

A5279

**Phase III Clinical Trial of Ultra-Short-Course Rifapentine/Isoniazid for the
Prevention of Active Tuberculosis in HIV-Infected Individuals with Latent
Tuberculosis Infection**

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

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and Infectious Diseases**

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STUDY MANAGEMENT

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Protocol e-mail Group

Sites planning to register 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.protA5279 e-mail group. Include the protocol number in the email subject line.

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

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For questions concerning entry criteria, toxicity management, concomitant medications, and coenrollment, contact the protocol Co-Chairs/Vice Chair. Send an e-mail message to actg.coreA5279@fstrf.org (ATTN: Richard Chaisson, MD; Susan Swindells, MBBS; Amita Gupta, MD, MHS). Include the protocol number, patient identification number (PID), and a brief relevant history.

Laboratory

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Data Management

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

- For transfers, reference the Patient Transfer from Site to Site SOP 119, and contact Ann Walawander, MA directly.
- For other questions, send an e-mail message to actg.coreA5279@fstrf.org (ATTN: Ann Walawander, MA).
- Include the protocol number, PID, and a detailed question.

Randomization/Participant Registration

For randomization/participant registration questions or problems and study identification number (SID) lists.

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

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- or call (716) 834-0900 x7302.

Protocol Document Questions

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STUDY MANAGEMENT (Cont'd)

Copies of the Protocol

To request hard copies of the protocol, send a message to ACTGNCC@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

To request copies of product package inserts, contact the DAIDS Regulatory Support Center (RSC):

- Send an e-mail message to 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 Product

For questions or problems regarding study product, dose, supplies, records, and returns, contact **Katherine Shin, PharmD**, Protocol Pharmacist:

- Send an e-mail message to kashin@niaid.nih.gov
- or call (301) 594-1517.

IND (Investigational New Drug) Number or Questions

For any questions about the IND, contact the DAIDS RSC:

- Send an e-mail message to Regulatory@tech-res.com
- or call (301) 897-1706.

Study Product Orders

Call the Clinical Research Products Management Center at (301) 294-0741.

Expedited Adverse Event (EAE) Reporting/Questions

To report an EAE or for questions related to EAE reporting, contact DAIDS through the RSC Safety Office:

- Send an e-mail message to 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.coreA5279@fstrf.org

Protocol-Specific Web Page

Additional information about the study may be found on the A5279 protocol-specific web page (PSWP).

GLOSSARY OF TERMS

AE	Adverse Event
ALT	Alanine Aminotransferase
ANC	Absolute Neutrophil Count
ART	Antiretroviral Therapy
AST	Aspartate Aminotransferase
ATS	American Thoracic Society
AUC	Area under the Concentration-Time Curve
BCG	Bacille Calmette-Guerin (TB vaccine)
CDC	Centers for Disease Control and Prevention
CFU	Colony-forming Units
CI	Confidence Interval
COD	Cause of Death
CLIA	Clinical Laboratory Improvement Amendments
CMV	Cytomegalovirus
CRF	Case Report Form
CRPMC	Clinical Research Products Management Center
CRS	Clinical Research Site
CSS	Community Scientific Subcommittee
DAERS	DAIDS Adverse Event Reporting System
DAIDS	Division of AIDS
DMC	Data Management Center
DOT	Directly Observed Therapy
DSMB	Data and Safety Monitoring Board
EAE	Expedited Adverse Event
EC	Ethics Committee
E/CIA	Enzyme or chemiluminescence
EMB	Ethambutol
EFV	Efavirenz
FDA	Food and Drug Administration
HBM	Human Biological Materials
IATA	International Air Transport Association
ICF	Informed Consent Form
ICH	International Conference on Harmonisation
IDSA	Infectious Diseases Society of America
IGRA	Interferon Gamma Release Assay
IND	Investigational New Drug
INH	Isoniazid
IPT	INH Preventive Therapy
IRB	Institutional Review Board
ITT	Intention-to-Treat
LTBI	Latent Tuberculosis Infection
LFU	Loss to Follow-Up
MAC	<i>Mycobacterium Avium</i> Complex
MDR TB	Multi-Drug-Resistant Tuberculosis
MTB	<i>Mycobacterium tuberculosis</i>
NIAID	National Institute of Allergy and Infectious Diseases

GLOSSARY OF TERMS (Cont'd)

NNRTI	Non-Nucleoside Reverse Transcriptase Inhibitor
NRTI	Nucleoside Reverse Transcriptase Inhibitor
NVP	Nevirapine
NWCS	New Work Concept Sheet
OHRP	Office for Human Research Protections
PBMC	Peripheral Blood Mononuclear Cell
PD	Pharmacodynamic
PI	Protease Inhibitor
PID	Patient Identification Number
PK	Pharmacokinetic
PPD	Purified Protein Derivative
PRO	Protocol Registration Office
PSWP	Protocol-Specific Web Page
PY	Person-Year
PZA	Pyrazinamide
RE	Regulatory Entity
RFB	Rifabutin
RIF	Rifampin
RPT	Rifapentine
RR	Relative Risk
RSC	Regulatory Support Center
SAE	Serious Adverse Event
SGOT	Serum Glutamic Oxaloacetic Transaminase
SGPT	Serum Glutamic Pyruvic Transaminase
SID	Study Identification Number
SOC	Standard of Care
SUSAR	Suspected Unexpected Serious Adverse Reaction
TB	Tuberculosis
TBTC	Tuberculosis Trials Consortium
TST	Tuberculin Skin Test
ULN	Upper Limit of Normal
U.S.	United States
WHO	World Health Organization
XDR TB	Extensively Drug-Resistant Tuberculosis

SCHEMA

A5279

Phase III Clinical Trial of Ultra-Short-Course Rifapentine/Isoniazid for the Prevention of Active Tuberculosis in HIV-Infected Individuals with Latent Tuberculosis Infection

<u>DESIGN</u>	This study is a multicenter, randomized, open-label, phase III clinical trial comparing a 4-week daily rifapentine (RPT)/isoniazid (INH) regimen to a standard 9-month daily INH regimen for the prevention of tuberculosis (TB) in HIV-infected participants without evidence of active TB. The primary objective will be efficacy of TB prevention. The study will also assess safety and tolerability of the regimens, adherence to the treatments, and patterns of antibiotic resistance among <i>Mycobacterium tuberculosis</i> (MTB) isolates in participants who fail on these prophylactic regimens.
<u>DURATION</u>	Each participant will be followed for 3 years (156 weeks) after the last participant is enrolled.
<u>SAMPLE SIZE</u>	3000 participants
<u>POPULATION</u>	<p>HIV-1 infected men and women ≥ 13 years old and ≥ 30 kg without evidence of active TB who:</p> <ol style="list-style-type: none"> 1. Have tuberculin skin test (TST) reactivity ≥ 5 mm or a positive interferon gamma release assay (IGRA), OR 2. Live in high TB burden areas, defined as areas with an estimated or reported TB prevalence of 60/100,000, according to the WHO or national or local health authorities. (Please refer to the A5279 protocol-specific web page [PSWP] for the WHO link to TB prevalence information by country. The protocol core team [actg.corea5279@fstrf.org] should be consulted if a site has data to suggest that the local TB burden differs significantly from the WHO country estimates and, therefore, should be considered in the application of this inclusion criterion.) <p>If taking antiretroviral therapy (ART) at study entry, only approved nucleoside reverse transcriptase inhibitors (NRTIs) with efavirenz (EFV) or nevirapine (NVP) for at least 4 weeks are permitted. A list of approved antiretroviral drugs is located on the A5279 PSWP. Participants on NVP must be dosed at 200 mg twice daily (BID).</p> <p>NVP trough levels will be evaluated in the first 90 participants in Arm A who are receiving NVP at entry and who meet other criteria in section 10.0, after which enrollment for participants on NVP may be temporarily halted. NVP pharmacokinetic (PK) data will be evaluated to determine whether standard NVP dosing results in adequate PK drug exposure in the presence of RPT treatment. If the A5279 team</p>

SCHEMA (Cont'd)

determines that concomitant dosing of NVP and RPT results in adequate drug exposure, the study may continue enrollment of participants receiving NVP.

EFV concentrations and pharmacogenetics will be evaluated in the first 90 participants who enroll in Arm B under Version 2.0 who are receiving EFV at entry and who meet other criteria in section 10.0. Additionally, under Version 2.0, EFV concentrations and pharmacogenetics will be evaluated in an additional 30 participants from Arm A who will undergo PK sampling at weeks 0, 2, 4, and 16.

NOTE: Participants randomized to Arm A may initiate any ART regimen after completing 4 weeks of RPT/INH. Participants randomized to Arm B may initiate any ART regimen after study entry.

STRATIFICATION Participants will be stratified based on (1) **the most recent CD4+ cell count obtained within 180 days prior to entry** (<100, 100-250, and >250 cells/mm³) and (2) ART use at entry (Yes/No).

REGIMEN Participants will be randomized within strata in a 1:1 ratio to receive either:

Arm A: 4-week daily regimen of weight-based RPT and INH, plus pyridoxine (vitamin B₆)

OR

Arm B: 9-month (36-week) daily INH regimen, plus pyridoxine (vitamin B₆)

1.0 HYPOTHESIS AND STUDY OBJECTIVES

1.1 Hypothesis

Ultra-short-course (4-week) daily rifapentine (RPT)/isoniazid (INH) is not inferior to a standard 9-month (36-week) daily INH regimen for the prevention of tuberculosis (TB) in HIV-infected individuals.

1.2 Primary Objective

To compare the efficacy of a 4-week daily regimen of weight-based RPT/INH to a standard 9-month (36 week) daily INH regimen for TB prevention in HIV-infected individuals.

1.3 Secondary Objectives

1.3.1 To compare safety and tolerability of the regimens

1.3.2 To compare overall and non-TB mortality rates among participants receiving the two regimens

1.3.3 To compare adherence rates in the two regimens

1.3.4 To investigate patterns of antibiotic resistance among *Mycobacterium tuberculosis* (MTB) isolates in participants failing prophylaxis

1.4 Supportive/Exploratory Objectives

The following objectives will be defined in detail in separate analysis plans.

1.4.1 To inform public health policy by comparing estimated costs and cost-effectiveness of the two regimens in various populations

1.4.2 To investigate the effect of RPT/**INH** on efavirenz (EFV) and nevirapine (NVP) plasma concentrations

1.4.3 To describe exposure-outcome relationships among EFV and NVP pharmacokinetic (PK) parameters and virologic failure, and safety and tolerance related to EFV and NVP

1.4.4 To investigate relationships among genetic characteristics of drug metabolizing enzymes and drug transporters and the PK characteristics of EFV, NVP, and RPT.

1.4.5 To determine the PK characteristics of EFV and its 7-OH-EFV and 8-OH-EFV metabolites when given in combination with RPT+INH (Arm A) and when given with INH alone (Arm B).

1.4.6 To compare EFV PK data obtained from combination therapy with RPT+INH and INH alone with a control group consisting of a set of plasma samples with participants receiving ART containing EFV but not RPT or INH, which will be collected from individuals in Arm A who have completed RPT/INH therapy and have allowed for a washout period.

2.0 INTRODUCTION

2.1 Background

The World Health Organization (WHO) estimates that in 2009, the last full year for which data collection is complete, there were 9.4 million new incident cases of TB, and 1.68 million deaths [1]. Among new incident cases of TB, 1.1 million were HIV-coinfected, and 35% of TB deaths were among HIV-coinfected individuals. In Africa, where AIDS is the leading cause of death (COD) from any disease, TB is the leading AIDS-related opportunistic infection [2]. South Africa has the highest national HIV burden in the world, with an estimated 1 of every 6 of the world's cases occurring there; South Africa also has the second highest estimated TB incidence rate per capita globally [3].

INH Treatment of Latent TB Infection (LTBI)

INH has been the cornerstone of treatment for LTBI to prevent active TB for more than 30 years; the first report of successful prevention of TB with INH was published in 1956 [4, 5]. In placebo-controlled trials of INH treatment of LTBI in persons in contact with persons with active TB who converted their tuberculin skin tests (TST) from negative to positive, the rate of developing active TB in the placebo groups was 12.9 cases/1000 person-years (PY) in the first year of follow-up, and 1.6 cases/1000 PY in the subsequent 7 years of follow-up [6]. Other placebo-controlled studies have further elucidated the background rates of developing active TB. Among British schoolchildren enrolled in a vaccine trial, placebo recipients who converted their TST from negative to positive during follow-up, the incidence of TB in the 15 years of follow-up was 4.7%, with the highest risk in the first 3 years after TST conversion [7]. Numerous randomized, placebo-controlled studies of the efficacy of INH given for 12 months were conducted in the 1950s and 1960s in countries with both high and low TB prevalence and across a broad spectrum of patient populations at risk for active TB. The efficacy based on the overall reduction in the incidence of active TB in these studies ranged from 25% to 92%; the protective efficacy when measured among those who completed a full course of treatment was approximately 90% [5]. Five-year TB incidence in the placebo groups of these trials ranged from 11.6 to 21.3/1000 PY. The effectiveness of INH preventive therapy (IPT) in non-HIV-infected populations is directly associated with duration of treatment with a reduction in development of active TB of 21% after 3 months, 65% after 6 months, and 75% after 12 months, although completion rates for 6-9 months of INH are unacceptably low, ranging from 20% to 70% [8]. Despite high levels of success and strong recommendations for use of INH for LTBI in high-resource countries where TB risk is low to moderate, uptake and completion of treatment remains less than optimal. In a recent study in the United States (US) and Canada, 17.1% of persons at risk who were offered INH after a positive TST declined treatment; persons recently in contact with persons with active TB were less likely to decline LTBI treatment [9]. Of those who

started INH treatment, 52.7% failed to complete the recommended course, with the recommendation of a 9-month regimen, residence in congregate settings, and injection drug use being among the strongest predictors of failure to complete LTBI treatment [9].

INH Treatment of LTBI in HIV-Infected Individuals

HIV infection contributes significantly to an increased risk of progression of LTBI to active TB. Published rates of progression based on data from a variety of studies range from 35 to 162 cases/1000 PY of observation, with an annual risk among HIV-infected persons with a positive TST of 45 cases/1000 PY [5, 10]. Debate also continues regarding the efficacy of LTBI treatment among HIV-infected individuals. In a Cochrane Database review of 12 randomized clinical trials of LTBI treatment in 8578 randomized HIV-infected persons, preventive therapy with any anti-TB drugs administered for 6-12 months versus placebo resulted in an overall 32% reduction in the incidence of active TB (relative risk [RR] 0.68; 95% confidence interval [CI] 0.54, 0.85) [11]. The effect was greater for those with a positive TST (62% reduction; RR 0.38; [95% CI 0.25, 0.57]) than for those with a negative TST (11% reduction; RR 0.89; [95% CI 0.64, 1.24]).

The efficacy was similar for all regimens but waned over time regardless of regimen. There was no reduction in all-cause mortality, but a favorable trend for mortality reduction among those with a positive TST. Among those studies reporting incidence rates for HIV-infected individuals in the placebo arm, they varied by population as indicated below:

Study	TST Status	TB Rate/ 100 person- years
Haiti, 1986-92	Purified Protein Derivative (PPD)+	10.0
	PPD-	5.7
Uganda, 1993-97	PPD+	3.4
	Anergic	3.06
Kenya, 1992-96	PPD+	8.03
	PPD-	2.73
Zambia, 1992-96	PPD+/-	8.06
U.S., 1991-96	Anergic	0.9
Zambia, 1998	PPD+/-	4.94
Haiti, 2001	PPD-	1.5
Spain, 2003	Anergic	3.1
South Africa, 2007	Anergic	11.6

Antiretroviral therapy (ART) was not available to participants followed in the majority of these trials. While more recent studies have indicated that INH administered for 6 months reduced the relative rate of TB by 55% to 67% when compared to placebo, the effect waned substantially within 6 months to 2.5 years after discontinuing INH [12, 13]. In a recently published study from South Africa, two clinical cohorts were evaluated in the context of incident TB during exposure to IPT and/or ART [14]. There were 267 incident TB cases diagnosed among 2778 HIV-infected patients followed for 4287 PY,

with an incident rate ratio of 6.2/100 PY. Compared to ART-naïve patients, those who received ART alone had a 64% decreased hazard for development of TB, and patients who received ART after receiving IPT had an 89% reduced hazard. In another recently reported study conducted in Botswana, 2000 HIV-infected patients were randomized to receive either 6 months or 36 months of INH to evaluate whether a longer duration of INH might have a more durable effect in reducing the incidence of TB [15]. The TB incidence rate was 2.22/100 PY in the 6-month INH arm and 0.57/100 PY in the 36-month arm, representing a 57% reduction overall in the 36-month INH arm. The percent reduction was largely driven by those who entered with a positive TST; those participants with a positive TST had a 92% reduction in the incidence of active TB after 36 months of INH. When evaluated according to the use of ART, those with a positive TST at entry who received both 36 months of INH and ART had an overall reduction of 96% in the annual incidence of TB. The effect of 6 months of INH began to wane immediately after discontinuation; the TB rate in this arm for those with a positive TST rose to 6.5/100 PY within approximately 1.5 years after stopping INH; the annual incidence in this arm was 2.5%. Conversely, in a randomized, controlled trial of 6 months of INH/ethambutol (EMB) versus 36 months of INH alone in 712 HIV-infected patients without evidence of active TB, the incidence rate of TB in the INH/EMB arm was 2.4/100 PY versus 1.6/100 PY for INH alone [16]. The historical background rate of TB in the population in the absence of INH was reported to be 7/100 PY. Similar to the Botswana study, the benefit for either arm was lost within 6 months after stopping preventive therapy. In both of these studies, there was no significant difference in TB rates between arms for those with a negative TST, and overall adverse event (AE) rates were low and not significantly different among the treatment arms, suggesting that all regimens tested were relatively safe.

Despite the favorable findings of these and previous studies, there has been little uptake of preventive therapy in regions of the world where it is most needed. Although longer courses of up to 36 months of IPT may further reduce the incidence rates of TB among HIV-infected individuals, the poor rates of uptake and the high proportion of individuals who fail to complete even 6 months of IPT highlight the need for alternative, more effective short-course approaches for treatment of LTBI. The TB rate per annum in persons living with HIV in high prevalence areas is still estimated to range from 2-7% depending on the geographic region, the coverage of ART, and the uptake of IPT.

Shortened Courses of LTBI Treatment

Alternative shortened courses of LTBI treatment have been evaluated in HIV-infected individuals. In a randomized clinical trial conducted prior to the advent of highly active ART [17] evaluated a 2-month regimen of daily rifampin (RIF) and pyrazinamide (PZA) compared with a 12-month regimen of daily INH in 1583 HIV-infected persons with a positive TST. Only 69% of patients completed 12 months of INH versus 80% for those randomized to RIF/PZA. However, there were no differences in rates for confirmed or probable TB, HIV disease progression, or death, although drug discontinuation rates were slightly higher in the RIF/PZA arm. This study was conducted in the US, Mexico, Haiti, and Brazil, and more than 70% of the patients were enrolled in the US; thus, it was not a test of short-course LTBI treatment in resource-limited settings with high endemic rates of TB. However, despite showing comparable results to IPT, there has been little uptake of this shortened course regimen in the US or other countries. This may reflect

ongoing uncertainty based on two other studies that evaluated short-course RIF/PZA in high TB endemic regions; one in Zambia where the regimen was administered twice weekly for 3 months, and one in Haiti where the regimen was administered twice weekly for 2 months [18, 19]. In both studies, the overall rate of TB was higher in the short-course LTBI treatment arms compared to the INH arms, although both studies used intermittent RIF/PZA. It is also possible that the lack of uptake reflects cases of severe liver injury associated with a 2-month regimen of RIF/PZA (albeit mostly in HIV-negative participants) after more widespread implementation of American Thoracic Society (ATS)/Centers for Disease Control and Prevention (CDC)/Infectious Diseases Society of America (IDSA) guidelines in 2000 [5].

Although these data support the benefit of LTBI treatment in HIV-infected individuals, including with the use of short-course RIF/PZA, data from large randomized clinical trials in HIV-infected patients exposed to TB in high TB prevalence resource-limited settings have only recently emerged. In a recently completed phase III clinical trial comparing 12 weeks of weekly RPT/INH (900 mg/ 900 mg) to 6 months of daily INH (300 mg) in South Africans with HIV and LTBI, the hazard of TB or death in the RPT/INH arm was 14% lower than for INH (HR=0.86, 95% CI 0.5-1.3, p=0.35) [20]. Although the difference was not statistically significant, the study was only powered to detect a 50% difference, and it is encouraging that RPT/INH given only once-weekly for 12 weeks could have similar efficacy to daily INH for 6 months. ACTG 5259/TBTC Study 26: "A Study of the Effectiveness and Tolerability of Weekly Rifapentine/Isoniazid for Three Months Versus Daily Isoniazid for Nine Months for the Treatment of Latent Tuberculosis Infection" has recently completed its preliminary analysis of more than 7500 patients at high risk for TB who were randomized to either 12 weekly doses of RPT 900 mg and INH 900 mg or 9 months of daily INH. The study found that RPT/INH was noninferior to standard INH and had significantly higher rates of treatment completion and lower rates of adverse events. The rates of TB in TBTC Study 26 were 0.13 cases per 100 PY in the INH arm and 0.07 cases per 100 PY in the RPT/INH arm. Only about 200 HIV-infected patients were included in this analysis, but a preliminary Cox proportional hazards analysis indicates that HIV was associated with an 8-fold increase in the hazard of TB, regardless of treatment arm. The ACTG has enrolled an additional approximately 200 HIV/TB-coinfected patients whose outcomes will be analyzed in several years; data from this trial will further inform the field. However, the HIV substudy is powered for tolerability rather than efficacy in the coinfecting cohort. People receiving or planning to receive ART within 90 days of enrollment are excluded because of the lack of PK/safety data with RPT and antiretroviral agents. Therefore, the study will provide limited information about this regimen in HIV-infected patients in resource-limited settings with high TB burden. At this point, the TB Trials Consortium (TBTC) is not planning more trials for LTBI. Building on this work, an efficacy trial by the ACTG in areas of high TB burden and in patients requiring ART is the next logical step.

Pre-clinical models of TB disease suggest that more frequent administration of RPT can lead to higher cure rates and shorter treatment duration. Although mice do not develop LTBI, a model in which mice are aerosol-immunized with Bacille Calmette-Guerin (BCG) vaccine prior to low-dose aerosol challenge with MTB produces an infection similar to human LTBI, based on the relatively small population (ie, 10^4 CFU [colony-forming units]) of non-multiplying bacilli that is contained by host immunity rather than TB drugs

[21]. A 3-month regimen of weekly RPT/INH in this model was shown to be equivalent to daily INH for 6-9 months and was subsequently demonstrated to have similar efficacy in humans [22, 23]. In the murine model of active TB, daily dosing of RPT was associated with substantially higher rifamycin exposure when compared with RIF, and reduced the duration of treatment needed to prevent relapse [24, 25]. Current experiments using a refined murine model of LTBI that reliably produces a lower bacterial burden by immunizing with recombinant BCG vaccine provide early evidence of the superior activity of daily RPT as compared to daily INH or other therapies. In the first experiment, mice received RPT 10 mg/kg administered 5 days/week (5/7), in doses comparable to humans, alone and with INH, PZA, or both, for 8 weeks. Control mice received RIF 10 mg/kg (5/7) alone and with INH, PZA, or both, for 8 weeks. The RPT-based regimens were significantly more active than their corresponding RIF-based controls. These regimens sterilized cultures more rapidly, with the exception of the comparison of the RPT/PZA and RIF/PZA, for which the trend favored RPT, but did not quite reach statistical significance after adjusting for multiple comparisons ($p=0.06$ for that comparison). All mice became culture negative by weeks 4-6 [26]. In a second experiment, RPT 10 mg/kg (5/7), with or without INH, was superior to INH alone, RIF alone, and RIF/INH control regimens. One month of RPT/INH (5/7) resulted in relapse rates similar to 4 months of RIF (5/7), 3 months of RIF/INH (5/7), and 3 months of RPT/INH (1/7) [E. Nuermberger, unpublished data]. Comparison to 6 months of INH (5/7) is pending. Treatment of mice in this model suggests that daily high-dose RPT should eliminate LTBI more quickly than conventional regimens.

These pre-clinical experiments serve as the basis for the ultra-short-course of RPT-based therapy proposed in this clinical trial, since the murine model of LTBI was previously found predictive of efficacy for the 2-month course RIF/PZA [27, 19, 17]. Furthermore, rifamycin PK is comparable between humans and mice. As indicated in the tables below, the 10 mg/kg dose in mice results in drug exposures that are remarkably similar to the exposures observed in healthy volunteers after the recommended human dose of 600 mg (ie, ~10 mg/kg). Steady-state RPT exposures observed in Ugandan TB patients receiving RPT 10 mg/kg (5/7) in combination with INH, PZA, and EMB in TBTC Study 29 were lower than exposures previously observed in mice and healthy volunteers (mean RPT $AUC_{0-24} = 179 \mu\text{g}\cdot\text{h}/\text{mL}$) [28]. A substantial portion of this difference could be due to the expected autoinduction of rifamycin metabolism with repeated dosing; although no autoinduction could be demonstrated after 7 consecutive daily administrations of 600 mg RPT [29], more recent investigations documented changes consistent with RPT autoinduction after 7 thrice weekly administrations of 900 mg RPT concomitant with daily moxifloxacin [30]. More importantly, RPT bioavailability being greatly increased (from 33 % to up to 86%) by food intake, fasting prior to drug administration in Study 29 is expected to have had a significant impact [Priftin package insert 2009, 31]. In addition, these fasting conditions may have enhanced the RPT and INH physico-chemical interaction expected to occur in acid conditions [32]. Pharmacogenetic differences also may underlie reduced RPT exposures among African patients, as recently observed for RIF [33]. An ongoing RPT dose escalation study among healthy volunteers (TBTC Study 29B) will determine safety, tolerability, and RPT exposures in fed patients receiving 7/7 dosing and should confirm the RPT dose necessary to produce in LTBI patients the same RPT exposures observed in mice receiving RPT 10 mg/kg (5/7). INH is cleared more rapidly in mice compared to humans,

so a higher mg/kg dose is necessary to achieve similar area under the concentration-time curve (AUC) values. The 10 mg/kg dose in mice most closely represents the INH exposures observed in humans who are rapid acetylators of INH. Compared to INH exposures in humans who are slow acetylators, the C_{max} in mice at this dose is 50% higher, but the AUC is 50-60% lower.

Mean PK parameter value in serum after a single RPT dose

Species	Humans [34]	Mice [24]
Dose	600 mg	10 mg/kg
PK parameter		
C_{max} ($\mu\text{g/ml}$)	15.8	13.0
AUC* ($\mu\text{g-h/ml}$)	386	417

*AUC_{0-∞} for humans, AUC_{0-48h} for mice

Mean PK parameter value in serum after a single RIF dose

Species	Humans [35]	Mice [36]
Dose	600 mg	10 mg/kg
PK parameter		
C_{max} ($\mu\text{g/ml}$)	14.9	12.1
AUC _{0-24h} ($\mu\text{g-h/ml}$)	118	116

Mean PK parameter value in serum after a single INH dose

Species	Humans* [37]	Mice [38]
Dose	300 mg	10 mg/kg
PK parameter		
C_{max} ($\mu\text{g/ml}$)	5.3-6.2	7.5
AUC _{0-24h} ($\mu\text{g-h/ml}$)	11.4-23.7	9.3

*Range shown is for rapid and slow acetylators of INH.

TB/HIV Drug Interactions

Rifamycin drugs such as RPT have the potential to cause drug-drug interactions of clinical importance. Rifampin (RIF), the most commonly-used rifamycin, is a potent inducer of multiple metabolizing enzymes, including cytochrome P450 enzymes, as well as P-glycoprotein and phase 2 enzymes [39]. Since most protease inhibitors (PI) and non-nucleoside reverse transcriptors (NNRTIs) are metabolized by cytochrome P450 3A4 isoenzyme (CYP3A4), induction of CYP3A4 by RIF can lead to reduced serum concentrations of antiretrovirals (ARVs) with a risk for treatment failure or emergence of resistance to ARVs. NVP and EFV are both subject to drug-drug interactions with RIF. EFV is cleared by CYP2B6 and CYP3A4 metabolizing enzymes, and EFV may act as a 3A4 inhibitor or inducer. NVP is eliminated via CYP3A4 and CYP2B6 and induces CYP3A4.

In patients who must be treated with RIF-based therapy for TB and require concurrent HAART, EFV is the NNRTI of choice. Since the PK of EFV 600 mg daily is similar to that of EFV 800 mg daily when coadministered with RIF in HIV/TB coinfecting patients [40, 41], some recommend that EFV dosing should be

increased in patients taking RIF; the US Food and Drug Administration (FDA) has recently approved a change in the label for EFV to increase dosage to 800 mg daily for patients weighing >50 kg when taking RIF. Despite somewhat diminished plasma concentrations of EFV in PK studies in patients taking RIF, however, pharmacodynamic (PD) studies in Brazil, South Africa, Thailand, and India in HIV/TB-coinfected patients receiving RIF have shown durable virologic and immunologic responses at the standard EFV dose of 600 mg daily [41--46]. These study findings suggest that a daily dose of 600 mg of EFV is safe and likely to be efficacious in patients being treated concurrently for HIV and TB with a RIF-based regimen. The effect of the physiological changes of pregnancy combined with RIF-based therapy on EFV concentrations and treatment outcomes among pregnant women is unknown.

NVP is frequently used in pregnancy and is widely available in fixed-dose combinations. When the standard dose of 200 mg twice daily is coadministered with RIF, serum concentrations of NVP are decreased by 20-30% [47]. One group found that coadministration of RIF with NVP caused significant decreases in the C_{max} (42%), trough concentration (53%), and AUC (46%) of NVP as well as significant increases in NVP oral clearance (Cl/F) [48]. However, studies evaluating the consequences of reduced NVP concentrations when given with RIF have yielded variable results. In one study, long-term CD4+ T-cell and HIV viral load values were similar in patients on NVP who had received a RIF-based regimen compared to those who had not. [47]. Conversely, two other studies have shown higher risk of virologic failure in patients taking NVP together with RIF [49]; The Thai Red Cross evaluated the efficacy of 600 mg NVP coadministered with RIF-containing TB regimen. They found the efficacy at 48 weeks to be similar to standard 400 mg dose, but there was a higher rate of NVP hypersensitivity in the higher dose group [50]. A recent study by Swaminathan and colleagues found higher rates of treatment failure and death in patients treated with RIF-based TB therapy and a NVP-based HIV regimen compared to patients receiving EFV-based HAART [51]. At this point, the optimal NVP dose when NVP is given together with a RIF-containing TB regimen is unclear.

It has long been thought that RPT causes less induction of P450 enzymes than RIF, but a new study in healthy volunteers by Dooley et al. has found that daily dosing of RPT is a more potent inducer than daily RIF [52]. Using midazolam (a CYP3A4-metabolized drug) as a substrate, these investigators found that RPT at doses of 5-20 mg/kg daily reduced AUCs by >90%, compared to a 75% reduction with RIF. Thus, coadministration of RPT with CYP3A4-metablized drugs such as PIs, raltegravir, and NNRTIs could result in clinically significant reductions in these agents.

INH inhibits CYP 2C19, 3A4 and, weakly, 2D6 [53]. INH is primarily metabolized via n-acetyl-transferase 2 (NAT2) to the inactive metabolite acetylisoniazid. The rate at which acetylisoniazid is formed is highly dependent on individual NAT2 genetics. INH is not currently recognized as having an interaction with EFV. However, studies performed in human liver microsomes have shown INH to inhibit CYP 1A2 and 2A6 [54]. Additionally, data recently presented by Bertrand et al. from patients

taking RIF and INH have shown there to be a concentration dependent inhibition effect of INH on EFV clearance, particularly evident in individuals with the CYP 2B6 516TT genotype and NAT2 slow acetylators [55]. These data allow the hypothesis that when EFV is coadministered with RIF (or RPT) and INH, then the inductive effect of RIF or RPT may be offset in some patients by the inhibitory effect of INH. This provides a plausible explanation for the contradictory results, seen largely between EFV-RIF PK studies in healthy volunteers and PK evaluations of EFV-RIF-INH coadministration in patients [56]. Whether or not the interaction between INH and the secondary metabolizing pathway of EFV (CYP2A6) is clinically significant in individuals taking RPT, INH, and EFV is unknown and requires investigation in HIV-infected persons.

Currently, there are no published data on the effects of RPT when administered with EFV in HIV-infected persons. Additionally, there are no data on plasma concentrations of EFV when given with RPT and INH. The possible interaction between INH and EFV in a select genotypic group of individuals may decrease or even cancel out the interaction between EFV and RPT caused by the enzyme inducing properties of RPT.

2.2 Rationale

Successful population-level treatment of LTBI has been hindered by several factors: (1) poor adherence to long courses of therapy; (2) the administrative burden of directly observed therapy (DOT); (3) toxicities related to INH; and (4) concerns related to the inability to effectively rule out subclinical TB and the attendant risk of drug resistance in the setting of possible INH monotherapy. In resource-limited settings with high TB prevalence, uptake of IPT remains dismally low as well, especially among HIV-infected patients. Estimates from the WHO indicate that in 2009, among HIV-infected persons screened and found not to have active TB, fewer than 1% were started on IPT [1]. Although longer durations of IPT may be more effective than conventional 6-12 month courses, similar considerations are likely to continue to impede implementation of IPT. New regimens that shorten treatment duration will improve adherence and, if more effective regimens are employed, will substantially reduce the burden on public health clinics associated with providing and monitoring prolonged DOT, and reduce the risk for the development and transmission of active TB in the most vulnerable settings.

While it is clear that adherence is better with shorter regimens, and that safety and efficacy in TB prevention is comparable to those measured in comparator arms with INH administered for 6-12 months, uptake of either INH or short-course RIF-containing regimens has been minimal in the very settings in which treatment for LTBI is most needed. Whether even shorter course LTBI treatment will be more acceptable and cost-effective in public health settings and sufficiently so to trigger broad uptake remains to be established. As well, the safety and efficacy of and adherence to a 1-month daily RPT/INH regimen have yet to be evaluated. We propose a randomized, controlled trial to compare the safety, tolerability, efficacy, and adherence of short-course, daily RPT/INH with the standard regimen for LTBI, 9 months of INH, in patients at high risk of developing active TB. As detailed in the package insert, RPT is an inducer of CYP450 enzymes [Priftin package insert 2009]. Concomitant use of RPT with other drugs

metabolized by these enzymes, such as PIs and NNRTI, may cause a significant decrease in plasma concentrations and loss of therapeutic effect of the PI or NNRTI. For this reason, patients requiring PI-based therapy during the first month of the trial will be excluded, and PK analyses of NNRTI levels will be performed as part of the study for those persons on a NNRTI regimen. In summary, development of a potent, ultra-short, effective treatment for LTBI could dramatically reduce the global incidence of active TB.

Cost-Effectiveness Analysis

The uptake of any new therapy is highly dependent on several factors, of which cost is one of the most significant. New therapies (especially those containing new drugs) are frequently significantly more expensive than standard regimens. Therefore, in programs with fixed and limited resources, these new regimens must be expected to provide either significant improvements in efficacy or long-term savings when compared to the current standard of care. Cost-effectiveness analysis performed in conjunction with a clinical trial can assist with this latter comparison and is most effective when performed in conjunction with the clinical trial [57].

We plan to examine the cost-effectiveness of RPT/INH compared with both 9 months of INH and other regimens. We would expect that the shorter regimen would lead to more patients completing a course of therapy, which should result in fewer cases of active TB over time. Also, because the costs of the RPT/INH regimen in most areas with high TB incidence are largely unknown, we can use modeling to determine price thresholds above which RPT/INH will no longer be cost-effective; these thresholds can be used by public health officials in setting local policy. Furthermore, while study participants will all be HIV-positive, any new regimen proven to be effective in this population will likely be used in other populations as well. Because most of these populations will have significantly lower baseline risk of TB activation than the study population, the benefits of a shorter-course regimen may not be as marked. Therefore, we will seek out cost-effectiveness thresholds for cost, efficacy, and underlying risk.

By performing this analysis in conjunction with the clinical trial, we will be able to collect detailed treatment data that can be used to estimate costs in a wide variety of settings. More importantly, if the study regimen proves effective, we will be able to provide guidance to public health officials as soon as study results become available.

Rationale for Choice of RPT

The rifamycins are the chief sterilizing drugs in the modern short-course regimen for treatment of active TB. Compared to RIF, RPT is more potent against MTB in vitro (MIC, 0.06 vs. 0.25 mg/L) [58] and provides greater drug exposures at a given mg/kg dose in mice and in humans, owing largely to its longer serum half-life (see below). In murine models of both active and latent TB infection, the increased rifamycin exposure obtained with substitution of RPT for RIF results in greater sterilizing activity and significant shortening of the duration of treatment needed to prevent relapse [36, 25, 26]. For example, in a murine model of active TB, substitution of RPT 10 mg/kg in place of RIF 10 mg/kg administered in combination with INH/PZA 5 days/week shortens the time needed to prevent relapse from 6 months to 3 months or less in all mice [24, 25]. In a murine model of latent TB infection, which provided the pre-clinical evidence base for clinical trials that proved the efficacy of the 2-month RIF/PZA combination for LTBI in

HIV-infected persons [17, 19, 27], RPT 10 mg/kg and the combination of RPT/INH administered 5 days/week were significantly more effective in reducing the rate of active TB than the same dose of RIF alone or RIF/INH [26]. In this experiment, all mice receiving RPT alone were rendered culture negative after 6 weeks, and 40%, 7%, and 0% of mice, respectively, developed culture-positive TB infection in the 3 months after completing treatment for 4, 6, or 8 weeks. RPT/INH rendered 4 of 5 mice culture negative after 4 weeks, and 86%, 14%, and 0% of mice, respectively, developed culture-positive TB infection in the 3 months after completing treatment for 4, 6, or 8 weeks. Among mice treated with RIF/INH, 100% and 47% of mice, respectively, developed culture-positive TB infection in the 3 months after completing treatment for 4 or 8 weeks (the efficacy of 6 weeks of RIF/INH was not assessed), consistent with the 3-month treatment duration recommended when RIF/INH is used for LTBI in humans [59]. RIF alone was less effective than RIF/INH. These results suggest that a regimen containing RPT at 10 mg/kg/day may treat LTBI in 2 months or less. Daily RPT/INH for 6-8 weeks (42-56 doses) would not offer cost-benefit advantage when compared to the upcoming 3-month once-weekly administration (12 doses) evaluated in TBTC Study 26. Data generated in the murine model at 4 weeks indicated that sterilization had occurred in a proportion of infected mice, suggesting that a 4-week regimen of daily RPT/INH could be sufficient to prevent development of active TB in patients. In a second experiment in the same model, one month of RPT/INH (5/7) resulted in relapse rates similar to 4 months of RIF (5/7), 3 months of RIF/INH (5/7), and 3 months of RPT/INH (1/7). These unpublished data showing comparable outcomes with three efficacious LTBI regimens provide further support for a 1-month treatment duration of RPT/INH treatment [E. Nuernberger, unpublished data].

The safety and tolerability of daily RPT has been evaluated in a phase I PK study in healthy volunteers [29]. Twenty-three healthy males were randomized to receive two of the following treatments in a 2-period, 4-treatment, incomplete block, cross-over design: single once-daily oral RPT at 150 mg, 300 mg, or 600 mg on study days 1 and 4 through 10, or single oral RPT 600 mg doses given every 3 days for 4 doses. All regimens reached steady state RPT concentrations and RPT was well tolerated in all four treatment periods. Urine discoloration was the most common AE, and occurred in all study participants. Other treatment-related AEs were upset stomach (n=4), lightheadedness (n=3), dry mouth (n=2), diarrhea (n=2), flatulence (n=1), and headache (n=1). No abnormalities of liver chemistries were reported.

TBTC Study 29, Evaluation of a Rifapentine-Containing Regimen for Intensive Phase Treatment of Pulmonary Tuberculosis, is a phase II trial comparing daily RPT (5 days per week) at 10 mg/kg to standard dose RIF in patients with newly diagnosed, smear-positive pulmonary TB. All patients also receive standard INH, PZA, and EMB. The primary endpoint is sputum culture conversion after 8 weeks. As of August 16, 2010, the study had recruited 465 patients and undergone six Data and Safety Monitoring Board (DSMB) reviews since enrollment began. No serious and unanticipated toxicities had been reported as of that date.

The safety and tolerability of RPT used daily has also been evaluated by the manufacturer in clinical phase II studies in AIDS patients with bacteremia caused by *Mycobacterium avium* complex (MAC):

Multicenter Dose Escalation Study to Evaluate Tolerance, Safety, and Activity of Rifapentine Alone and in Combination Therapy in AIDS Patients with MAC Bacteremia (Hoechst Marion Roussel protocol number 000473PR0005).

The primary objective of this phase II, open-label, multicenter, dose-escalation study was to determine the tolerance and safety of escalating RPT doses alone and in combination therapy for disseminated MAC bacteremic patients with AIDS. This study started in 1995 and ended in 1996. Patients were treated with RPT monotherapy for 14 days and then randomized to combination therapy with clarithromycin or combination therapy with clarithromycin/EMB. The combination therapy phase lasted 28 days. RPT was dosed once daily. Thirty patients were enrolled in the study; 8 received RPT 450 mg/day, and 22 received RPT 300 mg/day. All patients experienced one or more nonserious AEs; the high incidence was “indicative of the poor health status of this patient population”. Seventeen (56.7%) patients had one or more treatment-related AEs (AEs defined by the investigator as “definitely”, “probably”, or “possibly” related to study medication). Among these 17 patients, 6 (20% of total) had a hematologic AE (2 patients with anemia, 3 with neutropenia, and 1 with hemoglobin/hematocrit disease), 6 patients had a hepatic/biliary AE (5 with bilirubinemia, 1 with cholestatic hepatitis), 4 patients (13% of total) had a body-as-a-whole AE (3 with abdominal pain and 1 with ascites), and 3 (10% of total) had a gastrointestinal AE (2 with nausea and 1 with vomiting). There were 13 serious AEs (SAEs), 7 of which were death, and 6 of which were nonfatal. None of the deaths were judged to be related to study medication. Among the 6 nonfatal SAEs, 1 was judged not related to study medication, 1 was judged unlikely to be related to study medication (blindness in a patient known to have cytomegalovirus [CMV] retinitis); 2 were judged possibly related to study medication (depression and suicide attempt in 1 patient, and hepatic failure in 1 patient receiving 450 mg/day), and 2 were judged probably related to study medication (neutropenia in 1 patient receiving 300 mg/day, and dysarthria/confusion and AIDS in 1 patient). The rate of patient discontinuation due to treatment-related AEs was higher among patients receiving 450 mg/day (4 patients among 8 who received this dose) than among patients receiving 300 mg/day (5 patients among 22 who received this dose). However, among the 4 patients receiving 450 mg/day who discontinued, in only 1 patient was the AE attributed to study medication, and this AE was listed as “dysarthria/confusion/AIDS”.

Tolerance, Safety, and Activity of Rifapentine Alone and in Combination Therapy in AIDS Patients with *Mycobacterium avium* complex (MAC) Bacteremia (Hoechst Marion Roussel protocol number 000473PR0018).

The primary objective of this phase II, open-label, multicenter trial was to determine the tolerability of RPT alone and in combination therapy in disseminated MAC bacteremic patients with AIDS. This study started in 1995 and ended in 1997; enrollment was closed in 1997 because of the marked decrease in the incidence of disseminated MAC infection following the widespread availability of potent combination ART. Twenty-one patients were enrolled in this study. Four patients were enrolled to RPT monotherapy (3 received 300 mg/day and 1 received 450 mg/day); 3 patients completed 21 days of monotherapy and went on to complete 42 days of RPT-containing combination therapy. Seventeen patients were enrolled to RPT combination therapy only (11 received RPT 300 mg/day and 6 received RPT 450 mg/day); 13 completed 42 days of combination therapy. Twenty of 21 patients had ≥ 1 AE. As in the prior study, this was felt to be “indicative of the poor health status of this patient population.” Seven patients (33.3%) had ≥ 1 treatment-

related nonserious AE. Among these, 5 patients (23.8% of total patients) had a gastrointestinal AE, and 3 (14.3%) had a dermatologic AE. There were 17 SAEs (10 patients). Included among these SAEs were 3 deaths, none of which was judged by the investigator to be related to study drugs. There were 14 nonfatal SAEs, none of which was judged by the investigator to be related to study drugs. There were 4 permanent discontinuations due to AEs (3 deaths, plus 1 additional discontinuation due to an AE not related to study drugs), and 1 temporary discontinuation (due to rash; study drugs were stopped, and then reintroduced without return of the rash). Study conclusions were that AEs were overwhelmingly symptoms associated with AIDS and few were attributable to study drugs, and that RPT was well-tolerated at either dose level given as monotherapy or as combination therapy.

An Open-Label, Multicenter Extended Treatment Phase Study with Rifapentine in AIDS Patients Who Have Completed Protocol 000473PR0018 (Hoechst Marion Rousse) protocol number 000473PR0019).

The primary objective of this study was to provide RPT for extended treatment to patients who, in the opinion of the investigator, responded to treatment during the preceding RPT protocol (000473PR0018). Eight patients were enrolled in this extended use study, and the duration of treatment for a given patient was based on individual response. Seven patients received RPT 300 mg/day, and one patient received RPT 450 mg/day. Median number of weeks of RPT use in this study was 18 (range 4 to 52 weeks, mean 24.5 weeks). Four nonserious AEs were judged to be related (possibly, probably, or definitely) to study drugs: one patient each with dry mouth, conjunctival erythema, burning eyes, and erythematous ear canal. There were 14 SAEs including 3 deaths; none of the 14 SAEs was judged to be related to study drugs. Study conclusions were that AEs were overwhelmingly symptoms associated with AIDS and that RPT was well tolerated.

Importantly, individuals in the above studies had advanced AIDS complicated by disseminated MAC, each of which is associated with substantial morbidity and mortality. For example, Chaisson et al. reported in 1992 that the median duration of survival after disseminated MAC diagnosis in AIDS patients was 221 days, and that the probability of 1-year survival from the time of disseminated MAC diagnosis was 0.29 (95% CI 0.24-0.34) [60]. More recently, Benson et al. reported results of an ACTG study of three contemporary, clarithromycin-based regimens for treatment of disseminated MAC in AIDS patients [61]. Among the treatment groups, 8-25% died during the first 4 months of the study, and 28-50% died during the 48-week study period. Furthermore, 9-14% of patients stopped therapy due to protocol-defined toxicity, 9-25% had Grade 3 or higher anemia, and 6-14% had Grade 3 or higher hepatitis.

Impact of New PK Data on A5279

Previous research using intermittent doses of RPT had shown that P450 cytochrome induction was approximately 75-80% the magnitude of that caused by RIF. On this basis, Version 1.0 of the A5279 protocol originally excluded patients taking PI-containing ART regimens, but allowed enrollment of patients taking EFV- or NVP-containing regimens, and planned to include the first 90 of each group in a PK substudy of the interaction of RPT on trough concentrations of these agents. Recent data from TBTC Study 29B [62] reveal that daily dosing of RPT results in

greater induction of cytochromes than with RIF. The protocol pharmacologist and leadership team, as well as independent pharmacologists, reviewed the new data and concluded that while it is reasonable and safe to continue plans to enroll patients taking EFV, it would be most prudent to hold off on enrollment of patients taking NVP until more data were available. EFV is metabolized largely by CYP2B6 and to a lesser extent by CYP3A4, the isoenzyme induced by RPT. NVP, however, is largely metabolized by CYP3A4.

The protocol team accelerated the collection and analysis of PK data from the EFV substudy of A5279 to determine the potential effect that RPT might have on NVP PK. These PK analyses showed that concomitant dosing of EFV and RPT results in adequate drug exposure. Thus, patients taking NVP will be enrolled and similar PK analyses will be conducted.

RPT in Children

This study proposes to evaluate a shortened course of daily RPT and INH in adults and adolescents of age 13 and older. Data evaluating use of RPT in children are limited. However, PK data in children aged 2-12 years are available [63]. In this study, 24 were enrolled in a two-dose level, multicenter, PK study of orally administered RPT tablets. Single-dose PK data for children weighing 10-30 kg who received 150 mg RPT and children weighing 30-60 kg who received 300 mg RPT resulted in doses of 5-15 mg/kg, which approximates the labeled adult dose of RPT 600 mg. Overall, the mean peak RPT level was 7.26 +/- 2.64 mcg/mL; 6.87 +/- 2.82 mcg/mL among children who received 150 mg and 7.63 +/- 2.52 among children who received 300 mg (p=0.50). The mean time to peak level was 3.2 +/- 1.2 hours, and the $t_{1/2}$ was 20.5 +/- 18.0 hours. When stratified according to children who received 5-8.5 mg/kg vs. 8.6-11 mg/kg, there was no difference in peak concentration (7.36 vs. 7.19 mcg/mL; p=0.89), $t_{1/2}$ (18.9 vs. 21.8 hours; p=0.71), or AUC (117.8 vs. 119.0). There was no clear relationship between RPT dose and exposure, due primarily to a large degree of inter-individual variability. PK evaluation conducted in healthy patients 12-15 years old revealed PK parameters similar to those observed in healthy adults [Priftin package insert 2009; 64]. In this latter study, 12 adolescents with a mean age of 13.3 years were administered RPT 450 mg if <45kg, or 600 mg if ≥45 kg. The average weight of participants was 54.8 ± 10.4 kg. The RPT C_{max} and $AUC_{0-\infty}$ were 9.66 to 18.63 µg/mL and 397 ± 148 µg.h/L, respectively. Additional data will be available from TBTC Study 26, which is enrolling children and adolescents 2-18 years old.

Sample Storage

The protocol team feels it is important to store specimens on this study for future secondary work and New Work Concept Sheets (NWCS) in this population. However, the team also recognizes that storage of 5 years or more of longitudinal samples on 3000 participants, most of whom will not have TB on study, is not warranted nor cost-effective. The study will store plasma, serum, and peripheral blood mononuclear cells (PBMC) at entry and every 48 weeks on the first 30 participants enrolled by each site in a country with a high TB burden and on the first 50 participants enrolled by all U.S. sites combined. Samples will also be stored at TB diagnosis in any participant who develops active TB. This strategy will result in storage of longitudinal samples on a maximum of about 650 participants. Not all sites will enter 30 participants, and 40-50 of those with

longitudinal samples stored will be TB cases. Thus, this plan will store longitudinal samples on about 500 participants (controls) who never develop TB on study and about 40-50 participants (cases) who do develop TB. This will also provide one-time storage at the diagnosis of TB on about 200 other participants (cases) who do develop TB on study. This provides about a 2:1 ratio of controls to TB cases which will allow matching and subgroup analyses, as well as high power to detect differences if all participants are used. This also provides longitudinal storage on a reasonable number of eventual TB cases for intensive analyses. We envision the ACTG reserving the latter for targeted high-profile work and encouraging proposers to do pilot and developmental work on the larger group of TB cases with one-time storage.

3.0 STUDY DESIGN

This study is a multicenter, randomized, open-label, phase III clinical trial of an experimental TB treatment regimen (Arm A) of RPT/INH daily for 4 weeks compared to a standard TB treatment regimen (Arm B) of INH daily for 36 weeks in HIV-infected participants who do not have evidence of active TB. Randomization will be 1:1. Participants will be stratified based on (1) **the most recent CD4+ cell count obtained within 180 days prior to entry** (<100, 100-250, and >250 cells/mm³) and (2) ART use at entry (Yes/No). Each participant will be followed for 3 years (156 weeks) after the last participant is enrolled.

Weeks	Arm A (Experimental)	Arm B (Standard)
1 – 4	RPT weight-based dosing*/ INH 300 mg daily	INH 300 mg daily
5 – 36	No treatment	INH 300 mg daily
37-close to follow-up	No treatment	No treatment

*For weight 30 to <35 kg: RPT 300 mg once daily

*For weight 35 to ≤45 kg: RPT 450 mg once daily

*For weight >45 kg: RPT 600 mg once daily

*Average RPT dosage of ~10 mg/kg/administration

Participants must receive pyridoxine (vitamin B₆) 25 or 50 mg with each dose of INH. Sites will be expected to provide participants with the vitamin B₆ necessary for the study.

Under Version 1.0, EFV concentrations were evaluated early in the first 90 participants in Arm A who were receiving EFV at entry and who met other criteria in Section 10.0. EFV PK data were evaluated on an on-going basis, as described in Section 10.3, to determine whether standard EFV dosing results in adequate PK drug exposure in the presence of RPT treatment. The A5279 team determined that concomitant dosing of EFV and RPT results in adequate drug exposure; thus, the study was opened to participants receiving NVP. NVP concentrations will be evaluated in the first 90 participants in Arm A who are receiving NVP at entry and

meet other criteria in Section 10.0.

At the implementation of Version 2.0:

1. EFV concentrations and pharmacogenetics will be evaluated in an additional 30 participants from Arm A. These 30 participants will undergo PK sampling at weeks 0, 2, 4, and 16.
2. EFV concentrations and pharmacogenetics will be evaluated in the first 90 participants in Arm B who are receiving EFV at entry and who meet other criteria in Section 10.0. PK sampling will be performed at weeks 0, 2, and 4.

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 antigen, plasma HIV-1 RNA viral load. **Two or more HIV-1 RNA viral loads of >1,000 copies/mL are also acceptable as documentation of HIV infection.**

NOTE: The term 'licensed' refers to a 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-U.S. sites are encouraged to use FDA-approved methods for IND studies.

WHO and 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 or a plasma HIV-1 RNA viral load.

- 4.1.2 TST reactivity ≥ 5 mm, or a positive interferon gamma release assay (IGRA) at any time prior to study entry, OR living in a high TB burden area

NOTE A: In general, high TB burden areas are defined as areas with an estimated or reported TB prevalence of 60/100,000, according to the WHO or national or local health authorities. (Please refer to the A5279 protocol-specific web page [PSWP] for the WHO link to TB prevalence information by country. The protocol core team [actg.corea5279@fstrf.org] should be consulted if a site has data to suggest that the local TB burden differs significantly from the WHO country estimates and, therefore, should be considered in the application of this inclusion criterion.)

NOTE B: At entry, all participants must have a TST performed unless one has been performed within 60 days prior to entry, regardless of whether they live in a high TB burden area.

4.1.3 Laboratory values obtained within 30 days prior to entry

- Absolute neutrophil count (ANC) >750 cells/mm³
- Hemoglobin ≥ 7.4 g/dL
- Platelet count $\geq 50,000$ /mm³
- Aspartate aminotransferase (AST) (serum glutamic oxaloacetic transaminase [SGOT]) and alanine aminotransferase (ALT) (serum glutamic pyruvic transaminase [SGPT]) ≤ 3 X upper limit of normal (ULN)
- Total bilirubin ≤ 2.5 X ULN

4.1.4 **Chest radiograph or chest computed tomography (CT) scan without evidence of active tuberculosis, unless one has been performed within 30 days prior to entry.**

4.1.5 Female participants of reproductive potential must have a negative serum or urine pregnancy test performed within 7 days prior to study entry.

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, bilateral oophorectomy, or bilateral tubal ligation).

4.1.6 All participants must agree not to participate in a conception process (e.g., active attempt to become pregnant or to impregnate, donate sperm, in vitro fertilization) while receiving RPT and for 6 weeks after stopping this drug.

4.1.7 Female participants who are participating in sexual activity that could lead to pregnancy must agree to use one reliable non-hormonal form of contraceptive (i.e., **condoms, IUD, diaphragm with spermicide, or cervical cap with spermicide**) while receiving RPT and for 6 weeks after stopping this drug.

NOTE: 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 bilateral tubal ligation.

4.1.8 Men and women age ≥ 13 years

4.1.9 Weight ≥ 30 kg

4.1.10 Ability and willingness of participant or legal guardian to provide informed consent

4.2 Exclusion Criteria

4.2.1 Treatment for active or latent TB (pulmonary or extrapulmonary) within 2 years prior to study entry or, at screening, presence of any confirmed or probable TB based on criteria listed in the current ACTG Diagnosis Appendix

4.2.2 History of multi-drug resistant (MDR) or extensively-drug resistant (XDR) TB at any time prior to study entry

4.2.3 Known exposure to MDR or XDR TB (e.g., household member of a person with MDR or XDR TB) at any time prior to study entry

4.2.4 Treatment for >14 consecutive days with a rifamycin or >30 consecutive days with INH at any time during the 2 years prior to enrollment.

4.2.5 For participants taking ART at study entry, only **approved NRTIs with EFV or NVP for at least 4 weeks are permitted. Any other regimens at entry are exclusionary. A list of approved antiretroviral drugs is located on the A5279 PSWP. Participants on NVP must be dosed at 200 mg twice daily (BID).**

NOTE A: NVP trough levels will be evaluated in the first 90 participants in Arm A who are receiving NVP at entry and who meet other criteria in Section 10.0, after which enrolment for participants on NVP may be temporarily halted. NVP PK data will be evaluated to determine whether standard NVP dosing results in adequate PK drug exposure in the presence of RPT treatment. If the A5279 team determines that concomitant dosing of NVP and RPT results in adequate drug exposure, the study may continue enrollment of participants receiving NVP.

NOTE B: Participants randomized to Arm A may initiate any ART regimen after completing four weeks of RPT/INH. Participants randomized to Arm B may initiate any ART regimen after study entry.

4.2.6 History of liver cirrhosis at any time prior to study entry

4.2.7 Evidence of acute hepatitis, such as abdominal pain, jaundice, dark urine, and/or light stools within 90 days prior to entry

4.2.8 Diagnosis of porphyria at any time prior to study entry

4.2.9 Peripheral neuropathy \geq Grade 2 according to the December 2004 (Clarification, August 2009) Division of AIDS (DAIDS) Toxicity Table, within 90 days prior to study entry

- 4.2.10 Known allergy/sensitivity or any hypersensitivity to components of study drugs or their formulation
 - 4.2.11 Active drug or alcohol use or dependence that, in the opinion of the site investigator, would interfere with adherence to study requirements
 - 4.2.12 Serious illness requiring systemic treatment and/or hospitalization within 30 days prior to entry
 - 4.2.13 Breastfeeding
- 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 form 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 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. Protocol activation is also required before each non-U.S. site can enroll participants into the study, and may be required before each U.S. site can enroll any participants.

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 (or, when necessary, the parent or legal guardian if the participant is younger than 18 years of age or under guardianship) 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) Participant Enrollment System.

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

4.3.2 Randomization

Participants who meet eligibility criteria for A5279 will be randomized to A5279 according to standard ACTG DMC procedures.

4.4 Coenrollment Guidelines

Sites are encouraged to coenroll participants in A5128 or A5243. Coenrollment in A5128, "Plan for Obtaining Informed Consent to Use Stored Human Biological Materials (HBM) for Currently Unspecified Analyses," or A5243, "Plan for Obtaining Human Biological Samples at Non-U.S. Clinical Research Sites for Currently Unspecified Genetic Analyses," does not require permission from the A5279 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

Study treatment for Arm A participants is RPT plus INH for 4 weeks, followed by no treatment through week 36. Study treatment for Arm B participants is INH for a total of 36 weeks. All participants will be followed for 3 years (156 weeks) after enrollment of the last participant.

The study-provided **products** are rifapentine (RPT) and isoniazid (INH).

5.1 Regimens, Administration, and Duration

5.1.1 Regimens and Duration

At entry, participants will be randomized (1:1) to one of the following two arms:

Weeks	Arm A (Experimental)	Arm B (Standard)
1 – 4	Rifapentine (RPT, Priftin®), based on weight at entry For weight 30 to <35 kg: 300 mg once daily* For weight 35 to ≤45 kg: 450 mg once daily* For weight >45 kg: 600 mg once daily* PLUS Isoniazid (INH) 300 mg once daily	Isoniazid (INH) 300mg once daily
5 – 36	No treatment	Isoniazid (INH) 300mg once daily

* Average dosage of ~10 mg/kg/administration

All participants must receive pyridoxine (vitamin B₆) 25 or 50 mg with each dose of INH based on the current local, national, or international dosing guidelines. Sites will be expected to provide participants with the vitamin B₆ necessary for the study.

ART will not be provided by this study. Study clinicians, in conjunction with participants, should determine the optimal ART regimen for each participant, if indicated. However, for participants taking ART who are randomized to Arm A, only **approved NRTIs with EFV or NVP** are permitted for the first 4 weeks of study **treatment with RPT; a list of approved antiretroviral drugs is located on the A5279 PSWP**. If a participant must switch to an ART regimen that **includes an antiretroviral drug that is not on the approved list** while on RPT/INH, then RPT/INH must be discontinued; this participant will be followed off treatment, on study.

At the entry visit, the site pharmacist will dispense enough study products to last until the next study visit. Participants must return any remaining study product after the completion of randomized therapy. **Participants** in Arm A will have 8 weeks from enrollment to complete 4 weeks of treatment, and those in Arm B will have 54 weeks to complete 36 weeks of **treatment**.

5.1.2 Administration

RPT 300 mg: will be administered as two 150 mg tablets orally once daily with INH and is to be taken with food.

RPT 450 mg: will be administered as three 150 mg tablets orally once daily with INH and is to be taken with food.

RPT 600mg: will be administered as four 150 mg tablets orally once daily with

INH and is to be taken with food.

INH 300 mg: will be administered as one 300 mg tablet **or three 100 mg tablets** orally once daily*.

*NOTE: For Arm A participants, when INH is administered with RPT, both **products** will be taken together with food. For Arm B participants, when INH is administered alone (i.e., without RPT), INH may be taken with or without food.

Pyridoxine (vitamin B₆) 25 mg: will be administered as one 25 mg tablet orally once daily with INH.

Pyridoxine (vitamin B₆) 50 mg: will be administered as two 25 mg tablets or one 50 mg tablet orally once daily with INH.

5.2 Study Product Formulation and Preparation

Rifapentine will be supplied as tablets for oral administration, each containing 150 mg of rifapentine. Store at 25°C (77°F); excursions permitted from 15° – 30°C (59° – 86°F). Protect from excessive heat and humidity.

Isoniazid **provided through the study** will be supplied as tablets for oral administration, each containing 300 mg of isoniazid. **Store below 30°C (86°F).**

Isoniazid 100 mg or 300 mg tablets locally procured by the site and approved for use in A5279 by the protocol team must be stored in accordance with the manufacturer's instructions. INH locally procured by the site must be the same strength and formulation for the duration of the study.

5.3 Pharmacy: Product Supply, Distribution, and Accountability

5.3.1 Study Product Acquisition/Distribution

Rifapentine (RPT, Prifitin®) will be supplied by sanofi-aventis. Isoniazid (INH) will be supplied through the study with support from sanofi-aventis. Rifapentine (RPT, Prifitin®) and isoniazid (INH) will be available through the National Institute of Allergy and Infectious Diseases (NIAID) Clinical Research Products Management Center (CRPMC); **however, if INH is not available through the CRPMC, sites may obtain a supply of INH locally to be subsequently dispensed to the participant. The A5279 Site Implementation Plan (SIP) located on the A5279 PSWP must be completed by each site for protocol team notification and authorization of locally sourced INH.**

Any study product not provided by the study must comply with the NIAID (DAIDS) policy that outlines the process for authorizing the use of study products not marketed in the US in NIAID (DAIDS)-supported and/or sponsored clinical trials. This policy is available on the NIAID (DAIDS) website at:

<http://www.niaid.nih.gov/LabsAndResources/resources/DAIDSClinRsrch/Documents/NonFDAApprovedProducts.pdf>

If sites have received registration approval for A5279 Version 1.0 LOA #4 or Version 2.0, sites may order INH from the CRPMC and should begin to use that drug in lieu of any INH obtained locally (as previously outlined in A5279 Version 1.0, LOA #2). Sites may not order INH obtained from Macleods via the CRPMC until they have received registration approval for A5279 Version 1.0, LOA #4 or Version 2.0. Additionally, for sites switching from locally obtained INH to INH from the CRPMC, sites should document and notify the A5279 core team (actg.corea5279@fstrf.org) with the date that INH from Macleods Pharmaceuticals Limited is implemented at the site.

The site pharmacist can obtain the study products 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.

Pyridoxine (vitamin B₆) will not be supplied through the study and must be obtained locally by the site.

5.3.2 Study Product Accountability

The site pharmacist is required to maintain complete records of all study products received from the NIAID CRPMC **or other sources** and subsequently dispensed. At US CRSs, all unused study products must be returned to the NIAID CRPMC (or as otherwise directed by the sponsor) after the study is completed or terminated. The site pharmacists at non-US CRSs 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-provided products.

5.4 Concomitant Medications

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 on the ACTG Pharmacology drug table located at: <https://member.actgnetwork.org/cms/dl/12692>.

5.4.1 Required Medications

While on INH, pyridoxine (vitamin B₆) 25 or 50 mg once daily

5.4.2 Prohibited Medications

The A5279 prohibited medications are listed on the A5279 PSWP.

5.4.3 Precautionary Medications

The A5279 precautionary medications are listed on the A5279 PSWP. To avoid adverse drug interactions, package inserts of anti-TB agents, antiretroviral agents, and other concomitant medications should be referenced whenever a concomitant medication is initiated or dose changed, to avoid drug interaction AEs.

5.5 Adherence Assessment

Pill counts and self-report adherence interviews for both arms will be used to assess adherence during the treatment phase of each arm. Participants will also be asked to report on food consumption when taking RPT.

6.0 CLINICAL AND LABORATORY EVALUATIONS

6.1 Schedule of Events

Evaluation	Screening	Entry	Treatment Phase		Post-Treatment Phase (every 12 weeks, starting at week 48)	Diagnosis of TB	Premature Study Discontinuation
			Arm A: RPT/INH (weeks 2, 4, 8, 12, 16, 20, 24, 36)	Arm B: INH-only (weeks 2, 4, 8, 12, 16, 20, 24, 36)			
Documentation of HIV	X						
Medical History/Medication History	X						
Clinical Assessment ¹ (including TB assessment, adverse events, concomitant medications)	X	X	X	X	X	X	X
Chest Radiograph or Chest CT	X ²		If indicated	If indicated	If indicated	If indicated	
TST or IGRA	X ³	TST only ⁴					
Hematology	X	X	Week 4 and if indicated	Week 4 and if indicated	If indicated	If indicated	X
Liver Function Tests	X	X	Week 4 and if indicated	Week 4 and if indicated	If indicated	If indicated	X
Chemistry	X	X	Week 4 and if indicated	Week 4 and if indicated	If indicated	If indicated	X
Pregnancy Testing	X		If indicated	If indicated			

¹ A complete physical exam is required at entry; at post-entry visits, a targeted physical exam is required.

² **Chest radiograph or chest CT is required unless one has been performed within 30 days prior to entry.**

³ For participants not living in a high TB burden area, if prior positive TST/IGRA results are not available.

⁴ TST is required unless one has been performed within 60 days prior to entry **for all participants, regardless of whether they live in a high TB burden area.** An IGRA cannot be substituted at entry.

6.1 Schedule of Events (Cont'd)

Evaluation	Screening	Entry	Treatment Phase		Post-Treatment Phase (every 12 weeks, starting at week 48)	Diagnosis of TB	Premature Study Discontinuation
			Arm A: RPT/INH (weeks 2, 4, 8, 12, 16, 20, 24, 36)	Arm B: INH-only (weeks 2, 4, 8, 12, 16, 20, 24, 36)			
CD4+	X ⁵	X			Every 48 weeks		
Plasma HIV-1 RNA for Participants on ART		X					
Sputum Acid Fast Bacilli Smear and/or Xpert plus Sputum Culture	If indicated		If indicated	If indicated	If indicated	X	
Pill Count			Weeks 2 and 4 only	X			
Adherence Interview			Weeks 2 and 4 only	X			
Stored Plasma/PBMC/Serum ⁶		X			Every 48 weeks	X	
PK Samples ^{7, 8}		X	Weeks 2 and 4; plus week 16 for subset ¹⁰	Weeks 2 and 4			
Pharmacogenetic Sample ^{7, 9}		X					

⁵ A screening CD4+ cell count will only be collected if not done within 180 days prior to study entry.

⁶ These samples will be collected on a subset of participants; see section 6.3.13.

⁷ Only for participants who meet criteria in section 10.0. See section 10.0 for PK sampling directions.

⁸ A subset of the participants in the PK study will have a week 16 sample collected; see section 6.3.14.

⁹ If not collected at entry, this sample may be collected at week 2 or 4.

¹⁰Subset includes 30 patients in Arm A selected as EFV controls at implementation of protocol version 2.0

6.1 Schedule of Events (Cont'd)

Evaluation	Screening	Entry	Treatment Phase		Post-Treatment Phase (every 12 weeks, starting at week 48)	Diagnosis of TB	Premature Study Discontinuation
			Arm A: RPT/INH (weeks 2, 4, 8, 12, 16, 20, 24, 36)	Arm B: INH-only (weeks 2, 4, 8, 12, 16, 20, 24, 36)			
Stored Plasma for Virology ⁷			Week 8 only				

6.2 Timing of Evaluations

6.2.1 Screening Evaluations

Screening evaluations must occur prior to the participant's starting study medications. Screening evaluations to determine eligibility must be completed within 30 days prior to study entry unless otherwise specified.

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 log and entered into the ACTG database.

6.2.2 Entry Evaluations

On-study evaluations will occur after randomization. Entry evaluations must occur at least 24 hours after screening evaluations unless otherwise specified and be completed before initiating randomized treatment. Participants must begin treatment within 72 hours after randomization.

6.2.3 Post-Entry Evaluations

On-Treatment Evaluations

The window for the week 2 and week 4 study visits is +/- 7 days. The window for all other study visits during the treatment phase is +/- 14 days.

Post-Treatment Evaluations

During the follow-up phase, the window for study visits is +/- 14 days.

Diagnosis of TB

This visit should occur at the time of or as soon as possible after the diagnosis of TB, preferably within 4 weeks.

6.2.4 Discontinuation Evaluations

Evaluations for Randomized Participants Who Do Not Start Study Treatment

All case report forms (CRFs) must be completed and keyed for the period up to and including week 0 (entry).

Premature Treatment Discontinuation Evaluations

Participants who prematurely discontinue study treatment will continue to be followed on study, off study treatment for the remainder of the study follow-up, according to the schedule of events.

Premature Study Discontinuation Evaluations

Participants who prematurely discontinue the study will have evaluations performed as indicated in the schedule of events.

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 protocol-required 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 SAE:

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

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 Medical History

The medical history must include all prior TB, AIDS-defining events, and liver disease. In addition, it must include all diagnoses identified by the ACTG criteria for clinical events and other diagnoses within 30 days prior to study entry. For current criteria, refer to the appendix identified in the study CRF. Allergies to any medications and their formulations must be documented.

6.3.3 Medication History

A medication history including all prescription and nonprescription medications taken within 30 days prior to study entry must be present. Include actual or estimated start and stop dates. A complete HIV and active or latent TB treatment history must be present, with start and stop dates of any antiretroviral or TB medication (estimated if the exact dates cannot be obtained), immune-based therapy, or HIV-related vaccines, including blinded study medications.

6.3.4 Clinical Assessments

Complete Physical Exam

A complete physical examination at entry is to 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. The complete physical exam will also include signs and symptoms, diagnoses, vital signs (temperature, pulse, respiration rate, and blood pressure), height, and weight.

TB Assessment

To exclude active TB at study entry or to diagnose active TB on study, assessment of signs and symptoms should include **at least** the following:

- Any cough, fever, night sweats and/or involuntary weight loss
- Lymphadenopathy and/or abnormalities on lung examination

Targeted Physical Exam

A targeted physical examination at post-entry visits is to include vital signs (temperature, pulse, respiration rate, and blood pressure) and weight. It should be driven by any previously identified or new signs or symptoms including diagnoses that the participant has experienced since the last visit.

Signs and Symptoms

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

Diagnoses

Record all diagnoses identified by the ACTG criteria for clinical events and other diseases.

Concomitant Medications

All new concomitant medications, including all antiretroviral medications, taken since the last report and current concomitant medications modified since the last report should be recorded.

Study Treatment Modifications

Record all study drug modifications, including initial doses, participant-initiated and/or protocol-mandated modifications, inadvertent and deliberate interruptions (i.e., 3 or more missed doses) at each visit. Record permanent discontinuation of treatment.

6.3.5 Chest Radiograph or Chest CT

At screening, **or within 30 days prior to study entry**, and whenever active TB is suspected, a chest radiograph **or chest CT** should be performed.

6.3.6 TST or IGRA

For those participants who are not living in a high TB burden area, a TST or a licensed IGRA assay will be performed at screening if prior positive test results are not already available. High TB burden areas are defined as **areas** with all cases of TB prevalence $\geq 60/100,000$ of the country's population, according to the WHO (<http://apps.who.int/globalatlas/predefinedreports/tb/index.asp>).

All participants require a TST performed within 60 days prior to study entry or on the day of entry. If a TST was done at screening within 60 days of study entry, a repeat TST is not needed. If TB exposure was documented through an IGRA, or a TST that was performed more than 60 days prior to study entry, or by living in a high burden country, a TST must be performed within 60 days prior to study entry or at entry. Participants must return within 7 days to have the results read.

6.3.7 Laboratory Evaluations

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

Hematology

Hemoglobin, hematocrit, red blood cells, white blood cell count, ANC, and platelets.

Liver Function Tests

Total bilirubin, AST (SGOT), ALT (SGPT), and alkaline phosphatase. These tests should be performed at any time during the treatment and post-treatment phase if the participant exhibits signs suggestive of hepatitis (e.g., fatigue, weakness, malaise, anorexia, nausea, vomiting, abdominal pain, pale stools, dark urine, chills) or has signs of jaundice.

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).

6.3.8 Immunologic Studies

CD4+

CD4+ cell counts (both absolute and percentage counts) will be performed throughout the study at the same DAIDS-approved laboratory, if possible.

A screening CD4+ cell count will only be collected if not done within 180 days prior to study entry. A DAIDS-approved laboratory is not required for

the screening CD4+ count.

Because of the diurnal variation in CD4+ counts, determinations for individual participants should be obtained consistently in either the morning or the afternoon throughout the study, if possible.

NOTE: If the flow lab is using dual platform technology to obtain the results, each time a measurement is obtained, the local lab must perform a white blood cell count and differential from a sample collected at the same time.

6.3.9 Virologic Studies

Plasma HIV-1 RNA for Participants on ART

Quantitations must be performed at a DAIDS-approved laboratory in real time using a licensed assay.

6.3.10 Sputum Acid Fast Bacilli Smear and/or **Xpert plus** Sputum Culture

Whenever active TB is suspected, sputum AFB smear and/or **Xpert plus** sputum culture should be performed; **additional tests may be performed**. Positive cultures should undergo speciation, and drug susceptibility testing if positive for MTB. A regional or central reference laboratory may be used.

6.3.11 Pill Count

Pill counts for INH and RPT study treatment should be performed during the treatment phase as indicated in the schedule of events.

6.3.12 Adherence Interview

Self-report interviews on adherence to INH and RPT study treatment should be performed during the treatment phase as indicated in the schedule of events.

6.3.13 Stored Plasma/PBMC/Serum

Prior to June 1, 2014, the first 30 participants enrolled at each non-US site and the first 50 participants enrolled in the US were assigned to have plasma and serum stored at entry and every 48 weeks. Samples from these participants will continue to be collected for the duration of the study. In addition, at sites with the capability, viable PBMCs are being stored for future testing at all time points specified above for participants assigned to have PBMC stored.

Participants enrolled after May 31, 2014 will not be assigned to have plasma, serum, or PBMC samples collected at entry and every 48 weeks.

At the time of or as soon as possible after diagnosis (see section 6.2.3 of the protocol), all participants diagnosed with active TB, regardless of

enrollment date, will have plasma, serum, and PBMCs collected (where possible) for future testing. Participants already selected for plasma/PBMC/serum storage will continue to have samples taken every 48 weeks as previously scheduled. Otherwise, no additional plasma/PBMC/serum storage samples will be collected.

Sites will follow storage, testing, and shipping instructions provided on the A5279 PSWP.

6.3.14 PK Samples

Under Version 1.0, samples were collected from the first 90 participants in Arm A who were taking EFV at entry and meet other criteria in Section 10.0.

Samples will be collected from the first 90 participants in Arm A who are taking NVP and meet other criteria in Section 10.0.

Once Version 2.0 of this study is implemented:

- 1. EFV concentrations will be evaluated in an additional 30 participants from Arm A. These 30 individuals will serve as controls for the EFV analysis. A PK sample will be collected in these 30 individuals at weeks 0, 2 and 4 similar to the other EFV PK analysis; however, an additional week 16 sample will be collected as an “EFV only” sample. The week 16 sample will allow for a washout period after completion of RPT and INH.**
- 2. Samples will also be collected in the first 90 participants in Arm B enrolled into Version 2.0 who are taking EFV at entry and meet other criteria in Section 10.0.**

6.3.15 Pharmacogenetic Sample

This sample will be collected from those participants in Arm A **and Arm B** who are taking part in the PK study. **This will include those individuals in Arm A who are serving as controls for EFV PK**, and have consented to the collection of this sample. It should be collected at entry; however, if it is not collected at entry, it may be collected at week 2 or 4.

6.3.16 Stored Plasma for Virology

For those participating in the PK portion of the study, plasma will be collected **at week 8** and stored **for HIV virology**.

7.0 CLINICAL MANAGEMENT ISSUES

This study will use 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/>.

7.1 Toxicity

If study drugs are held for toxicity, participants in Arm A will have 8 weeks from enrollment to complete 4 weeks of treatment, and those in Arm B will have 54 weeks to complete 36 weeks of treatment.

Grades 1 and 2: Participants may continue INH and RPT, at the discretion of the site investigator with careful follow-up.

Grades 3 and 4: Study drugs should be held until return to baseline (entry visit levels) if baseline was >Grade 2, or until ≤Grade 2 or within normal limits if baseline was ≤Grade 2. Study drugs may be permanently discontinued at the discretion of site investigator.

Gastrointestinal

For nausea/vomiting and/or diarrhea ≥Grade 3 or Grade 2 toxicity if symptoms were not present at the previous visit, all study drugs should be held until the symptoms have resolved. Reintroduce study drugs with caution.

Antiemetic and antidiarrheal medication may be used at the site investigator's discretion.

If nausea and vomiting occur as a result of hepatitis that is not due to study drugs, every effort should be made to reintroduce the study drugs after the symptoms subside to baseline levels.

Cutaneous

If Grade 2 or 3 or showing a significant increase over baseline, all study drugs should be held until the toxicity resolves. Study drugs should be reintroduced with caution. Grade 4 cutaneous or Grade 4 mucocutaneous rash is a major toxicity, and all study drugs should be interrupted pending resolution of the toxicity. Study drugs may be permanently discontinued if believed to be the cause of toxicity. Study drugs may also be interrupted and reintroduced at the discretion of the site investigator.

Drug-Associated Fever

If ≥Grade 3, all study drugs should be held until the temperature returns to normal. Study drugs should be reintroduced with caution. Recurrence of symptoms on reintroduction will result in permanent discontinuation of the responsible agent. No alteration of dose will occur.

Elevated Liver-Associated Enzymes

If AST (SGOT), ALT (SGPT), or total bilirubin increase two grades over baseline (if baseline is <Grade 2) to maximum of Grade 3, study drugs should be held until the levels return to baseline or Grade 2. Reintroduce the study drug(s) with caution.

If baseline was Grade 2 and liver-associated enzyme(s) increase to Grade 3, no action is required.

Grade 4 is a major toxicity, and study drugs will be interrupted pending resolution of the toxicity. Permanent discontinuation of study drugs is at the site investigator's discretion.

Peripheral Neuropathy

Peripheral neuropathy associated with INH is usually avoided by the concurrent administration of vitamin B₆. In this study, all participants will take vitamin B₆ concomitantly with INH. If peripheral neuropathy develops, every effort should be made to determine the etiology (i.e., whether the neuropathy is due to INH toxicity, alcohol, or other factors). Participants with peripheral neuropathy <Grade 2 may be entered into the study, but should be monitored carefully for any progression of peripheral neuropathy.

For Grade 1 or 2, continue the study drugs and follow the participant more frequently for progression of peripheral neuropathy. Consider increase in vitamin B₆ dose. For Grade 3 or 4, discontinue INH until toxicity resolves to Grade ≤ 2 ; then INH may be reintroduced at the site investigator's discretion. If peripheral neuropathy does not resolve despite discontinuation of INH, the INH may be reintroduced at the site investigator's discretion.

7.2 Pregnancy

Pregnant women will discontinue RPT and be treated according to in-country standard of care. They will be encouraged to continue on study and complete the evaluations per the schedule of events. At the end of the pregnancy, the outcome and AEs for the participant and the infant will be recorded on an outcome CRF.

Disclosure of pregnancy to parents of participants who are minors will be handled according to in-country standard of care.

Pregnancies that occur on study in female participants receiving ART should be reported by the CRS to The Antiretroviral Pregnancy Registry. More information is available at www.apregistry.com. For U.S. sites: Phone: 800-258-4263; Fax: 800-800-1052. For non-U.S. sites: Phone: 910-679-1598; Fax: 44 1628-789-666 or 910-246-0637

8.0 CRITERIA FOR DISCONTINUATION

8.1 Permanent Treatment Discontinuation

- Drug-related toxicity (see section 7.1)
- Requirement for prohibited medications (see section 5.4)
- Pregnancy or breastfeeding while receiving RPT
- Reaching a defined clinical endpoint
- Completion of treatment phase as defined by 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

8.2 Premature Study Discontinuation

- **3 or more consecutive missed study visits**
- Request by the participant to withdraw

- Request of the primary care provider if s/he 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, NIAID, IRB or EC, US FDA, Office for Human Research Protections (OHRP), investigator, pharmaceutical supporter, or other government agencies as part of their duties to ensure that research participants are protected.

9.0 STATISTICAL CONSIDERATIONS

9.1 General Design Issues

This is an open-label, randomized, phase III study to evaluate whether a short-course, 4-week RPT/INH regimen is non-inferior to a standard 9-month daily INH regimen (9-INH) for the prevention of active TB in HIV-infected participants. We intend to recruit 3000 participants. Each participant will be followed until 3 years after entry of the last participant. We anticipate accrual to occur at the rate of approximately 100-120 participants per month, once a substantial number of sites that intend to participate have initiated accrual.

9.2 Endpoints

9.2.1 Primary Endpoint: time from randomization to first diagnosis of active TB

9.2.2 Secondary Endpoints

9.2.2.1 Safety and tolerability:

9.2.2.1.1 Safety endpoints:

- a) Occurrence of one or more SAEs vs. no SAEs
- b) Highest reported grade of each new Grade 3 or 4 laboratory value or sign or symptom that is at least one grade increase from baseline for targeted events [i.e., nausea and vomiting, cutaneous, drug-associated fever, elevated AST (SGOT), ALT, (SGPT), or bilirubin, and peripheral neuropathy]

9.2.2.1.2 Tolerability:

Ordered categorical variable indicating most stringent level of study drug management due to toxicity that was required over the treatment period:

1. Premature permanent treatment discontinuation
2. Treatment hold for more than 7 consecutive days
3. None of the above

9.2.2.2 Time from randomization to death from any cause

- 9.2.2.3 Time from randomization to death due to a non-TB event
- 9.2.2.4 EFV plasma concentrations at weeks **0, 2 and 4** in the first 90 participants **randomized to Arm A** who enter the study taking EFV and who meet dose timing criteria; **and, under Version 2.0, at weeks 0, 2, 4, and 16 in the first 30 participants randomized to Arm A who enter the study taking EFV and who meet dose timing criteria.**
- 9.2.2.5 NVP plasma concentrations at weeks **0, 2 and 4** in the first 90 participants **randomized to Arm A** who enter the study taking NVP and who meet dose timing criteria.
- 9.2.2.6 Under Version 2.0, EFV plasma concentrations at weeks 0, 2, and 4 in the first 90 participants randomized to Arm B who enter the study taking EFV and who meet dose timing criteria.**
- 9.2.3 Additional secondary endpoints for supportive/exploratory analyses that will be defined in more detail in separate analysis plans:
 - 9.2.3.1 Adherence to TB treatment: self-reported number of pills missed since last visit and pill count while on study drug
 - 9.2.3.2 Antibiotic resistance pattern of MTB isolates in participants who develop active TB
 - 9.2.3.3 HIV-1 RNA changes from baseline to week 8 in the first 90 participants entering the study taking EFV and who meet PK analysis dose timing criteria and in the first 90 participants entering the study taking NVP and who meet PK analysis dose timing criteria (may be evaluated only in a subset, e.g., those with very low EFV or NVP levels)
 - 9.2.3.4 Polymorphisms in host genes involved in metabolism or transport of EFV, NVP, and RPT including: CYP2B6, CYP3A4/5, SLCO1B1, CYP2A6, UGT2B7, PXR (pregnane X receptor), CAR (constitutive androstane receptor), and HFN4A (hepatocyte nuclear factor).
 - 9.2.3.5 Cost-effectiveness measures
- 9.3 Randomization and Stratification

Participants will be randomized in a 1:1 ratio to the two arms using permuted blocks. Randomization will be stratified by: CD4+ cell count <100, 100-250, and >250 cells/mL; ART, receiving ART at entry versus not.
- 9.4 Sample Size and Accrual

In a recently-completed phase III clinical trial comparing 6 months of daily INH (6-INH) to 12 weeks of weekly RPT/INH or RIF/INH and to continuous INH, the rate of active TB

(including death ascribed to TB) was 1.77/100 PY both in the 6-INH arm (N=328) and in the study as a whole (N=1150) with no attenuation over time [65]. This study excluded participants with an indication for ART and whose CD4+ cell counts were relatively high. A5279 will enroll participants with any CD4+ cell counts; thus, the team anticipates a higher rate of active TB. In addition, a survey of ACTG studies conducted at non-U.S. sites found that approximately 15% of deaths occurring at non-U.S. sites had an unknown cause (including causes such as “HIV disease” or “natural causes” as unknown). This is fewer deaths with unknown COD than in the TB study referenced above [personal communication]. Both because we anticipate entering participants with lower CD4+ cell counts and because we anticipate identification of nearly all TB-related deaths, we expect the rate of active TB (including death ascribed to TB) will be at least 2.00/100 PY, and possibly higher. We will use a noninferiority design to test the hypothesis that the ultra-short-course RPT/INH regimen has efficacy that is no worse than the 9-INH control arm (standard of care [SOC]) within an accepted tolerance to define noninferiority. We will perform the study with a one-sided 0.025 significance level (i.e., 2-sided 0.05-level) and will target 90% power to confirm noninferiority if it is, in fact, true. Follow-up will continue to 3 years beyond entry of the last participant. Participants lost to follow-up and those who die from causes unrelated to TB will be censored. Participants with an unknown COD will be considered to be TB endpoints. Non-TB mortality (including unknown COD) is expected to be lower than the rate of active TB, and the number of deaths with unknown COD should be minimal: nonetheless, sensitivity analyses described below will be conducted.

The following table provides total sample sizes needed to confirm the noninferiority of short-course RPT/INH for TB incidence rates of 2.00 and 2.25/100 PY on the SOC arm and a range of tolerance expressed as TB incidence rate per 100 PY of observation. The 9-INH arm is the SOC. To provide concrete numbers for comparison and to put the tolerance regions in scale, the table provides the 3- and 5-year percentages of active TB for the control (9-INH) arm and for a range of noninferiority tolerance rates of TB per 100 PY. We anticipate accrual will be 2 years, but could be 1.5 to 2.5 years from the time when substantial sites have joined the study.

	Rate/ 100PY	Active TB Percent		Total accrual given accrual duration and target baseline TB rates/100PY					
		3yr %	5yr %	1.5yr acc		2.0yr acc		2.5yr acc	
				2.00	2.25	2.00	2.25	2.00	2.25
SOC arm	2.00	5.9%	9.6%						
	2.25	6.6%	10.8%						
Tolerance	3.00	8.7%	14.1%	3723	6587	3410	6224	3335	5945
	3.25	9.4%	15.2%	2596	4025	2452	3804	2326	3608
	3.5	10.1%	16.3%	1950	2782	1842	2628	1747	2494
	3.75	10.8%	17.4%	1544	2449	1459	1968	1383	1867

This has been adjusted for 10% total loss to follow-up (LFU) and non-TB death by 3 years which has been modeled as an exponential competing risk, and for interim monitoring (2% increase by multiplication).

Given substantial issues of adherence, which can lead to drug resistance, failure to complete the full 9 months of INH, and cost in use of 9-INH in clinical practice, the team feels an incidence rate of 3.25/100 PY as the tolerance boundary for evaluation of short-course RPT/INH would be acceptable. This leads to a sample size of around 2452 participants. The team proposes to accrue 3000 participants to allow essential subgroups, such as the CD4+ cell count and ART strata, to be evaluated with some degree of certainty. Should a stratum break 60:40, with 3000 participants, there is 80% power (2-sided alpha=0.05) to test non-inferiority within the larger stratum with the same 3.25/100 PY tolerance. With the larger sample size, the confidence bounds on the difference in the TB incidence rate between the arms in the full study will be narrower than required to rule out the tolerance of TB incidence of 3.25/100 PY. Thus, should the true difference be much smaller, this can be detected to inform the field.

When setting the tolerance region for a study such as this, an important consideration is whether the tolerance region is therapeutic. Section 2.1 contains a table of studies reporting placebo arm TB incidence rates in studies in HIV-infected individuals. A5279 requires PPD or IGRA positivity or residence in an area with a high TB burden. This table presents the 3- and 5-year percentages of active TB for a range of incidence rates for active placebo in participants who were PPD+ or who were PPD+/- in a country with a high TB burden.

	Rate/ 100PY	Active TB Percent	
		3yr %	5yr %
Placebo	5.00	14.3%	22.6%
	8.00	22.1%	34.1%
	10.00	27.1%	41.0%

The targeted tolerance region for this study demonstrates a considerable reduction in active TB compared to the reported rates with placebo. It should also be remembered that the tolerance region represents the limits of a 95% CI; that is, if noninferiority is confirmed, the actual observed rate in the short-course regimen will be substantially less than the tolerance boundary.

9.5 Monitoring

This study will be reviewed at least annually by the NIAID African DSMB. For all reviews, the DSMB will be provided detailed information on safety (including mortality and regimen tolerability) and administrative aspects (screening failures, accrual, compliance with visits, specimen collection, and participant retention).

We anticipate the first efficacy analysis will be performed at approximately the second annual review. Should accrual initiate rapidly, the review may be accelerated to ensure the DSMB has considered early information on the rates of active TB before accrual closes. Especially early in the study, an important function of the DSMB will be to consider the consistency of the magnitude of event rates with the design assumptions. The timing of subsequent efficacy reviews will be decided in conjunction with the DSMB.

A Peto use function will be employed for formal between-arm comparisons.

The primary focus of this study is relatively long-term outcomes. The team urges caution in considering early stopping or release of information on this study, especially if interim results are based on short follow-up. The team suggests that the following guidance be considered in deliberations:

- If there is early evidence of the noninferiority of short-course RPT/INH, the team intends that the study continue to full accrual and follow-up to confirm that long-term results are consistent with early evidence, and to evaluate the possible superiority of short-course RPT/INH.
- If the 99.9% CI at early interim analysis excludes an IRD of 0.00/100PY in favor of the RPT arm (i.e., early evidence of the superiority of RPT), the team intends that the study continue to full accrual and follow-up to confirm that long-term results are consistent with early evidence.
- If the 99.9% CI at early interim analysis excludes an IRD of 0.00/100PY in favor of the 9-INH arm, the team intends that the study continue with close monitoring.
- If the 99.9% CI at interim analysis excludes an IRD of 1.25/100PY suggesting the RPT arm is significantly worse than the allowed tolerance boundary, the team intends that consideration be given to stopping the study.

Reports on safety will be provided to the DAIDS Clinical Representative every 6 months. In addition, periodic reports of data pooled over arm will be provided to the team that detail accrual, participant status, and the delinquency of forms and specimens. The study co-chairs will receive pooled safety information periodically. The form and schedule of these will be detailed in the Monitoring Plan to be developed by SDAC, the DMC, and the team. Some secondary objectives will not be evaluated until the end of the study either because they are based on subgroups that will be identified retrospectively or because they are not related to safety or the primary outcomes, but study monitoring will include assessment of the availability of data needed for identified analyses (eg, isolates from prophylaxis failures).

The team will conduct monitoring for EFV and NVP PK as described in Section 10.0.

9.6 Analyses

Primary

The primary objective will be evaluated by calculating a CI around the difference between the observed TB incidence rates with the confidence level adjusted for stratification and interim monitoring. Data from prior studies are consistent with a constant TB rate, but this will be confirmed in these data. If this assumption does not hold, other methods will be employed (e.g., piece-wise models) to confirm whether non-inferiority holds or not over the time frame of the study. As noted above, deaths attributed to TB will be considered to be endpoints. Deaths attributed to causes other than TB will be censored. Deaths from unknown causes are expected to be minimal. For the primary analysis, deaths from unknown causes will be coded as TB events. Sensitivity analyses will include censoring all deaths from unknown causes, including all nontraumatic deaths as events, and use of weighted modeling that attributes portions of

deaths from unknown causes to be due to TB or non-TB causes based on predictors of COD in deaths with known COD.

This is functionally a strategy study, comparing 9 months of treatment to an ultra-short-course. While strict intention-to-treat (ITT) analyses are preferred in classical superiority studies, they can bias noninferiority studies to erroneously confirm noninferiority if non-compliant participants in both arms dilute the treatment difference. However, in this study, clinical practice in long-term INH prophylaxis suffers from noncompliance both in terms of adherence and also drop-off. A 9-INH arm that includes participants with non-adherence and courses that are shorter than 9 months is the true comparator arm. Thus, for this noninferiority study, the ITT analysis will be primary. An 'as treated' analysis confined to those with pre-specified adherence levels and/or full course treatment (we anticipate poorer adherence in the 9-INH arm) will be performed for exploratory purposes.

We will also perform multi-covariate analyses of predictors of active TB. As required by NIH, interactions of gender and race/ethnicity with treatment will be formally tested and presented. As noted above, we will evaluate the noninferiority of short-course RPT/INH within the CD4+ cell count and ART strata as differences could be important to inform the field. There will be no adjustment to the alpha level for multiple comparisons, and results will be presented cautiously.

Secondary

Safety analyses will consider the rates and nature of SAEs and of Grades 3 and 4 events, treatment modifications including temporary holds, and treatment discontinuations. These will be analyzed as dichotomous measures (percent of participants who meet a given event criterion), failure time measures (eg, time to first treatment modification; time to first safety event), and counts (eg, number of combined SAE + Grades 3 and 4 events per person).

Overall mortality and non-TB mortality, including all deaths as events and possibly censoring traumatic death, will be evaluated with log rank tests stratified by CD4+ count and ART use. If there are sufficient deaths, proportional hazards modeling will be performed to evaluate risk factors.

Adherence will be evaluated with the results of self-report interviews and pill counts. Associations of adherence and outcome will be explored using pre-defined levels of adherence. We will also explore whether there are adherence differences between the arms during the first month when both arms receive active intervention.

The rate and pattern of antibiotic resistance among participants who are diagnosed with active TB will be described. Should active TB rates be around 2.00/100 PY in each arm, there will be about 8% TB overall on the study or 240 cases which will provide some opportunity to compare the rates of resistance, patterns of antibiotics to which the MTB organisms are resistant, and time trends in resistance.

An exploratory analysis among participants in the PK study (see Section 10.0) will evaluate the association of HIV virologic outcomes (eg, 'blips', confirmed loss of virologic

control) and safety with both the directly observed concentrations of EFV and NVP and also the trough antiretroviral levels and select PK parameters (eg, AUC) derived from the Bayesian modeling. The EFV and NVP parameters will be evaluated both as continuous measures and also dichotomized at 1 mg/L (EFV) and 3 mg/L (NVP), levels that define acceptance in Section 10.0.

9.7 Cost-Effectiveness Analysis

A previously described model of LTBI treatment will be used to estimate the costs and cost-effectiveness of RPT/INH as compared with other treatment strategies and no treatment [66]. Efficacy, adherence, and toxicity data for RPT/INH will be obtained from the trial, with other parameters taken from the available literature. The underlying probability of activation will be varied using a risk multiplier to simulate various high-risk populations not included in the study (HIV-negative contacts, diabetes mellitus, end-stage renal disease, etc.).

In the best-case scenario, costs for treatment of LTBI and active TB will be based on current U.S. practice. Because the costs of treating LTBI and active TB in most high-incidence areas are largely unknown, we will make certain assumptions and then perform a sensitivity analysis over a wide range of estimates.

Costs and cost-effectiveness (measured in cost per quality-adjusted life-years) will be calculated for all regimens. Analysis will focus on determining thresholds for cost, efficacy, and adherence parameters above (or below) which the optimal strategy changes. Calculations will be repeated for other simulated high-risk populations to inform public health policy on the appropriate use of the new regimen in various TB control programs.

10.0 PHARMACOLOGY PLAN

10.1 Pharmacology Objectives

10.1.1 Primary: To investigate the effects of concomitant RPT/**INH** administration on EFV or NVP PK and assess these concentrations relative to baseline values and historical controls with and without RIF, and accepted minimal effective EFV and NVP concentrations.

For this study, the historical control for EFV PK data will be from the pharmacology substudy conducted as part of A5095. This study population consisted of HIV-infected persons who were treatment-naïve with plasma HIV RNA levels >400 copies/mL and not receiving concomitant agents that interact with EFV. The first choice for historical control data for NVP, like EFV, will be from ACTG studies. One published population PK study of NVP is from ACTG 241, a study in HIV-infected persons who also received ZDV and ddI [67].

10.1.2 Secondary: To investigate the PK of RPT.

10.1.3 Secondary: To investigate relationships among genetic characteristics of drug metabolizing enzymes and drug transporters and the PK characteristics of EFV, NVP, and RPT.

10.1.4 Determine the PK characteristics of EFV and its 7-OH-EFV and 8-OH-EFV metabolites when given in combination with RPT+INH (Arm A) and when given with INH alone (Arm B).

10.1.5 Compare EFV PK data obtained from combination therapy with RPT+INH and INH alone with a control group consisting of a set of plasma samples with participants receiving ART containing EFV but not RPT or INH, which will be collected from individuals in Arm A that have completed RPT/INH therapy and have allowed for a washout period.

10.2 Pharmacology Study Design

The pharmacologic evaluations are designed to provide information on whether RPT, because of its CYP3A-inducing properties, decreases the concentrations of the NNRTIs, EFV and NVP, which are both substrates for CYP3A. The hierarchy for rifamycin enzyme-inducing potency is: RIF > RPT > rifabutin (RFB). RIF reaches maximal enzyme induction at a dose of 600 mg once daily. RPT enzyme induction exhibits dose dependency. At a RPT dose of 600 mg once daily, the enzyme induction appears close to that of RIF at 600 mg once daily; lower RPT doses of 300 mg once daily or 600 mg every 3 days produce less enzyme induction than RPT at 600 mg once daily and RIF at 600 mg once daily [30]. There is considerable information on the PK of EFV and NVP when given with RIF; there are no data available on the effect of RPT on the PK of EFV and NVP. The pharmacologic evaluations for A5279 are designed to provide data on the effects of RPT on the PK of EFV and NVP.

The effect of RPT on the PK of EFV was evaluated before participants on NVP were allowed to enroll into this study. The A5279 team reviewed the EFV PK data on an on-going basis, as described in section 10.3. Since these data showed adequate EFV exposure in the presence of RPT treatment, the study is open to participants on NVP, and NVP PK will be evaluated in the first 90 participants in Arm A taking NVP at entry. NVP PK will be evaluated in a similar manner as the EFV PK analysis was conducted.

Data are accumulating to suggest that INH affects EFV clearance primarily through the CYP2A6 pathway. The effect of RPT on EFV clearance is expected to occur through induction of the CYP2B6 pathway. Each of these two pathways leads primarily to different metabolites of EFV. The 8-hydroxy-efavirenz metabolite is the primary metabolite formed via the CYP2B6 pathway, while the 7-hydroxy-efavirenz metabolite is the primary metabolite formed via the CYP2A6 pathway. Therefore, quantitation of these metabolites of EFV will allow investigation of the separate effects of RPT and INH on EFV metabolism.

At the implementation of Version 2.0:

1. EFV concentrations will be evaluated in an additional 30 participants from Arm

- A. These 30 participants will serve as controls for the EFV analysis. A PK sample will be collected in these 30 individuals at weeks 0, 2, and 4 similar to the other EFV PK analysis; however, an additional week 16 sample will be collected as an “EFV only” sample. The week 16 sample will allow for a washout period after completion of RPT and INH.**
- 2. Additional pharmacologic assessments will be made in Arm B (INH only) to investigate the effect of INH on EFV metabolism. Arm B participants receive 9 months of daily INH therapy. Pharmacologic evaluations, similar to those performed in the first 90 participants in Arm A, will be made in the first 90 subjects in Arm B who are taking EFV at entry at the time of implementation of protocol Version 2.0. These PK assessments will take place at weeks 0, 2, and 4, as they are in Arm A. EFV and its major metabolites, 7-OH-EFV and 8-OH-EFV will be quantified in human plasma. Concentrations of EFV and its metabolites will also be determined from the samples already collected from first 90 participants in Arm A. The addition of these assessments from Arm B patients will allow the team to better understand what role each of the anti-tuberculosis drugs, INH and RPT, individually have on EFV metabolism. At present, there are no such data available.**

A sparse sampling approach will be used in A5279. The rationale for this approach is based on the following considerations. First, data exist on the PK of EFV and NVP in HIV-infected participants with and without concomitant RIF administration [67; 68, 69, 70]; unpublished data from ACTG studies A5095/A5097s and A5221]. Second, RPT at a dose of 600 mg/day is not expected to produce enzyme induction any greater than that of RIF 600 mg/day [29]. Therefore, third, if RPT indeed reduces EFV and NVP concentrations, this reduction should not be greater than that observed with RIF. These considerations allow a sparse sampling approach (versus an intensive dose-interval PK study) to investigate whether EFV and NVP concentrations in the presence of RPT are more comparable to historical controls who are receiving RIF, or to historical controls who are not receiving RIF.

Exposure-response relationships between EFV and NVP concentrations and virologic failure have been demonstrated. For example, Cohen recently reported that in an evaluation of 142 HIV-infected persons, EFV concentrations <1 mg/L were strongly associated with an increased risk for virologic failure (odds ratio 12.5, 95% CI, 2.7-57.3) [69]. The collective data for EFV indicate an increased risk of virologic failure if trough (or mid-interval) concentrations are less than 1 mg/L. EFV PK data from A5097 indicate that 21% of participants receiving the standard dose of EFV had trough concentrations less than 1 mg/L. These data provide a basis to select for this study that the proportion of participants who have trough concentrations less than 1 mg/L when EFV is combined with RPT is not greater than 20%. Several investigations have found relationships between low NVP trough concentrations and an increased risk of virologic failure. de Vries-Sluijs reported a 5-fold increased risk of virologic failure in participants who had NVP trough concentrations less than 3 mg/L. A NVP trough of less than 3 mg/L is the present consensus threshold for an increased risk of virologic failure [71]. In adults receiving the usual NVP dose of 200 mg twice daily, the proportion of participants who are expected to have concentrations less than 3 mg/L appears to range from 7% to 25%.

These data form a basis, like that for EFV, that proportion of participants with trough NVP concentrations less than 3 mg/L is not greater than 20%.

Differences among patients in their PK characteristics of EFV, NVP, and RPT are known to arise as a result of differences in genes that encode for drug-metabolizing enzymes and drug transporters. Because PK variability has been associated with differences in drug response, understanding whether the differences in concentrations has a genetic basis in how the drug is metabolized, or a nongenetic basis (e.g., patient medication adherence) is important to understand the treatment outcomes of A5279. Participants will be asked to provide informed consent to study polymorphisms in host genes involved in metabolism or transport of EFV, NVP and RPT. Consent for genetic testing is optional, and a participant may refuse genetic sampling and still participate in the study. The genes of interest for A5279 are: CYP2B6, CYP3A4/5, SLCO1B1, CYP2A6, UGT2B7, PXR (pregnane X receptor), CAR (constitutive androstane receptor), and HFN4A (hepatocyte nuclear factor).

1. EFV Sample Size: 90 participants receiving EFV and RPT/INH (**Arm A**) **sampled at weeks 0, 2, and 4.**

Version 2.0 will also include the following EFV evaluations:

- a. **30 additional participants receiving EFV from Arm A sampled at weeks 0, 2, 4, and 16, to serve as controls**
 - b. **90 participants receiving EFV and INH (Arm B) sampled at weeks 0, 2, and 4.**
2. NVP Sample Size: 90 participants receiving NVP and RPT/INH (**Arm A**) **sampled at weeks 0, 2, and 4.**
3. EFV Sampling Strategy
The sampling strategy for EFV assumes that EFV doses will be taken in the evening. Blood samples for quantitation of EFV will be obtained at three study visits: entry (prior to the start of RPT and INH, Arm A) and the weeks 2 and 4 study visits. **The control participants from Arm A (n=30), who will be enrolled with Version 2.0, will have an additional PK sample obtained at week 16, in addition to weeks 0, 2 and 4.** One blood sample will be obtained at each visit. With the dose taken the night before, this sample should be approximately 12 hours post dose, but should not be drawn any sooner than 10 hours after the previous evening's dose or any later than 24 hours after the dose.

If the study participant is taking EFV in the morning, the participant should change to evening dosing for the PK studies. After completion of the week 4 PK study, the participant may then change back to morning dosing, **with the exception of controls who should wait until after the week 16 sample has been drawn to change their dosing time.** The following schedule may be used for the conversion from morning to evening dosing.

Entry Day -4	Four days prior to the entry (week 0) PK visit, the morning dose should be taken as usual.
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Entry Day -3	Three days prior to the entry visit and the pre-RPT PK sample, a morning dose should be taken as usual. Additionally on this day, a bedtime dose should be taken; this dose will be taken approximately 12 hours after the morning dose.
Entry Day -2	NO morning dose should be taken. A bedtime dose of EFV should be taken.
Entry Day -1	A bedtime dose should be taken.
Entry/PK Study Day 0	Blood samples for the PK study will be taken as described above. A bedtime dose of EFV should be administered. The bedtime dosing schedule for EFV should be maintained through the week 4 PK sample, or week 16 for the controls.
+1 day after week 4 (or 16 in a subset) PK	A morning dose of EFV should be taken; this dose will be approximately 12 hours after the evening dose given on Study Day 0. NO bedtime dose should be taken.
+2 day after week 4 (or 16 in a subset) PK	The participant's usual dosing schedule for EFV should be resumed.

4. NVP Sampling Strategy

The sampling strategy for NVP assumes twice daily administration with one dose in the morning and one dose in the evening. Blood samples for quantitation of NVP will be obtained at three study visits: entry (prior to the start of RPT and INH, Arm A) and the weeks 2 and 4 study visits. One blood sample will be obtained at each visit. This sample should be obtained before the morning dose of NVP is administered, and thus should be approximately 12 hours after the prior evening's dose. This sample should not be taken any earlier than 10 hours or later than 14 hours after the prior dose.

5. Medication Adherence

In all cases, the times and dates of all doses of RPT and either EFV or NVP taken in the previous 3 days must be recorded on the CRF. Samples should not be collected from participants who have missed any doses of RPT and EFV, or NVP within 3 days prior to the study visit.

6. EFV, 7-OH-EFV, 8-OH-EFV, and NVP Quantitation

EFV, **7-OH-EFV, 8-OH-EFV**, and NVP concentrations will be determined in a Clinical Laboratory Improvement Amendments (CLIA)-certified laboratory. The goal is for EFV and NVP concentration information from the entry and weeks 2 and 4 (**and 16 in a subset**) samples to be available for evaluation by the A5279 team during the course of the study.

7. RPT PK

At the time that a blood sample is obtained for EFV or NVP at the weeks 2 and 4 visits, an additional blood sample will be obtained for RPT. RPT has an approximate 15-hour half-life which allows sampling at the same time that samples are collected for EFV or NVP.

8. Pharmacogenetics.

An optional blood sample for genetic testing of variations in drug metabolizing enzymes and drug transporters for EFV, NVP, and RPT will be collected at the entry visit (prior to the start of RPT and INH) from participants who are also having an entry sample obtained for measurement of either EFV or NVP. If this sample is not collected at entry, it may be collected at week 2 or 4.

10.3 Primary and Secondary Data, Modeling, and Data Analysis

1. The EFV PK data will be judged acceptable if **we have evidence that >80%** of participants have EFV concentrations ≥ 1 mg/L.
2. The NVP PK data will be judged acceptable if **we have evidence that >80%** of participants have NVP concentrations ≥ 3 mg/L.

Any participant who has a baseline (pre-RPT) sample **or a week 2 or 4 sample in which the concentration for the relevant ARV** is below the limit of quantitation will be deemed to be non-adherent, and the PK data will not be evaluable. The observed concentrations of EFV and NVP and the times post dose that these concentrations were obtained will be summarized. In addition, because exact trough levels (pre-dose concentrations) are not required to be obtained, the PK characteristics of EFV and NVP may be estimated for each individual participant and trough concentrations estimated using these EFV and NVP PK parameters. Parameter estimation will be accomplished using Bayesian estimation methods implemented in ADAPT II (Biomedical Simulations Resource at the University of Southern California, Los Angeles, CA). This approach utilizes maximum a posteriori Bayesian estimation (MAP) to estimate individual PK parameters utilizing prior information for the population mean and variances of the PK characteristics of EFV. Prior PK data for EFV indicate that its PK characteristics are sufficiently well described with a 1-compartment structural model. A proportional variance model will be used to describe the output error associated with the concentration-time data (variance model). Each observation will be inversely weighted by the model-based estimated variance (of the corresponding predicted value), assuming the variance is proportional to the predicted value and coefficient of variation of 10% for the assay. The primary estimated PK parameters will include the volume of the distribution (V), and elimination rate constant (k_e). Apparent oral clearance (CL/F), elimination half-life ($T_{1/2}$), and AUC will be calculated from these parameters using standard equations.

The team wishes to detect any issues that might exist with EFV or NVP concentrations very early in accrual of participants receiving these ARVs. The team will assess the proportion of participants who have **acceptable** (as defined above) EFV and NVP concentrations **up to four times** during the study for EFV and NVP separately. **The first phase of the evaluation will be conducted in the first 31 evaluable participants who are distributed across key geographic regions, 18 years or older, and receiving an ARV.** The second phase assessment will be made when trough levels are available for a total of approximately 90 evaluable participants at weeks 2 and 4. **Samples in the first phase (first 31 evaluable participants who are 18 years or older) will be shipped and assayed frequently to facilitate rapid**

evaluation and decision making in this early phase. Should early accrual of participants receiving EFV or NVP be so rapid that a substantial number of the 90 would be entered before the first 31 who are 18 years or older can be evaluated, accrual of participants receiving that ARV may be suspended pending results of the first phase assessment. Accrual of participants receiving that ARV would be resumed if the results in the first phase were acceptable.

The first phase assessment will be conducted in 2 or 3 stages depending on the rate of accrual of evaluable participants. Accrual for the PK evaluation may pause within the first phase for evaluation of data, such as adherence or the metabolizer and transporter genes noted above, should early results be of concern. Assuming the first phase is conducted in three stages, the first evaluation for each agent will be made when weeks 2 and 4 trough levels are available for 9 evaluable participants; if ≤ 4 of the 9 have acceptable ARV levels at both weeks 2 and 4, the team would consider this to be of concern. The second evaluation will be made when weeks 2 and 4 trough levels are available for 21 evaluable participants; if ≤ 12 of the 21 have acceptable ARV levels at both weeks 2 and 4, the team would consider this to be of concern. The third evaluation will be made when weeks 2 and 4 trough levels are available for 31 evaluable participants; if ≤ 20 of the 31 have acceptable ARV levels at both weeks 2 and 4, the team would consider this to be of concern. This rule was developed to have a high likelihood (95% or higher) of continuing to accrue participants if the true underlying rate of having acceptable ARV concentrations is greater than 80% and meets both Optimum and Min/Max criteria [72; conducted with PASS 2011]. Should accrual of participants receiving an ARV be so rapid that the first phase evaluation with 21 participants would be uninformative, it will not be performed and the first and third evaluation rules will apply: ie, the team would be concerned if $\leq 4/9$ or $\leq 20/31$ participants have acceptable ARV levels.

The following table provides overall probabilities that ARV levels will be found acceptable in the first phase assessment for a range of values for the true underlying proportion who fail to have acceptable ARV levels at weeks 2 and 4. These probabilities are provided for the 3-stage and 2-stage options in the first 31 evaluable participants.

Underlying rate Failing criteria	Prob finding Acceptable 3-stage	Prob finding Acceptable 2-stage
0.20	0.951	0.954
0.40	0.225	0.221
0.45	0.096	0.098
0.50	0.033	0.033
0.60	0.001	0.002

That is, if the true probability of failing to meet the ARV level is 20% (so greater than 80% having acceptable drug levels), there is greater than 95% likelihood of finding the drug levels at weeks 2 and 4 to be acceptable. If, however, the true probability of failing to meet the ARV level criterion is 45% (so showing evidence

that the true rate achieving acceptable levels might be only 55%), there is less than a 10% chance of erroneously concluding the drug levels at weeks 2 and 4 to be acceptable in the first 31 evaluable participants. This design has very low likelihood of failing to detect very high probabilities of low drug concentrations, and we will be conducting a second phase assessment in 90 participants that will have a high likelihood of detecting true smaller proportions with unacceptable drug levels. As noted above, PK samples in the first 31 participants will be assayed rapidly; should the pharmacologists note early issues before an assessment stage is accrued (e.g., if it becomes clear before 9 participants have data that only 4 or fewer evaluable participants will have acceptable drug levels), the A5279 core team will be notified. Of note, the 3- and 2-stage designs have very similar probabilities of finding various proportions acceptable; however, the 3-stage design provides an earlier time point to detect unacceptable levels should the accrual rate be modest.

The second phase assessment will include all 90 participants with detectable ARV levels at baseline and weeks 2 and 4, and will also consider all participants with a detectable level at baseline. The primary evaluation will consist of constructing a lower 95% confidence interval (CI) on the proportion of participants who have acceptable drug levels at both weeks 2 and 4. The CI in all 90 will not be adjusted for the first phase assessment as the first phase is conducted only in those 18 years of age or older. If the first 31 were a true subset of all 90, adjustment for the multi-phase (with 2 or 3 stages in the first phase) would 'shift' the lower 95% CI on the observed success rate upward in a more favorable direction. Thus, not making an adjustment in all 90 is conservative. We will confirm this by constructing an adjusted CI for the proportion who have acceptable drug levels in all participants 18 years or older among the 90 in the primary analysis.

The team may also apply a bioequivalence approach for an evaluation of the baseline (pre-RPT) and the weeks 2 and 4 samples. This approach will evaluate whether the 90% CIs of the ratios of plus RPT trough concentrations of EFV and NVP relative to the baseline (or no RPT) troughs are contained within a specified no effect boundary. The usual FDA no effect range is 0.80 to 1.25. However, where exposure-response data exist, these data may be used to establish the no effect boundary. The threshold troughs for EFV and NVP, which have clinical support, could be used as these no-effect boundaries. If the 90% CI for exposure ratios falls entirely within the equivalence range we could conclude that a clinically significant effect of RPT on EFV and NVP is not found.

Prior to the implementation of Version 2.0 of the protocol, the A5279 team reviewed the EFV PK data, as described in section 10.3. Since these data showed adequate EFV exposure in the presence of RPT treatment, the study was opened to participants on NVP, and NVP PK will be evaluated in the first 90 participants in Arm A taking NVP at entry. NVP PK will be evaluated in a similar manner as the EFV PK analysis was conducted.

Relationships between concentrations of EFV, its 7 and 8 hydroxy metabolites, and patient-specific genetic status will be gathered. The 7-hydroxy metabolite of

EFV is predominantly formed via the CYP2A6 pathway whereas the 8-hydroxy metabolite is formed via the CYP2B6 pathway. Metabolite profiles will yield insight into which pathway is the dominant metabolizing pathway in genetic subsets of individuals taking EFV and INH ± RPT. Additionally, analyzing metabolite profiles will separate the interactions of INH and RPT with EFV. Geometric mean ratios (GMR) will be developed for estimated clearance values for the populations in each study arm. The GMR of EFV clearance from the control group of participants on EFV (no RPT or INH) to the clearance of those participants on Arm B (INH) of the study will give the field important insight into what effect INH has on EFV clearance. CYP2A6 status will be defined as a covariate for this analysis. Secondly, a GMR for control (EFV only) to Arm A (RPT+INH) participants' clearance will be developed. From this data, we will be able to test whether the induction effects of RPT on CYP2B6 are negated by INH inhibition of CYP2A6, and what the overall effect on EFV metabolism is, again using participants' genotypes as covariates for the analysis. The control EFV participants will be established from a set of participants in Arm A on EFV containing regimens. These participants will serve as the EFV only controls and will have a PK sample drawn at weeks 0, 2, 4, and additionally week 16.

Pharmacodynamic (PD) Modeling

For this analysis, the PK characteristics of EFV and NVP will be evaluated using NONMEM version V (GloboMax, Hanover, MD), which uses mixed effects (random and fixed) regression to estimate population means and variances of PK parameters and to identify patient characteristics (covariates) that may influence these parameters. Base models will be developed using first-order conditional estimation with interaction (FOCE-I). A stepwise procedure will be used to determine whether a 1- or 2-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 inpatient (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. Covariates including sex, age, weight, race, and genetic characteristics of drug metabolizing enzymes and transporters will be investigated. The influence of each covariate on the PK characteristics of EFV and NVP will be tested sequentially. 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. 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, HIV-1 RNA) is replaced. This is analogous to the commonly used F test to select among regression models. The outcome of this analysis is to identify the model that best describes the plasma PK of EFV and NVP, and to investigate whether any patient characteristics influence the PK of these antiretroviral agents. Following finding the model that best describes the plasma PK characteristics of EFV and NVP, we will next develop a linked PK and PD model to investigate relationships among the PK parameters of EFV and NVP, and virologic response (or loss of response) and measures

of safety and tolerance such as liver function tests. These PD models may be in the form of a linear or a sigmoid E_{max} relationship where, for example, lower EFV concentrations are related to detectable levels of HIV-1 RNA in plasma.

RPT PK

The observed concentrations of RPT and the times post dose that these concentrations were obtained will be summarized. The concentration data will be evaluated for evidence of adherence to RPT. Additionally, a population PK analysis using an approach as described above for EFV and NVP may be performed. Finally, RPT concentration information may be used in the evaluation of the primary (efficacy) and secondary (safety, adherence, and resistance) endpoints of the A5279 study.

10.4 Anticipated Outcomes

At present, there are no data on the PK of EFV or NVP when combined with RPT. These PK evaluations will provide information on EFV and NVP concentrations when given concomitantly with RPT and whether the proportion of participants who have EFV or NVP concentrations less than the accepted minimum values is higher than observed in participants taking EFV and NVP without inducers of drug metabolism. Information will be obtained as to whether host genetic differences contribute to differences among participants in EFV, NVP, and RPT concentrations. The pharmacologic data from A5279 should provide guidance as to whether a significant drug-drug interaction exists that would warrant further evaluation, or in the absence of such a signal, information for clinicians that EFV and NVP may be combined with RPT.

11.0 DATA COLLECTION AND MONITORING AND ADVERSE EVENT REPORTING

11.1 Records to Be Kept

CRFs 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 CRSs 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 or EC, the site monitors, the US FDA, the NIAID, the OHRP, and the pharmaceutical supporter or designee, or other government agencies for confirmation of the study data.

11.4 Expedited Adverse Event (EAE) Reporting

11.4.1 AE Reporting to DAIDS

Requirements, definitions, and methods for expedited reporting of AEs are outlined in Version 2.0 of the DAIDS EAE Manual, which is available on the RSC website at <http://rsc.tech-res.com/safetyandpharmacovigilance/>.

The DAIDS Adverse Events Reporting System (DAERS), an internet-based reporting system must be used for EAE reporting to DAIDS. In the event of system outages or technical difficulties, EAEs 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 EAEs 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 from the time of enrollment until 8 weeks after the participant permanently discontinues all study agents. After this time, the SUSAR Reporting Category will be used.

The study agents for which expedited reporting are required are rifapentine and isoniazid.

11.4.3 Grading Severity of Events

The DAIDS Table for Grading the Severity of Adult and Pediatric Adverse Events (DAIDS AE Grading Table), Version 1.0, December 2004 (Clarification dated August 2009) must be used and is available on the DAIDS RSC Web site at: <http://rsc.tech-res.com/safetyandpharmacovigilance/>.

11.4.4 EAE Reporting Period

The EAE reporting period for this study is the entire study duration for an individual participant (from study enrollment until study completion or discontinuation of the participant from study participation for any reason).

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 (e.g., from publicly available information).

12.0 HUMAN PARTICIPANTS

12.1 Institutional Review Board (IRB) Review and Informed Consent

This protocol and the informed consent document (Appendix I) and any subsequent modifications will be reviewed and approved by the IRB or EC responsible for oversight of the study. A signed consent form will be obtained from the participant (or parent or legal guardian for 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 or EC, NIAID, US FDA, OHRP, the pharmaceutical supporter or designee, or other government agencies.

12.3 Study Discontinuation

The study may be discontinued at any time by the ACTG, NIAID, IRB or EC, US FDA, OHRP, the pharmaceutical supporter, 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 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 CDC 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 protocol:

A5279: Phase III Clinical Trial of Ultra-Short-Course Rifapentine/Isoniazid for the Prevention of Active Tuberculosis in HIV-Infected Individuals with Latent Tuberculosis Infection, FINAL Version 2.0, dated 08/28/14

SHORT TITLE FOR THE STUDY: Short-course RPT/INH for latent TB in HIV-infected individuals

INTRODUCTION

You are being asked to take part in this research study because you are infected with HIV (the virus that causes AIDS) and either have tested positive for the bacteria that causes tuberculosis (TB) or live in an area where TB infection occurs frequently. This study is sponsored by the National Institutes of Health (NIH). 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 know 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?

Some people are infected with the bacteria that cause TB, but their immune systems (the system in a person's body that helps fight infections) prevent the bacteria from multiplying and they do not have any symptoms from the infection; these people are said to have latent TB infection. Latent TB can develop into active disease and cause sickness, especially in people with weakened immune systems, such as those with HIV.

The standard way to keep latent TB from becoming active is treatment with 6 to 9 months of daily isoniazid, an anti-TB drug. ACTG researchers are interested in seeing if shorter treatments work just as well as this standard treatment. This study will compare the standard treatment with a much shorter treatment (4 weeks) of the anti-TB drugs rifapentine and isoniazid, to find if this shorter treatment is as good. The study will also compare the safety and tolerability of the two treatments. Both rifapentine and isoniazid are approved by the United States (US) Food and Drug Administration (FDA).

APPENDIX I (Cont'd)

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

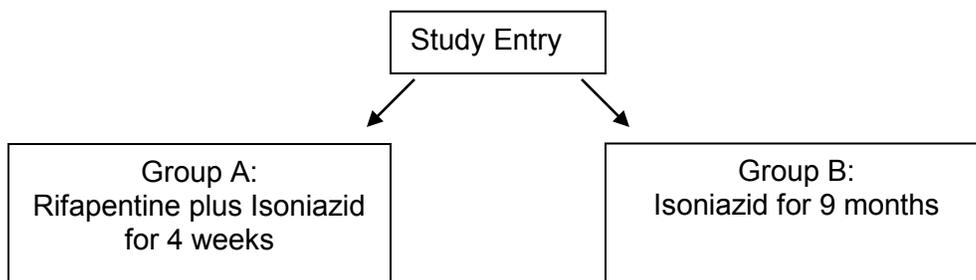
If you decide to join this study, you will need to be seen in the clinic about 10 times in the first 9 months and then about every 3 months for as long as you are on the study, which may be 3 to 5 years or longer. The evaluations required at most visits will take about 1 hour to complete, although you may need to be at the clinic longer than this. The schedule of visits and study procedures are explained in Appendix I-A.

If you do not join 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. As part of this screening visit, some demographic (for example, age, gender, race), clinical (for example, disease condition, diagnosis), and laboratory information is being collected from you so that ACTG researchers may help determine whether there are patterns or common reasons why people do not join a study.

If you enter the study

At the study entry visit, you will be assigned to one of these two treatment groups:



Because your assignment is random, like the flip of a coin, you will have an equal chance of being in either group. You will not be able to choose your group, but you and the study doctor, as well as the study staff, will know which group you are in.

If you are in Group A, you will take rifapentine and isoniazid for 4 weeks. Depending on your weight, you will take 2, 3, or 4 tablets of rifapentine and one tablet of isoniazid with food once a day. Rifapentine and isoniazid will be provided to you.

If you are in Group B, you will take isoniazid for 9 months. You will take one tablet of isoniazid with or without food once a day. Isoniazid will be provided to you.

Regardless of which group you are in, you must also take vitamin B₆ once a day while taking isoniazid, to help prevent possible side effects of isoniazid. Vitamin B₆ will be provided to you.

While you are in the study, you will be asked to tell the study doctor if you have signs that you might have active TB. If you have symptoms such as cough, fever, night sweats, or weight loss, you should contact the study doctor right away.

APPENDIX I (Cont'd)

Other

If you are one of the first 90 people enrolled **in Group A** who is taking efavirenz, or one of the first 90 people enrolled **in Group A** who is taking nevirapine, an additional blood sample will be collected from you at entry and again at weeks 2 and 4. This blood will be tested for levels of rifapentine and either efavirenz or nevirapine. In addition, at week 8, you will have some blood collected and stored for future testing to look at your HIV viral load (a test that shows how much HIV is in your blood) and the levels of study drugs in your body.

Once Version 2.0 of this study is started:

- 1. If you are one of the first 90 people enrolled into Version 2.0 in Group B who is taking efavirenz, additional blood samples will be collected from you at entry and again at weeks 2 and 4. This blood will be tested for levels of efavirenz and its metabolites.**
- 2. If you are one of the 30 efavirenz control participants in Group A, blood samples will be collected at entry and again at weeks 0, 2, 4, and 16. This blood will be tested for concentrations of efavirenz and its major metabolites. At week 8, you will have some blood collected and stored for future testing to look at your HIV viral load and the levels of study drugs in your body.**

If you are part of this group of people who will have levels of rifapentine and either efavirenz or nevirapine tested, you will be asked to have another blood sample collected and stored for genetic testing, to see if differences in certain genes may affect the levels of some anti-HIV and study drugs in the blood. The facilities where this blood will be stored for genetic testing will not have information that identifies you. Since this genetic testing is optional, please indicate below if you agree to have this blood collected. If you do not agree, then this sample will not be collected. If you agree now and later change your mind, your sample will not be used for genetic testing. No matter what you decide, it will not affect your participation in the A5279 study.

_____ YES, I agree to have blood collected and stored for this genetic testing.

_____ NO, I do not agree. Do not collect this extra blood sample from me.

If you agree, some of your blood that is left over after all required study testing is done may be stored (with usual protections of your identity) and used for future ACTG-approved research that is separate from this study. Genetic testing will not be done on these blood samples. Samples collected from you will be stored in the US. These samples may be stored for an indefinite period of time. Results of testing performed on these samples will not be given to you. You may withdraw your consent for research on stored specimens at any time and the specimens will be discarded. No matter what you decide, it will not affect your participation in the study.

_____ YES, I agree to have my leftover blood stored.

_____ NO, I do not agree.

APPENDIX I (Cont'd)

HOW MANY PEOPLE WILL TAKE PART IN THIS STUDY?

About 3000 people will take part in this study.

HOW LONG WILL I BE IN THIS STUDY?

This study will last for about 3 years after the last participant is enrolled. You will be in this study between 3 and 5 years, or maybe even longer, depending on the how long it takes the study to fill up and when you join.

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 stopped or cancelled.
- A Data Safety Monitoring Board (DSMB) recommends that the study be stopped early. (A DSMB 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 drugs without your permission if:

- continuing the study drugs may be harmful to you
- you need a treatment that you may not take while taking the study drugs
- you become pregnant or begin breastfeeding and are taking rifapentine

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

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

After you have completed your study treatment period, the study will not be able to continue to provide you with rifapentine and/or isoniazid. 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.

APPENDIX I (Cont'd)

Risks of Antibacterials

Some medications used to treat TB are antibacterials that may be associated with diarrhea, including bloody diarrhea, which may be severe.

Isoniazid (INH)

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

Serious and sometimes life threatening liver damage may develop even after many months of treatment. Older age, already having some liver disease, drinking alcohol regularly and using injection drugs are all associated with an increased risk of developing liver damage. Woman, particularly black and Hispanic woman, or if they are pregnant or recently gave birth to a baby, may also be at increased risk of life threatening liver damage. If you develop any of the following symptoms, you should call your doctor right away:

- unexplained loss of appetite
- nausea and or vomiting
- pale colored stools
- yellowing of the eyes or skin
- pain in the upper abdomen
- dark urine

Additional side effects may include:

- tingling and numbness in the hands and feet
- memory loss, confusion, trouble sleeping, changes in behavior or mood
- unsteadiness or dizziness
- seizures
- low blood counts
- rash and itching
- high blood sugar
- joint pain
- reduced vitamin B₆ levels (a vitamin that helps with many functions in your body)

Rifapentine (RPT, Priftin)

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

- reddish coloring of urine, sweat, sputum, saliva, tears, and breast milk. Contact lenses and dentures may be permanently stained.
- liver damage that may include abnormal liver function tests. If you develop any of the following symptoms of liver damage, you should call your doctor right away:
 - unexplained loss of appetite
 - nausea and/or vomiting
 - pale-colored stools
 - yellowing of the eyes or skin
 - pain in the upper abdomen
 - dark urine
- loss of appetite

APPENDIX I (Cont'd)

- low blood counts
- low blood sugar
- upset stomach or vomiting
- decreased effectiveness of hormonal contraceptives and other medications, including some anti-HIV medications. Tell your doctor about all medications that you are taking.

Non-Study Medications

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. In addition, you must tell the study doctor or nurse before enrolling in any other clinical trials while on this study.

Risks of Drawing Blood

Taking blood may cause some discomfort, bleeding, or bruising where the needle enters the body, lightheadedness, and in rare cases, fainting or infection.

Risks of TB Skin Test

In rare cases, a TB skin test can cause severe redness and swelling of the arm in people who had a positive TB skin test in the past. There have even been a few cases where this reaction was seen in people who had not had this test before.

Risks of Chest X-ray

The amount of high-energy radiation used in a chest x-ray is relatively small and does not pose any significant risk to you.

Risks of Social Harm

It is possible that participating in this study will make it difficult for you to keep your HIV or TB status secret from people close to you. This may lead to unwelcome discussions about or reactions to your HIV or TB status. Please talk with the study staff if you have any concerns in this regard.

ARE THERE RISKS RELATED TO PREGNANCY?

Rifapentine may be unsafe for unborn babies. If you are having sex that could lead to pregnancy, you must agree not to become pregnant while you are taking rifapentine and for 6 weeks after stopping this drug. You must use one of the following barrier methods of birth control that you discuss with the study staff:

- male or female condoms
- diaphragm or cervical cap with a cream or gel that kills sperm
- intrauterine device (IUD)

APPENDIX I (Cont'd)

A barrier method of birth control is required because rifapentine can prevent birth control pills and other hormonal birth control methods from working.

[Insert language describing how your site will handle pregnancies in minors.]

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. For example, the TB treatment you receive could help prevent you from developing TB. 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 risk the possibility of having 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 or the study doctor will explain the risks and benefits of these choices.

WHAT ABOUT CONFIDENTIALITY?

For US Sites: We will do everything we can to protect your privacy. In addition to the efforts of the study staff to help keep your personal information private, we have gotten a Certificate of Confidentiality from the U.S. Federal Government. This certificate means that researchers cannot be forced to tell people who are not connected with this study, such as the court system, about your participation. Also, any publication of this study will not use your name or identify you personally.

People who may review your records include the ACTG, Office of Human Research Protections (OHRP), FDA, (insert name of site) Institutional Review Board (IRB) or Ethics Committee (EC), NIH, study staff, study monitors, the drug company supporting this study, and its designees. Having a Certificate of Confidentiality does not prevent you from releasing information about yourself and your participation in the study.

Even with the Certificate of Confidentiality, if the study staff learns of possible child abuse and/or neglect or a risk of harm to yourself or others, we will be required to tell the proper authorities.

OR

APPENDIX I (Cont'd)

For Non-US Sites: 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. Any publication of this study will not use your name or identify you personally.

Your records may be reviewed by the ACTG, OHRP, FDA, (insert name of site) IRB or EC, NIH, national regulatory/health agencies, study staff, study monitors, and the drug company supporting this study, and its designees.

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

WHAT ARE THE COSTS TO ME?

Taking part in this study may lead to added costs to you and your insurance company. 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.

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 NIH. You will not be giving up any of your legal rights by signing this consent form.

WHAT ARE MY RIGHTS AS A RESEARCH PARTICIPANT?

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 affect medical care you receive at this site.

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 participant, contact:

- name or title of person on the IRB, EC, or other organization appropriate for the site
- telephone number of above

APPENDIX I (Cont'd)

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 I-A: A5279 STUDY VISITS

The study staff can answer any questions you have about individual study visits, how long they will last, or about the tests that will occur. The table below can be used as a quick reference for you, along with the explanations that follow.

I. Study Schedule

Evaluation or Procedure	Screening ¹	Entry ²	Visits in First 9 Months ³	Follow-up Visits ⁴	Diagnosis of TB ⁵	Early Discontinuation ⁶
Consent & contact information collected	√					
HIV confirmed	√					
TB test	√	√				
Chest x-ray	√		If needed			
Physical exam	√	√	√			√
Blood collected	√	√	√		√	√
Pregnancy test	√		If needed			
Sputum collected	If needed		If needed		√	
Pill count			√			
Adherence questions			√			

¹Screening Visit: After you have read and signed the consent form, you will have several tests done to make sure that you meet the requirements for joining the study.

²Entry Visit: If you are able to join the study, you will come to the clinic to enter the study and receive your treatment assignment. At this visit, you will find out if you receive rifapentine plus isoniazid for 4 weeks or isoniazid for 9 months.

³Visits in First 9 Months: You will return to the clinic at weeks 2, 4, 8, 12, 16, 20, 24, and 36 after the entry visit.

⁴Follow-up Visits: After the first 9 months, you will have visits every 12 weeks for the rest of the time you are on the study, which may be 3 to 5 years or longer.

⁵Diagnosis of TB: If you develop TB, you will come to the clinic for an extra visit.

⁶Early Discontinuation: If you stop the study early, you will be asked to come in for a final visit.

APPENDIX I-A (Cont'd)

II. Explanation of Evaluations

Below are descriptions of the evaluations. You will be told the results of all tests performed with the exception of those tests to look at the levels of study drugs in your body and those performed on blood stored for future virology and pharmacology tests and for future ACTG-approved testing.

Consent and contact information collected

After you read the consent and have had a chance to ask questions about the study, you will sign the consent form if you want to continue and join the study. You will also be asked how to be contacted in case you miss a visit or there are problems with your tests, and whether you give the study team permission to contact you.

HIV infection confirmed

If there is no record available, another HIV test will be done. If an HIV test has to 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.

TB test

If you do not live in an area where TB occurs often, **at screening**, you may be asked to have a test to see if you have latent TB, unless you have results from a previous test for latent TB. For this test, you will either have a small amount of blood drawn (about 5 mL or 1 teaspoon) or an injection into the skin on the underside of your lower arm (called a tuberculin skin test or TST). When you enter the study, you will be required to have a TST if you have not had one in the past 60 days, **regardless of whether you live in an area where TB occurs often**.

Chest x-ray

You will have a chest x-ray during screening. If your doctor thinks that you may have active TB at any time during the study, you will have another chest x-ray.

Physical examination

You will have a physical exam and will be asked questions about your health and about any medicines you have taken or are taking now.

Blood collected

Between 5 and 60 mL (1 teaspoon to 4 tablespoons) of blood may be collected at any one visit.

Blood will be collected from you for various tests during the study. These include: routine blood tests for safety, HIV viral load, CD4+ count (a test that shows how many infection-fighting cells you have in your blood), liver function tests, and possibly a TB test.

At entry and again at 2, 4, and possibly 16 weeks after entry, you may have some blood collected for tests to look at the levels of some anti-HIV and study drugs in your body. If you agree, at entry, you may also have some blood collected for genetic testing, to see if differences in specific genes may affect the levels of some anti-HIV and study drugs in the blood. Collection of blood for this genetic testing is optional.

At week 8, you may also have some blood collected and stored for future testing to look at your HIV viral load and the levels of study drugs in your body. The study staff will tell you if you will have blood drawn for this testing.

APPENDIX I-A (Cont'd)

At entry and every 48 weeks for the duration of the study, if you agree, some of the blood that is collected will be stored for future ACTG-approved testing. The study staff will tell you if you will have blood drawn for this future testing.

Pregnancy test

If you are a woman who is able to become pregnant, you will be asked to give a small urine or blood sample (about 5 mL or 1 teaspoon) for a pregnancy test at screening and anytime during the first 9 months of the study, if you think you might be pregnant.

Sputum collected

If your doctor or the study doctor thinks that you may have active TB at any time during the study, you will be asked to provide a sputum sample that will be used to confirm whether you have TB. To provide this sample, you will be asked to cough deeply and then spit into a cup. If you need help to cough deeply, the clinic staff may ask you to briefly breathe a mist of saltwater through a tube or a mask.

Pill count

While you are taking study drug, you will be asked to bring in your study drug at each visit so that the study staff may count the number of pills.

Adherence questions

At the visits that occur while you are taking study drugs, you will be asked questions about how well you remember to take the study drugs. When you are taking rifapentine, you will also be asked about taking this drug with food.