum age of consent, as defined by the local IRB.

4.1.12 Ability to swallow oral medications.

4.1.13 Ability and willingness of participant or legal guardian/representative to provide informed consent.

4.2 Exclusion Criteria

4.2.1 History of completed TB treatment and resolution of TB symptoms less than 1 year prior to the current TB episode at study entry, or incomplete treatment for a prior episode of TB (i.e., defaulted past TB treatment) at any time prior to the current TB episode.

NOTE: Completed TB treatment is defined as completion of an 8-week intensive phase of TB treatment with INH and RIF plus at least 2 other anti-TB drugs, followed by a 16-week continuation phase of TB treatment with INH and RIF for a total duration of at least 24 weeks of TB treatment.

4.2.2 Documented multidrug-resistant tuberculosis (MDR TB) or extensively drug-resistant (XDR) TB.

NOTE: MDR TB is defined as TB with resistance to RIF and INH. XDR TB is defined as MDR TB plus resistance to fluoroquinolones and to at least one second-line injectable anti-TB drug. If MDR TB or XDR TB is determined based on locally-obtained drug susceptibility testing after study entry, the participants will be discontinued from the study and referred to their primary clinician/clinical facility or TB and ART program and treated with the best available TB and ART according to local standards of care.

4.2.3 Participants infected with a rifamycin resistant strain of TB as determined by HAIN GenoType MTBDR Plus line probe assay or, GeneXpert® MTB/RIF assay (or, following approval of the core team, a result from another locally-obtained standardized RIF drug susceptibility test). Participants found to have a rifamycin-resistant strain of TB should be referred for management according to the site's standard of care.

NOTE A: Participants may be enrolled pending the results of RIF drug susceptibility testing if a rapid HAIN GenoType MTBDR Plus line probe

assay, GeneXpert® MTB/RIF assay, or other rapid MTB RIF drug resistance assay result is not yet available. However, if RIF drug-susceptibility test results are not available within 60 days after study entry or if any drug susceptibility testing subsequently demonstrates RIF resistance, participants will be discontinued from the study and referred to their primary clinician/clinical facility or TB and ART program and treated with the best available TB and ART according to local standards of care.

NOTE B: All specimens available from participants at entry should also be tested for INH drug susceptibility (as per the SOE and section 6.3.2), however, INH monoresistance (i.e., the baseline isolate is resistant only to INH) is not an exclusion criterion for enrollment. If the HAIN GenoType MTBDR Plus line probe assay is used or if any other rapid drug susceptibility test is used that also supplies information on INH susceptibility, these results will be recorded. If a GeneXpert MTB/RIF assay is used, which only detects RIF resistance, then samples should also be tested with another standardized method that also evaluates INH susceptibility.

4.2.4 Receipt of more than 28 cumulative days of anti-TB treatment for the current TB episode prior to study entry.

NOTE: Receipt of therapy for latent TB is permitted as is receipt of short-term augmentin or a fluoroquinolone (for < 14 days) for treatment of bacterial infections.

4.2.5 Active drug or alcohol use or dependence that, in the opinion of the site investigator, would interfere with adherence to study requirements.

4.2.6 Active illness requiring systemic treatment and/or hospitalization within 30 days prior to study entry, or that in the opinion of the site investigator, might otherwise interfere with adherence to study requirements.

4.2.7 Pregnant or breastfeeding.

4.2.8 Anticipated receipt of any of the prohibited medications listed in section 5.4.2.

4.2.9 Known intolerance/allergy/sensitivity or any hypersensitivity to components of study drugs or their formulations.

4.2.10 History of close contact with known MDR or XDR TB patients at any time prior to study entry.

NOTE: Close contact is defined as participant history of prolonged, frequent, or intense contact approximating > 8 hours per day with a person known to have infectious MDR or XDR TB e.g., household, other congregate living or incarceration contacts.

4.3 Study Enrollment Procedures

4.3.1

Prior to implementation of this protocol, and any subsequent full version amendments, each site must have the protocol and the protocol consent forms approved, as appropriate, by their local institutional review board (IRB)/ethics committee (EC) and any other applicable regulatory entity (RE). Upon receiving final approval, sites will submit all required protocol registration documents to the Division of AIDS (DAIDS) Protocol Registration Office (PRO) at the Regulatory Support Center (RSC). The DAIDS PRO will review the submitted protocol registration packet to ensure that all of the required documents have been received.

For studies at non-US sites, protocol activation is required prior to enrolling participants into the study.

Site-specific informed consent forms (ICFs) WILL be reviewed and approved by the DAIDS PRO, and sites will receive an Initial Registration Notification from the DAIDS PRO that indicates successful completion of the protocol registration process. A copy of the Initial Registration Notification should be retained in the site's regulatory files.

Upon receiving final IRB/EC and any other applicable RE approvals for an amendment, sites should implement the amendment immediately. Sites are required to submit an amendment registration packet to the DAIDS PRO at the RSC. The DAIDS PRO will review the submitted protocol registration packet to ensure that all the required documents have been received. Site-specific ICFs WILL NOT be reviewed and approved by the DAIDS PRO, and sites will receive an Amendment Registration Notification when the DAIDS PRO receives a complete registration packet. A copy of the Amendment Registration Notification should be retained in the site's regulatory files.

For additional information on the protocol registration process and specific documents required for initial and amendment registrations, refer to the current version of the DAIDS Protocol Registration Manual.

Once a candidate for study entry has been identified, details will be carefully discussed with the participant. The participant will be asked to read and sign the approved protocol consent form. For participants from whom a signed informed consent has been obtained, an ACTG Screening Checklist must be entered through the Data Management Center (DMC) Subject Enrollment System.

4.3.2 Randomization/Subject Registration

For participants from whom informed consent has been obtained, but who are deemed ineligible or who do not enroll into the initial protocol step, an ACTG Screening Failure Results form must be completed and keyed into the database.

4.4 Coenrollment Guidelines

Sites are encouraged to coenroll participants in A5243, "Plan for Obtaining Human Biological Samples at Non-US Clinical Research Sites for Currently Unspecified Genetic Analyses." Coenrollment in A5243 does not require permission from the A5290 protocol chairs. For specific questions and approval for coenrollment in other studies, sites must contact the protocol chairs via e-mail as described in the Study Management section.

5.0 STUDY TREATMENT

5.1 Regimens, Administration, and Duration

5.1.1 For Participants Enrolled During Accrual Period 1

At entry, participants will be randomized (1:1:1) to one of the following three arms: Arm A, Arm B, and Arm C as further defined in this section. Anti-TB therapy with study-provided RBT or non-study-provided RIF and non-study-provided INH, EMB, and PZA should be started within 72 hours of randomization. ART should be started as soon as possible after initiating anti-TB therapy, but may be delayed for up to 7-14 days after initiation of anti-TB therapy to allow for assessment of initial tolerability of TB medications.

5.1.1.1 Arm A

ART
<u>Entry through Week 72</u>

- LPV 400 mg/ RTV 100 mg orally twice daily plus 2 NRTIs
- After completion of TB treatment, ART will continue at initial dosing through week 72: LPV 400 mg/ RTV 100 mg orally twice daily plus 2 NRTIs

Anti-TB Therapy
Participants will receive the following anti-TB medications with recommended dosing, unless dose adjustments are required (see Table 5.1):

<u>Entry through Week 8 study visit (or until completion of intensive TB treatment as determined after dose adjustment in accrual period 1 participants)</u>

- INH 300 mg orally once daily
- RBT 300 mg orally once daily, then 150 mg orally once daily upon initiation of ART*
- EMB (15 to 20 mg/kg) orally once daily
- PZA (20 to 30 mg/kg) orally once daily (not to exceed 2 g per day)
- Pyridoxine 25 mg orally once daily

Week 8 study visit through Week 24 (or as determined by primary clinician if longer anti-TB treatment required)

- INH 300 mg orally once daily
- RBT 150 mg orally once daily
- Pyridoxine 25 mg orally once daily
- INH, RBT, and pyridoxine will continue through week 24 for a minimum total duration of 24 weeks

INH, RBT, and pyridoxine may continue beyond 24 weeks to a maximum of 48 weeks at the discretion of the primary clinician, and the protocol core team must be notified.

5.1.1.2 Arm B

ART
Entry through Week 72

- LPV 800 mg/ RTV 200 mg orally twice daily plus 2 NRTIs, unless dose adjustments are required (see Table 5.1)
- After completion of TB treatment, ART will change to standard dosing (LPV 400 mg/RTV 100 mg orally twice daily plus 2 NRTIs) through week 72

Anti-TB Therapy
Participants will receive the following anti-TB medications with recommended dosing:

Entry through Week 8 study visit (or until completion of intensive TB treatment as determined after dose adjustment in accrual period 1 participants)

- INH 300 mg orally once daily
- RIF (weight-based dose; for weight < 45 kg: 450 mg orally once daily; for weight $\geq$ 45 kg: 600 mg orally once daily) orally once daily
- EMB (15 to 20 mg/kg) orally once daily
- PZA (20 to 30 mg/kg) orally once daily (not to exceed 2 g per day)
- Pyridoxine 25 mg orally once daily

Week 8 study visit through Week 24 (or as determined by primary clinician if longer anti-TB treatment required)

- INH 300 mg orally once daily
- RIF (weight-based dose; for weight < 45 kg: 450 mg orally once daily; for weight $\geq$ 45 kg: 600 mg orally once daily) orally once daily
- Pyridoxine 25 mg orally once daily
- INH, RIF, and pyridoxine will continue through week 24 for a minimum total duration of 24 weeks

INH, RIF, and pyridoxine may continue beyond 24 weeks to a maximum of 48 weeks at the discretion of the primary clinician and the protocol core team must be notified.

5.1.1.3 Arm C

ART
Entry through Week 72

- LPV 400 mg/ RTV 100 mg orally twice daily plus 2 NRTIs
- RAL 400 mg orally twice daily
- After completion of TB treatment, ART will continue at initial entry dosing through week 72: LPV 400 mg/ RTV 100 mg orally twice daily plus 2 NRTIs and RAL 400 mg orally twice daily

Anti-TB Therapy
Participants will receive the following anti-TB medications with recommended dosing, unless dose adjustments are required (see Table 5.1):

Entry through Week 8 study visit (or until completion of intensive TB treatment as determined after dose adjustment in accrual period 1 participants)

- INH 300 mg orally once daily
- RBT 300 mg orally once daily, then 150 mg orally once daily upon initiation of ART*
- EMB (15 to 20 mg/kg) orally once daily
- PZA (20 to 30 mg/kg) orally once daily (not to exceed 2 g per day)
- Pyridoxine 25 mg orally once daily

Week 8 study visit through Week 24 (or as determined by primary clinician if longer anti-TB treatment required)

- INH 300 mg orally once daily
- RBT 150 mg orally once daily
- Pyridoxine 25 mg orally once daily
- INH, RBT, and pyridoxine will continue through week 24 for a minimum total duration of 24 weeks

INH, RBT, and pyridoxine may continue beyond 24 weeks to a maximum of 48 weeks at the discretion of the primary clinician, and the protocol core team must be notified.

*NOTE: In Arms A and C, RBT should be administered at a dose of 300 mg daily until the start of antiretroviral therapy at which time the dose should be reduced to the 150 mg daily dose. All participants will receive TB treatment according to in-country TB guidelines for daily TB treatment and Directly Observed Therapy (DOT), except that all study participants will receive daily TB treatment 7 days

per week, i.e., participants will not use a 5 days per week schedule that may be recommended in some in-country TB programs.

If dose adjustments of LPV/r or RBT are deemed necessary, the intensive TB treatment phase will be extended at the adjusted dose for the relevant participants in the affected treatment arm, and participants will undergo additional drug level assessment (see detailed description in section 3.0).

Any participants determined to have clearly inadequate RBT concentrations during the accrual period 1 PK evaluation should be monitored closely after dose adjustments for TB outcomes throughout the course of their TB treatment.

If LPV/r is prematurely discontinued at any time during TB treatment, the team should be notified, and the RBT dose should be increased to 300 mg daily pending further instructions from the team.

Site pharmacists must receive new prescriptions from an authorized prescriber for dosing changes.

NOTE: A two accrual period design will be used as previously described. Because participants enrolled in the accrual period 1 will be undergoing treatment for active TB, they will continue on their randomized regimen pending the outcome of the accrual period 1 interim PK and safety evaluations. No participants will be enrolled in the accrual period 2 until completion of the accrual period 1 analysis and determination of subsequent dosing for LPV/r and RBT is made.

If, based on the SMC's determination, unacceptable PK or safety criteria are met within two treatment arms, then further enrollment into the study may be stopped, and the accrual period 1 participants will be managed according to best available local TB and antiretroviral treatment. These participants will be followed off study medication for the remainder of study follow-up (up to 72 weeks).

Table 5.1. LPV/r and RBT Dose Adjustment Table

	LPV/r Dose Adjustment	Rifabutin Dose Adjustment
Arm A	No dose adjustment	RBT PK parameters low: Adjust RBT to RBT 300 mg orally three times weekly (TIW) or 300 mg orally once daily (see section 10.4). RBT PK parameters high: Decrease RBT to RBT 150 mg orally TIW NOTE: The RBT C_{max} will be used for the purpose of individual dose adjustment for low or high RBT concentrations. A low RBT concentration will be < 250 ng/mL. A high

		RBT C_{max} will be greater than 900 ng/mL.
Arm B	• LPV Cmin < 1 mg/L and Cmax < 12 mg/L: add LPV 200 mg/RTV 50 mg (one additional fixed-dose combination tablet) twice daily • LPV Cmin < 1 mg/L and Cmax > 12 mg/L: add one additional RTV 100 mg tab tablet twice daily NOTE: A LPV C_{12} (or trough) will be used to define whether an individual subject's LPV/r dose is too low.	N/A
Arm C	No dose adjustment	RBT PK parameters low: Adjust RBT to RBT 300 mg orally TIW or 300 mg orally once daily (see section 10.4). RBT PK parameters high: Decrease RBT to RBT 150 mg orally TIW NOTE: See Arm A for definition of RBT low and high concentrations.

Rifabutin Dose Adjustment:
RBT concentrations clearly associated with therapeutic success or an increased incidence of toxicity have not been established, although the range of 300-900 ng/mL for C_{max} has been associated with acceptable TB outcomes in a small number of patients. The RBT C_{max} will be used for the purpose of individual dose adjustment for low or high RBT concentrations. A low RBT C_{max} will be defined as < 250 ng/mL. This concentration represents the 25th percentile of RBT C_{max} values in 14 HIV and TB infected persons receiving a RBT dose of 150 mg once daily given in conjunction with LPV/RTV[40]. A high RBT C_{max} will be greater than 900 ng/mL. This concentration is greater than 2 standard deviations in healthy volunteers receiving a 300 mg once daily RBT dose[43]. The 300 mg RBT once daily dose is the usual RBT dose prior to an adjustment for the drug-drug interaction with LPV/RTV; a C_{max} > 900 ng/mL would represent an exposure above that usually seen in healthy volunteers or persons with TB.

LPV/r Dose Adjustment:
A LPV C_{12} (or trough) less than 1 mg/L will be used to define whether an individual participant's LPV/r dose is too low. A C_{12} value less than 1 mg/L is less than the 25th percentile of C_{12h} concentrations in a small study of HIV and TB infected persons receiving double dose LPV/RTV (i.e. 800/200 twice daily) with RIF, 600 mg once daily[27]. A 12-hour post dose plasma concentration (C_{12h}) value less than 1 mg/L is also considered the minimum threshold value for LPV by the DHHS Guidelines Panel. A C_{max} value > 12 mg/L is ≥ the 75th percentile in HIV-infected persons receiving the usual twice daily 400/100 LPV/RTV dose.

NOTE: No substantive effect of RBT on LPV concentrations is expected based on prior PK data with this combination; however, if LPV levels in the ranges noted for Arm B are observed in Arm A or Arm C, then dose adjustments will be the same as for Arm B.

5.1.2 For Participants Enrolled During Accrual Period 2

Once the accrual period 1 PK and safety analysis is completed and a determination is made to begin enrollment to accrual period 2, additional participants will be randomized into one of three treatment arms: Arm A, Arm B, and Arm C. Dosing for each treatment arm in accrual period 2 will be based on final dosing from the corresponding treatment arm during the dose-finding period in accrual period 1 participants.

5.1.3 Administration

LPV 400 mg/ RTV 100 mg will be administered as two 200 mg/ 50 mg fixed-dose combination tablets orally twice daily.

LPV 800 mg/ RTV 200 mg will be administered as four 200 mg/ 50 mg fixed-dose combination tablets orally twice daily.

Additional LPV/r doses, if required as part of dose adjustments, will be administered as one 200 mg/ 50 mg fixed-dose combination tablet orally twice daily added to the original dose.

Additional RTV doses, if required as part of dose adjustments, will be administered as one 100 mg tablet orally twice daily.

RAL will be administered as one 400 mg tablet orally twice daily.

RBT 150 mg will be administered as one 150 mg capsule orally once daily, or if dose adjusted, as one 150 mg capsule orally three times weekly.

RBT 300 mg will be administered as two 150 mg capsules orally once daily, or when dose adjusted, as 300 mg (two 150 mg capsules) orally three times weekly.

All TB medications and pyridoxine obtained locally by the site will be administered as per manufacturer information or package insert.

For accrual period 1 participants in Arms A and C, it is necessary for the once daily dose of RBT to be taken with the morning dose of LPV/RTV, and for Arm C participants that the morning dose of RAL be taken with the morning dose of LPV/RTV and RBT.

In general, RBT, LPV/r, and RTV if used separately, should be taken with food; however, high fat meals should be avoided. Other anti-TB medications should be taken on an empty stomach, unless otherwise specified. Site staff should advise

the participant that if he/she does eat prior to coming to the clinic to avoid high fat meals. Specific timing of doses for PK assessments may differ from these general instructions and are indicated in section 10.0 (also see section 6.3.11).

5.1.4 Duration

ART will continue through week 72 after study entry. Anti-TB treatment will continue for a minimum total duration of 24 weeks to a maximum of 48 weeks as specified by the participant's local primary clinician.

5.2 Study Product Formulation and Preparation

5.2.1 Lopinavir/Ritonavir (LPV/RTV, Aluvia, Kaletra): 200 mg LPV and 50 mg RTV in each fixed-dose, film-coated tablet. Store at 20°-25°C (68°-77°F); excursions permitted to 15°-30°C (59°-86°F). Dispense in original container. Exposure of this product to high humidity outside the original container for longer than 2 weeks is not recommended.

5.2.2 Raltegravir (RAL, Isentress): 400 mg tablets must be dispensed in the original bottle with the desiccant provided. Store at 20°-25°C (68°-77°F); excursions permitted to 15°-30°C (59°-86°F).

5.2.3 Ritonavir (RTV, Norvir): 100 mg tablets. Store at 20°-25°C (68°-77°F); excursions permitted to 15°-30°C (59°-86°F). Exposure of this product to high humidity outside the original or USP equivalent container for longer than 2 weeks is not recommended.

5.2.4 Rifabutin (RBT, Mycobutin): 150 mg capsules. Keep tightly closed and dispense in a tight container as defined in the USP. Store at 25°C (77°F); excursions permitted to 15°-30°C (59°-86°F).

5.2.5 All other TB medications and pyridoxine obtained locally by the site will be stored as per manufacturer information or package insert.

5.3 Pharmacy: Product Supply, Distribution, and Accountability

5.3.1 Product Supply

Lopinavir/ritonavir and ritonavir will be supplied by Abbott Laboratories.

Raltegravir will be supplied by Merck & Co., Inc.

Rifabutin will be supplied by Pfizer Inc.

Lopinavir/ritonavir, ritonavir, raltegravir, and rifabutin will be made available through this study. Isoniazid, rifampin, ethambutol, pyrazinamide, pyridoxine and NRTI background will not be provided through the study and must be obtained by non-study prescription.

Fixed-dose combination TB treatment tablets will be permitted for this study only for participants randomized to Arm B. Fixed-dose combination tablets containing INH, RIF, EMB, and PZA may be used during the intensive phase of TB treatment and fixed-dose combination tablets containing INH and RIF may be used for the continuation phase of TB treatment.

Fixed-dose combination TB treatment tablets will not be permitted for participants randomized to Arms A or C.

5.3.2 Study Product Acquisition/Distribution

All study-provided ARVs and rifabutin will be available through the NIAID Clinical Research Products Management Center (CRPMC). The site pharmacist can obtain study product for this protocol by following the instructions in the manual *Pharmacy Guidelines and Instructions for DAIDS Clinical Trials Networks* in the section Study Product Management Responsibilities.

No other TB treatment agents will be provided through this study.

5.3.3 Study Product Accountability

The site pharmacist is required to maintain complete records of all study products received from the NIAID CRPMC and subsequently dispensed. At non-US clinical research sites, the site pharmacist must follow the instructions provided in the manual *Pharmacy Guidelines and Instructions for DAIDS Clinical Trials Networks* in the section Study Product Management Responsibilities for the destruction of unused study products.

5.4 Concomitant Medications

Below are lists of selected concomitant medications. These lists are only current as of the date of this protocol. Therefore, whenever a concomitant medication or study agent is initiated or a dose changed, investigators must review the concomitant medications' and study agents' most recent package inserts, Investigator's Brochures, or updated information from DAIDS to obtain the most current information on drug interactions, contraindications, and precautions.

Additional drug information may be found in the ACTG Drug Interaction Database on the ACTG website at: https://actgnetwork.org/ACTG-Drug-Interactions-Database.

5.4.1 Required Medications

None.

5.4.2 Prohibited Medications

For a list of prohibited medications, refer to the PSWP.

5.4.3 Precautionary Medications

For a list of precautionary medications, refer to the PSWP.

5.5 Adherence Assessment

Adherence to ARVs and TB treatment will be assessed using study-specific CRFs. Pill counts will also be performed. Participants who are receiving TB treatment outside the study clinic will be expected to bring their TB treatment records with them to each visit.

6.0 CLINICAL AND LABORATORY EVALUATIONS

6.1 Schedule of Events

Evaluation	Screening	Entry	PK Visit Day 12 ± 2 days after initiation of ART***	Post-Entry Evaluations (Weeks)											Time of MTB IRIS	Virologic Failure	Time of Suspected TB Treatment Failure or Recurrence	Premature ARV and/or TB Treatment and Premature Disc. Evals
				Visit Window ± 7 days														
				2	4	8	12	16	20	24	32	40	48	72				
Documentation of HIV-1	X																	
AFB, TB Culture, and Drug Sensitivity*		X				X	X	If still TB-positive, repeat every 4 weeks until 2 consecutive TB-negative cultures									X	
Medical History/Medication History		X																
Clinical Assessments, Including TB Evaluations	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Adherence Assessment - Pill Counts					X	X	X		X	X	X		X	X	X	X	X	X
TB Treatment Status and Outcome Determination										At comple-tion of TB treat-ment			X	X			X	X
Chest X-Ray	X					X							X	X			X	X
Hematology	X	X			X	X		X		X			X	X	X			X
Liver Function Tests	X	X		X		X		X		X			X	X				X
Blood Chemistries	X	X				X		X		X			X	X				X
Pregnancy Test**	X	X		Repeat as indicated														
CD4+/CD8+	X	X				X				X			X	X	X	X		X

Evaluation	Screening	Entry	PK Visit Day 12 ± 2 days after initiation of ART***	Post-Entry Evaluations (Weeks)											Time of MTB IRIS	Virologic Failure	Time of Suspected TB Treatment Failure or Recurrence	Premature ARV and/or TB Treatment and Premature Disc. Evals
				Visit Window ± 7 days														
				2	4	8	12	16	20	24	32	40	48	72				
Plasma HIV-1 RNA	X	X				X		X		X			X	X	X	X		X
HIV Resistance Testing (Stored Plasma)		X	Collect at confirmation of virologic failure															
Stored Plasma and PBMC		X								X			X	X	X	X		X
Population PK for Accrual Period 2 (see section 10.5.2)				X		X												
Intensive Pharmacokinetic Studies for Accrual Period 1 (refer to section 10.2.2)			X															
Stored Serum		X								X			X	X	X	X		X
Stored Urine		X				X				X			X	X	X	X		X
Sputum Sample Storage		X				X				X							X	

* If the participant has exclusively extrapulmonary TB and sputum cannot be induced, a sputum sample is not required, but a specimen from any clinically relevant extrapulmonary site, if available (e.g., pleural, pericardial, or peritoneal fluid or tissue biopsy; aspirate of lymph node, cold abscess, bone marrow or joint fluid; cerebrospinal fluid; liver, bone marrow or other tissue biopsy or; blood) should be submitted for AFB smear, mycobacterial culture, and TB drug susceptibility testing (see section 6.2.6). Drug susceptibility results for both RIF and INH should be recorded when available.

** The pregnancy test must be negative within 7 days prior to study entry and 72 hours of starting study medications.

***Unless the week 2 or week 4 visit did not take place, the full Clinical Assessment does not need to be conducted. If the week 2 visit or week 4 visit did take place, only the vital signs and weight need to collected.

6.2 Timing of Evaluations

6.2.1 Screening Evaluations

Screening evaluations must occur prior to randomization. Screening evaluations to determine eligibility must be completed within 14 days prior to study entry unless otherwise specified. The pregnancy test must be negative within 7 days prior to study entry and 72 hours of starting study medications. CD4+/CD8+ T-cell count, and viral load should be completed up to 30 days prior to study entry. In addition to data being collected on participants who enroll into the study, demographic, clinical, and laboratory data on screening failures will be captured in a Screening Failure Results form and entered into the ACTG database. A Screening Failure Results form must be completed for consented individuals who do not enter the study.

6.2.2 Randomization and Entry Evaluations

Entry evaluations will occur after randomization. Entry evaluations and initiation of anti-TB therapy with study provided RIF or RBT and non-study provided INH, EMB and PZA should be started within 72 hours of randomization. ART should be started as soon as possible after initiating anti-TB therapy, but may be delayed for up to 7-14 days after initiation of anti-TB therapy to allow participants sufficient time to assess tolerability of TB medications. Dates of initiation of all study provided and non-study provided anti-TB and ART medications will be entered into the ACTG database.

6.2.3 Post-Entry Evaluations

Study visits must be scheduled ± 7 days of the weeks indicated in the Schedule of Events (SOE). There should be no study visits after the week 72 (final study) visit.

NOTE: The PK visit on day 12 (after initiation of ART) has a window of ± 2 days, and therefore, could be combined with the week 2 or 4 visit.

6.2.4 Time of MTB IRIS

Participants who develop symptoms consistent with IRIS or MTB IRIS at any time through week 72 should have the evaluations listed in the SOE as soon as possible after presentation. See the ACTG definition of MTB IRIS in the current ACTG diagnosis appendix or on the ACTG website under Protocol Support Resources (the definition is identified on the CRF). MTB IRIS will be reported on the MTB IRIS CRF.

Sites must remember that reporting of an IRIS or MTB IRIS event includes recording information concerning any invasive procedures and hospitalizations

related to the IRIS episode on the appropriate IRIS Update Form, as well as subsequently recording eventual resolution of that event.

6.2.5 Virologic Failure

The visit evaluations required at the time of confirmation of virologic failure (as per the SOE) will be determined after the results of the second consecutive (confirmatory) specimen are available; virologic failure is defined as a confirmed HIV-1 RNA level ≥ 1000 copies/mL at or after 16 weeks and before 24 weeks of ART or ≥ 400 copies/mL at or after 24 weeks of treatment.

6.2.6 Time of Suspected TB Treatment Failure or Recurrence

A participant must undergo the evaluations indicated in the SOE under TB treatment failure or recurrence within 28 days of the site becoming aware of a possible TB treatment failure or recurrence of TB disease as indicated below. TB treatment failure should be suspected for participants who have not resolved their signs and symptoms related to the qualifying episode of TB or have a persistently positive AFB smear in sputum or other body fluid or tissue sample after completion of the intensive phase of TB treatment. TB treatment failure is confirmed if a TB-positive mycobacterial culture is obtained from any site after week 16 of TB treatment.

Participants who have resolved their signs and symptoms related to the qualifying episode of TB and have negative AFB smears and mycobacterial cultures, if available, but have a recurrence of signs or symptoms of TB at any time at or after week 24 and before the week 72 endpoint should return for an interim visit as soon as possible after presentation. A sputum sample should be obtained for AFB smear and culture, and a chest x-ray or other radiographic evaluation as indicated should be performed. Any results from repeated sputum and chest x-ray evaluations must be documented. If the participant enrolled with exclusively extrapulmonary TB and no new pulmonary signs or symptoms are present, a sputum sample is not required, but a specimen from any clinically relevant extrapulmonary site, if available (e.g., pleural, pericardial, or peritoneal fluid or tissue biopsy; aspirate of lymph node, cold abscess, bone marrow or joint fluid; cerebrospinal fluid; liver, bone marrow or other tissue biopsy or; blood) should be submitted for AFB smear, mycobacterial culture, and TB drug susceptibility testing. Any information that is provided by the local TB clinic related to TB recurrence must be recorded on the CRFs when received, as noted for TB evaluations above. Any positive sputum or other body fluid or tissue culture should be stored at the site or in the local TB laboratory as appropriate to site procedures.

6.2.7 Discontinuation Evaluations

<u>Evaluations for Randomized Participants Who Do Not Start Study Treatment</u>
All CRFs must be completed and keyed for the period up to and including week 0.

Premature ARV and/or TB Treatment and Premature Discontinuation Evaluations
Participants who prematurely discontinue from the study, and participants who prematurely discontinue ARV and/or TB treatment, will have the discontinuation evaluations performed as noted in the SOE within 4 weeks after the discontinuation. If the participant discontinues any study-provided ARV, he/she will continue on the remaining study-provided ARVs and the date of the discontinuation of any study-provided (or study treatment) ARV drug and reason for discontinuation will be entered on the Antiretroviral Regimen Record. If the participant discontinues any study-provided TB drug, he/she will continue on the remaining TB drugs and the date of the discontinuation of the study-provided (or study treatment) TB drug and the reason for discontinuation will be entered on the TB Treatment Record.

When the participant takes the last dose of the last study-provided (or study treatment) drug (ARV and/or TB drugs), the Permanent Discontinuation of Study Drugs form will be completed with the date of study drug discontinuation and the reason for discontinuation. If the participant discontinues all study-provided (or study treatment) ARV or TB drugs prematurely, he/she will be encouraged to continue on study, off study treatment, and receive all evaluations as per the SOE through week 72.

6.3 Instructions for Evaluations

All clinical and laboratory information required by this protocol is to be present in the source documents. Sites must refer to the Source Document Guidelines on the DAIDS Web site for information about what must be included in the source document: http://www.niaid.nih.gov/labsandresources/resources/daidsclinrsrch/documents/sourcedocappndx.pdf.

All stated evaluations are to be recorded on the CRF and keyed into the database unless otherwise specified. This includes events that meet the International Conference on Harmonisation (ICH) definitions for a serious adverse event (SAE), regardless of relatedness or association to study medications. Refer to section 11.4.2 for the lists of SAEs and additional events required to be recorded on the CRF and keyed into the database.

To grade diagnoses, signs and symptoms, and laboratory results, sites must refer to the DAIDS Table for Grading the Severity of Adult and Pediatric Adverse Events (DAIDS AE Grading Table), Version 1.0, December 2004 (Clarification, August 2009), which can be found on the DAIDS RSC Web site: http://rsc.tech-res.com/safetyandpharmacovigilance/.

6.3.1 Documentation of HIV-1

Please refer to section 4.1.1 regarding assay requirements for HIV-1 documentation. HIV-1 documentation is not recorded on the CRF.

6.3.2 Acid Fast Bacilli (AFB), TB Culture, and Drug Sensitivity

At or within 30 days prior to study entry, all participants should have a sputum sample collected for AFB smear, mycobacterial culture, speciation (if culture positive), and TB drug susceptibility (if MTB culture positive) testing to be performed locally or at a reference laboratory. The ability to produce a sputum sample is not a requirement for enrollment into the study; however, once entered, site staff must attempt to obtain a sputum sample and can induce a sputum sample if the participant is not able to produce one on his/her own.

NOTE: If the participant has exclusively extrapulmonary TB and sputum cannot be induced, a sputum sample is not required, but a specimen from any clinically relevant extrapulmonary site (e.g., pleural, pericardial, or peritoneal fluid or tissue biopsy; aspirate of lymph node, cold abscess, bone marrow or joint fluid; cerebrospinal fluid; liver, bone marrow or other tissue biopsy or; blood), if available, should be submitted for AFB smear, mycobacterial culture, and TB drug susceptibility testing.

Documentation for the current episode of TB should include any TB treatment initiated for the qualifying (current) episode prior to randomization, any known TB diagnostic test results available (e.g., culture from any samples, including blood, or cerebrospinal fluid (CSF), drug susceptibility test results, and histopathology results), and any radiologic exams documenting manifestations of TB. Record this information on the CRFs.

At week 8 and week 12, a sputum sample will be collected and tested as above. See below for additional sputum collection instructions if the culture is positive for TB.

<u>Entry and Subsequent Sputum Collections</u>
At entry (not required if obtained within 3 days prior to entry), week 8, week 12, and at the time of suspected TB treatment failure/TB recurrence, participants will be given sterile collection containers to collect first morning expectorated sputum the day of their clinic visit. These specimens will be collected by induction if they cannot be spontaneously produced.

Sputum will be collected as described below:

- If the final dose of intensive phase of INH, RIF or RBT, EMB and PZA coincides with the week 8 visit, collect sputum samples within 72 hours of ingestion of the final dose of intensive phase of TB treatment and prior to the ingestion of the second dose of continuation phase TB medications.

- If the final dose of intensive phase INH, RIF or RBT, EMB and PZA does NOT coincide with the week 8 visit, (a) collect a sputum sample at week 8, and (b) schedule a separate visit within 72 hours of ingestion of the final dose of intensive phase of TB treatment and prior to the ingestion of the second dose of continuation phase TB medications.

- From week 16 onward, collect single sputum samples every 4 weeks (monthly) for smear and cultures if sputum culture results have not demonstrated two consecutive TB-negative cultures after week 12, and discontinue monthly smear and cultures once there are two consecutive TB-negative sputum cultures. Drug susceptibility testing on available samples should be done if the sputum culture remains MTB positive after the week 8 timepoint.

If the sputum sample does not become TB-negative by the week 16 time point, the participant has failed TB treatment. The participant will be taken off study TB medications and will be treated for possible drug-resistant TB at the discretion of the primary clinician according to local, national, or international guidelines used for treatment of drug-resistant TB. These participants will be followed on study, but off study-provided TB drugs until week 72. If the participant must discontinue study-provided TB treatment, he/she may still continue to take study-provided ARVs.

Collect sputum in a sterile single-use collection container. If possible, the oral cavity should be rinsed with clean water that is expectorated prior to giving the sample. The specimen should contain 3-5 mL of sputum.

Participants who are unable to expectorate or who submit an inadequate specimen may have sputum collected in the clinic by study staff. Induction by aerosolized inhalation of sterile nebulized saline will be required for participants who cannot expectorate. Participants who cannot produce sputum even with induction will have this noted on the CRF. At subsequent visits, these participants will not undergo sputum induction if they remain without a cough, with the exception of week 8, at which point all participants will attempt to provide sputum, via induction, if necessary. Collection method, timing, volume, and appearance of sputum must be recorded on the CRF. Specimens should be refrigerated at 4°C within 1 hour of collection whenever possible and should be transported on ice or cold pack, if available, to the lab as soon as possible.

NOTE: If the participant entered the study with exclusively extrapulmonary TB and does not develop pulmonary signs, symptoms, or cough at any time during follow-up, he/she will not have sputa submitted.

6.3.3 Medical History

The medical history must include all diagnoses identified by the ACTG criteria for clinical events and other diagnoses. For current criteria, refer to the appendix identified in the study CRF. Any allergies to any medications and their formulations must be documented.

Documentation of historical information for all prior TB episodes will include any available information about diagnosis dates, and any available results of TB cultures, AFB smear results, TB drug susceptibility testing, and TB treatment information. History of prior TB episodes with dates and TB treatment (with start

and stop dates if known or estimated duration of prior TB treatment if start and stop dates are unavailable), and all other information for prior TB episodes should be documented in the source document only.

All other diagnoses identified by the ACTG criteria for clinical events and other diseases must be recorded on the CRF and in the source document.

6.3.4 Medication History

A medication history must be present, including start and stop dates. The table below lists the medications that must be included in the history.

Medication Category	Complete History or Timeframe	CRF / Source Document
TB therapy for the current episode	Complete history	CRF and source document
Immune-based therapy	Complete history	CRF and source document
Blinded study treatment	Complete history	CRF and source document
HIV-1-related vaccines	Complete history	CRF and source document
Prescription drugs for treatment of opportunistic infections	Complete history	CRF and source document
Prescription drugs for prophylaxis of opportunistic infections	Within 30 days prior to study entry	CRF and source document
ART	Complete history	CRF
Prescription drugs (other)	Within 30 days prior to study entry	CRF and source document
Non-prescription drugs	Within 30 days prior to study entry	Source document
Alternative therapies	Currently being taken	Record as yes/no on CRF; if yes, record details in source document
Dietary supplements	Currently being taken	CRF

6.3.5 Clinical Assessments, Including TB Evaluations

Complete Physical Exam
A complete physical examination will be performed at screening only and will include at a minimum an examination of the skin, head, mouth, and neck; auscultation of the chest; cardiac exam; abdominal exam; examination of the lower extremities for edema; and Karnofsky performance score. The complete physical exam will also include signs and symptoms, diagnoses, vital signs (temperature, pulse, respiration rate, and blood pressure), and a measurement of height and weight. Standardized blood pressure is not required for A5290.

Targeted Physical Exam
After screening, a targeted physical examination is to be driven by any previously identified or new signs or symptoms including diagnoses that the participant has experienced since the last visit. This examination will include weight, vital signs

(temperature, pulse, respiration rate, and blood pressure), examination for the presence of thrush, lymphadenopathy, presence of rash, and lung examination.

Signs and Symptoms
At entry, all grades that occurred within 30 days prior to study entry must be recorded; post-entry, all signs and symptoms ≥ Grade 3 must be recorded. Record all signs and symptoms that led to a change in treatment, regardless of grade.

At entry, all TB-related signs and/or symptoms that occurred within 30 days prior to study entry must be recorded. These include, but are not limited to, fever, weight loss, lymphadenopathy, pulmonary signs and symptoms, and evidence of extrapulmonary disease (e.g., meningitis), presence of wasting, cold abscesses, or abdominal disease.

After entry, resolution of TB-related signs and symptoms reported at entry will be recorded. Any new or resolved Grade ≥ 2 TB signs or symptoms reported after entry will be recorded on the CRF.

TB Evaluations
A review of all reported results from evaluations for the qualifying episode of TB performed at the local clinical or TB program site must be completed for all participants. At each visit, all diagnostic, laboratory and radiology results, and treatment information available regarding the qualifying (current) episode of TB, including any that is provided by the local TB clinic, must be recorded on the CRFs when received. This will include TB-related radiologic results, including most recent chest x-ray, AFB smear and culture results, and other evaluations related to TB diagnosis and evaluation of TB status. Any changes in results from repeated radiologic evaluations must be documented.

Participants whose qualifying episode of TB is later identified as drug-resistant according to the inclusion and exclusion criteria in section 4.0 will be discontinued from the study and referred to their primary clinician/clinical facility or TB and ART program and treated with the best available TB and ART according to local standards of care. Sites must notify the A5290 core team by e-mail (actg.corea5290@fstrf.org) within 2 weeks after learning that the participant's TB has been identified as drug-resistant.

Participants whose qualifying episode of TB was later deemed to be not TB will continue to be followed on study, off study-provided TB treatment, but on study-provided ART, for safety and ART endpoints.

Cultures from study samples identified as TB-positive, including any sample that is positive for drug-resistance, must be stored at the site laboratory or the local TB laboratory performing the TB testing (as appropriate to site procedures).

Diagnoses
Diagnoses identified by the ACTG criteria for clinical events and other diseases received since the last visit must be recorded. Refer to the study CRF for the appropriate appendix used for the current ACTG criteria.

Concomitant Medications
After entry, all concomitant prescription medications, excluding TB medications, started or stopped since the last visit must be recorded on the CRF. Nonprescription medications will be recorded in the source documents only. Non-study provided TB medications will be recorded on the TB Treatment CRF and all non-study provided ART will be recorded on the ARV Treatment CRF.

HIV and TB Study Treatment Modifications
Record all ARV and anti-TB study drug modifications, including initial doses, modifications that were participant-initiated and/or protocol-mandated and/or according to local/national/international guidelines, and inadvertent and deliberate interruptions of ARVs for > 3 days and anti-TB medications for > 7 days at each visit. Record any permanent discontinuation of any ARV or anti-TB drug.

6.3.6 Adherence Assessment - Pill Counts

Pill counts for all prescribed ARVs and TB medications will be conducted according to the SOE.

6.3.7 TB Treatment Status and Outcome Determination

At completion of the entire course of TB treatment, TB treatment status/outcome must be recorded on the CRF, and should also be documented again at weeks 48 and 72, at the time of detection/diagnosis of TB treatment failure or TB relapse/recurrence or at the time of premature discontinuation or death.

TB treatment status/outcome will be classified according to the following, adapted from ATS guidelines[42].

Cure: Completion of all recommended doses of medication *and* 2 consecutive TB-negative mycobacterial cultures.

Treatment failure: TB-positive mycobacterial culture after 16 weeks of TB treatment for a participant who was documented to be taking TB medications.

Died: Participant who died for any reason before the completion of TB-treatment.

Default: Participant whose TB-treatment was interrupted for 2 or more consecutive months and did not reinitiate TB therapy.

Transfer out/lost to follow-up (LTFU): Participant who was transferred to another treatment facility or LTFU and for whom the TB treatment outcome is not known.

Treatment ongoing: At time of evaluation, participant is still undergoing treatment for TB. Documentation should be made of why prolonged TB treatment is occurring, including: default with reinitiation of TB treatment, initial TB treatment failure, and persistent TB-positive mycobacterial cultures.

Relapse/recurrence: Participant who has 2 consecutive TB-negative mycobacterial cultures and who subsequently has clinical or radiographic deterioration consistent with active TB at or after week 24 and before the week 72 endpoint.

Treatment completed: Participant who has completed TB treatment but who does not meet the criteria to be classified as a cure or a failure.

NOTE: For participants who are enrolled with probable TB and do not have a positive mycobacterial culture from any site available to meet these outcome definitions, but who have specimens with a positive AFB smear, the AFB smear result will be substituted for the mycobacterial culture result in assessing TB outcomes. If there are no positive AFB smear results, then the assessment of TB outcomes will be based on best clinical judgment and further reviewed by the team and an independent endpoint reviewer.

6.3.8 Chest X-Ray

A chest X-ray must be performed within 30 days prior to study entry, at weeks 8, 48, and 72, at the time of suspected TB treatment failure or relapse/recurrence, and at premature study discontinuation. Interpretation of the x-ray is to be performed by a clinician.

6.3.9 Laboratory Evaluations

At screening and entry all protocol required laboratory values must be recorded on the CRFs. For post-entry assessments, record all Grade ≥ 3 laboratory values. All laboratory toxicities that led to a change in treatment, regardless of grade, must be recorded.

Hematology
Hemoglobin, hematocrit, red blood cells, mean corpuscular volume, white blood cell count (WBC), differential WBC, ANC, and platelets.

Liver Function Tests
Total bilirubin, AST (SGOT), ALT (SGPT), and alkaline phosphatase.

Blood Chemistries
Sodium, potassium, chloride, bicarbonate, creatinine, and albumin.

Pregnancy Test
For women with reproductive potential: Serum or urine β-HCG (urine test must have a sensitivity of 15-25 mIU/mL).

CD4+/CD8+
Obtain absolute CD4+/CD8+ count and percentages within 30 days prior to study entry from a laboratory that is certified for protocol testing by the DAIDS Immunology Quality Assurance (IQA) Program. For entry and post-entry evaluations, the laboratory must be certified by the DAIDS Immunology Quality Assurance (IQA) Program.

6.3.10 Virologic Studies

Plasma HIV-1 RNA
Screening HIV-1 RNA must be performed within 30 days prior to study entry by a laboratory that possesses a CLIA certification or equivalent.
For entry and post-entry evaluations, the laboratory must be certified by the DAIDS Virology Quality Assurance (VQA) Program.

HIV Resistance Testing (Stored Plasma)
HIV resistance testing will be performed retrospectively (not in real time), using a VQA certified method. Refer to the A5290 Laboratory Processing Chart (LPC) for additional details.

Stored Plasma and PBMC
Plasma will be stored for future virology testing as indicated in the SOE. Refer to the A5290 LPC for details of collection, processing, shipping, and designated laboratory. At sites that are able to, PBMCs (viable, whenever possible) will be cryopreserved for future virology and immunology testing.

6.3.11 Pharmacokinetic Studies

See section 10.0, Pharmacology Plan.

Participants do not have to be fasting when they come to the clinic for their PK study. Site staff should advise the participant that if he/she does eat prior to coming to the clinic to avoid high fat meals. If the sites provide a meal on the PK day, it should not be a high fat meal and it should be provided 3 hours after the dose of LPV/RTV and either RBT or RIF has been given. Any kind of a snack or meal can be provided after that 3 hour post dose meal. (See section 5.1.3.)

Participants' PK samples collected during the dose-finding period in accrual period 1 will be batched and shipped to the ACTG repository every 2 weeks with immediate re-shipping to the PK laboratory. Otherwise, PK samples will be batched and shipped to the ACTG repository periodically. Refer to the A5290 LPC for additional instructions.

6.3.12 Stored Serum

Serum samples will be collected as per the SOE and stored for future immunology testing. Refer to the A5290 LPC.

6.3.13 Stored Urine

Urine will be stored for future TB biomarker testing as per the SOE. Refer to the A5290 LPC.

6.3.14 Sputum Sample Storage

Samples will be collected as per the SOE and stored as per the A5290 LPC.

7.0 CLINICAL MANAGEMENT ISSUES

A5290 will use the Division of AIDS Table for Grading the Severity of Adult and Pediatric Adverse Events Version 1.0, December 2004, Clarification August 2009, as a guideline for grading toxicities.

Toxicity management at non-US sites may require reliance on clinical symptoms, clinician judgment, and available laboratory markers, since alternatives to study-provided ARV drugs may be very limited and baseline levels of certain laboratory parameters (e.g., hemoglobin) may be different than in other settings.

This section provides guidelines for management of pregnancy and breastfeeding and of toxicities related to study-provided drugs LPV/r, RBT, and RAL only. When one of the ARV drugs is held for resolution of toxicity, all drugs in the ARV regimen should be held concurrently. With the exception of RBT, toxicity management of the TB medications will be performed by local TB control programs or the site investigator according to local standards in close communication with the A5290 protocol team.

Every attempt should be made to continue to follow participants who discontinue ARVs and/or TB drugs because of a Grade 3 or 4 AE until resolution of the adverse event can be documented.

The A5290 Clinical Management Committee (A5290 CMC) is available to discuss toxicity management of study-provided and other ARVs and TB drugs with investigators. The A5290 CMC consists of the A5290 protocol chairs, statisticians, DAIDS medical officer, DAIDS pharmacist, data managers, clinical trials specialist, and other protocol team members selected by the A5290 protocol chairs.

7.1 Toxicity Management

Grade 1 or 2
Participants who develop a Grade 1 or 2 AE or toxicity may continue ARVs and TB drugs without alteration of the dosage. Participants experiencing Grade 1 or 2 toxicities will be managed at the discretion of the site investigator.

Grade 3
If there is compelling evidence that the AE has NOT been caused by the study-provided drugs, dosing may continue at the discretion of the site investigator/clinician. Except as stated in the following sections, participants who develop a Grade 3 AE or toxicity thought to be secondary to study-provided drugs or of unknown etiology may have all of their ARVs and/or TB drugs withheld, at the site investigator's discretion. Investigators are welcome to discuss toxicity management with the A5290 CMC. The participant should be reevaluated weekly if at all possible until the AE returns to Grade ≤ 2 or until stabilized and no longer in need of such frequent monitoring, as determined by the site investigator, at which time ART and/or anti-TB treatment may be reintroduced at the discretion of the site investigator or according to standard practice.

Grade 4
Participants who develop a symptomatic Grade 4 AE or toxicity, not specifically addressed below, will have all medications withheld and should be reevaluated weekly if at all possible until the AE returns to Grade ≤ 2 or until stabilized and no longer in need of such frequent monitoring, as determined by the site investigator. However, under certain circumstances the ARV or TB drug thought most likely to be related to the AE may be resumed at the discretion of the site investigator. However, if study-provided ARV or TB drugs are permanently discontinued due to a toxicity not otherwise specified in section 7.2, then the participant should continue to be followed on study, off-study-provided medications and referred to their primary clinician for best available management.

Participants with Grade 4 asymptomatic laboratory abnormalities, not specifically addressed below, may continue ART and anti-TB treatment if the site investigator has compelling evidence that the toxicity is NOT related to the ART or anti-TB treatment, or if benefit of the ART or anti-TB treatment outweighs the potential risk.

7.2 Specific Management of Toxicities Related to Study-Provided Drugs

7.2.1 AST and ALT Elevation

ARVs, INH, RIF, RBT, and PZA can all cause alterations in liver function tests. Concomitant illnesses, including TB, may also alter these laboratory parameters. Therefore, changes in AST or ALT should be evaluated within the clinical context of the abnormalities.

Participants entering this trial will potentially have advanced HIV disease and active TB. Elevation in ALT and AST is expected. Because this study is designed to assess the risk/benefit ratio of second-line ART with varying doses of LPV/r

and RBT as an alternative for RIF in this population, participants with ≤ 2 x ULN for ALT will be allowed to enroll in accrual period 1 and participants with ≤ 5 x ULN for both parameters will be allowed to enroll in accrual period 2 of the study. If the AST or ALT elevation is considered most likely to be due to concomitant illness or medication, standard management, including discontinuation of the likely causative agent, should be undertaken.

For asymptomatic or symptomatic elevation of AST or ALT > 7.5 × ULN (Grade 3), all medications should be discontinued and held until levels and symptoms are Grade ≤ 2, at which time therapy may be reintroduced. All medications may be restarted if the laboratory abnormalities were thought secondary to a concomitant illness.

If the elevation of AST or ALT is thought to be due to RBT, anti-TB medications should be reintroduced one at a time in 3-7 day increments, and if all other anti-TB medications are tolerated, RBT should be added last, initially at a reduced dose according to Table 5.1. If the participant was already receiving RBT at a reduced-dose then the re-challenge dose should be the dose the participant was previously receiving. If the RBT dose is tolerated upon re-challenge for 7 days, then the ARVs should be restarted. If Grade 3 or higher elevation of AST or ALT recurs with the reintroduction of RBT then RBT should be permanently discontinued and the participant should be referred to his/her primary clinician or local TB program, provided the best available anti-TB therapy according to local standards, and the participant should continue to be followed on study but off study-provided anti-TB medications.

If the elevation of AST or ALT is thought to be due to LPV/r, anti-TB medications should be reintroduced one at a time in 3-7 day increments as described above, and if all anti-TB medications are tolerated upon re-challenge, then LPV/r should be re-introduced at the reduced dose according to Table 5.1 together with the NRTIs. If the participant was already receiving a reduced dose of LPV/r, then the re-challenge dose of LPV/r should be the dose the participant was previously receiving. If the LPV/r dose is tolerated upon re-challenge for 7 days, then the previous dose the participant was receiving, if applicable, may be restarted after discussion with the A5290 CMC. If Grade 3 or higher elevation of AST or ALT recurs with the reintroduction of LPV/r then LPV/r should be permanently discontinued, the participant should be referred to his/her primary clinician or local TB program and provided the best available ART according to local standards, and the participant should continue to be followed on study but off study-provided anti-HIV medications.

7.2.2 Bilirubin

Participants entering this trial will potentially have advanced HIV disease and active TB. Elevation in bilirubin is common in this situation; however, asymptomatic or symptomatic elevation of bilirubin may also occur with RBT, RIF, or LPV/r. Because this study is designed to assess the risk/benefit ratio of second-line ART with varying doses of LPV/r and RBT as an alternative for RIF

in this population, participants with ≤ 2.5 X ULN of bilirubin will be allowed to enroll in accrual period 1 and participants with ≤ 5 X ULN of bilirubin will be allowed to enroll in accrual period 2 of the study. If the bilirubin elevation is considered most likely to be due to concomitant illness or medication, standard management, including discontinuation of the likely causative agent, should be undertaken.

For new Grade 3 bilirubin, study medications can be continued if, in the opinion of the site investigator, the possible benefits of therapy outweigh the risks.

For asymptomatic or symptomatic new elevation of bilirubin > 5 x ULN (Grade 4), all medications must be discontinued and held until levels are Grade ≤ 2, at which time therapy may be reintroduced. All medications may be restarted if the laboratory abnormalities are thought to be secondary to a concomitant illness. If the elevation of bilirubin is thought to be due to RBT, anti-TB medications should be reintroduced one at a time in 3-7 day increments, and if all other anti-TB meds are tolerated, RBT should be added last, initially at a reduced dose according to Table 5.1. If the participant was already receiving RBT at a reduced dose then the re-challenge dose should be the dose the participant was previously receiving. If the RBT dose is tolerated upon re-challenge for 7 days, then the ARVs should be restarted. If Grade 4 elevation of bilirubin recurs with the reintroduction of RBT, then RBT should be permanently discontinued and the participant should be referred to his/her primary clinician or local TB program, provided the best available anti-TB therapy according to local standards, and the participant should continue to be followed on study but off study-provided anti-TB medications.

If the elevation of bilirubin is thought to be due to LPV/r, anti-TB medications should be reintroduced one at a time in 3-7 day increments as described above, and if all anti-TB medications are tolerated upon re-challenge, then LPV/r should be re-introduced at the reduced dose according to Table 5.1 together with the NRTIs. If the participant was already receiving a reduced dose of LPV/r, then the re-challenge dose of LPV/r should be the dose the participant was previously receiving. If the LPV/r dose is tolerated upon re-challenge for 7 days, then the previous dose the participant was receiving, if applicable, may be restarted after discussion with the A5290 CMC. If Grade 4 elevation of bilirubin recurs with the reintroduction of LPV/r, then LPV/r should be discontinued, the participant should be referred to his/her primary clinician or local TB program and provided the best available ART according to local standards, and the participant should continue to be followed on study but off study-provided anti-HIV medications.

7.2.3 Uveitis

Uveitis presents with eye pain, redness, photophobia, blurred vision and/or decreased visual acuity. The most likely study drug to be associated with uveitis is RBT. Uveitis is reported to occur at a rate of ~3% in persons receiving RBT in doses of 450-600 mg/d. If signs or symptoms of uveitis occur in a participant assigned to a RBT regimen, RBT should be temporarily held, and the participant

should be referred to a local ophthalmologist or primary clinician for evaluation and symptomatic treatment, which may include topical (eye drops) mydriatics and/or corticosteroids. Once symptoms resolve, RBT may be restarted at a reduced dose according to Table 5.1. If the participant was already receiving a reduced dose of RBT, re-challenge with RBT at the previous reduced dose may be considered after discussion with the A5290 CMC. If uveitis recurs after re-challenge with the reduced dose, RBT should be permanently discontinued, the participant should be referred to his/her primary clinician or local TB program, and provided the best available anti-TB therapy according to local standards, and the participant should continue to be followed on study but off study-provided anti-TB medications.

7.2.4 Neutropenia

Participants entering this trial will potentially have advanced HIV disease and active TB. Neutropenia is expected. Because this study is designed to assess the risk/benefit ratio of second-line ART with varying doses of LPV/r and RBT as an alternative for RIF in this population, participants with ≥ Grade 2 neutropenia will be allowed to enroll in accrual period 1 and participants with ≥ Grade 3 neutropenia will be allowed to enroll in accrual period 2 of the study. RBT may be associated with neutropenia. If Grade 4 neutropenia develops after study entry and RBT is considered the likely causative agent, the dose of RBT should be reduced according to recommendations in Table 5.1, and the neutrophil count should be repeated within 72 hours of the dose reduction. If the participant is already receiving a reduced dose of RBT, or if the repeat neutrophil count has not improved to Grade 3 or less, then RBT should be held, and the neutrophil count should be repeated within 72 hours. If the neutrophil count has improved to Grade 3 or less, RBT may be restarted at the reduced dose. If Grade 4 neutropenia recurs, RBT must be permanently discontinued, the participant should be referred to his/her primary clinician or local TB program, and provided the best available anti-TB therapy according to local standards, and the participant should continue to be followed on study but off study-provided anti-TB medications.

7.2.5 Severe Rash/Cutaneous Reaction

Moderate to severe rash potentially related to drug hypersensitivity may occur with any of the study provided drugs, although the likeliest agents to cause rash in this setting are RIF, RBT, and RAL. It may not be possible to determine which, if any of the study drugs is the cause. Participants should be instructed to immediately stop taking RIF, RBT, RAL or other suspect drugs, and seek medical attention if they develop a rash of Grade 3 or higher, or any rash of Grade 2 or higher associated with any of the following symptoms that may be signs of a more serious reaction, such as Stevens-Johnson syndrome, toxic epidermal necrolysis, or severe hypersensitivity: fever, generalized malaise or fatigue, muscle or joint aches, blisters, oral lesions, eye inflammation, facial swelling, swelling of the eyes, lips, mouth, breathing difficulty, and/or signs and symptoms of liver abnormalities (e.g., jaundice, dark or tea colored urine, pale colored

stools/bowel movements, nausea, vomiting, loss of appetite, or right upper quadrant abdominal pain). If the rash and symptoms are thought to be due to RIF, RBT, or RAL, and no other cause can be determined, then RIF, RBT, or RAL must be permanently discontinued, the participant should be referred to his/her primary clinician or local TB program (if the suspect agent is RIF or RBT), and provided the best available anti-HIV and/or anti-TB therapy according to local standards. The participant should continue to be followed on study but off-study-provided RIF, RBT, or RAL.

7.2.6 Nausea and Vomiting

Although common, nausea following initiation of therapy with ARV medications and/or TB treatment usually subsides or resolves during the first few weeks of treatment.

Steps in the management of nausea include taking the medication with food and administration of antiemetics.

7.2.7 Diarrhea

Diarrhea is a common side effect of infection and medication toxicity. If no infectious cause of diarrhea is found and onset is temporally related to new medication, symptomatic management with antidiarrheal agents is appropriate.

7.2.8 Recommendations for Management of Immune Reconstitution Inflammatory Syndromes

Inflammatory syndromes in participants with TB may occur shortly after the initiation of either anti-TB treatment or ART. When these syndromes are suspected, the management plan presented below should be followed. Consultation with the A5290 CMC is recommended. Note that MTB IRIS may be observed in participants who have not yet initiated or switched to second-line ART.

- Continue ART.
- Evaluate for new diagnosis of opportunistic infection or worsening of TB, as indicated.
- Continue or initiate specific therapy for the infection, if present.
- Initiate anti-inflammatory agents, initially non-steroidals or, if needed, corticosteroids at the discretion of the site investigator.

7.3 Pregnancy and Breastfeeding

If a participant becomes pregnant during the study, she may choose to continue study-provided medications during pregnancy and breastfeeding, after discussion with her primary clinician and the A5290 CMC, given the lack of optimal alternatives for TB treatment in the setting of a PI-based ART regimen. Participants who choose to continue all study-provided medications will be followed on study through the completion of the

pregnancy and the outcome of the pregnancy will be recorded on the CRF. If a participant chooses not to continue either study-provided anti-TB or antiretroviral medications, she will be referred to local clinics and will receive the best available TB or ART as determined by her primary clinician, but will continue to be followed on study but off study-provided anti-TB or antiretroviral medications, or both, and the outcome of the pregnancy will be recorded on the CRF.

If a woman has completed the study or chooses to discontinue from the study before the end of the pregnancy, the site staff should request permission to contact her regarding pregnancy outcomes at the end of the pregnancy. If the information is obtained, pregnancy outcomes will be submitted on a CRF at the end of the pregnancy. A5290 will not provide prenatal or postpartum care to infants born to women on study through the protocol; however, women who become pregnant on study will continue to be followed as described above but will be referred to local clinics and/or other research studies for prenatal and postpartum care.

Pregnancies that occur on study will be reported to The Antiretroviral Pregnancy Registry. Intrapartum complications and/or pregnancy outcome will be recorded on the CRFs and also reported to The Antiretroviral Pregnancy Registry. More information is available at www.apregistry.com. Phone: 800-258-4263; Fax: 800-800-1052.

8.0 CRITERIA FOR DISCONTINUATION

8.1 Permanent ARV Treatment Discontinuation

- Drug-related toxicity (see section 7.1).
- Requirement for prohibited concomitant medications (see section 5.4).
- Stopping the last component of study-provided ART.
- Request by participant to terminate treatment.
- Clinical reasons believed life threatening by the physician, even if not addressed in the toxicity section of the protocol.

NOTE: Participants must be referred to their primary care clinician/clinical facility or ART program and treated with the best available ART if they permanently discontinue study-provided ARVs.

8.2 Permanent TB Treatment Discontinuation

- Qualifying episode of suspected TB determined not to be TB.
- Drug-related toxicity (see section 7.1).
- Requirement for prohibited concomitant medications (see section 5.4).
- Stopping the study-provided TB drug.
- Completion of TB treatment as defined in the protocol.
- Request by participant to terminate treatment.
- Clinical reasons believed life threatening by the physician, even if not addressed in the toxicity section of the protocol.

NOTE: Participants must be referred to their primary care clinician/clinical facility or TB program and treated with the best available TB treatment if they permanently discontinue study-provided anti-TB treatment.

8.3 Premature Study Discontinuation

- Failure by the participant to attend 3 consecutive clinic visits.
- RIF resistance found after study entry.
- Request by the participant to withdraw.
- Request of the primary care provider if he/she thinks the study is no longer in the best interest of the participant.
- Participant judged by the investigator to be at significant risk of failing to comply with the provisions of the protocol as to cause harm to self or seriously interfere with the validity of the study results.
- At the discretion of the ACTG, institutional review board (IRB)/ethics committee (EC), US Food and Drug Administration (FDA), Office for Human Research Protections (OHRP), NIAID, investigator, pharmaceutical supporter(s), or local governmental authorities.

9.0 STATISTICAL CONSIDERATIONS

9.1 General Design Issues

This is an open-label, randomized, phase 2b study to evaluate whether a standard dose lopinavir/ritonavir (LPV/r) regimen, with or without raltegravir (RAL), coupled with rifabutin (RBT)-based TB treatment is superior to a double dose LPV/r regimen coupled with rifampin (RIF)-based TB treatment. We intend to recruit 471 HIV-infected participants with active TB who require protease inhibitor (PI)-based antiretroviral therapy (ART). Each participant will be followed until week 72. We anticipate accrual to occur at the rate of approximately 4-5 participants per month per site once all sites are registered and enrolling participants.

9.2 Primary Endpoints

9.2.1 Accrual Period 1 PK Study Endpoints

9.2.1.1 LPV plasma concentrations at day 12 ± 2 (after initiation of ART) in Arms A, B, and C.

9.2.1.2 RBT plasma concentrations at day 12 ± 2 (after initiation of ART) in Arms A and C.

9.2.1.3 Grade 3 or 4 laboratory value or sign or symptom attributed to study-provided medication(s) by 28 days of ART.

9.2.1.4 Discontinuation of study-provided drug(s) for treatment-limiting toxicity or intolerance (such that PK assessments within the day 12 ± 2 (after initiation of ART) window cannot be completed).

9.2.2 Primary endpoint: HIV virologic suppression is defined as plasma HIV-1 RNA level < 400 copies/mL at 48 weeks.

9.2.3 Secondary Endpoints

9.2.3.1 TB treatment outcomes: mycobacterial culture conversion at week 8, occurrence of TB treatment failure at or after week 24, and occurrence of TB relapse/recurrence by week 72.

NOTE A: TB treatment outcomes for participants who enroll with probable TB for whom week 8 mycobacterial culture conversion cannot be assessed will include week 8 AFB smear conversion coupled with resolution of signs, symptoms, and radiographic abnormalities on which the diagnosis of probable TB was based or solely resolution of signs, symptoms, and radiographic abnormalities for participants with negative AFB smears or AFB smears that are not available at baseline, in addition to TB treatment failure at or after week 24, and TB relapse/recurrence by week 72.

NOTE B: Participants who cannot produce sputum even with induction, as noted on the CRF, will be considered MTB culture negative and AFB smear negative in analyses.

9.2.3.2 HIV virologic suppression based on two definitions: plasma HIV RNA level < 400 copies/mL at 48 weeks and < 50 copies/mL at 48 weeks.

9.2.3.3 Safety and tolerability:

9.2.3.3.1 Highest reported grade of each new Grade 3 or 4 laboratory value or sign or symptom that is at least a one grade increase from baseline.

9.2.3.3.2 Ordered categorical variable indicating most stringent level of ARV drug management due to toxicity that was required over the co-treatment period: premature permanent treatment discontinuation; treatment hold for more than 3 consecutive days; and none of the above.

9.2.3.3.3 Ordered categorical variable indicating most stringent level of TB drug management due to toxicity that was required over the co-treatment period: premature permanent treatment discontinuation; treatment hold for more than 7 consecutive days; and none of the above.

9.2.3.4 HIV virologic failure is defined as two consecutive plasma HIV-1 RNA levels ≥ 1000 copies/mL at or after 16 weeks and before 24 weeks of ART or ≥ 400 copies/mL at or after 24 weeks of treatment.

NOTE: This definition of virologic failure will be applied regardless of whether or not randomized ART is being taken at the time of failure.

9.2.3.4.1 Occurrence of HIV virologic failure.

9.2.3.4.2 Time to HIV virologic failure.

9.2.3.5 TB drug resistance patterns in participants who have TB treatment failure or relapse/recurrence of TB.

9.2.3.6 Occurrence of MTB IRIS events.

9.2.3.7 Predictors of disease progression:

9.2.3.7.1 CD4+ T-cell counts at baseline and at weeks 8, 24, 48, and 72.

9.2.3.7.2 Occurrence of new AIDS-defining illnesses.

9.2.3.7.3 Occurrence of HIV-disease progression (defined as new AIDS-defining illness or death).

9.2.3.7.4 Occurrence of death.

9.2.4 Additional endpoints for supportive/exploratory analyses that will be defined in more detail in separate analysis plans:

9.2.4.1 HIV-1 drug resistance patterns in participants who have HIV virologic failure.

9.2.4.2 LPV plasma concentrations in Arm B, RBT plasma concentrations in Arms A and C, and RAL plasma concentration in Arm C at weeks 2 and 8 in accrual period 2 participants.

9.2.4.3 Cost-benefit measures related to adding RAL.

9.3 Randomization and Stratification

The participants will be randomized 1:1:1 to three open-label arms using permuted blocks. Randomization will not be stratified.

9.4 Sample Size and Accrual

Accrual will take place in two periods. Accrual period 1 will enroll participants who will undergo an initial dose-finding period before continuing regular study follow-up through 72 weeks. Once review of the dose-finding period in accrual period 1 participants is complete, accrual period 2 will begin.

9.4.1 Sample Size and Accrual for Dose-Finding Study in Accrual Period 1 Participants

For the study design of the dose-finding study in participants enrolled during the accrual period 1, the primary driver is equivalence comparing day 12 ± 2 (after initiation of ART) RBT 24-hour AUC with control data derived from prior PK studies[40,43]. Subject-level data for 500 studies were simulated with pre-specified sample sizes and no-effect boundaries (NEBs). For the simulation study data, geometric mean ratios (GMRs), mean GMR, and 90% confidence intervals were calculated. Based on this simulation study, eighteen evaluable participants per arm are needed for the dose-finding study in accrual period 1 participants to adequately evaluate PK parameters and safety. As shown in Table 9.1 below, a CV of 32% was assumed with three different NEBs. There is more than 90% power to have the 90% CI around the GMR fall entirely within the pre-specified NEB of 67%-150%.

Table 9.1. Probability (%) of Declaring Equivalence for the RBT PK Objective

Sample size		% diff	Prob declare equiv for NEB			Simulated data	
Alone	Co-drug	AUC	50%-200%	67%-150%	80%-125%	Mean GMR	Typical 90% CI
14	14	-30	87%	11%	1%	69.7%	(57.1%, 85.2%)
		-20	98%	44%	4%	79.9%	(65.4%, 97.6%)
		-10	100%	76%	12%	89.2%	(73.1%, 108.9%)
		-5	100%	89%	19%	95.4%	(78.2%, 116.3%)
		5	100%	90%	18%	104.2%	(85.4%, 127.1%)
		10	100%	83%	13%	109.2%	(89.4%, 133.4%)
		20	100%	57%	6%	120.4%	(98.7%, 146.8%)
		30	96%	32%	1%	130.1%	(106.5%, 158.9%)
18	18	-30	93%	9%	0%	69.9%	(58.7%, 83.2%)
		-20	100%	52%	5%	80.1%	(67.3%, 95.4%)
		-10	100%	90%	24%	90.3%	(75.9%, 107.5%)
		-5	100%	93%	30%	94.2%	(79.2%, 112.1%)
		5	100%	94%	30%	105.5%	(88.7%, 125.5%)
		10	100%	90%	26%	110.0%	(92.4%, 131.0%)
		20	100%	70%	9%	119.0%	(99.9%, 141.7%)
		30	99%	36%	2%	130.6%	(109.6%, 155.7%)
22	22	-30	98%	13%	0%	69.8%	(59.6%, 81.8%)
		-20	100%	55%	4%	79.5%	(68.0%, 93.0%)
		-10	100%	93%	31%	90.3%	(77.0%, 105.9%)

Sample size		% diff	Prob declare equiv for NEB			Simulated data	
Alone	Co-drug	AUC	50%-200%	67%-150%	80%-125%	Mean GMR	Typical 90% CI
		-5	100%	98%	45%	95.0%	(81.3%, 111.1%)
		5	100%	98%	46%	104.8%	(89.5%, 122.8%)
		10	100%	94%	31%	110.5%	(94.5%, 129.3%)
		20	100%	77%	10%	120.0%	(102.6%, 140.2%)
		30	100%	44%	3%	129.5%	(110.6%, 151.7%)

Participants who do not have day 12 ± 2 (after initiation of ART) PK samples will not be replaced. Thus, we will enroll 20 participants in each arm, expecting 18 participants in each arm with evaluable PK data. (However, the accrual period 1 PK and safety interim analysis may lead to proposing additional accrual period 1 participants to assure an adequate PK assessment.)

Accrual will be suspended after the last participant is enrolled into the accrual period 1.

9.4.2 Overall Sample Size

For the overall study design, we assume that the standard dose LPV/r regimen with or without RAL coupled with RBT-based anti-TB therapy will be superior to a double-dose LPV/r regimen with RIF-based anti-TB therapy. We estimate the virologic suppression rate at 48 weeks for the double-dose LPV/r treatment arm will be approximately 50%, for the LPV/r with RBT-based anti-TB therapy to be approximately 70%, and for the LPV/r plus RBT plus RAL arm to approach 80-90%. These numbers are based on the following considerations: 1) the standard of care in the US is to switch ART for a failing regimen at earlier time points based on viral load monitoring such that background rates of concomitant NRTI resistance are relatively low, while this is not the case in resource-constrained settings where viral load monitoring is less frequent or not routinely done; 2) there are only a limited number of drugs available for use in second-line therapy in most resource-constrained settings making it difficult to construct a second-line ART regimen with three or more known active drugs; 3) there may be more variability in PK with LPV/r coupled with RBT than has been previously appreciated, and this might compromise virologic outcomes; 4) there are insufficient data available to address this point, which is, in part, why we propose to do this study; and 5) we anticipate that there will be an appreciable rate of adverse effects of anti-TB treatment as well as of ARTs (especially in the double-dose LPV/r arm which could lead to poorer adherence and early treatment discontinuation, thus, lower efficacy) that might result in repeated episodes of short-term treatment interruption for management of side effects, as has been observed in A5221 and other TB treatment studies. For these reasons, the 85-90% virologic suppression rates reported at 48 weeks for studies in resource-rich settings may not be achievable in the context of active TB in resource-constrained settings.

Because the primary objective entails comparing virologic efficacy of Arm A versus Arm B and Arm C versus Arm A, we will have two hypothesis tests and will use an alpha-level of 0.025 for each test (thus, overall alpha-level = 0.05). If we assume the overall virologic efficacy of the double-dose LPV/r arm is 50%, and the standard LPV/r dosed arm coupled with RBT is 70% by 48 weeks (and 80-90% for LPV/r and RAL with RBT-based anti-TB treatment), 147 participants per arm will provide 90% power to detect a 20% difference in virologic response rates by 48 weeks between the double-dose LPV/r arm and the standard LPV/r plus RBT arm and adequate power for the comparison of the standard LPV/r plus RBT arm and adequate power for the comparison of the standard LPV/r plus RBT plus RAL arm compared to both other treatment arms. This assumes using a two-sample, two-sided 0.025-level asymptotically-normal binomial test. Participants lost to follow-up will be considered as failures. Participants determined to have RIF-resistant TB isolates after enrollment will be taken off study, referred to their local clinician or clinical facility to receive best available local standard of care, and will not be replaced. Assuming that 3% of participants will have RIF resistance at entry and be taken off study, we will need to adjust the sample size to require 152 participants per arm. Adjusting the sample size again by 3% for interim analyses requires 157 participants per arm. Based on these data and assumptions, the estimated overall sample size will be 471 participants.

9.4.3 Overall accrual

Accrual period 1 will open once at least 4-5 sites have all regulatory approvals completed and are ready to enroll participants immediately. The team estimates that these 4-5 sites should be able to accrue approximately 4-6 participants per month per site. As other sites begin accrual period 1, the team anticipates that accrual period 1 (n=60) should be completed within approximately 2-4 months.

Accrual period 2 will open once the accrual period 1 interim PK and safety analysis is completed. The team anticipates ultimately 15 sites each enrolling 4-5 participants per month. Thus, taking into account a slow, early accrual period, accrual period 2 (n=411) is anticipated to take approximately nine months.

Not accounting for the time during which accrual is suspended after the accrual period 1 closes and until the accrual period 1 interim PK and safety analysis is completed, the expected time to reach full accrual (n=471) is approximately 13 months.

9.5 Monitoring

9.5.1 Monitoring During the Dose-Finding Period in Accrual Period 1 Participants

Since initiation of ART may be delayed for up to 7-14 days after starting anti-TB therapy to allow participants sufficient time to assess tolerability of TB medications, PK assessments will be timed based on initiation of ART. Until the final SMC review during the dose-finding period in accrual period 1 participants,

the core team will closely monitor adverse events (AEs) and drug concentrations. The protocol data manager will provide unblinded detailed AE summary reports to the core team on a weekly basis. These reports will be discussed on weekly core team calls.

PK and Safety Criteria

- For RBT (Arms A and C), equivalence analyses will compare day 12 ± 2 (after initiation of ART) RBT 24-hour AUC and C_{max} with control data derived from prior PK studies, as determined by whether the 90% confidence intervals of the ratios of the RBT concentrations (when co-administered with LPV/r) relative to daily RBT concentrations in the absence of LPV/r are fully contained within the pre-specified NEB of 67%-150%. RBT concentrations in Arms A and C will be judged acceptable if equivalence is declared according to these PK parameters.
- For LPV in Arm B, the primary PK parameter is the day 12 ± 2 (after initiation of ART) C_{min} (C_{12}), and the acceptable lower limit value is ≥ 1 mg/L. LPV concentrations in Arm B will be judged acceptable if no more than three participants have a C_{min} < 1 mg/L.
- No more than three participants in any treatment arm experience a Grade 3 or Grade 4 AE attributable to study-provided medication by 28 days after ART initiation.
- No more than three participants in any treatment arm discontinue study-provided drug(s) for treatment-limiting toxicity or intolerance (such that PK assessments within the day 12 ± 2 (after initiation of ART) window cannot be completed).

The justification behind the RBT PK criterion is given in section 9.4.1. The other three criteria depend on the number of events (i.e., no more than 3). Based on Table 9.2 below, supposing the underlying rate is 10%, with X=3, there is an 87% chance of the study regimen in a particular arm going forward to accrual period 2.

Table 9.2. Probability (%) of Deciding the Criterion is Acceptable Based on a Range of Underlying Rates

Underlying Rate	Probability of X or Fewer Events in 20 Participants Given the Underlying Toxicity Rate:				
	X=1	X=2	X=3	X=4	X=5
0.05	0.736	0.925	0.984	0.997	0.999
0.10	0.392	0.677	*0.867*	0.957	0.989
0.15	0.176	0.405	0.648	0.830	0.933
0.20	0.069	0.206	0.411	0.630	0.804
0.25	0.024	0.091	0.225	0.415	0.617

The core team will also examine the LPV concentrations in Arms A and C in order to determine if RBT affects LPV concentrations. Any dose modifications of

LPV in Arms A and C will be the guided by the modifications proposed for Arm B (see Table 5.1 in section 5.1.1).

While the intent is to conduct the accrual period 1 PK and safety interim analysis after 54-60 accrual period 1 participants have completed 28 days of ART, available drug concentrations and safety data will be assessed weekly by the core team in an unblinded fashion as follows. Sites will be asked to batch PK samples and ship them every two weeks to the ACTG repository with immediate re-shipping to the PK laboratory. The PK laboratory will measure drug concentrations as soon as possible after receipt of shipments and will report results within 2 weeks of receiving the samples. The core team will monitor all available concentrations weekly for those results received to date. An early interim analysis of PK results and safety criteria will be evaluated after the first 10-12 participants in each treatment arm complete 28 days of ART and the day 12 ± 2 drug concentrations are available to assess any early trends suggesting lower or higher than expected concentrations of any study-provided drug(s). (Please see the Study Monitoring Plan for more details on how this early PK assessment will be completed.) If the early assessments indicate concentrations out of acceptable ranges for more than three participants in a treatment arm or trends related to safety concerns, an early ACTG Study Monitoring Committee (SMC) evaluation will be triggered. Any dose adjustments recommended by the SMC in consultation with the core team after this interim evaluation will be implemented for any new accrual period 1 participants enrolled as soon as possible after the review and for any already enrolled participants who have drug concentrations clearly out of acceptable ranges. However, the decision to revise dose schedules and treatment duration of participants with inadequate drug concentrations would be made based not just on the drug concentrations, but also on all available clinical data regarding TB and HIV endpoints. While true real-time reporting of drug concentrations will not be possible, individual participants identified, either during weekly core team monitoring or during any early SMC monitoring assessments, who have clearly inadequate concentrations of any study-provided drug would be reported to the sites as soon as that determination is made, and individual dose adjustments may be recommended according to the dose adjustment schedule in Table 5.1 in section 5.1.1 Accrual period 1 participants for whom early dose adjustments are recommended will have drug concentrations repeated 12 ± 2 days after initiating the adjusted dose. If no early PK or safety trends are identified during core team or early SMC monitoring, dosing will continue in participants enrolled during accrual period 1 as per assigned treatment arm.

NOTE: Any participants determined to have clearly inadequate RBT concentrations during the accrual period 1 PK evaluation should be monitored closely after dose adjustments for TB outcomes throughout the course of their TB treatment.

After 54-60 accrual period 1 participants have completed 28 days of ART and have drug concentrations available, the core team, together with the SMC, will review the results of the full accrual period 1 interim PK and safety analysis.

If the acceptable PK criteria for RBT and LPV are met, and if three or fewer participants in each treatment arm report ≥ Grade 3 AEs attributed to study-provided drugs(s) by 28 days of ART, and if three or fewer participants in each treatment arm discontinue study-provided drug(s) for treatment-limiting toxicity or intolerance (such that PK assessments cannot be completed), then accrual period 2 will open at the planned dose schedules of LPV/r and RBT.

If acceptable PK criteria are not met, or if more than three participants in one or more treatment arms report ≥ Grade 3 AEs attributed to study-provided drug(s) by 28 days of ART, or if more than three participants in one or more treatment arms discontinue study-provided drug(s) for treatment-limiting toxicity or intolerance (such that PK assessments cannot be completed), the SMC, in consultation with the core team, may elect to adjust the doses of RBT and/or LPV/r, as described above for all participants in the affected arm identified with inadequate study-provided drug concentrations. Repeat steady-state (day 12 ± 2 after dose adjustment) drug concentrations will be obtained for only the study arm participants in whom a dose was adjusted. A second accrual period 1 PK and safety interim analysis will be conducted after all accrual period 1 participants undergoing dose adjustment have completed 28 days of dose-adjusted treatment and when day 12 ± 2 post-dose adjustment levels are. This second analysis will include all accrual period 1 participants with available data.

The core team and SMC will then review the results of the second accrual period 1 interim PK and safety analysis. If acceptable PK criteria are not met, or if more than three participants in one or more treatment arms report ≥ Grade 3 AEs attributed to study-provided drug(s) by 28 days of ART, or if more than three participants in one or more treatment arms discontinue study-provided drug(s) for treatment-limiting toxicity or intolerance (such that PK assessments cannot be completed), then a decision will be made about whether to continue, modify (e.g., add additional participants in the accrual period 1 to assure adequate PK assessment are completed), or halt the treatment arm(s) in question, based on analysis of the nature of the AEs and reasons for study-provided drug discontinuation, and the degree of PK criteria failure. At this second interim review, if three or fewer participants report ≥ Grade 3 AEs attributed to study-provided drug(s), and if three or fewer participants discontinue study-provided drug(s) for treatment-limiting toxicity or intolerance (such that PK assessments cannot be completed), and if acceptable PK criteria are met for at least two of the treatment arms, the SMC, in consultation with the core team, will determine whether accrual period 2 will open.

If, based on the SMC's determination, unacceptable PK and/or safety criteria are met within two treatment arms, then further enrollment into the study may be stopped, and accrual period 1 participants will be managed according to best available local TB and ARV treatment. These participants will be followed off study drug for the remainder of study follow-up (up to 72 weeks).

If the SMC determines that accrual period 2 enrollment should proceed, accrual period 2 participants will then be randomized 1:1:1 to Arm A, B, or C (or with

equal probability to the remaining sample size in the remaining treatment arms) at the doses determined during the dose-finding period in accrual period 1 participants. No individual dose adjustments will be made based on drug concentrations for participants enrolled during the accrual period 2.

Based on this monitoring, if criteria are determined to be unacceptable in any treatment arm before the three accrual period 1 cohorts are fully enrolled, further accrual to the arm in question may be stopped.

9.5.2 Overall Study Monitoring

Early deaths, defined as those occurring within the first two months on study, will be monitored by the core team. The cumulative number of deaths during the first two months on study will be combined across the treatment arms and will be calculated on a monthly basis using a Kaplan-Meier estimator and reported to the core team. Should more than 15% of the number of participants enrolled die during the first two months on study, the team will request that the NIAID DSMB review the study for safety. This review will include both safety data and efficacy data through week 48, as available.

After the final SMC review of the PK and safety data during the dose-finding period in accrual period 1 participants, this study will be reviewed at least annually by the NIAID Data Safety and Monitoring Board (DSMB). This DSMB will receive a copy of the full accrual period 1 PK and safety interim analysis. For all annual reviews, the DSMB will be provided detailed information on safety (including mortality and regimen tolerability) and administrative aspects (accrual, baseline characteristics of participants, compliance with specimen storage, and retention). The first safety review will take place approximately one year after the final SMC review. The first efficacy review will be timed to occur while enrollment is ongoing so any required changes to the protocol may be made before accrual ceases. Thus, the first efficacy review will take place when approximately 25% of all participants have completed 48 weeks of follow-up. The timing of the first efficacy review will be decided at the first safety review. Efficacy reviews will employ group sequential monitoring of survival probabilities with boundaries defined by the Haybittle-Peto rule, with repeated 99.995% confidence intervals on the difference in proportions with HIV RNA level < 400 copies/mL at 48 weeks (Arm B versus Arm A and Arm B versus Arm C). For monitoring efficacy, there are three scenarios with respect to the confidence intervals:

1. The lower bound of the CI is >0%
2. The CI includes 0%
3. The upper bound of the CI is <0%.

If the lower bound of the 99.995% CI on the difference is greater than 0%, then the experimental Arm (A or C) is superior to Arm B as hypothesized and the team intends for the study to continue to full accrual and follow-up. If the 99.995% CI on the difference includes 0%, then superiority has not been demonstrated (yet) and the team intends to evaluate this finding in conjunction with predicted interval

plots[39] to evaluate the possibility of demonstrating superiority with trial continuation (e.g., evaluate futility) and the team intends for the study to continue to full accrual and follow-up since collecting secondary endpoints is desirable in this population regardless of possible futility. If the upper bound of the 99.995% CI on the difference is less than 0%, meaning Arm (A or C) is inferior, the team intends to evaluate this finding in the context of the toxicity and TB endpoints to determine whether the study or one of the treatment arms should be stopped while using predicted interval plots to evaluate the possibility of demonstrating superiority with trial continuation (e.g., evaluate futility).

The efficacy reviews will also include monitoring the TB cure rate. Since the team anticipates that Arm A will be non-inferior to Arm B and Arm C will be non-inferior to Arm B, there are two contrasts (Arm A vs. Arm B and Arm C vs. Arm B). A one-sided 97.5% CI for the difference in cure rates (i.e., A-B and C-B) will be calculated for each contrast and the lower bound of the interval will be compared to -10% (i.e., 10% is the non-inferiority margin). For interim monitoring of the TB cure rate, CIs for the difference in TB cure rates will be constructed as above. Again, there are three possible scenarios:

1. The lower bound of the CI is >0%
2. The lower bound of the CI is >-10% but <0%
3. The lower bound of the CI is <-10%.

If the lower bound of the CI is >0%, then the experimental arm (A or C) is superior to Arm B with respect to the TB cure rate and the team intends to evaluate this finding in the context of the HIV RNA and toxicity endpoints to determine whether the study should be stopped. If the lower bound of the CI is >-10% but <0%, then Arm A or C is non-inferior to Arm B and the team intends for the study to continue to full accrual and follow-up as designed. If the lower bound of the CI is <-10%, then non-inferiority has not been demonstrated (yet) and the team intends to evaluate this finding in conjunction with predicted interval plots to evaluate the likelihood of demonstrating non-inferiority with trial continuation (e.g., evaluate futility). The team discussed the possibility of a futility analysis and decided the study should continue to full accrual and follow-up as designed since collecting secondary endpoints is desirable in this population.

The number and timing of reviews will depend on the accrual rate and will be decided in conjunction with the DSMB.

Reports on adverse events pooled over arms, but summarized by accrual period, will be provided to the Division of AIDS Medical Officer every 6 months.

When approximately 25% of participants have completed 48 weeks of follow-up, overall sample size will be re-evaluated based on the current study rate of HIV virologic suppression in Arm B only. If the suppression rate is much higher than the hypothesized 50%, the protocol team will need to consider increasing the sample size in order to have sufficient power to detect smaller treatment differences (since the hypothesized 70% HIV virologic suppression in Arm A will

still hold). If the suppression rate is much lower than the hypothesized 50%, the protocol team discussed the possibility of doing a futility analysis but decided that collecting secondary endpoints is desirable in this population given that Arm B is standard of care in many resource-constrained settings. As the primary endpoint involves comparisons with Arm B, monitoring the Arm B (standard of care/control) rate alone will not affect the alpha level for the primary objective.

9.6 Analyses

9.6.1 Accrual Period 1 PK and Safety Interim Analyses

Interim PK and safety analyses will be conducted when the first 10-12 accrual period 1 participants per treatment arm have completed 28 days of ART and day 12 ± 2 (after initiation of ART) drug concentrations are available. These early assessments will try to identify any early trends suggesting lower or higher than expected concentrations of any study-provided drug(s). If early assessments indicate concentrations out of acceptable ranges for more than three participants in a treatment arm or trends related to safety criteria, an early ACTG Study Monitoring Committee (SMC) evaluation will be triggered.

The accrual period 1 PK and safety interim analysis will be conducted when 54-60 accrual period 1 participants have completed 28 days of ART and day 12 ± 2 (after initiation of ART) PK results are available. Study participants who discontinue study follow-up prior to day 28 will have their safety data included in the safety analysis. Furthermore, study participants who are lost-to-follow-up prior to day 28 will be considered failures in the safety analysis. Because these participants will be undergoing treatment for active TB, they will continue on their randomized therapy pending the results of this interim PK and safety analysis, but accrual will be suspended until the final accrual period 1 PK and safety interim analysis has been reviewed by the SMC.

For RBT (Arms A and C), an equivalence approach will be used to compare day 12 ± 2 (after initiation of ART) RBT 24-hour AUC and C_{max} with control data derived from prior PK studies, as determined by whether the 90% CI of the ratios of the RBT concentrations (when co-administered with LPV/r) relative to daily RBT concentrations in the absence of LPV/r are fully contained within the pre-specified NEB of 67%-150%. RBT concentrations in Arms A and C will be judged acceptable if equivalence is declared according to these PK parameters. (Please note: the control data derived from prior PK studies are described in section 10.3.)

For LPV (Arm B), the primary PK parameter is the C_{min} (trough or 12-hour post dose concentration), and the acceptable lower limit value is ≥ 1 mg/L. LPV/r concentrations in Arm B will be judged acceptable if no more than three participants have a C_{min}< 1 mg/L.

For all treatment arms, the safety endpoint is all ≥ Grade 3 AEs attributable to study-provided drug(s) by 28 days after ART initiation and all discontinuations of

study-provided drug(s) for treatment-limiting toxicity or intolerance (such that PK assessments within the days 12 ± 2 (after initiation of ART) window cannot be completed). The arms will be judged to pass the safety criteria if no more than three participants have reported ≥ Grade 3 AEs attributable to study-provided drug(s) by 28 days after ART initiation and if no more than 3 participants discontinued study-provided drug(s) for treatment-limiting toxicity or intolerance (such that PK assessments could not be completed).

9.6.2 Analysis of the Primary Objective

All participants enrolled into A5290 will be included in the analysis of all the overall study objectives regardless of any required dose adjustments for accrual period 1 participants. The protocol team discussed the effect of including participants enrolled during accrual period 1 who underwent dose adjustments in the final analysis of the primary endpoint. The protocol team acknowledges that it is possible that those enrolled during accrual period 1 who had low LPV concentrations and required a dose adjustment might have worse HIV viral load responses at week 48, or alternatively, those who underwent a dose adjustment of one or more study-provided drugs might have greater toxicity that could adversely affect adherence, early treatment discontinuation, and HIV viral load responses at week 48. There remains significant uncertainty around what the major drivers will be of the week 48 virologic outcomes in this setting, such that including all participants in an intent-to-treat analysis accounting for all factors that might have contributed to the endpoint, including low levels requiring dose adjustment, higher toxicity leading to non-adherence or dose interruptions, prolonged intensive TB treatment phase, etc. will be a part of the study analysis plan. The protocol team also acknowledges that it is possible that those enrolled during the accrual period 1 could be different than those enrolled during the accrual period 2. Besides seeking as homogeneous a population as possible, baseline tables of factors that could affect drug concentrations (e.g., sex, prior ART experience, body weight, etc.) will be summarized by accrual period.

The primary outcome variable will be the rates of virologic suppression at 48 weeks within each treatment arm. Participants lost-to-follow-up or without virologic data will be considered failures (i.e., not suppressed). The rate in the double-dose LPV/r arm will be separately compared to the standard dose LPV/r arms in two analyses. The rates between the two arms will be compared using an asymptotic normal binomial test (Arm A versus Arm B; Arm C versus Arm B).

9.6.3 Analysis of the Secondary Objectives

Secondary objectives and additional analyses will be evaluated with statistical techniques appropriate to the data type and specific question, including but not limited to Wilcoxon tests and logistic regression for dichotomous endpoints and Cox proportional hazards regression for time-to-event endpoints. Some analyses will consider change between baseline and target time points, such as weeks 24 and 48. Continuous variables may be dichotomized based on conventional cut points (e.g., median or CD4 <50). Except for select analyses of virologic

suppression that are reviewed by the DSMB, the alpha-level for these exploratory and hypothesis-generating analyses will not be adjusted for multiple testing.

10.0 PHARMACOLOGY PLAN

10.1 Pharmacology Objectives

10.1.1 To evaluate LPV PK characteristics (AUC, C_{max}, C_{min}) in study participants enrolled in Arms A, B, and C, accrual periods 1 and 2.

10.1.2 To evaluate the RBT PK characteristics (AUC, C_{max}, C_{min}) in study participants enrolled in Arms A and C, accrual periods 1 and 2.

10.1.3 To evaluate the RAL PK characteristics (AUC, C_{max}, C_{min}) in study participants enrolled in Arm C, accrual period 2.

10.2 Pharmacology Study Design for the Dose-Finding Study in Accrual Period 1 Participants

A5290 is a prospective evaluation in participants undergoing treatment for confirmed or probable TB and who require PI-based ART. The dose-finding study in accrual period 1 participants of A5290 is designed to evaluate two primary questions: 1) Is a RBT dose of 150 mg once daily when given with LPV/r adequate? and 2) Is an LPV/r dose of 800/200 mg BID when given with RIF adequate? Intensive PK evaluations will be performed on day 12 ± 2 (after initiation of ART) of concomitant TB and HIV therapy on all accrual period 1 participants.

10.2.1 Sample Size

The sample size for the dose-finding study in accrual period 1 participants will be 20 participants per treatment arm, randomized 1:1:1 for a total of 60 participants.

10.2.2 Sampling Strategy

Arms A and C, RBT pharmacokinetics. Plasma samples will be obtained just prior (pre-dose) and for 24 hours after administration of the morning dose of RBT at the following times: 2, 4, 5, 6, and 24 hours (next day) after the dose. Plasma will be frozen and batch shipped every 2 weeks to the ACTG repository, which will immediately re-ship them to the designated ACTG Pharmacology Support Laboratory (PSL). Refer to the A5290 LPC for additional instructions.

Arms A, B, and C LPV pharmacokinetics. Plasma samples will be obtained just prior to administration of the morning dose of LPV/r, and at the following times: 2, 4, 5, and 6 hours after the dose. A pre-dose concentration will be taken to be a 12-hour post dose concentration. Plasma will be frozen and batch shipped every 2 weeks to the ACTG repository, which will immediately re-ship them to the designated PSL. Refer to the A5290 LPC for additional instructions.

This sampling strategy requires that the once daily dose of RBT be taken with the morning dose of LPV/RTV for Arms A and C, and that the morning dose of RAL for Arm C be taken with the morning dose of LPV/RTV.

10.2.3 Medication Adherence

All participants should be counseled to ensure strict compliance with their TB and HIV medications. Participants should be queried as to the number of doses of TB and HIV medications not taken in the previous 3 days, and this number should be recorded on the CRF. The time and date of all doses of all TB and HIV medications taken the day prior to the PK study day (i.e., day 12 ± 2 of concomitant therapy) must be recorded on the CRF. The time of all doses of TB and HIV medications given on the day of the PK study should be recorded on the CRF. The PK study should not be performed if participants report missing any doses of any TB or HIV medication on the day prior to the PK study. If this situation occurs, the participant should be counseled about medication adherence, and a repeat PK study may be performed ≥ 5 days later, and no more than 12 days later than the originally scheduled PK study. If on this second PK day, the same participant should report missing any doses on the day prior to the PK study, the PK study should not be performed and this individual will not be considered eligible for the PK study.

A measured LPV pre-dose (or 12-hour post dose concentration) that is below the limit of quantitation (BLQ, < 20 ng/mL) will be taken as objective evidence for non-adherence. Any participant in Arm B of the accrual period 1 with a LPV C12 that is BLQ will not be considered for assessment of the accrual period 1 LPV PK passing criterion. Similarly, a measured RBT pre-dose concentration that is BLQ will be taken as objective evidence of non-adherence for participants in Arms A and C of the accrual period 1. Any participant with a RBT pre-dose concentration that is BLQ will not be included in evaluation of the accrual period 1 RBT PK passing criterion evaluation. Any participants determined to have clearly inadequate RBT concentrations during accrual period 1 evaluation should be monitored closely for TB outcomes throughout the course of their TB treatment.

10.2.4 RBT and LPV Quantitation

RBT and LPV concentrations will be determined in an ACTG CLIA-certified pharmacology laboratory. The goal is for RBT and LPV concentration information from the day 12 ± 2 PK study to be available for evaluation by the A5290 core team during the dose-finding period in accrual period 1 participants. Accrual period 1 participants for whom early dose adjustments are recommended will have drug concentrations repeated 12 ± 2 days after initiating the adjusted dose. If no early PK or safety trends are identified during core team or SMC monitoring, dosing will continue in participants enrolled during accrual period 1 as per assigned treatment arm.

10.3 Primary and Secondary Data, Modeling, and Data Analysis for the Dose-Finding Study in Accrual Period 1 Participants

The observed concentrations of RBT and LPV and the times post dose that these concentrations were obtained will be summarized.
The primary PK characteristics for RBT are: C_{max}, time to maximum plasma concentration (T_{max}), 24-hour post dose plasma concentration (C_{24h}), area under the concentration-time curve (AUC_{0-24}), and apparent oral clearance (CL/F). Standard noncompartmental techniques will be used to assess PK parameters. The AUC will be determined using the trapezoidal rule. C_{max} will be taken as the maximum observed concentration. T_{max} is the time at which C_{max} occurs. If more than one C_{max} and T_{max} occur in a given profile, the median of these values will be taken. The 24-hour post dose concentrations will be the directly measured value. Apparent oral clearance will be calculated as CL/F = dose/AUC_{0-24}. The elimination half-life is considered a secondary parameter and will be determined using regression analysis when possible.

The primary PK characteristics for LPV are: C_{max}, T_{max}, C_{12h}, AUC_{0-12}, and CL/F. Standard noncompartmental techniques will be used to assess PK parameters. The AUC will be determined using the trapezoidal rule. C_{max} will be taken as the maximum observed concentration. T_{max} is the time at which C_{max} occurs. If more than one C_{max} and T_{max} occur in a given profile, the median of these values will be taken. The pre-dose concentration will be taken as the 12-hour post dose concentration, and will be the directly measured value. CL/F will be calculated as CL/F = dose/AUC_{0-12}. The elimination half-life is considered a secondary parameter and will be determined using regression analysis when possible.

For RBT (Arms A and C), an equivalence approach will be used to compare RBT AUC and $\mathbf{C_{max}}$ with those of two control datasets from previous PK studies, as described below. This approach will evaluate whether the 90% CIs of the ratios of the RBT + LPV/r relative to daily RBT PK characteristics are fully contained within a specified no effect boundary. A no effect range of 0.67 to 1.50 will be used. Arms A and C will be judged to pass the RBT PK criterion if equivalence is declared.

For LPV in Arm B, the primary PK parameter is the $\mathbf{C_{min}}$ (trough or 12-hour post dose concentration), and the acceptable lower value is ≥ 1 mg/L. Arm B will be judged to pass the LPV $\mathbf{C_{min}}$ criterion if no more than three participants have a $\mathbf{C_{min}}$ < 1 mg/L.

RBT pharmacokinetics will be evaluated in Arms A and C of A5290 to investigate the question of whether a RBT dose of 150 mg once daily is adequate when given with LPV/r. An equivalence approach will be used to compare the RBT AUC and C_{max} with those of two historical controls. For this comparison, we have selected a recent publication describing a drug-drug interaction study of darunavir/ritonavir and RBT. In this healthy volunteer study, one arm contained RBT only given for 12 days at a dose of 300 mg once daily. The strength of this control dataset is the 300 mg RBT dose and an intensive pharmacokinetic study. The recommended dose reduction strategy for RBT to 150 mg once daily when given with a ritonavir-boosted PI is intended to approximate the exposure of the standard, 300 mg once daily dose. Thus, this selected control dataset provides the appropriate comparison for the 150 mg once daily dose of RBT in A5290

and the necessary PK data[43]. A second control dataset will also be examined. Some RBT PK data are now beginning to become available from studies conducted in HIV- and TB-infected persons. One study is that of Naiker, et al[40]. This study is another good comparison for A5290 because of similarities in patients, drugs and dosing regimens. However, because this study is only available in abstract form, has a limited sample size (n=16), and the majority of the available RBT PK data are from studies conducted in healthy volunteers, this study will not be used as the sole, control dataset but will be used as a supplementary control to the data from the darunavir/ritonavir and RBT PK study previously described.

10.4 Anticipated Outcomes for the Dose-Finding Study in Accrual Period 1 Participants

These data will provide guidance to the A5290 core team and SMC prior to the opening of accrual period 2 as to whether the current management approach for the drug-drug interaction between RBT and LPV/r (a RBT dose of 150 mg once daily) produces RBT plasma concentrations comparable to those of RBT 300 mg once daily without LPV/r observed in prior PK studies. Additionally, these accrual period 1 PK evaluations will provide guidance as to whether the management strategy for the drug-drug interaction between LPV/r and RIF (Arm B) of using double-dose LPV/r (i.e., 800/200 mg BID) achieves adequate LPV concentrations.

If the RBT PK data fall outside the effective ranges and the team determines that a dose adjustment is warranted, the team will consider two possibilities – an adjustment to 300 mg TIW as indicated in Table 5.1 or a change to 300 mg daily based on the RBT PK from the accrual period 1 dose-finding period and the assessment of which dose adjustment would best approximate the reference PK parameters for RBT 300 mg once daily given without LPV/r, as described above in section 10.3. If the team determines a RBT dose decrease is warranted, the dose will be reduced to the 150 mg TIW dose currently recommended. No substantive effect of RBT on LPV/r concentrations is expected based on prior PK data with this combination; however, if levels in the ranges noted for Arm B are observed in Arm A or Arm C, then dose adjustments will be the same as for Arm B.

10.5 Population Pharmacokinetic Study Design in Participants Enrolled During Accrual Period 2

10.5.1 Sample Size for Accrual Period 2

411 participants will be randomized 1:1:1 to Arm A, B, or C (or with equal probability to the remaining sample size in the remaining treatment arms) at the doses determined during the dose-finding period in accrual period 1 participants, and with a population PK approach in the accrual period 2.

10.5.2 Sampling Strategy – Specimen Collection

Blood samples for population PK studies will be collected at the week 2 and week 8 clinic visits. Two blood samples, if possible, will be collected at each of these clinic visits. These sampling strategies apply to all three arms of A5290.

Plasma will be frozen and periodically batch shipped to the ACTG repository, which will re-ship them to designated ACTG PSL. Refer to the A5290 LPC for additional instructions.

At week 2, the priority blood sample should be collected within a window of 6-12 hours after administration of a dose of LPV/r. This dose of LPV/r may be either the evening dose the day before the clinic visit or the morning dose the day of the clinic visit. The second blood sample may be collected at any time before or after this sample, as long as there is at least a 2-hour interval between sample collections.

At week 8, the first and priority blood sample should be collected within a window of 2 to 4 hours after administration of RBT. A second blood sample may be collected at any time after this blood sample, as long as there is at least a 2-hour interval between sample collections.

For participants in Arm C, samples obtained from this sampling schedule at weeks 2 and 8 will also be suitable for RAL.

10.5.3 Medication Adherence

All participants should be counseled to ensure strict compliance with their TB and HIV medications. Participants should be queried as to the number of doses of TB and HIV medications not taken in the previous 3 days, and this number should be recorded on the CRF. The time and date of all doses of all TB and HIV medications taken the day prior to the PK study day (i.e., weeks 2 and 8) must be recorded on the CRF. The time of all doses of TB and HIV medications given on the day of the PK study should be recorded on the CRF. The PK study should not be performed if participants report missing any doses of any TB or HIV medication on the day prior to the PK study. If this situation occurs, the participant should be counseled about medication adherence, and a repeat PK study may be performed ≥ 5 days later, and no more than 12 days later than the originally scheduled PK study. If on this second PK day, the same participant should report missing any doses on the day prior to the PK study, the PK study should not be performed and this individual will not be considered eligible for the PK study.

10.5.4 RBT, LPV, and RAL Quantitation

RBT, LPV, and RAL concentrations will be determined in an ACTG CLIA-certified pharmacology laboratory.

10.6 Primary and Secondary Data, Modeling, and Data Analysis for the Population PK Study in Accrual Period 2 Participants

For this analysis, the primary interest will be the PK characteristics of RBT and LPV; the PK characteristics of RAL are a secondary objective. PK characteristics will be evaluated using NONMEM version VI (GloboMax, Hanover, MD). NONMEM uses mixed effects

(random and fixed) regression to estimate population means and variances of PK parameters and identify factors, such as body weight, gender or concomitant drug that may influence these parameters. Base models will be developed using first-order conditional estimation with interaction. A stepwise procedure will be used to determine whether a one- or two-compartment model best fits the plasma data under the principle of parsimony. An exponential error distribution will be assumed for the description of both interpatient and intrapatient (residual) PK parameter variability. Residual error will be modeled as an additive plus proportional error model. If necessary, poorly identified structural parameters, such as the absorption rate constant, may be fixed to usual adult values. The following covariates will be collected at baseline or during follow-up visits: sex, age, weight, race, markers of renal function (estimate creatinine clearance), HIV regimen (e.g., Arm A, B, or C) and HIV response markers, and TB regimen and response markers. The influence of each covariate on the PK characteristics of RBT and LPV will be tested sequentially. At each step, the goodness of fit plots will also be evaluated.

At the end of the analysis, all covariates that show an influence on the parameters will be evaluated again by comparison of the full model (with all factors included) with a model from which each of the factors is deleted sequentially. For forward addition and backward elimination a decrease in objective function value by 3.84 ($p \leq 0.05$) and 6.64 ($p \leq 0.01$), respectively, would advocate sufficiently influential covariates. NONMEM uses extended least squares to calculate the objective function and the difference in the value of the objective function between models is approximately chi-squared distributed. A difference in objective function of greater than 6.6 is considered significant (6.6 corresponds to a chi-square for $p=0.01$ with 1 degree of freedom) when one parameter is added or the covariate (e.g., body weight) is replaced. This is analogous to the commonly used F test to select among regression models. The primary outcome of this analysis is to identify the model that best describes the plasma PK of RBT, LPV, and RAL and to investigate whether any of the covariates influence the PK of these ART and TB agents. The final model will include all significant covariates (if any) and the parameter estimates for all parameters together with the estimates of residual and interpatient variability. The accuracy and robustness of the final population model will be assessed using a bootstrap method. A secondary objective of this combined analysis will be to develop a linked population PK-PD model in NONMEM to evaluate potential relationships between these plasma concentrations/PK characteristics and therapeutic outcomes (i.e., response to HIV therapy and to TB treatment, and adverse events).

10.7 Anticipated Outcomes in the Population PK Study in Accrual Period 2 Participants

These population PK studies will provide data on whether the PK basis for the selection of the RBT and LPV dosing strategies during the dose-finding period in accrual period 1 participants can be confirmed in a much larger population of participants enrolled during accrual period 2. Additionally, these population PK data will provide information on the concentrations of RAL for participants in Arm C. The PK data for RBT, LPV, and RAL will be used to investigate exposure-response relationships among RBT, LPV, and RAL and measures of response to HIV therapy and TB therapy, and these data may fill gaps in our knowledge, for example, of whether threshold concentrations of RBT are associated with positive or negative (e.g., acquired rifamycin resistance) TB treatment outcomes.

11.0 DATA COLLECTION AND MONITORING AND ADVERSE EVENT REPORTING

11.1 Records to Be Kept

Case report forms (CRF) will be provided for each participant. Participants must not be identified by name on any CRFs. Participants will be identified by the patient identification number (PID) and study identification number (SID) provided by the ACTG DMC upon randomization.

11.2 Role of Data Management

11.2.1 Instructions concerning the recording of study data on CRFs will be provided by the ACTG DMC. Each CRS is responsible for keying the data in a timely fashion.

11.2.2 It is the responsibility of the ACTG DMC to assure the quality of computerized data for each ACTG study. This role extends from protocol development to generation of the final study databases.

11.3 Clinical Site Monitoring and Record Availability

11.3.1 Site monitors under contract to the NIAID will visit participating clinical research sites to review the individual participant records, including consent forms, CRFs, supporting data, laboratory specimen records, and medical records (physicians' progress notes, nurses' notes, individuals' hospital charts), to ensure protection of study participants, compliance with the protocol, and accuracy and completeness of records. The monitors also will inspect sites' regulatory files to ensure that regulatory requirements are being followed and sites' pharmacies to review product storage and management.

11.3.2 The site investigator will make study documents (e.g., consent forms, drug distribution forms, CRFs) and pertinent hospital or clinic records readily available for inspection by the local IRB/EC, the site monitors, the US FDA, the NIAID, the OHRP, the local governmental authorities, and the pharmaceutical supporter(s) or designee for confirmation of the study data.

11.4 Expedited Adverse Event Reporting to DAIDS

11.4.1 Adverse Event Reporting to DAIDS

The Serious Adverse Event (SAE) Reporting Category will be used for this study. Requirements, definitions, and methods for SAE and expedited reporting of Adverse Events (AEs) are outlined in Version 2.0 of DAIDS EAE Manual, which is available on the RSC website at http://rsc.tech-res.com/safetyandpharmacovigilance/.

The DAIDS Adverse Events Reporting System (DAERS) internet-based reporting system must be used for expedited AE reporting to DAIDS. In the event of system outages or technical difficulties, expedited AEs may be submitted via the DAIDS EAE Form. For questions about DAERS, please

contact DAIDS-ES at DAIDS-ESSupport@niaid.nih.gov. Site queries may also be sent from within the DAERS application itself.

Sites where DAERS has not been implemented will submit expedited AEs by documenting the information on the current DAIDS EAE Form. This form is available on the RSC website: http://rsc.tech-res.com/safetyandpharmacovigilance/. For questions about EAE reporting, please contact the RSC (DAIDSRSCSafetyOffice@tech-res.com).

11.4.2 Reporting Requirements for this Study

- The SAE Reporting Category, as defined in Version 2.0 of the DAIDS EAE Manual, will be used for this study.
- The study agents for which expedited reporting is required are: LPV/r, RTV, RBT, and RAL.
- As per the SAE and EAE Reporting Categories identified above, any of the following SAEs require expedited reporting regardless of relatedness or association with the study agents listed:

  - Results in death
  - Life-threatening
  - Requires inpatient hospitalization or prolongation of existing hospitalization
  - Results in persistent or significant disability/incapacity
  - Congenital anomaly/birth defects/fetal losses
  - Other important medical events (may not be immediately life-threatening or result in death or hospitalization but may jeopardize the participant or may require intervention to prevent one of the events listed above).

- In addition to the SAEs listed above, additional events required to be reported in an expedited manner for this protocol include the following:

  - Cancers with no other event, regardless of the association
  - All overdoses of study medications
  - IRIS events that are grade 3 or 4
  - All abnormal outcomes of pregnancies occurring at $\geq$ 20 weeks gestation.

11.4.3 Grading Severity of Events

The most current Division of AIDS Table for Grading the Severity of Adult and Pediatric Adverse Events (DAIDS AE Grading Table) is used and is available on the RSC website at http://rsc.tech-res.com/safetyandpharmacovigilance/.

11.4.4 Expedited AE Reporting Period

- The expedited AE reporting period for this study is as per the EAE manual.
- After the protocol-defined AE reporting period, unless otherwise noted, only suspected, unexpected serious adverse reactions (SUSARs), as defined in Version 2.0 of the EAE Manual, will be reported to DAIDS if the study staff become aware of the events on a passive basis (from publicly available information).

12.0 HUMAN PARTICIPANTS

12.1 Institutional Review Board (IRB) Review and Informed Consent

This protocol and the informed consent documents (Appendix I and Appendix II) and any subsequent modifications will be reviewed and approved by the IRB or ethics committee responsible for oversight of the study. A signed consent form will be obtained from the participant (or parent, legal guardian, or person with power of attorney for participants who cannot consent for themselves, such as those below the legal age of consent). The consent form will describe the purpose of the study, the procedures to be followed, and the risks and benefits of participation. A copy of the consent form will be given to the participant, parent, or legal guardian, and this fact will be documented in the participant's record.

12.2 Participant Confidentiality

All laboratory specimens, evaluation forms, reports, and other records that leave the site will be identified by coded number only to maintain participant confidentiality. All records will be kept locked. All computer entry and networking programs will be done with coded numbers only. Clinical information will not be released without written permission of the participant, except as necessary for monitoring by ACTG, IRB/EC, the US FDA, the NIAID, the OHRP, the local governmental authorities, or the pharmaceutical supporter(s) or designee.

12.3 Study Discontinuation

The study may be discontinued at any time by the ACTG, IRB/EC, the NIAID, the pharmaceutical supporter(s), the US FDA, the OHRP, or other government agencies as part of their duties to ensure that research participants are protected.

13.0 PUBLICATION OF RESEARCH FINDINGS

Publication of the results of this trial will be governed by ACTG policies. Any presentation, abstract, or manuscript will be made available for review by the pharmaceutical supporter(s) prior to submission.

14.0 BIOHAZARD CONTAINMENT

As the transmission of HIV and other blood-borne pathogens can occur through contact with contaminated needles, blood, and blood products, appropriate blood and secretion precautions will be employed by all personnel in the drawing of blood and shipping and handling of all specimens for this study, as currently recommended by the Centers for Disease Control and Prevention and the National Institutes of Health.

All dangerous goods materials, including diagnostic specimens and infectious substances, must be transported using packaging mandated by CFR 42 Part 72. Please refer to instructions detailed in the International Air Transport Association (IATA) Dangerous Goods Regulations.

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APPENDIX I

DIVISION OF AIDS
AIDS CLINICAL TRIALS GROUP (ACTG)
SAMPLE INFORMED CONSENT FOR ACCRUAL PERIOD 1 (1st ENROLLMENT PERIOD)

For protocol:
A Randomized, Phase 2b Study of a Double-Dose Lopinavir/Ritonavir-Based Antiretroviral Regimen with Rifampin-Based Tuberculosis Treatment versus a Standard-Dose Lopinavir/Ritonavir-Based Antiretroviral Regimen with Rifabutin-Based Tuberculosis Treatment with or without Raltegravir in HIV-1-Infected Persons Requiring Treatment for Active TB and HIV
A5290, FINAL Version 1.0, Dated 01/31/12

SHORT TITLE FOR THE STUDY: Rifampin-Based TB Treatment vs. Rifabutin-Based TB Treatment in HIV, A5290, FINAL Version 1.0

INTRODUCTION

You are being asked to take part in this research study because you are infected with HIV (the virus that causes AIDS), you are taking or planning to take an anti-HIV therapy (ART) regimen that contains a protease inhibitor drug (one of several different types of drugs used for treating HIV), and your doctor has determined that you may have tuberculosis (TB). This study is sponsored by the National Institutes of Health (NIH) in the United States (US). The doctor in charge of this study at this site is: (insert name of Principal Investigator). Before you decide if you want to be a part of this study, we want you to have information about the study.

This is a consent form. It gives you information about this study. The study staff will talk with you about this information. You are free to ask questions about this study at any time. If you agree to take part in this study, you will be asked to sign this consent form. You will get a copy to keep.

WHY IS THIS STUDY BEING DONE?

The current preferred treatment for people with TB and HIV starting their first anti-HIV treatment regimen contains efavirenz, an anti-HIV drug, called a non-nucleoside reverse transcriptase inhibitor (NNRTI). However, not all people with HIV-related TB can be treated with efavirenz, Some people cannot tolerate the side effects of efavirenz. Efavirenz also cannot be used in women who may be or may become pregnant. Some people may have been previously treated with efavirenz or other NNRTI anti-HIV drugs and may have developed resistance to NNRTI anti-HIV drugs, meaning the drugs are no longer working. In addition, the current standard treatment for TB includes rifampin, an anti-TB drug that can reduce the amount of certain anti-HIV drugs, particularly protease inhibitor drugs, in the blood to levels that are not able to treat HIV. For this reason, when protease inhibitor anti-HIV treatment is needed in people with TB and HIV, either a higher dose of the protease inhibitor or a different drug that works similarly to rifampin, called rifabutin, is sometimes used instead of rifampin. Even so, the doses of the

protease inhibitor or the rifabutin may need to be adjusted so the amounts in the blood are able to treat both HIV and TB. However, the most appropriate doses of protease inhibitors and of rifabutin have not been fully studied in people with TB and HIV. Therefore, treatment with protease inhibitors or alternative anti-HIV drugs may be necessary for people with HIV and TB. The purpose of this study is to find a safe treatment that contains either rifampin or rifabutin that works against TB in people who have HIV and are being treated with protease-inhibitor anti-HIV drugs. Another purpose of this study is to see how well people are able to take the TB treatment that includes a standard amount of rifampin with a double amount of lopinavir/ritonavir instead of the regular recommended amounts of lopinavir/ritonavir and rifabutin.

This study will enroll participants in two enrollment periods. The first part of this study (participants joining during the 1st enrollment period) will enroll 60 participants and is being performed to find out how protease inhibitors act together with certain anti-TB drugs in your body. If you join during the 1st enrollment period, you will have the amount of protease inhibitors and of certain anti-TB drugs measured in your blood to determine whether these amounts are safe enough or whether different doses of these drugs will be needed to continue with the second part of the study (participants joining during the 2nd enrollment period). If the amount of the protease inhibitor or the anti-TB drug called rifabutin are higher or lower than expected, some participants in the 1st enrollment period will have their doses of these drugs changed, and they might need to be continued on their assigned TB medications for a longer period of time to allow drug levels to be measured again. The results from the 1st enrollment period will be used to find a safe amount of study medications to use in the second period of the study (2nd enrollment period). The 2nd enrollment period of this study will enroll 411 additional participants and is being done to see how well the amount of the protease inhibitor and certain anti-TB drugs selected from the 1st enrollment period work to treat HIV and TB.

You are being asked to take part in 1st enrollment (the first part) of this study now and if the results show that a safe combination of study medications can be used together in people with HIV and TB, you will continue on study for a total of 72 weeks.

This study will compare three different combinations of both anti-HIV drugs and anti-TB drugs, as shown in Table 1 below. Each of the three drug combinations includes the protease inhibitor drug lopinavir/ritonavir.

Table 1. Drug Combinations

Group (Combination of Drugs)	HIV Drugs	TB Drugs
A	• lopinavir/ritonavir • two nucleoside analogue reverse transcriptase inhibitors (NRTIs)	• isoniazid • rifabutin • ethambutol • pyrazinamide • pyridoxine (vitamin B6)
B	• double-dose lopinavir/ritonavir • two NRTIs	• INH • rifampin • ethambutol • pyrazinamide • pyridoxine (vitamin B6)

Group (Combination of Drugs)	HIV Drugs	TB Drugs
C	• lopinavir/ritonavir • two NRTIs • raltegravir	• isoniazid • rifabutin • ethambutol • pyrazinamide • pyridoxine (vitamin B6)

If you decide to join the study, you will receive lopinavir/ritonavir (combined in a fixed dose tablet). You might also receive raltegravir, another anti-HIV drug in another class of HIV medications called an integrase inhibitor, if you are assigned to Group C. You will also be asked to take either rifabutin or rifampin during the study. Rifabutin will be given to you as part of the study, but rifampin will not be provided to you through the study. If you are assigned to a Group receiving rifampin, this will be provided to you by prescription locally together with your other TB medications.

Lopinavir/ritonavir and raltegravir are approved by the US Food and Drug Administration (FDA) for treating HIV. Rifampin is approved by the FDA for treating TB. Rifabutin is used as an alternative to rifampin in multiple-drug treatments for TB in people infected with HIV who are taking certain anti-HIV drugs that when used together with rifampin makes either the anti-HIV drug or rifampin not work effectively. Rifabutin is not approved by the FDA for treating TB.

WHAT DO I HAVE TO DO IF I AM IN THIS STUDY?

If you decide to join this study and enroll in the first part of this study (1st enrollment period), you will be required to be seen in the clinic about 14 times over 18 months. Most visits will take about one hour to complete. Sometimes, a study visit may take longer. The study staff should be able to tell you about how long each visit will take. You may need to come to the clinic for extra visits if you develop new symptoms of TB, side effects of your medication, or if you switch drugs. If the amounts of study medications in your blood measured are higher or lower than expected, you might have your dose of one or more study medications changed, and you may need to continue your TB medications for a longer duration, up to 8 more weeks, and to come in to the clinic for additional visits to measure amounts of study medications in your blood.

Screening Visit

After you have read and signed this consent form, you will have several tests done to make sure that you meet the requirements for joining the study.

- We will check to see if you have HIV. If there is no record, another HIV test will be done. You may have to sign a separate consent form before this is done. You will be told the results of the HIV test as soon as it is available. If the test results show that you are HIV-positive, the study staff will give you HIV counseling.
- You will be asked about information related to your TB infection. You may be asked to bring your medical records to the clinic at your next visit so the study doctor can review your test results and medications prescribed by your doctor from the TB clinic. If you will get TB treatment outside of the study clinic, you will be asked to bring your TB treatment records to all study visits.

- You will have a physical examination and will be asked questions about your health and about any medicines you have taken or are taking now.
- You will have a chest x-ray if you have not had one within the past 30 days.
- About 20 mL (about 1 ½ tablespoons) of blood will be drawn for routine lab tests, CD4/CD8 cell count (a test that shows how many infection-fighting cells you have in your blood), liver function tests, and HIV viral load (a test that shows how much HIV is in your blood).
- If you are a woman who is able to become pregnant, you will have a pregnancy test done. You will be asked to give a small urine or blood sample for the pregnancy test. You cannot enter the study if you are pregnant or breastfeeding.
- You will be asked whether you give permission, and if so, how you can be contacted in case you miss a visit or there are problems with your tests.

You will receive the results of the CD4/CD8 count, HIV viral load, and other blood tests as soon as they are available. If you have a pregnancy test, you will be told the result as soon as it is available.

<u>If you do not enroll into the study</u>
If you decide not to take part in this study or if you do not meet the eligibility requirements, we will still use some of your information collected during the screening visit. As part of this screening visit, demographic (for example, your age, gender, race), clinical (for example, disease condition, diagnosis), and laboratory (for example, routine lab tests, CD4/CD8 cell count, HIV viral load, and liver function tests) information is being collected from you. This information may be used by ACTG researchers to help determine whether there are patterns or common reasons why people do not join a study. The information may also help ACTG researchers understand more about HIV and TB treatment.

<u>Entry Visit</u>
If you are eligible and you agree to join the study, you will be assigned to one of three treatment groups that will include both anti-HIV therapy and treatment for TB. Your assignment is random (like the flip of a coin), and you will not be able to choose your group. The three groups are treatment Groups A, B and C, as listed in the table at the beginning of this form. Both you and your doctor will know which of the groups you are in (see Table 1 showing drug combinations A, B, and C). No matter which group you are in, you should continue to take your medicines according to your doctor's instructions. You will need to obtain some of your anti-HIV and anti-TB medicines by prescription from your doctor(s) or through your local TB or HIV clinic. The study staff will explain to you how you should obtain any required medicines that are not provided by the study.

At this visit, you will also have the following evaluations:
- You may be asked to provide some sputum (phlegm from your lungs) by coughing and then spitting into a cup; if you have trouble coughing, you may be asked to breathe a mist of saltwater through a tube or mask and then to spit into a cup. Your sputum will be tested to detect TB-like organisms. The test will see if TB can be grown in the laboratory from your sputum sample. We will also test your sputum to see if regular TB drugs work for you; a sample of your sputum will be saved for future testing for biomarkers of anti-TB drug activity.

- You will have a physical examination and will be asked questions about your health, about symptoms you may have related to TB, and about any changes in the medications you have been taking.
- About 20 mL (about 1 ½ tablespoons) of blood will be drawn for routine lab tests, HIV viral load, CD4/CD8 count, and liver function tests. The results of these tests will be provided to you and your doctor.
- If you are a woman who is able to become pregnant, you will have a pregnancy test done.
- You will be asked questions about how well you are taking your medicines.
- About 30 mL (about 2 tablespoons) of blood will be drawn and about 20 mL of urine will be obtained for future HIV tests and TB tests after the study is over.

Scheduled Clinic Visits

At each of the scheduled visits, you will have the following evaluations:

- You will have a physical examination and will be asked questions about your health and about any changes in the medicines you have been taking.
- If you are a woman who is able to become pregnant, you may have a pregnancy test done.

At some study visits you will also have one or more of the following evaluations:

- About 10 mL (about 2 teaspoons) of blood will be drawn for routine lab tests and liver function tests. The results of these tests will be provided to you and your doctor.
- You will have about 20 mL (about 1 ½ tablespoons) of blood drawn for HIV viral load and CD4/CD8 count. The results of these tests will be provided to you and your doctor.
- After about 8 weeks and 24 weeks on study, you will be asked to provide another sputum sample for a TB smear, culture and a test to see if regular TB drugs are still working for you. A portion of your sputum sample will be saved for future TB testing.
- After about 8 weeks, 48 weeks, and 72 weeks on study, you will have another chest x-ray.
- About 30 mL (about 2 tablespoons) of blood will be drawn and about 20 mL of urine will be obtained for future HIV tests and TB tests after the study is over.
- You will be asked how well you have taken the study medications and if you have missed any doses.
- If you will get TB treatment outside of the study clinic, you will be asked to bring your TB treatment records to all study visits.

For the day 12 visit, you will be asked to remain at the clinic for about 6 hours. You will have about an additional 20 mL (about 1 ½ tablespoons) of blood drawn for pharmacokinetic (PK) studies that will measure the amounts of lopinavir/ritonavir and rifampin or rifabutin in your blood. If you are taking drug combination A or C, you will have blood drawn just before you take your medicine, and at 2, 4, 5, and 6, and 24 hours (the next day) after you take your medicine. If you are taking drug combination B, you will have blood drawn in the morning, just before you take your medicine, and at 2, 4, 5, and 6 hours after you take your medicine. If the amounts of lopinavir/ritonavir and/or rifabutin in your blood are higher or lower than expected, your dose of lopinavir/ritonavir and/or rifabutin may be changed, and you will continue to be followed after you have started the new dose of your study medication(s). If your dose(s) of study medication(s) are changed, you may be asked to continue being followed for up to an additional 8 weeks on your TB medications, and some of the procedures described above will be repeated according to the same schedules.

You will be asked to take your drugs for HIV with a low fat meal. You will be asked to take your drugs for TB on an empty stomach.

Some of your blood will be stored (with usual protectors of identity) and used for immunologic and viral testing that is required for this study.

Other
Some of your blood that is left over after all required study testing is done may be stored with your permission (with usual protectors of identity) and used for ACTG-approved HIV-related or TB-related research.

Also, If you agree, about an extra 2 tablespoons of blood will be taken and stored (with usual protectors of identity), and may be used for future ACTG-approved HIV-related or TB-related research. Please indicate if you agree to this or not by initialing by the yes or no below.

_____ YES _____ NO

Urine and sputum samples will also be stored for future use and testing as part of the study.

HOW MANY PEOPLE WILL TAKE PART IN THIS STUDY?

About 60 people will take part in the first part (1st enrollment) of the study. An additional 411 people will take part in the second part (2nd enrollment) of the study.

HOW LONG WILL I BE IN THIS STUDY?

You will be in this study for about 72 weeks.

WHY WOULD THE DOCTOR TAKE ME OFF THIS STUDY EARLY?

The study doctor may need to take you off the study early without your permission if:

- the study is cancelled.
- a Data Safety Monitoring Board (DSMB) or Study Monitoring Committee (SMC) recommends that the study be stopped early (A DSMB or SMC is an outside group of experts who monitor the study.)
- you are not able to attend the study visits as required by the study

The study doctor may also need to take you off the study drug(s) without your permission if:

- continuing the study drug(s) may be harmful to you
- you need a treatment that you may not take while on the study
- you are not able to take the study drug(s) as required by the study

If you must stop taking the study drug(s) before the study is over, the study doctor may ask you to continue to be part of the study and return for some study visits and procedures.

If I have to permanently stop taking study-provided drugs, or once I leave the study, how would they be provided?

During the study:

If you must permanently stop taking study-provided drugs before your study participation is over, the study staff will discuss other options that may be of benefit to you.

After the study:

After you have finished your study participation, the study will not be able to continue to provide you with the drugs you received on the study. If continuing to take these or similar drugs would be of benefit to you, the study staff will discuss how you may be able to obtain them.

WHAT ARE THE RISKS OF THE STUDY?

Risks of 1st Enrollment Period

It is possible that you may not continue to have high enough levels of drugs in your blood and continue to take your assigned treatment regimen over time. If you are not able to maintain adequate levels of drugs in your blood, there is a risk that the drugs might not work as well against HIV or TB (in other words your symptoms or levels of HIV or TB might worsen) or that you might have more side effects of the medications. It is also possible that you may be asked to continue taking certain anti-TB drugs for a longer duration than is usually needed. This might be required if you need to have doses of your study drugs changed because you are not able to maintain adequate levels of certain drugs in your blood with your first assigned treatment regimen or because you have more severe TB and your doctor thinks longer anti-TB treatment is needed. Other risks include unknown side effects and your ability to take the different doses of lopinavir/ritonavir along with the anti-TB drugs. We will monitor your drug levels and any side effects, and report to your site any concerns as soon as the information is available.

Risks of CD4 Counts < 50 cells/µL

It is possible that you may have a CD4 cell (a type of white blood cell that is a measure of how well your immune system works when you are infected with HIV) count of less than 50 cells/µL in your blood at the time you enroll in this study. People with this CD4 cell count level are at increased risk of dying from their HIV or from TB. Research has shown that the risk of death might be decreased in some people with TB and HIV who have CD4 cell counts less than 50 cells/µL if anti-HIV drugs are started earlier after starting anti-TB treatment. Therefore, your doctor and the study team will work to get you started on your anti-HIV study medications as soon as possible after you have started your anti-TB medications. In addition, some studies have shown that some people with HIV and TB who have CD4 cell counts less than 50 cells/µL might have lower than expected amounts of anti-TB drugs in their blood during TB treatment. We will monitor your drug levels and any side effects and activity of your medications against TB and HIV, and report to your site any concerns as soon as the information is available.

Risks of Study Drugs

The drugs used in this study may have side effects, some of which are listed below. Please note that these lists do not include all the side effects seen with these drugs. These lists include the more serious or common side effects with a known or possible relationship. If you have questions concerning the additional study drug side effects please ask the medical staff at your site.

There is a risk of serious and/or life-threatening side effects when non-study medications are taken with the study drugs. For your safety, you must tell the study doctor or nurse about all medications you are taking before you start the study and also before starting any new medications while on the study. Also, you must tell the study doctor or nurse before enrolling in any other clinical trials while on this study.

Use of Combination Antiretroviral Drugs

Immune Reconstitution Syndrome: In some people with advanced HIV infection, signs and symptoms of inflammation from other infections may occur soon after anti-HIV treatment is started.

The use of strong anti-HIV drug combinations may be associated with an abnormal placement of body fat and wasting. Some of the body changes include:

- Increase in fat around the waist and stomach area
- Increase in fat on the back of the neck
- Thinning of the face, legs, and arms
- Breast enlargement

Use of Protease Inhibitors

The use of protease inhibitors may be related to the following:

- Increases in the amount of triglycerides and/or cholesterol in the blood
- Development of diabetes or the worsening of high blood sugar

There have been reports of increased bleeding in HIV-infected persons with hemophilia who were treated with protease inhibitors. It is not known if protease inhibitors were the cause of these bleeding episodes.

Lopinavir/Ritonavir (LPV/r)

The following serious side effects are associated with the use of LPV/r and some of these could occur more often or be more severe if the levels of LPV/r in your blood are higher than expected as a result of the doses used in this study:

- Abnormal heart rhythm and electrocardiogram (EKG) changes. These changes can lead to serious heart problems. Your risk for these problems may be higher if you:
    - Already have a history of abnormal heart rhythm or other types of heart disease
    - Take other medicines that can affect your heart rhythm while you take LPV/r

If you develop abnormal heart rhythm you may experience lightheadedness, fainting spells or an abnormal heart beat.

- Pancreatitis (inflammation of the pancreas), which may cause death. If you develop pancreatitis, you may have one or more of the following:
    - Stomach pain, nausea, vomiting or abnormal pancreatic function blood tests
    - Large increases in triglycerides and cholesterol in the blood
    - Liver problems and worsening liver disease, which may result in death. People with these conditions may have abnormal liver function blood tests. If you are developing liver problems, you may have one or more of the following: yellowing of the skin or whites of your eyes, dark urine, pain on the right side of your stomach, loss of appetite, upset stomach or vomiting, pale colored stools, itchy skin.
    - Rash, which could blister, and may be severe or life-threatening

Additional side effects may include:
- Abnormal bowel movements (stools), including loose or watery stools, upset stomach and stomach pain
- Feeling weak and tired
- Headache

Ritonavir (RTV)
The following side effects have been associated with the use of RTV and some of these could occur more often or be more severe if the levels of RTV in your blood are higher than expected as a result of the doses used in this study:

- Feeling weak and tired
- Stomach and bowel problems including abdominal pain, upset stomach, vomiting, abnormal stools, and loose or watery stools
- Loss of appetite
- Headache
- Dizziness
- Abnormal increases in triglycerides and cholesterol in blood
- Numbness and tingling in the arms, legs and around the mouth
- Rash
- Abnormal liver function blood tests which may be due to possible liver problems. Liver problems including cases of death have occurred in people taking RTV.
- A change in the sense of taste
- Pancreatitis, which may cause death. If you develop pancreatitis, you may have one or more of the following: stomach pain, nausea, and vomiting.
- Abnormal heart rhythm and EKG changes. If you develop abnormal heart rhythm you may experience lightheadedness, fainting spells or an abnormal heart beat.
- Allergic reactions that can be serious that may include symptoms like hives, trouble breathing and mild to severe skin rashes or reactions

Raltegravir (RAL)
The following side effects have been associated with the use of RAL:

- Upset stomach
- Headache
- Tiredness

- Weakness
- Trouble sleeping
- Rash, which can be severe
- Feeling anxious
- Depression, suicidal thoughts and actions
- Paranoia (an abnormal sense of fear)
- Low blood platelet count
- Muscle tenderness, weakness or injury which can be serious and lead to kidney damage

Severe and potentially life-threatening rash has been reported with the use of raltegravir. You should immediately contact the study staff if you develop rash. The study staff will ask you to immediately stop taking raltegravir and possibly other study drugs. If you develop a rash with any of the following side effects it may be a sign of a more serious reaction such as Stevens-Johnson syndrome, toxic epidermal necrolysis, or severe hypersensitivity: fever, generally ill feeling, extreme tiredness, muscle or joint aches, blisters, oral lesions, eye inflammation, facial swelling, swelling of the eyes, lips, mouth, breathing difficulty, and/or signs and symptoms of liver problems (yellowing of the skin or whites of the eyes, dark or tea colored urine, pale colored stools/bowel movements, nausea, vomiting, loss of appetite, or pain, aching or sensitivity on the right side below the ribs). If you develop a severe rash, you will be closely followed and appropriate therapy will be started.

Rifabutin (RBT)
The following side effects have been associated with the use of RBT and some of them could occur more often or be more severe if the levels of RBT in your blood are higher than expected as a result of the doses used in this study:

- Abnormal urine discoloration
- Digestive system side effects, including nausea, vomiting, indigestion, belching, and taste changes
- Abdominal pain
- Rash
- Fever
- Headache
- Diarrhea, including diarrhea due to Clostridium difficile, a bacteria that interferes with the normal function of the bowel
- Loss of appetite
- Jaundice (yellow skin)
- Muscle pain
- Insomnia
- Fatigue
- Decrease in neutrophil count (a type of white blood cell which aids in fighting some types of infections, or modest suppression of the total white blood cell counts
- Decrease in platelet counts (a component in blood that helps blood to clot)
- Eye inflammation (uveitis) which can produce eye redness, pain, sensitivity, and decreased vision
- Decrease in effectiveness of oral contraceptives (birth control pills) or Norplant
- Decrease in methadone effectiveness

- Urine, sweat, sputum, tears, and skin may be colored brown-orange

Rifampin (RIF)
RIF is commonly prescribed in the United States and worldwide to treat TB, and is generally well tolerated. RIF turns urine, sweat, sputum, and tears a red-orange color. The red-orange color in urine may stain undergarments. Soft contact lenses may be permanently stained by RIF. Less common side effects include:

- Hepatitis (inflammation of the liver). This has caused deaths in patients who already had liver disease or who were taking other drugs that were toxic to the liver.
- Increases in liver function tests
- Increased bilirubin, which may be associated with yellowing of the eyes
- Upset stomach, vomiting, and diarrhea
- Abdominal pain
- Reduced levels of some of your body's hormones
- Reduced levels of calcium and phosphate in blood
- Decreased effectiveness of hormonal contraceptives and many other medications
- Reduced blood cell counts
- Headache
- Rash and itching
- Fever
- Kidney failure

Risks of Drawing Blood
Taking blood may cause discomfort, bleeding, and bruising where the blood is drawn. Occasionally, there is swelling in the area where the needle enters the body and there is a small risk of infection. There is also a risk of lightheadedness, fainting, and blood clots.

Risks of Chest X-rays
You will be exposed to very small amounts of radiation. The scanning machines will not cause any physical discomfort other than from having to be still for the test.

Other Risks
By taking part in this study, it is possible that it might be difficult for you to keep your HIV status secret from people close to you. This may lead to unwelcome discussions about or reactions to your HIV status. Please talk with the clinic staff if you have any concerns about this.

You may also have some anxiety or depression regarding the study testing, treatment, and results.

ARE THERE RISKS RELATED TO PREGNANCY?

It is not known if some of the drug combinations in this study would cause harm to unborn babies. If you are having sex that could lead to pregnancy, you must agree not to become pregnant, or, if you are a man, you must agree not to attempt to make a woman pregnant or participate in sperm donation.

Because of the risk involved, you and your partner must use two methods of birth control that you discuss with the study staff. You must continue to use both methods until at least 6 weeks after you stop the study drug. If you are having sex that could lead to pregnancy, and do not use 2 types birth control, your study doctor will take you off of the study drugs. You may choose two of the birth control methods listed below (one type should be a barrier method):

- condoms (barrier method), with or without a spermicidal agent
- a diaphragm or cervical cap (barrier method) with spermicide
- an IUD (intrauterine device)
- hormone-based contraceptive

If you are pregnant, you cannot enter the study. If you think you may be pregnant at any time during the study, tell your study staff right away. The study staff will ask you to stay in the study so that you can be evaluated. If you become pregnant during the study, after discussion with your doctor and the study team, you may choose to continue your study-provided anti-HIV or anti-TB medications during your pregnancy and you may choose to breastfeed your baby. If you choose to continue your assigned study medications you will be asked to continue on the study and information about the outcome of your pregnancy will be recorded in study records. If you choose not to continue study-provided anti-HIV or anti-TB medications, you and your doctor will decide on the best available HIV and/or TB medications for you to use, but the study staff will ask you to stay in the study so that you can continue to be evaluated. If you leave the study before the end of your pregnancy, the study staff will request permission for you to be contacted at the end of your pregnancy so that you and your baby can be evaluated.

If you become pregnant while you are in the study, your pregnancy will be reported to the Antiretroviral Pregnancy Registry.

ARE THERE BENEFITS TO TAKING PART IN THIS STUDY?

If you take part in this study, there may be a direct benefit to you, but no guarantee can be made. It is also possible that you may receive no benefit from being in this study. Information learned from this study may help others who have HIV and TB.

WHAT OTHER CHOICES DO I HAVE BESIDES THIS STUDY?

Instead of being in this study you have the choice of:

- treatment with prescription drugs available to you
- treatment with experimental drugs, if you qualify
- no treatment

Please talk to your doctor about these and other choices available to you. Your doctor will explain the risks and benefits of these choices.

WHAT ABOUT CONFIDENTIALITY?

The study team will provide you with an identification number. The identification number (not your name or other information that could be used to identify you) will be used for laboratory tests or blood work stored for testing in future studies. Your medical records and the list of names, addresses, and identification numbers will be kept in a locked room. Only the study staff will have the keys. No publication of this study will use your name or identify you personally.

Efforts will be made to keep your personal information confidential. We cannot guarantee absolute confidentiality. Your personal information may be disclosed if required by law. Your records may be reviewed by the ACTG, US Office for Human Resource Protections (OHRP), FDA, the drug companies supporting the study, the local institutional review board or ethics committee (insert name of site IRB/EC), National Institutes of Health (NIH), your country's national health agency or other regulatory authorities, study staff, and study monitors.

A description of this clinical trial will be available on ClinicalTrials.gov, as required by US law. This website will not include information that can identify you. At most, the web site will include a summary of the results. You can search this Web site at any time.

WHAT ARE THE COSTS TO ME?

There will be no cost to you for study-related visits, study-provided drugs, physical examinations, laboratory tests, or other procedures. You, your insurance company, or your health care system, may need to pay the cost of anti-HIV and anti-TB drugs not provided by the study. *(Delete references to insurance company or health care system if not applicable at site.)* In some cases, it is possible that your insurance company will not pay for these costs because you are taking part in a research study.

The study will not provide prenatal care, postpartum testing, or care to infants born to women who become pregnant while on study.

WILL I RECEIVE ANY PAYMENT?

Insert site-specific information on compensation to study participants.

WHAT HAPPENS IF I AM INJURED?

If you are injured as a result of being in this study, you will be given immediate treatment for your injuries. The cost for this treatment will be charged to you or your insurance company. There is no program for compensation either through this institution or the US NIH. You will not be giving up any of your legal rights by signing this consent form.

WHAT ARE MY RIGHTS AS A RESEARCH SUBJECT?

Taking part in this study is completely voluntary. You may choose not to take part in this study or leave this study at any time. Your decision will not have any impact on your participation in other studies conducted by NIH and will not result in any penalty or loss of benefits to which you are otherwise entitled.

We will tell you about new information from this or other studies that may affect your health, welfare, or willingness to stay in this study. If you want the results of the study, let the study staff know.

WHAT DO I DO IF I HAVE QUESTIONS OR PROBLEMS?

For questions about this study or a research-related injury, contact:

- name of the investigator or other study staff
- telephone number of above

For questions about your rights as a research subject, contact:

- name or title of person on the Institutional Review Board (IRB) or other organization appropriate for the site
- telephone number of above

SIGNATURE PAGE

If you have read this consent form (or had it explained to you), all your questions have been answered and you agree to take part in this study, please sign your name below.

_____	_____
Participant's Name (print)	Participant's Signature and Date
_____	_____
Participant's Legal Guardian (print) (As appropriate)	Legal Guardian's Signature and Date
_____	_____
Study Staff Conducting Consent Discussion (print)	Study Staff's Signature and Date
_____	_____
Witness's Name (print) (As appropriate)	Witness's Signature and Date

APPENDIX II

DIVISION OF AIDS
AIDS CLINICAL TRIALS GROUP (ACTG)
SAMPLE INFORMED CONSENT FOR ACCRUAL PERIOD 2 (2nd ENROLLMENT PERIOD)

For protocol:
A Randomized, Phase 2b Study of a Double-Dose Lopinavir/Ritonavir-Based Antiretroviral Regimen with Rifampin-Based Tuberculosis Treatment versus a Standard-Dose Lopinavir/Ritonavir-Based Antiretroviral Regimen with Rifabutin-Based Tuberculosis Treatment with or without Raltegravir in HIV-1-Infected Persons Requiring Treatment for Active TB and HIV
A5290, FINAL Version 1.0, Dated 01/31/12

SHORT TITLE FOR THE STUDY: Rifampin-Based TB Treatment vs. Rifabutin-Based TB Treatment in HIV, A5290, FINAL Version 1.0

INTRODUCTION

You are being asked to take part in this research study because you are infected with HIV (the virus that causes AIDS), you are taking or planning to take an anti-HIV therapy (ART) regimen that contains a protease inhibitor drug (one of several different types of drugs used for treating HIV), and your doctor has determined that you may have tuberculosis (TB). This study is sponsored by the National Institutes of Health (NIH) in the United States (U.S). The doctor in charge of this study at this site is: (insert name of Principal Investigator). Before you decide if you want to be a part of this study, we want you to have information about the study.

This is a consent form. It gives you information about this study. The study staff will talk with you about this information. You are free to ask questions about this study at any time. If you agree to take part in this study, you will be asked to sign this consent form. You will get a copy to keep.

WHY IS THIS STUDY BEING DONE?

The current preferred treatment for people with TB and HIV starting their first anti-HIV treatment regimen contains efavirenz, an anti-HIV drug called a non-nucleoside reverse transcriptase inhibitor (NNRTI). However, not all people with HIV-related TB can be treated with efavirenz. Some people cannot tolerate the side effects of EFV. EFV also cannot be used in women who may be or may become pregnant. Some people may have been previously treated with efavirenz or other NNRTI anti-HIV drugs and may have developed resistance to NNRTI anti-HIV drugs, meaning the drugs are no longer working. Therefore, treatment with protease inhibitors or alternative anti-HIV drugs may be necessary for people with HIV and TB. In addition, the current standard treatment for TB includes rifampin, an anti-TB drug that can reduce the amount of certain anti-HIV drugs, particularly protease inhibitor drugs, in the blood to levels that are not able to treat HIV. For this reason, when protease inhibitor anti-HIV treatment is needed in people with TB and HIV, either a higher dose of the protease inhibitor or a different drug that

works similarly to rifampin called rifabutin is sometimes used instead of rifampin. Even so, the doses of the protease inhibitor or the rifabutin may need to be adjusted so the amounts in the blood are able to treat both HIV and TB. However, the most appropriate doses of protease inhibitors and of rifampin or rifabutin to use have not been fully studied in people with TB and HIV. Therefore, the purpose of this study is to find a safe treatment that contains either rifampin or rifabutin that works against TB in people who have HIV and are being treated with protease-inhibitor anti-HIV drugs. Another purpose of this study is to see how well people are able to take the TB treatment that includes a standard amount of rifampin with a double amount of lopinavir/ritonavir instead of the regular recommended amounts of lopinavir/ritonavir and rifabutin.

This study will enroll participants in two enrollment periods. The first part of this study (participants joining during the 1st enrollment period) will enroll 60 participants and is being performed to find out how protease inhibitor anti-HIV drugs act together with certain anti-TB drugs in the body. Participants enrolled in the 1st enrollment period will have the amount of protease inhibitors and of certain anti-TB drugs measured in the blood to determine whether these amounts are safe enough or whether different doses of these drugs will be needed to continue with the second part of the study (participants joining during the 2nd enrollment period). The results from the 1st enrollment period will be used to find a safe amount of study medications to use in the 2nd enrollment period of the study (participants joining during the 2nd enrollment period). The 2nd enrollment period of this study will enroll 411 additional participants and is being done to see how well the amount of the protease inhibitor and certain anti-TB drugs selected from the 1st enrollment period work to treat HIV and TB.

You are being asked to take part in the 2nd enrollment (the second part) of this study now. This study will compare three different combinations of both anti-HIV drugs and anti-TB drugs, as shown in Table 1 below. Each of the three drug combinations includes the protease inhibitor drug lopinavir/ritonavir.

Table 1. Drug Combinations

Group (Combination of Drugs)	HIV Drugs	TB Drugs
A	• lopinavir/ritonavir • two nucleoside analogue reverse transcriptase inhibitors (NRTIs)	• isoniazid • rifabutin • ethambutol • pyrazinamide • pyridoxine (vitamin B6)
B	• double-dose lopinavir/ritonavir • two NRTIs	• isoniazid • rifampin • ethambutol • pyrazinamide • pyridoxine (vitamin B6)
C	• lopinavir/ritonavir • two NRTIs • raltegravir	• INH • RBT • EMB • pyrazinamide • pyridoxine (vitamin B6)

If you decide to join the study, you will receive lopinavir/ritonavir (combined in a fixed dose tablet). You might also receive raltegravir, another anti-HIV drug in another class of HIV medications called an integrase inhibitor, if you are assigned to Group C. You will also be asked to take either rifabutin or rifampin during the study. Rifabutin will be given to you as part of the study, but rifampin will not be provided to you through the study. If you are assigned to a Group receiving rifampin, this will be provided to you by prescription locally together with your other TB medications.

Lopinavir/ritonavir and raltegravir are approved by the US Food and Drug Administration (FDA) for treating HIV. Rifampin is approved by the FDA for treating TB. Rifabutin is used as an alternative to rifampin in multiple-drug treatments for TB in people infected with HIV who are taking certain anti-HIV drugs when used together with rifampin makes either the anti-HIV drug or rifampin not work effectively. Rifabutin is not approved by the FDA for treating TB.

WHAT DO I HAVE TO DO IF I AM IN THIS STUDY?

If you decide to join this study and enroll into the second part of this study (2nd enrollment period), you will be required to be seen in the clinic about 14 times over 18 months. Most visits will take about one hour to complete. Sometimes, a study visit may take longer. The study staff should be able to tell you about how long each visit will take. You may need to come to the clinic for extra visits if you develop new symptoms of TB, side effects of your medication, or if you switch drugs.

Screening Visit

After you have read and signed this consent form, you will have several tests done to make sure that you meet the requirements for joining the study.

- We will check to see if you have HIV. If there is no record, another HIV test will be done. You may have to sign a separate consent form before this is done. You will be told the results of the HIV test as soon as it is available. If the test results show that you are HIV-positive, the study staff will give you HIV counseling.
- You will be asked about information related to your TB infection. You may be asked to bring your medical records to the clinic at your next visit so the study doctor can review your test results and medications prescribed by your doctor from the TB clinic. If you will get TB treatment outside of the study clinic, you will be asked to bring your TB treatment records to all study visits.
- You will have a physical examination and will be asked questions about your health and about any medicines you have taken or are taking now.
- You will have a chest x-ray if you have not had one within the past 30 days.
- About 20 mL (about 1 ½ tablespoons) of blood will be drawn for routine lab tests, CD4/CD8 cell count (a test that shows how many infection-fighting cells you have in your blood), liver function tests, and HIV viral load (a test that shows how much HIV is in your blood). The results of these tests will be provided to you and your doctor.
- If you are a woman who is able to become pregnant, you will have a pregnancy test done. You will be asked to give a small urine or blood sample for the pregnancy test. You cannot enter the study if you are pregnant or breastfeeding.
- You will be asked whether you give permission, and if so, how you can be contacted in case you miss a visit or there are problems with your tests.

You will receive the results of the CD4/CD8 count, HIV viral load, and other blood tests as soon as they are available. If you have a pregnancy test, you will be told the result as soon as it is available.

If you do not enroll into the study

If you decide not to take part in this study or if you do not meet the eligibility requirements, we will still use some of your information collected during the screening visit. As part of this screening visit, demographic (for example, your age, gender, race), clinical (for example, disease condition, diagnosis), and laboratory (for example, routine lab tests, CD4/CD8 cell count, HIV viral load, and liver function tests) information is being collected from you. This information may be used by ACTG researchers to help determine whether there are patterns or common reasons why people do not join a study. The information may also help ACTG researchers understand more about HIV and TB treatment.

Entry Visit

If you are eligible and you agree to join the study, you will be assigned to one of three treatment groups that will include both anti-HIV therapy and treatment for TB. Your assignment is random (like the flip of a coin), and you will not be able to choose your group. The three groups are treatment Groups A, B and C, as listed in the table at the beginning of this form. Both you and your doctor will know which of the groups you are in (see Table 1 showing drug combinations A, B, and C). No matter which group you are in, you should continue to take your medicines according to your doctor's instructions. You will need to obtain some of your anti-HIV and anti-TB medicines by prescription from your doctor(s) or through your local TB or HIV clinic. The study staff will explain to you how you should obtain any required medicines that are not provided by the study.

At this visit, you will also have the following evaluations:

- You may be asked to provide some sputum (phlegm from your lungs) by coughing and then spitting into a cup; if you have trouble coughing, you may be asked to breathe a mist of saltwater through a tube or mask and then to spit into a cup. Your sputum will be tested to detect TB-like organisms. The test will see if TB can be grown in the laboratory from your sputum sample. We will also test your sputum to see if regular TB drugs work for you; a sample of your sputum will be saved for future testing for biomarkers of anti-TB drug activity.
- You will have a physical examination and will be asked questions about your health, about symptoms you may have related to TB, and about any changes in the medications you have been taking.
- About 20 mL (about 1 ½ tablespoons) of blood will be drawn for routine lab tests, HIV viral load, CD4/CD8 count, and liver function tests. The results of these tests will be provided to you and your doctor.
- If you are a woman who is able to become pregnant, you will have a pregnancy test done.
- You will be asked questions about how well you are taking your medicines.
- About 30 mL (about 2 tablespoons) of blood will be drawn and about 20 mL of urine will be obtained for future HIV tests and TB tests after the study is over.

Scheduled Clinic Visits

At each of the scheduled visits, you will have the following evaluations:

- You will have a physical examination and will be asked questions about your health and about any changes in the medicines you have been taking.

- If you are a woman who is able to become pregnant, you may have a pregnancy test done.

At some study visits you will also have one or more of the following evaluations:

- About 10 mL (about 2 teaspoons) of blood will be drawn for routine lab tests and liver function tests. The results of these tests will be provided to you and your doctor.
- You will have about 20 mL (about 1 ½ tablespoons) of blood drawn for HIV viral load and CD4/CD8 count. The results of these tests will be provided to you and your doctor.
- After about 8 weeks and 24 weeks on study, you will be asked to provide another sputum sample for a TB smear, culture and a test to see if regular TB drugs are still working for you. A portion of your sputum sample will be saved for future TB testing.
- After about 8 weeks, 48 weeks, and 72 weeks on study, you will have another chest x-ray.
- About 30 mL (about 2 tablespoons) of blood will be drawn and about 20 mL of urine will be obtained for future HIV tests and TB tests after the study is over.
- You will be asked how well you have taken the study medications and if you have missed any doses.
- If you will get TB treatment outside of the study clinic, you will be asked to bring your TB treatment records to all study visits.

For the week 2 and week 8 visits, you will have blood drawn for pharmacokinetic (PK) studies that will measure the amounts of lopinavir/ritonavir and rifampin or rifabutin in your blood. At week 2, you will have blood collected within 6-12 hours after you receive lopinavir/ritonavir. You may receive this dose of lopinavir/ritonavir either the night before your clinic visit or the morning of the clinic visit. A second blood sample will be collected at any time before or after this sample, as long as there is at least a 2 hour time period between the two blood draws. At week 8, you will have blood drawn 2 to 4 hours after you take rifabutin. After at least 2 hours have passed, you will have a second blood draw. If you are in Group C, you will also have these blood draws done.

You will be asked to take your drugs for HIV with a low fat meal. You will be asked to take your drugs for TB on an empty stomach.

Some of your blood will be stored (with usual protectors of identity) and used for immunologic and viral testing that is required for this study.

<u>Other</u>
Some of your blood that is left over after all required study testing is done may be stored with your permission (with usual protectors of identity) and used for ACTG-approved HIV-related or TB-related research.

If you agree, about an extra 2 tablespoons (10 mL) of blood will be taken. This blood will be stored (with usual protectors of identity) and may be used for future ACTG-approved HIV-related or TB-related research. Please indicate if you agree to this or not by initialing by the yes or no below.

_____ YES _____ NO

Urine and sputum samples will also be stored for future use and testing as part of the study.

HOW MANY PEOPLE WILL TAKE PART IN THIS STUDY?

About 411 people will take part in this part of the study (2nd enrollment period). About 60 people will take part in the first part (1st enrollment period) of the study.

HOW LONG WILL I BE IN THIS STUDY?

You will be in this study for about 72 weeks.

WHY WOULD THE DOCTOR TAKE ME OFF THIS STUDY EARLY?

The study doctor may need to take you off the study early without your permission if:

- the study is cancelled.
- a Data Safety Monitoring Board (DSMB) or Study Monitoring Committee (SMC) recommends that the study be stopped early (A DSMB or SMC is an outside group of experts who monitor the study.)
- you are not able to attend the study visits as required by the study

The study doctor may also need to take you off the study drug(s) without your permission if:

- continuing the study drug(s) may be harmful to you
- you need a treatment that you may not take while on the study
- you are not able to take the study drug(s) as required by the study

If you must stop taking the study drug(s) before the study is over, the study doctor may ask you to continue to be part of the study and return for some study visits and procedures.

<u>If I have to permanently stop taking study-provided drugs, or once I leave the study, how would they be provided?</u>

During the study:

If you must permanently stop taking study-provided drugs before your study participation is over, the study staff will discuss other options that may be of benefit to you.

After the study:

After you have finished your study participation, the study will not be able to continue to provide you with the drugs you received on the study. If continuing to take these or similar drugs would be of benefit to you, the study staff will discuss how you may be able to obtain them.

WHAT ARE THE RISKS OF THE STUDY?

The drugs used in this study may have side effects, some of which are listed below. Please note that these lists do not include all the side effects seen with these drugs. These lists include the more serious or common side effects with a known or possible relationship. If you have questions concerning the additional study drug side effects please ask the medical staff at your site.

There is a risk of serious and/or life-threatening side effects when non-study medications are taken with the study drugs. For your safety, you must tell the study doctor or nurse about all medications you are taking before you start the study and also before starting any new medications while on the study. Also, you must tell the study doctor or nurse before enrolling in any other clinical trials while on this study.

Risks of 2nd Enrollment Period

It is possible that the amounts of anti-HIV and anti-TB drugs that you receive together will result in amounts of anti-TB drugs in your blood that may not be able to cure TB. It is also possible that the combination will result in amounts of anti-HIV drugs that may not be as able to treat your HIV as what could be prescribed for you outside of the study.

Risks of CD4 Counts < 50 cells/µL

It is possible that you may have a CD4 cell (a type of white blood cell that is a measure of how well your immune system works when you are infected with HIV) count of less than 50 cells/µL in your blood at the time you enroll in this study. People with this CD4 cell count level are at increased risk of dying from their HIV or from TB. Research has shown that the risk of death might be decreased in some people with TB and HIV who have CD4 cell counts less than 50 cells/µL if anti-HIV drugs are started earlier after starting anti-TB treatment. Therefore, your doctor and the study team will work to get you started on your anti-HIV study medications as soon as possible after you have started your anti-TB medications. In addition, some studies have shown that some people with HIV and TB who have CD4 cell counts less than 50 cells/µL might have lower than expected amounts of anti-TB drugs in their blood during TB treatment. We will monitor your drug levels and any side effects and activity of your medications against TB and HIV, and report to your site any concerns as soon as the information is available.

Use of Combination Antiretroviral Drugs

Immune Reconstitution Syndrome: In some people with advanced HIV infection, signs and symptoms of inflammation from other infections may occur soon after anti-HIV treatment is started.

The use of strong anti-HIV drug combinations may be associated with an abnormal placement of body fat and wasting. Some of the body changes include:

- Increase in fat around the waist and stomach area
- Increase in fat on the back of the neck
- Thinning of the face, legs, and arms
- Breast enlargement

Use of Protease Inhibitors
The use of protease inhibitors may be related to the following:

- Increases in the amount of triglycerides and/or cholesterol in the blood
- Development of diabetes or the worsening of high blood sugar

There have been reports of increased bleeding in HIV-infected persons with hemophilia who were treated with protease inhibitors. It is not known if protease inhibitors were the cause of these bleeding episodes.

Lopinavir/Ritonavir
The following serious side effects are associated with the use of lopinavir/ritonavir:

- Abnormal heart rhythm and electrocardiogram (EKG) changes. These changes can lead to serious heart problems. Your risk for these problems may be higher if you:
    - Already have a history of abnormal heart rhythm or other types of heart disease
    - Take other medicines that can affect your heart rhythm while you take lopinavir/ritonavir

If you develop abnormal heart rhythm you may experience lightheadedness, fainting spells or an abnormal heart beat.

- Pancreatitis (inflammation of the pancreas), which may cause death. If you develop pancreatitis, you may have one or more of the following:
    - Stomach pain, nausea, vomiting or abnormal pancreatic function blood tests
    - Large increases in triglycerides and cholesterol in the blood
    - Liver problems and worsening liver disease, which may result in death. People with these conditions may have abnormal liver function blood tests. If you are developing liver problems, you may have one or more of the following: yellowing of the skin or whites of your eyes, dark urine, pain on the right side of your stomach, loss of appetite, upset stomach or vomiting, pale colored stools, itchy skin.
    - Rash, which could blister, and may be severe or life-threatening

Additional side effects may include:

- Abnormal bowel movements (stools), including loose or watery stools, upset stomach and stomach pain
- Feeling weak and tired
- Headache

Ritonavir (RTV)
The following side effects have been associated with the use of RTV:

- Feeling weak and tired
- Stomach and bowel problems including abdominal pain, upset stomach, vomiting, abnormal stools, and loose or watery stools
- Loss of appetite
- Headache
- Dizziness

- Abnormal increases in triglycerides and cholesterol in blood
- Numbness and tingling in the arms, legs and around the mouth
- Rash
- Abnormal liver function blood tests which may be due to possible liver problems. Liver problems including cases of death have occurred in people taking RTV.
- A change in the sense of taste
- Pancreatitis, which may cause death. If you develop pancreatitis, you may have one or more of the following: stomach pain, nausea, and vomiting.
- Abnormal heart rhythm and EKG changes. If you develop abnormal heart rhythm you may experience lightheadedness, fainting spells or an abnormal heart beat.
- Allergic reactions that can be serious that may include symptoms like hives, trouble breathing and mild to severe skin rashes or reactions

Raltegravir
The following side effects have been associated with the use of raltegravir:

- Upset stomach
- Headache
- Tiredness
- Weakness
- Trouble sleeping
- Rash, which can be severe
- Feeling anxious
- Depression, suicidal thoughts and actions
- Paranoia (an abnormal sense of fear)
- Low blood platelet count
- Muscle tenderness, weakness or injury which can be serious and lead to kidney damage

Severe and potentially life-threatening rash has been reported with the use of raltegravir. You should immediately contact the study staff if you develop rash. The study staff will ask you to immediately stop taking raltegravir and possibly other study drugs. If you develop a rash with any of the following side effects it may be a sign of a more serious reaction such as Stevens-Johnson syndrome, toxic epidermal necrolysis, or severe hypersensitivity: fever, generally ill feeling, extreme tiredness, muscle or joint aches, blisters, oral lesions, eye inflammation, facial swelling, swelling of the eyes, lips, mouth, breathing difficulty, and/or signs and symptoms of liver problems (yellowing of the skin or whites of the eyes, dark or tea colored urine, pale colored stools/bowel movements, nausea, vomiting, loss of appetite, or pain, aching or sensitivity on the right side below the ribs). If you develop a severe rash, you will be closely followed and appropriate therapy will be started.

Rifabutin
The following side effects have been associated with the use of rifabutin:

- Abnormal urine discoloration
- Digestive system side effects, including nausea, vomiting, indigestion, belching, and taste changes
- Abdominal pain

- Rash
- Fever
- Headache
- Diarrhea, including diarrhea due to Clostridium difficile, a bacteria that interferes with the normal function of the bowel
- Loss of appetite
- Jaundice (yellow skin)
- Muscle pain
- Insomnia
- Fatigue
- Decrease in neutrophil count (a type of white blood cell which aids in fighting some types of infections, or modest suppression of the total white blood cell counts
- Decrease in platelet counts (a component in blood that helps blood to clot)
- Eye inflammation (uveitis) which can produce eye redness, pain, sensitivity, and decreased vision
- Decrease in effectiveness of oral contraceptives (birth control pills) or Norplant
- Decrease in methadone effectiveness
- Urine, sweat, sputum, tears, and skin may be colored brown-orange

Rifampin

Rifampin is commonly prescribed in the United States and worldwide to treat TB, and is generally well tolerated. RIF turns urine, sweat, sputum, and tears a red-orange color. The red-orange color in urine may stain undergarments. Soft contact lenses may be permanently stained by rifampin. Less common side effects include:

- Hepatitis (inflammation of the liver). This has caused deaths in patients who already had liver disease or who were taking other drugs that were toxic to the liver.
- Increases in liver function tests
- Increased bilirubin, which may be associated with yellowing of the eyes
- Upset stomach, vomiting, and diarrhea
- Abdominal pain
- Reduced levels of some of your body's hormones
- Reduced levels of calcium and phosphate in blood
- Decreased effectiveness of hormonal contraceptives and many other medications
- Reduced blood cell counts
- Headache
- Rash and itching
- Fever
- Kidney failure

Risks of Drawing Blood

Taking blood may cause discomfort, bleeding, and bruising where the blood is drawn. Occasionally, there is swelling in the area where the needle enters the body and there is a small risk of infection. There is also a risk of lightheadedness, fainting, and blood clots.

Risks of Chest X-rays
You will be exposed to very small amounts of radiation. The scanning machines will not cause any physical discomfort other than from having to be still for the test.

Other Risks
By taking part in this study, it is possible that it might be difficult for you to keep your HIV status secret from people close to you. This may lead to unwelcome discussions about or reactions to your HIV status. Please talk with the clinic staff if you have any concerns about this.

You may also have some anxiety or depression regarding the study testing, treatment, and results.

ARE THERE RISKS RELATED TO PREGNANCY?

It is not known if some of the drug combinations in this study would cause harm to unborn babies. If you are having sex that could lead to pregnancy, you must agree not to become pregnant, or, if you are a man, you must agree not to attempt to make a woman pregnant or participate in sperm donation.

Because of the risk involved, you and your partner must use two methods of birth control that you discuss with the study staff. You must continue to use both methods until at least 6 weeks after you stop the study drug. If you are having sex that could lead to pregnancy, and do not use 2 types birth control, your study doctor will take you off of the study drugs. You may choose two of the birth control methods listed below (one type should be a barrier method):

- condoms (barrier method), with or without a spermicidal agent
- a diaphragm or cervical cap (barrier method) with spermicide
- an IUD (intrauterine device).
- hormone-based contraceptive.

If you are pregnant, you cannot enter the study. If you think you may be pregnant at any time during the study, tell your study staff right away. The study staff will ask you to stay in the study so that you can be evaluated. If you become pregnant during the study, after discussion with your doctor and the study team, you may choose to continue your study-provided anti-HIV or anti-TB medications during your pregnancy and you may choose to breastfeed your baby. If you choose to continue your assigned study medications you will be asked to continue on the study and information about the outcome of your pregnancy will be recorded in study records. If you choose not to continue study-provided anti-HIV or anti-TB medications, you and your doctor will decide on the best available HIV and TB medications for you to use, but the study staff will ask you to stay in the study so that you can continue to be evaluated. If you leave the study before the end of your pregnancy, the study staff will request permission for you to be contacted at the end of your pregnancy so that you and your baby can be evaluated.
If you become pregnant while you are in the study, your pregnancy will be reported to the Antiretroviral Pregnancy Registry.

ARE THERE BENEFITS TO TAKING PART IN THIS STUDY?

If you take part in this study, there may be a direct benefit to you, but no guarantee can be made. It is also possible that you may receive no benefit from being in this study. Information learned from this study may help others who have HIV and TB.

WHAT OTHER CHOICES DO I HAVE BESIDES THIS STUDY?

Instead of being in this study you have the choice of:

- treatment with prescription drugs available to you
- treatment with experimental drugs, if you qualify
- no treatment

Please talk to your doctor about these and other choices available to you. Your doctor will explain the risks and benefits of these choices.

WHAT ABOUT CONFIDENTIALITY?

The study team will provide you with an identification number. The identification number (not your name or other information that could be used to identify you) will be used for laboratory tests or blood work stored for testing in future studies. Your medical records and the list of names, addresses, and identification numbers will be kept in a locked room. Only the study staff will have the keys. No publication of this study will use your name or identify you personally.

Efforts will be made to keep your personal information confidential. We cannot guarantee absolute confidentiality. Your personal information may be disclosed if required by law. Your records may be reviewed by the ACTG, US Office for Human Resource Protections (OHRP), FDA, the drug companies supporting the study, the local institutional review board or ethics committee (insert name of site IRB/EC), NIH, your country's national health agency or other regulatory authorities, study staff, and study monitors.

A description of this clinical trial will be available on ClinicalTrials.gov, as required by US law. This website will not include information that can identify you. At most, the web site will include a summary of the results. You can search this Web site at any time.

WHAT ARE THE COSTS TO ME?

There will be no cost to you for study-related visits, study-provided drugs, physical examinations, laboratory tests, or other procedures. You, your insurance company, or your health care system, may need to pay the cost of anti-HIV and anti-TB drugs not provided by the study. *(Delete references to insurance company or health care system if not applicable at site.)* In some cases, it is possible that your insurance company will not pay for these costs because you are taking part in a research study.

The study will not provide prenatal care, postpartum testing, or care to infants born to women who become pregnant while on study.

WILL I RECEIVE ANY PAYMENT?

Insert site-specific information on compensation to study participants.

WHAT HAPPENS IF I AM INJURED?

If you are injured as a result of being in this study, you will be given immediate treatment for your injuries. The cost for this treatment will be charged to you or your insurance company. There is no program for compensation either through this institution or the US NIH. You will not be giving up any of your legal rights by signing this consent form.

WHAT ARE MY RIGHTS AS A RESEARCH SUBJECT?

Taking part in this study is completely voluntary. You may choose not to take part in this study or leave this study at any time. Your decision will not have any impact on your participation in other studies conducted by NIH and will not result in any penalty or loss of benefits to which you are otherwise entitled.

We will tell you about new information from this or other studies that may affect your health, welfare, or willingness to stay in this study. If you want the results of the study, let the study staff know.

WHAT DO I DO IF I HAVE QUESTIONS OR PROBLEMS?

For questions about this study or a research-related injury, contact:

- name of the investigator or other study staff
- telephone number of above

For questions about your rights as a research subject, contact:

- name or title of person on the Institutional Review Board (IRB) or other organization appropriate for the site
- telephone number of above

SIGNATURE PAGE

If you have read this consent form (or had it explained to you), all your questions have been answered and you agree to take part in this study, please sign your name below.

_____	_____
Participant's Name (print)	Participant's Signature and Date
_____	_____
Participant's Legal Guardian (print) (As appropriate)	Legal Guardian's Signature and Date
_____	_____
Study Staff Conducting Consent Discussion (print)	Study Staff's Signature and Date
_____	_____
Witness's Name (print) (As appropriate)	Witness's Signature and Date