IMPAACT 2001

A Phase I/II Trial of the Pharmacokinetics, Tolerability, and Safety of Once-Weekly Rifapentine and Isoniazid in HIV-1-infected and HIV-1-uninfected Pregnant and Postpartum Women with Latent Tuberculosis Infection

A Study of the International Maternal Pediatric Adolescent AIDS Clinical Trials Network

Sponsored by:
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ABBREVIATIONS AND ACRONYMS

3HP	Rifapentine (900mg) and isoniazid (900mg) weekly for 3 months
3TC	Lamivudine, Epivir
9H	INH 300mg daily for 9 months
ACTG	AIDS Clinical Trials Group
AE	Adverse Event
AIDS	Acquired Immunodeficiency Syndrome
ALT	Alanine Transaminase
ART	Antiretroviral Therapy
ARV	Antiretroviral
AST	Aspartate Aminotransferase
AUC	Area Under the Curve
BSV	Between subject variability
cART	Combination ART
CBC	Complete Blood Count
CDC	Centers for Disease Control and Prevention
CFR	Code of Federal Regulations
CI	Confidence interval
CL/F	Clearance
CLIA	Clinical Laboratory Improvement Amendments
C_{max}	Peak Plasma Concentration
CMC	Clinical Management Committee
C_{min}	Minimum Plasma Concentration
CRF	Case Report Form
CRPMC	Clinical Research Products Management Center
CRS	Clinical Research Site
D4T	Stavudine
DAERS	DAIDS Adverse Event Reporting System
DAIDS	Division of AIDS
DAIDS PRO	DAIDS Protocol Registration Office
DDI	Didanosine
desRPT	Desacetyl-rifapentine
DMC	Data Management Center
DNA	Deoxyribonucleic Acid
DOT	Directly Observed Therapy
DSMB	Data and Safety Monitoring Board
EAE	Expedited Adverse Event
EC	Ethics Committee
EFV	Efavirenz
EIA	Enzyme Immunoassay
EQA	External quality assurance
FDA	(US) Food and Drug Administration
FSTRF	Frontier Science and Technology Research Foundation
GCLP	Good Clinical Laboratory Practice

GCP	Good Clinical Practices
HAART	Highly Active Antiretroviral Therapy
HIV-1	Human Immunodeficiency Virus Type 1
IATA	International Air Transport Association
ICF	Informed Consent Form
ICH	International Conference on Harmonisation
IGRA	Interferon Gamma Release Assay
IMPAACT	International Maternal Pediatric Adolescent AIDS Clinical Trials Network
IND	Investigational New Drug
INH	Isoniazid
INR	International Normalized Ratio
IRB	Institutional Review Board
IoR	Investigator of Record
LAR	Legally Authorized Representative
LC	IMPAACT Laboratory Center
LTBI	Latent Tuberculosis Infection
MDR TB	Multi-drug resistant tuberculosis
MOH	Ministry of Health
MOP	Manual of Procedures
MTB	Mycobacterium tuberculosis
MUAC	Middle Upper Arm Circumference
NIAID	National Institute of Allergy and Infectious Diseases
NICHD	Eunice Kennedy Shriver National Institute of Child Health and Human Development
NIH	National Institutes of Health
NRTI	Nucleoside Reverse Transcriptase Inhibitor
NVP	Nevirapine
OHRP	Office for Human Research Protections
OCSO	Office of Clinical Site Oversight
PCR	Polymerase Chain Reaction
PEPFAR	President's Emergency Plan for AIDS Relief
PI	Protease Inhibitor
PK	Pharmacokinetics
PT	Prothrombin Time
PTT	Partial Thromboplastin Time
RNA	Ribonucleic Acid
RPT	Rifapentine
RSE	Relative standard error
SAE	Serious Adverse Event
SDMC	Statistical and Data Management Center
SES	Subject Enrollment System
SoE	Schedule of Evaluations
SOP	Standard Operating Procedure
SSE	Stochastic simulation-estimation
SUSAR	Suspected Unexpected Serious Adverse Reaction
TB	Tuberculosis
TBTC	Tuberculosis Trials Consortium
TST	Tuberculin Skin Test
ULN	Upper Limit of Normal
US	United States of America
WHO	World Health Organization
XDR	Extensively drug-resistant tuberculosis

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SCHEMA

Purpose:	To describe the pharmacokinetics, tolerability, and safety of 12 once-weekly doses of rifapentine (RPT) and isoniazid (INH) in pregnant and postpartum women with latent tuberculosis (TB) and inform the practice on usage of this regimen in the second and third trimesters of pregnancy.
Design:	Prospective, open-label, multi-center study
Study Population:	HIV-1-infected and HIV-1-uninfected pregnant women with latent TB and their infants, enrolled in two cohorts based on gestation: • Cohort 1: Enrolled in second trimester (≥14 to <28 weeks) and on study drug for 12 weeks • Cohort 2: Enrolled in third trimester (≥28 to ≤34 weeks) and on study drug for 12 weeks
Sample Size:	Up to 82 pregnant women (and their infants) will be enrolled to yield a minimum of 25 evaluable women in each cohort. Within each cohort, enrollment of at least 10 evaluable HIV-1-infected women will be targeted. This sample size is selected to achieve a relative standard error (RSE) of five percent for estimation of clearance.
Study Treatment:	Twelve directly observed once-weekly doses of RPT (900mg) and INH (900mg) taken with pyridoxine (25 to 100mg). An interim analysis will be performed to assess the clearance of RPT compared to non-pregnant historical controls, and a dose adjustment may be recommended based on this analysis.
Study Duration:	Approximately 24 months total. Accrual is expected to require approximately 12 months, and each enrolled woman will be followed through pregnancy and 24 weeks postpartum. Infants will be followed for 24 weeks from birth.

Primary Objectives

- To estimate the population pharmacokinetics (PK) (CL/F, absorption, volume of distribution) of RPT and its desacetyl-rifapentine metabolite (desRPT) among pregnant women during the second trimester and third trimester who are receiving once-weekly RPT (900mg or the new study dose, if a dose adjustment is indicated by the interim analysis) and once-weekly INH (900mg).

- To estimate the incidence of serious adverse events (SAEs) related to RPT + INH dosed once weekly for 12 weeks in pregnant women.

- To describe the infant safety outcomes among infants born to women receiving once-weekly RPT + INH.

Secondary Objectives

- To estimate the population pharmacokinetics (PK) (CL/F, absorption, volume of distribution) of RPT and its desacetyl-rifapentine metabolite (desRPT) among pregnant women during the postpartum period who are receiving once-weekly RPT (900mg or the new study dose, if a dose adjustment is indicated by the interim analysis) and once-weekly INH (900mg).

- To assess the impact of covariates (gestational age, weight, age, HIV status) on primary PK parameters using population PK modeling.

- To compare RPT and desRPT exposure pharmacokinetic parameters (AUC, C_{max}, C_{min}) for RPT in pregnant and postpartum women versus non-pregnant historical controls, using noncompartmental analyses.

- To determine the RPT dose in pregnancy that achieves similar estimated exposure (AUC) of RPT as non-pregnant adults at standard doses.

- To quantify RPT and desRPT concentrations at delivery among infants born to women receiving once-weekly RPT + INH.

- To describe the tolerability of RPT + INH dosed once weekly for 12 weeks in pregnant and postpartum women.

- To assess incidence of active TB in mother-infant pairs up to 24 weeks postpartum.

- To explore the population pharmacokinetics (PK) (CL/F, absorption, volume of distribution) of INH in HIV-1-infected and HIV-1-uninfected pregnant and postpartum women (i.e., women who are and are not taking efavirenz (EFV)) who are receiving once-weekly RPT (900mg or the new study dose, if a dose adjustment is indicated by the interim analysis) and once-weekly INH (900mg).

Exploratory Objectives

- To quantify RPT and desRPT concentrations in breast milk of postpartum women receiving once-weekly RPT + INH.

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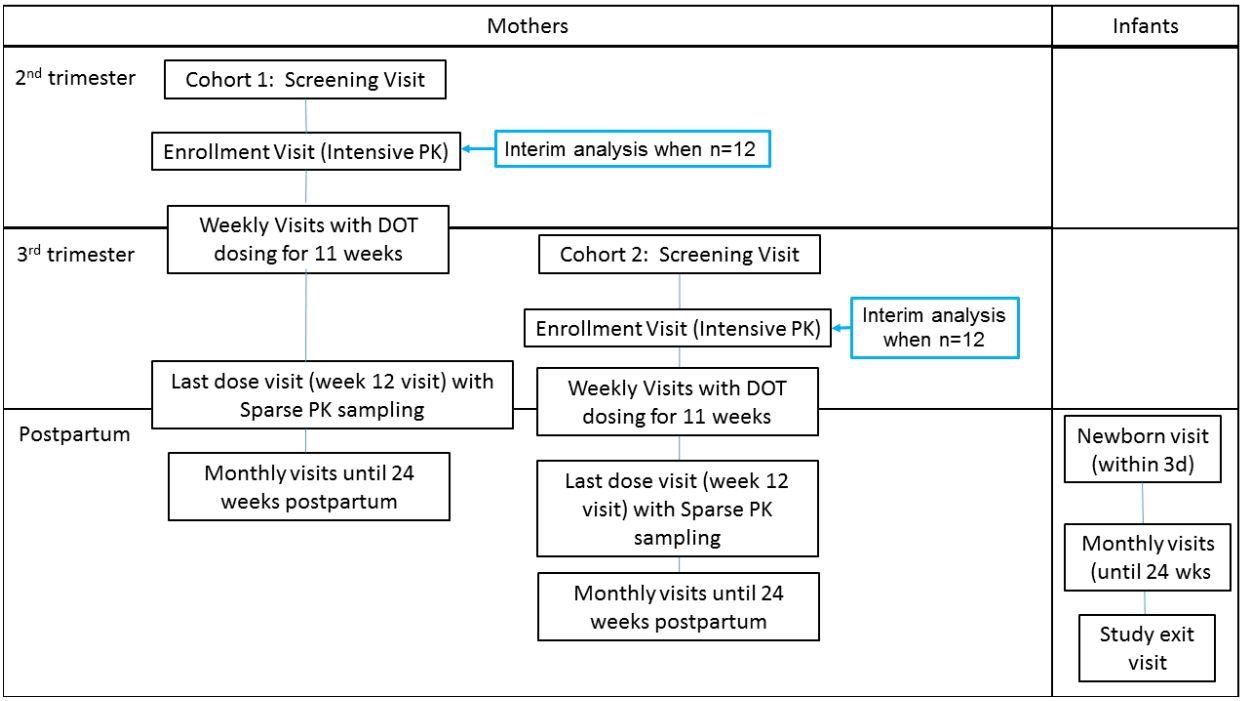
Figure 1: Study Visit Schedule - Mothers and Infants



1 INTRODUCTION

1.1 Background

An estimated two billion persons carry latent Mycobacterium tuberculosis (MTB). Treatment of latent tuberculosis infection (LTBI) is critical to global tuberculosis (TB) control and elimination (1, 2). Globally, the most commonly used current LTBI treatment regimen is six to nine months of INH (3, 4). Treatment completion rates of this regimen, however, are suboptimal, ranging from 5-64% in high-burden TB settings (5-7). Furthermore, potential concerns about the selection of drug resistance and drug toxicity, particularly hepatotoxicity, have hampered implementation of this regimen (8-10).

Pregnant women: LTBI and its treatment
Prevalence of latent LTBI in pregnant women is similar to that of the general population. Studies report a prevalence of 18%–34% among HIV-negative pregnant women in India and up to 49% in HIV-positive pregnant women in South Africa (8, 11). Pregnant women are at increased risk of progressing from latent LTBI to active tuberculosis (TB) because pregnancy suppresses the Th1 immune response (12-14). Symptoms of active TB may not be seen until after delivery, when Th1 suppression reverses and symptoms are exacerbated (13). A large study recently found that early postpartum women are twice as likely to develop TB as non-pregnant women, suggesting that biologic changes in pregnancy and postpartum influence TB epidemiology (15-19).

The World Health Organization (WHO) currently recommends treating LTBI with daily INH for all HIV-infected pregnant women, but few programs have implemented this policy. Adherence and toxicity concerns remain the main barriers to treatment. Adherence rates for daily INH among postpartum Hispanic women in the US, for example, are as low as 6-21% (20). Pregnancy and infant outcomes of women taking INH for active TB treatment are comparable to normal pregnant women not receiving TB treatment, but toxicity concerns persist due to the suboptimal quality of existing studies (21). NIH-funded studies are under way to assess the optimal timing of initiation of INH for TB prophylaxis for HIV-1-infected women (IMPAACT P1078), the pharmacology of first-line TB drugs for TB disease in HIV-1-infected and HIV-1-uninfected pregnant and postpartum women (IMPAACT P1026s and R01HD06435), and pregnancy and treatment outcomes among pregnant women with tuberculosis and HIV (R01HD06435).

The US Centers for Disease Control and Prevention (CDC) recommends the use of either nine months of daily INH monotherapy or a newer regimen of three months of weekly INH and RPT. The INH/RPT regimen is recommended in otherwise healthy patients over the age of 12 years who have LTBI. Though the CDC states that the regimen can be considered in other populations when it offers “practical advantages,” the regimen is not recommended in pregnant women, because the safety of the regimen in pregnancy is unknown. This study aims to address this gap in knowledge.

Pharmacokinetics in pregnancy
The physiologic changes associated with pregnancy can impact drug disposition significantly. Gastrointestinal motility, stomach pH, protein binding, hepatic metabolism, and renal blood flow are all altered by pregnancy and can affect drug absorption, distribution, metabolism, and clearance. Pregnant women experience increased gastrointestinal transit time, which can alter the extent of drug absorption. They also have decreased albumin, which can affect protein binding and drug distribution, as well as free drug concentrations. Moreover, progesterone increases CYP3A4 activity, while estrogen inhibits CYP1A2 and CYP2C19 (22, 23). The combination of these effects complicates dosing regimens for many medications. In HIV management, for example, the dose of lopinavir and darunavir need to be doubled

during pregnancy, but only during the third trimester (24). Clearly, given the complex physiologic changes that occur with pregnancy, a thorough understanding of the pharmacokinetics of new drugs or regimens in this population is needed before they can be administered safely and effectively to pregnant women.

1.2 Prior Research

RPT and LTBI

In the past four years, there have been three major studies published on the use of this regimen in different populations. These studies and their major findings are summarized here:

- TB Trials Consortium (TBTC) Study 26: Recently, a large TBTC-sponsored open-label randomized non-inferiority trial comparing three months of directly observed once-weekly rifapentine (RPT) (900mg) plus INH (900mg) (3HP) versus nine months of self-administered daily INH (300mg) (9H) (TBTC Study 26) demonstrated that 3HP was as effective as (and potentially superior to) the standard 9H regimen and was associated with a higher completion rate (82% versus 69%) and less drug-related hepatotoxicity (0.4% versus 2.7%) (25). Women on 3HP were more likely to have drug-associated "possible hypersensitivity" reactions than men, but severe reactions were very rare, only occurring in 0.37% of all people taking RPT/INH (25).
    - In a substudy of TBTC Study 26, the 3HP regimen was also better tolerated in HIV-1-infected participants compared to HIV-1-uninfected participants. Moreover, HIV-1-infected patients had experienced fewer adverse events with the 3HP than 9H (26, 27).

- PREVENT TB Trial: This trial was conducted through TBTC and IMPAACT in children and adolescents from international sites and the US, to assess safety and efficacy of 3HP versus 9H regimen in this population. Treatment with 3HP resulted in higher adherence rates (88% in 3HP versus 81% in 9H). Importantly, neither arm exhibited any hepatotoxicity, Grade 4 adverse events or treatment-attributed deaths. None of the children in the 3HP arm developed active TB versus 3 (0.74%) of the children in the 9H arm (28).

Furthermore, there have been no reports of hemorrhage in studies of RPT for LTBI treatment. (A full summary of adverse events seen in trials using RPT/INH is shown in Table 1). In November 2014, the US FDA granted RPT a supplemental indication for LTBI treatment. 3HP is now being recommended by the CDC as an appropriate alternative for latent TB treatment in people ≥12 years old who are at high risk of developing active TB (e.g., recent exposure to known TB contact, conversion from negative to positive latent TB test, radiographic evidence of healed pulmonary TB, HIV-positive not on antiretrovirals) (29) . The CDC states that the regimen can be considered in other populations when it offers "practical advantages" but does not recommend its use in pregnant women because the safety of the regimen in unknown. IMPAACT 2001 aims to address this gap in knowledge.

Table 1. Drug-related adverse events in trials of RPT/INH for LTBI treatment

Adverse Event	*TBTC 26 (HIV-negative) n=1861**	*TBTC 26 (HIV-positive) n= 207*	*Martinson, et al Soweto study (HIV-positive) n=328*
Hepatotoxicity	11 (0.59%)	3 (1.4%)	5 (1.5%)
Rash	15(0.8%)	1 (0.5%)	0 (0%)
Possible hypersensitivity	85(4.6%)	2 (1%)	0 (0%)

* confirmed HIV-uninfected

RPT pharmacokinetics in adults

RPT is well absorbed and reaches a peak concentration in non-pregnant adults approximately five hours after ingestion. Bioavailability is improved when ingested with food, though lipid content does not appear to impact the magnitude of this effect (30). In a substudy of TBTC 26, gender was not associated with variability in RPT PK parameters by population PK modeling (31). RPT's half-life ($t_{1/2}$) is five times longer than that of rifampin (11-18 hours versus 2-5 hours), resulting in measurable concentrations at and beyond 24 hours (32). Rifampin, a structurally similar rifamycin antibiotic, induces its own metabolism leading to reductions in half-life and AUC with repeat daily dosing. RPT also induces its own metabolism, but because of its longer half-life, accumulation occurs with multiple dosing (33, 34). RPT metabolism is not dependent on cytochrome P450. The effects of RPT on antiretrovirals' concentrations is currently under investigation, but, in ACTG 5279, no clinically significant reductions in efavirenz (EFV) concentrations were seen among 30 patients receiving daily RPT 10 mg/kg and isoniazid together with EFV-based combination ART (35). Preliminary results from a Phase I trial sponsored by Sanofi also demonstrated that once-weekly RPT did not reduce EFV concentrations appreciably, so it is likely that these drugs can be used safely together (36, 37).

EFV concentrations are marginally decreased among women in late pregnancy (38). However, few studies have evaluated this, and the numbers are small, largely because until recently, EFV was not used in pregnancy in many settings. EFV is now used without dose adjustment in pregnancy globally. There are no data about CYP2B6 activity among pregnant women taking EFV. Rifampin does not reduce EFV concentrations in pregnant women; in some women, INH increases EFV concentrations (depending on NAT2 genotype and CYP2B6 genotype).

Further evaluations are being conducted to optimize RPT-containing regimens for LTBI and to extend the use of the 12-week RPT/INH regimen to all populations. A pharmacokinetic study was being conducted through TBTC (TBTC-S35) to determine the appropriate doses of RPT for young children (ages 0-2). Of note, dosing for children aged two years and older has been established and is in the product label (37). An actively enrolling ACTG clinical trial is assessing an ultra-short course of four weeks of daily INH (300mg) and RPT (450mg or 600mg, depending on weight) among non-pregnant HIV-1-infected persons greater than 13 years old (ACTG 5279). The PK and safety of these novel regimens have not been tested in pregnant women.

Safety and tolerability of RPT in pregnancy and breastfeeding

Like rifampin, which is routinely used for the treatment of active TB during pregnancy, RPT is a rifamycin derivative and was categorized as FDA Pregnancy Category C. This meant that animal studies showed adverse effects on the fetus, but, because there are no adequately controlled trials in humans, the use of the drug in pregnancy may be acceptable if the benefits are thought to outweigh the risks. RPT, like all rifamycins, may increase the risk of maternal hemorrhage and bleeding in the infant, although in an evaluation of six women on RPT during pregnancy, none had bleeding events (32). Fourteen patients with active tuberculosis that were treated with an anti-tuberculosis regimen that included rifapentine became pregnant during clinical studies. Six delivered normal infants; four had first trimester spontaneous abortions (of these, one patient abused ethanol and another patient was HIV-infected); one had an elective abortion; and outcome was unknown in three patients (37). None of these studies had pregnancy outcomes as a primary outcome, and the quality of reporting therefore varied by study. Moreover, the effect of rifapentine, specifically, could not be separated from the possible effect of the other TB drugs included in the active TB regimen. An ongoing study in South Africa examined safety events in pregnant women taking daily rifampin as part of an active TB regimen and found there were no associated bleeding events (39).

In Study 26, 116 women became pregnant while on study (71 in 9H arm, 45 in 3HP arm). All women were taken off study drug at the time pregnancy was diagnosed. There were no drug-related bleeding events reported in TBTC 26. Occurrences of spontaneous abortions and live births were comparable between the two study arms as well as compared to the general population (see Table 2 below). No mortality (maternal or perinatal) or congenital anomalies were reported (40). Sixteen spontaneous

abortions occurred during the study, with major malformations either not detected or considered unknown in 15, and one fetus that screened positive for Down syndrome. A total of 12 elective abortions were reported during the study. Reasons for elective abortion were due to fetal diagnosis of Turner syndrome in one case and unknown reasons in 11 cases (37).

Table 2: Pregnancy outcomes from TBTC - Study 26 versus general population[a]

	No treatment[b] (n=6,578,000)	9 INH (n=71)	3 RPT/INH (n=45[c])
Spontaneous abortion	1.12 million (17%)	9 (13%)	7 (16%)
Elective abortion	1.21 million (18%)	6 (8.4%)	6 (13%)
Live births	4.25 million (65%)	54 (76%)	31 (69%)
Postpartum hemorrhage [d]	124,708 (2.9%)	0 (0%)	0 (0%)

a – 2 pregnancies with unknown outcomes occurred in each treatment group
b – From Ventura, et al. – Pregnancy rates for 1900-2008 in the USA
c – 1 patient had 2 pregnancies during the study (1 outcome spontaneous abortion and one live birth)
d – From Callaghan, et al. – Trends in postpartum hemorrhage: United States 1994-2006, n=10,481,197

Ventura S.J., Curtain S.C., Abma J.C. et al: National Vital Statistics Reports June 20, 2013. Volume 60 number 7.

There are no data on RPT concentrations in breast milk, and it is unknown whether RPT is secreted in breast milk. The FDA label recommends discontinuation of the drug or nursing because of the lack of data. However, the CDC recommends that breastfeeding should not be discouraged in women taking this drug. For rifampicin, a related rifamycin antibiotic, breast milk concentrations are very low. Peak levels of 0.05% of those plasma levels are seen in breast milk with standard dosing for TB treatment (41, 42). The WHO also recommends that use of rifampicin is compatible with breastfeeding mothers (43). Of note, rifampicin given for TB treatment is given daily, whereas RPT in this study will be given once weekly.

RPT, like other rifamycins, causes red-orange discoloration of body fluids. In trials where RPT was combined with INH and other antituberculosis drugs, rates of adverse reactions were similar between rifampin and RPT, with increased liver aminotransferase activity in about 5% of patients. No serious bleeding events were noted (32). In TBTC 26, 3HP was also well-tolerated among study participants compared to 9H. Clinical trials evaluating the efficacy of RPT as replacement for rifampin during the intensive phase of treatment for active TB in adults with and without HIV-1 infection have been completed or are in late stages of development; pregnant women, however, have been excluded from all of these trials (44, 45).

Safety and tolerability of INH in pregnancy and breastfeeding:
INH is used in pregnancy to treat active TB, where its benefit clearly exceeds the risk. It is an FDA Category C drug due to its limited data in pregnant women. INH crosses the placental barrier. It is not known to be associated with an increased rate of congenital abnormalities, and it is not considered to be teratogenic. INH is also reported to be safe and compatible with breastfeeding but does have potential for interference with nucleic acid metabolism, and hepatotoxicity has been documented in infants on treatment doses of INH (46-48).

Safety and tolerability of vitamin B_6 in pregnancy and breastfeeding:
Pyridoxine (vitamin B_6) is recommended with INH. In absence of INH, pyridoxine is safe to be used in pregnancy and postpartum at doses up to 100mg (49).

1.3 Rationale

Pregnancy is an important entry point for women to seek health care. Moreover, pregnant and postpartum women with LTBI are immunologically at higher risk of developing active TB. Maternal TB can lead to infant TB, which is even more difficult to diagnose, and is also associated with an increased risk of neonatal death, fetal distress, low birth weight, and prematurity (17, 43, 50-53). If a mother is co-infected with HIV and TB, she has double the risk of transmitting HIV to her infant (54). Children under five years of age have an eight times increased risk of death simply by living in the same home as a mother with active TB (55). Therefore, prevention of TB in pregnant women is an important priority for maternal and child health. Antenatal visits present an opportunity to screen women for both active and latent TB and to implement LTBI therapies to benefit the mother, her infant, and the household, especially in settings where HIV is highly prevalent. A three-month LTBI regimen during pregnancy would improve completion rates and allow close monitoring for drug toxicities compared to longer regimens. Once-weekly RPT/INH offers the additional benefit of once-weekly dosing, which may improve adherence. In the mouse model, addition of INH to a three-month regimen of RPT improved activity against MTB compared to RPT alone (56). The three-month regimen of weekly RPT and INH (3HP) was also shown to be safe and efficacious in non-pregnant humans, including those with HIV who were on an EFV-based ART regimen (25, 26). However, trials with RPT have excluded pregnant and postpartum women, a group that has a higher risk of TB than the general population and for whom the disease has negative consequences for both maternal and infant health, particularly if the woman is HIV-1-infected (15, 17, 43, 54, 57). The complex physiologic changes of pregnancy underscore the need for pharmacokinetic studies before newer regimens can be administered at the proper dose, safely and effectively to pregnant women. Furthermore, given the favorable safety profile, ease of use, potential advantages in cost and programmatic delivery, and opportunity for completing LTBI treatment during pregnancy, the three-month combination Study 26 regimen has substantial potential benefits for this population.

Rationale for study design
IMPAACT 2001 will be the first detailed study of the newer, shorter, and more tolerable regimen of RPT and INH with a focus on the metabolic alterations associated with pregnancy. The dose selected is the standard of care for adults based on TBTC 26 (see Section 1.2) and what is known about the metabolism of rifapentine in other populations (see Appendix II). This dose is expected to be appropriate for pregnant women as well.

The sampling strategy planned for IMPAACT 2001 is consistent with PK sampling in adults participating in TBTC trials of RPT, which will allow for comparison of the proposed IMPAACT 2001 study data with data from non-pregnant adults. Specifically, TBTC 26 used clearance as the main PK parameter, which will also be used as the primary PK parameter in IMPAACT 2001 for comparison with the non-pregnant historical controls (58). The sampling schedule is based on the expected PK profiles of RPT. The use of an intensive sampling strategy will support development of a model that estimates RPT PK well among pregnant women, including estimates for typical values and variability around absorption and elimination of the drug in this special population. The population PK modeling will be used to examine covariate effects (such as gestational age and weight) on PK parameters. With the sample size of 50 evaluable subjects, there will also be 90% power to detect one or more safety events for which the true rate of occurrence is 5 per 100 women or infants treated. The use of an interim analysis is a conservative approach, because there may be several different scenarios and variations in PK for RPT (e.g., changes in second trimester only, changes in third trimester only, similar changes in both trimesters, different changes in each trimester). With this approach, there will be power to detect all of them. To this end, a relatively large sample size is preferred to account for variability of the drug, itself, and possible physiologic differences between the second and third trimesters. Enrollment of half of each of the cohorts will provide sufficient power to detect a trimester-to-trimester effect.

The key limitations of using historical controls include the possibilities that controls and treated individuals (a) represent incomparable populations, and/or (b) differ systematically on key factors that affect the relationship between treatment and endpoint, and/or (c) encounter important differences in

ancillary aspects of medical care as practices change over time. Because historical controls represent a source of information on level and variability of objectively measured endpoints, the limitations do not seem to indicate a serious risk of bias for this trial. Furthermore, there is a very good understanding of historic controls of measured endpoints that obviates repeating this again and an excellent understanding of RPT (see Appendix II).

In summary, using these tools, this study will estimate the PK, safety and tolerability of rifapentine (RPT) and isoniazid (INH) dosed once weekly for 12 weeks in HIV-1-infected and high-risk HIV-1-uninfected pregnant women residing in moderate to high TB burden settings. The goal is to inform practice on appropriate use of this regimen in pregnant and postpartum women that achieves concentrations similar to non-pregnant adults, in whom efficacy has been established. The preliminary safety and tolerability of this regimen in this population will also be evaluated. It is anticipated that this study will generate useful PK data to help inform next steps for an amendment to this protocol or a separate future study.

1.4 Hypotheses

Standard doses of once-weekly 900mg RPT and 900mg INH, when given to pregnant women in the second trimester, third trimester, and postpartum will have pharmacokinetic parameters within 25% of a well-established cohort of non-pregnant historical controls. At this dose, there will be no serious adverse events or safety concerns for pregnant women taking the regimen or their infants, respectively.

2 OBJECTIVES

2.1 Primary Objectives

2.1.1 To estimate the population pharmacokinetics (PK) (CL/F, absorption, volume of distribution) of RPT and its desacetyl-rifapentine metabolite (desRPT) among pregnant women during the second trimester and third trimester who are receiving once-weekly RPT (900mg or the new study dose, if a dose adjustment is indicated by the interim analysis) and once-weekly INH (900mg).

2.1.2 To estimate the incidence of serious adverse events (SAEs) related to RPT + INH dosed once weekly for 12 weeks in pregnant women.

2.1.3 To describe the infant safety outcomes among infants born to women receiving once-weekly RPT + INH.

2.2 Secondary Objectives

2.2.1 To estimate the population pharmacokinetics (PK) (CL/F, absorption, volume of distribution) of RPT and its desacetyl-rifapentine metabolite (desRPT) among pregnant women during the postpartum period who are receiving once-weekly RPT (900mg or the new study dose, if a dose adjustment is indicated by the interim analysis) and once-weekly INH (900mg).

2.2.2 To assess the impact of covariates (gestational age, weight, age, HIV status) on primary PK parameters using population PK modeling.

2.2.3 To compare RPT and desRPT exposure pharmacokinetic parameters (AUC, C_{max}, C_{min}) for RPT in pregnant and postpartum women versus non-pregnant historical controls, using noncompartmental analyses.

2.2.4 To determine the RPT dose in pregnancy that achieves similar estimated exposure (AUC) of RPT as non-pregnant adults at standard doses.

2.2.5 To quantify RPT and desRPT concentrations at delivery among infants born to women receiving once-weekly RPT + INH.

2.2.6 To describe the tolerability of RPT + INH dosed once weekly for 12 weeks in pregnant and postpartum women.

2.2.7 To assess incidence of active TB in mother-infant pairs up to 24 weeks postpartum.

2.2.8 To explore the population pharmacokinetics (PK) (CL/F, absorption, volume of distribution) of INH in HIV-1-infected and HIV-1-uninfected pregnant and postpartum women (i.e., women who are and are not taking efavirenz (EFV)) who are receiving once-weekly RPT (900mg or the new study dose, if a dose adjustment is indicated by the interim analysis) and once-weekly INH (900mg).

2.3 Exploratory Objectives

2.3.1 To quantify RPT and desRPT concentrations in breast milk of postpartum women receiving once-weekly RPT + INH.

3 STUDY DESIGN

3.1 Identification of Study Design

IMPAACT 2001 is an open-label, multi-center, intensive PK study to evaluate the pharmacokinetics, safety, and tolerability of RPT and INH dosed once weekly for 12 doses in HIV-1-infected and HIV-1-uninfected pregnant women with latent TB infection at high risk for development of TB. Infants will also be enrolled, and breast milk samples from postpartum women who are still taking RPT/INH will be collected.

Each enrolled woman will receive the study drug regimen and will be followed for 24 weeks postpartum, regardless of when she delivers. Therefore, it is expected that some women will continue the study drug regimen postpartum, while some women may have completed the study drug regimen prior to delivery. It is possible that a woman enrolled in Cohort 1 could continue the study drug regimen postpartum (e.g., if she delivers her infant pre-term).

Two study cohorts are planned:
Cohort 1: Pregnant women ≥14 weeks gestation through <28 weeks gestation (second trimester)
Cohort 2: Pregnant women ≥28 weeks gestation through ≤34 weeks gestation (third trimester)

An interim analysis to assess the PK of RPT will be conducted, and a dose adjustment may be indicated for each cohort (see Section 10). Dose adjustments indicated for Cohort 2 will be implemented for Cohort 1 women as they enter their third trimester of pregnancy. See Section 3.4 for accrual into the cohorts, and Section 10.3 (Interim Analysis and Dose Adjustment) for further details regarding the interim analysis and dose adjustment.

3.2 Summary of Major Outcomes

Outcomes are listed in Section 9.2.

3.3 Time to Complete Accrual

Accrual is expected to be completed within 12 months from when the first woman is enrolled.

3.4 Accrual into Cohorts

Both cohorts will open to accrual at the same time.

The interim analysis for Cohort 1 will occur *either* after the first 12 women are enrolled into Cohort 1 *or* after the first 12 women are enrolled into Cohort 2, whichever event occurs first. (If there are effects of pregnancy on drug disposition, those effects are likely to be most prominent late in pregnancy (i.e., in the third trimester)). Once PK samples for the 12th woman have been submitted, enrollment into Cohort 1 will be paused for three months or until results of the RPT exposure analysis are available, whichever event occurs first.

The interim analysis for Cohort 2 will occur after the first 12 women are enrolled into Cohort 2. Once PK samples for the 12th woman have been submitted, enrollment into Cohort 2 will be paused for three months or until results of the RPT exposure analysis are available, whichever event occurs first.

Following the interim analysis in each cohort, the appropriate accrual plan as outlined below will be conducted for the respective cohort:

3.4.1 If a dose adjustment is not indicated, women will continue to be enrolled at the original dose to complete the remaining accrual target of 25 evaluable women for that cohort.

3.4.2 If a dose adjustment to a higher dose is indicated, a target of 25 new evaluable women will be enrolled at the higher dose.

3.4.3 If a dose adjustment to a lower dose is indicated, subsequent newly-enrolled women will be given the lower dose. The accrual target in that cohort will remain at 25 evaluable women in total. That is, the 25 evaluable women will include some women who received the 900mg dose and some who received the lower dose.

Women are considered evaluable if they meet any of the following criteria:

- Contribute any data to the Intensive PK or Sparse PK sampling collections
- Complete the study drug regimen (see Section 5.1.2 for adherence definition)

Women who enroll into Cohort 1 will not contribute toward the Cohort 2 accrual target during their third trimester of pregnancy. See Section 10 (Clinical Pharmacology Plan) below for further details regarding interim analysis timing and dose adjustment determinations.

Any pause in accrual to allow for an interim analysis and any changes in the dosing of the study drug regimen will be communicated by the IMPAACT 2001 Core Team to all participating sites.

3.5 Expected Duration of Study Participation

After completing the study drug regimen, all women will be followed once monthly until 24 weeks postpartum to assess for the development of active TB disease. Infants will also be followed once monthly for the first 24 weeks of life.

3.6 Sites

This study will be conducted at the IMPAACT sites listed in the Site Roster.

4 STUDY POPULATION

This study will be conducted among at least 50 evaluable pregnant women, and their infants, enrolled at study sites in Haiti, Kenya, Malawi, South Africa, Thailand, the United States, and Zimbabwe. Up to 82 women will be enrolled across sites to yield a minimum of 25 evaluable women in each of two cohorts based on gestation. Women in Cohort 1 will be enrolled in the second trimester of pregnancy (≥14 to <28 weeks); women in Cohort 2 will be enrolled in the third trimester of pregnancy (≥28 to ≤34 weeks). Within each cohort, enrollment of at least 10 evaluable HIV-1-infected women will be targeted.

Women will be selected for the study according to the criteria in Sections 4.1 and 4.2 and the guidelines in Section 4.3. The study-specific approach to recruitment, screening, and enrollment is described in Section 4.4. Considerations related to participant retention are provided in Section 4.5.

4.1 Inclusion Criteria

Women must meet all of the following criteria for inclusion in this study:

4.1.1 Age ≥ 18 years, or minimum age of consent according to locally applicable laws or regulations at screening, verified per site SOPs; and able and willing to provide written informed consent for study at screening

4.1.2 At screening, evidence by ultrasound of a viable singleton pregnancy with an estimated gestational age at enrollment of ≥ 14 weeks through ≤ 34 weeks as per screening ultrasound (see Section 6.7.3)

4.1.3 Has at least one of the following risk factors for TB:

- Per participant report, household contact* with a known active pulmonary TB patient
- Per medical records, confirmation of HIV-1 infection (see Section 4.1.5) with single positive TST or IGRA at any time in the past. If not available in medical record, perform at screening.

*Note: A household contact is defined as a person who currently lives or lived in the same dwelling unit and shares or shared the same housekeeping arrangements and who reports exposure within the past two years to an adult index case with pulmonary TB.

4.1.4 Documentation of HIV-1 infection status, or confirmation of HIV-1 infection status (if unknown or undocumented)

Confirmation of HIV-1 infection is defined as positive results from <u>two</u> samples (described below) collected at <u>different</u> time points. All samples tested must be whole blood, serum, or plasma. As this study is being conducted under an IND, all test methods should be FDA-approved, if available. If FDA-approved methods are not available, test methods should be verified according to GCLP and approved by the IMPAACT Laboratory Center.

If a participant has a negative result per medical history, or if her status is unknown, HIV-1-uninfected status must be confirmed per Sample #1 requirements below within 14 days prior to enrollment.

- Sample #1 may be tested by non-study public or PEPFAR programs. However, both the result and the assay date must be recorded in participant's chart. Source documentation (e.g., participant's medical record/chart, Ministry of Health (MOH) registers, laboratory results, etc.) must be available if requested.
- Sample #1 may be tested using any of the following:
  - Two rapid antibody tests from different manufacturers or based on different principles and epitopes

- One enzyme immunoassay (EIA) OR Western Blot OR immunofluorescence OR chemiluminescence
- One HIV DNA PCR
- One quantitative HIV RNA PCR (above the limit of detection for evidence of infection)
- One qualitative HIV RNA PCR
- One HIV total nucleic acid test

If Sample #1 is negative, the participant should be enrolled as HIV-1-uninfected with testing repeated as clinically indicated. If Sample #1 is positive, then collect and test Sample #2.

- Sample #2 must be tested in a CAP/CLIA-approved laboratory (for US sites) or in a laboratory that operates according to GCLP guidelines and participates in appropriate external quality assurance program (for international sites).
- Sample #2 may be tested using any of the following:
  - Rapid antibody test. If this option is used in combination with two rapid tests for Sample #1, at least one of the three rapid tests must be FDA-approved, and the third rapid test must be from a third manufacturer or based on a third principle or epitope.
  - One EIA OR Western Blot OR immunofluorescence OR chemiluminescence
  - One HIV DNA PCR
  - One quantitative HIV RNA PCR (above the limit of detection for evidence of infection)
  - One qualitative HIV RNA PCR
  - One HIV total nucleic acid test

4.1.5 If HIV-1-infected, documented current prescription of EFV + 2 NRTI regimen and reports taking regimen for at least two weeks prior to enrollment (regimens containing protease, integrase, or entry inhibitors are not permitted)

4.1.6 Documented laboratory values obtained within 30 days prior to enrollment:
- Hemoglobin $\geq$ 7.5 g/dL
- ALT $\leq$ 3 times the upper limit of normal (ULN)
- Total bilirubin $\leq$ 2.5 times the ULN
- Absolute neutrophil count (ANC) $\geq$ 750 cells/mm^3
- Platelet count $\geq$ 100,000/mm^3

4.1.7 Per participant report at screening, intent to remain in the current geographical area of residence for the duration of the study

4.1.8 Per participant report at screening, able to swallow whole tablets

4.1.9 Per participant report, intention to keep the pregnancy

4.1.10 Per participant report, willingness to permit infant to participate in the study

4.2 Exclusion Criteria

Women who meet any of the following criteria will be excluded from this study:

4.2.1 Evidence of confirmed or probable active TB disease per WHO symptom screen and confirmation by Gene Xpert, shielded chest x-ray, or sputum sample

4.2.2 Participant report of personal history of INH- or rifampin-resistant, multi-drug resistant (MDR), or extensively drug-resistant (XDR) TB

4.2.3 Participant report of personal history of active TB in the past 2 years

4.2.4 Participant report of previous treatment for LTBI

4.2.5 Household contact (as defined above) with known active MDR or XDR TB disease

4.2.6 Known major fetal abnormality as detected on ultrasound

4.2.7 Known allergy/sensitivity or any hypersensitivity to components of study drugs or their formulation

4.2.8 Known history of liver cirrhosis at any time prior to study entry

4.2.9 Per participant report and/or medical records, evidence of acute clinical hepatitis, such as a combination of abdominal pain, jaundice, dark urine, and/or light stools within 90 days prior to entry

4.2.10 Participant report and/or medical records of peripheral neuropathy Grade 2 or higher within 90 days prior to entry

4.2.11 Current use or history of 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 Participant report and/or clinical evidence of porphyria

4.2.13 Any other condition that, in the opinion of the IoR/designee, would preclude informed consent, make study participation unsafe, complicate interpretation of study outcome data, or otherwise interfere with achieving the study objectives, including taking the study medication

4.2.14 Planned or current participation in an interventional drug study

4.2.15 Current use of any prohibited or precautionary medications (see Section 5.5), including didanosine (DDI) or stavudine (D4T)

4.3 Co-Enrollment Considerations

Participants (i.e., women or infants) cannot be co-enrolled in an interventional drug study. Co-enrollment in other types of studies will be considered on a case-by-case basis. Sites will consult with the IMPAACT 2001 Core Team, impaact.core2001@fstrf.org, and the other study team for co-enrollment considerations and questions.

4.4 Recruitment, Screening, and Enrollment Process

Study visits and procedures are described in detail in Section 6.

Recruitment: As part of participant outreach and recruitment strategies, study staff may pre-screen potential study participants at either on-site or off-site locations. It is anticipated that many women will be recruited from the antenatal clinic at the site. During these interactions, study staff may explain the study to potential participants and ascertain elements of presumptive eligibility (e.g., age, gestational age), to be confirmed at on-site screening visits. Process information (e.g., number of potential participants contacted, number presumptively eligible) may be recorded and stored at the study site in the absence of written informed consent, provided the information is collected in such a manner that it cannot be linked to potential participant identifiers. At each site, procedures and documentation will comply with local IRB/EC requirements.

Screening: Once referred, study staff will obtain written informed consent. Written informed consent for study participation must be obtained before any study-related procedures are performed. After informed consent is obtained from the woman, a study-specific screening number will be acquired for the mother-infant pair through completion of the IMPAACT Screening Checklist. The checklist is part of the Subject Enrollment System (SES) located on the IMPAACT Data Management Center (DMC) website (at https://www.fstrf.org). Participant ID Numbers (PIDs) will be assigned at the site to both the woman and the infant. A PID is retrieved from the site's PID list, which is generated at the DMC and sent to the sites. The screening visit procedures are found in Section 6.

Enrollment: For mother-infant pairs who are found to be eligible for the study, enrollment will occur upon successful entry of required eligibility data into the SES (See Section 6.1). Successful entry into the SES will generate a study identification number (SID) for both the woman and the infant, as well as prescribing information for the study drug regimen. For pairs who are found ineligible or who do not enroll in the study for any reason, a Screening Failure Results case report form will be completed to record the screening outcome. The Entry Visit procedures are found in Section 6.

The DMC will generate monthly screening and enrollment reports. Using these reports, the Protocol Team will monitor accrual closely, relative to the study-specific accrual plan that has been established in collaboration with the study sites. Based on this plan, accrual is projected to be completed within 12 months. Each site must establish and implement SOPs to achieve the projected rates of enrollment specified in the accrual plan. Accrual will be assessed on team calls for each site, with an assessment of any issues surrounding enrollment. Should accrual rates fall below projections, the Protocol Team will work with study sites to take action as needed.

4.5 Participant Retention

Once a woman enrolls in this study, the study site will make every effort to retain her and her infant for the protocol-specified duration of follow-up and thereby minimize potential biases associated with loss to follow-up. Each site must establish and implement SOPs that target retention rates that are sufficient to allow the primary study outcomes to be reliably estimated (a maximum 10% loss to follow-up is assumed in sample size calculations).

The DMC will generate monthly reports of the number and percentage of participants completing follow-up visits throughout the course of the study. Based on these reports, the Protocol Team will track retention closely and work with study sites as needed to take any required action to address below-target rates.

5 STUDY TREATMENT

Study treatment for women consists of 12 once-weekly doses of RPT, INH, and pyridoxine (vitamin B_6). All HIV-1-infected women are required to have been on efavirenz (EFV) + 2 NRTIs (not provided through the study) for at least two weeks prior to enrollment.

Both RPT and INH will be provided through the study.

5.1 Regimens, Administration and Duration of Regimen

5.1.1 Regimens and Administration

The study drug regimen consists of 12 directly observed once-weekly doses of rifapentine (RPT) 900mg (six 150mg tablets), isoniazid (INH) 900mg (three 300mg tablets), and pyridoxine (vitamin B_6) 25mg to 100mg. HIV-1-infected and HIV-1-uninfected pregnant women with latent TB and their infants will be enrolled into two cohorts based upon gestation:

Cohort 1: Pregnant women in the second trimester (≥14 to <28 weeks gestation).
Cohort 2: Pregnant women in the third trimester ≥28 to ≤34 weeks gestation) and postpartum.

Both cohorts will receive the study drug regimen weekly with food as described in the MOP. The study drug regimen dosing may be adjusted based on an interim analysis (see Section 10 (Clinical Pharmacology Plan)). Doses should be given 7 days part (± 2 days). Women will be provided a meal within 30 minutes prior to each dose. Following this meal, women will swallow whole RPT, whole INH, and whole or crushed pyridoxine tablets under direct observation of site staff (i.e., directly observed therapy, DOT).

Women must receive the appropriate dose of pyridoxine 25mg to 100mg based on the current local, national, or international dosing guidelines. Pyridoxine can be taken as a whole tablet or crushed.

5.1.2 Duration and Adherence

All enrolled women will receive 12 weekly directly observed doses of the study regimen and will be followed until 24 weeks postpartum. Infants will not directly receive the study drug regimen but will be followed on study for the first 24 weeks of life.

Adequate adherence to the study drug regimen is defined as receipt of at least 90% of the prescribed doses. Women are to receive 12 weekly doses within a 16-week window (12 weeks consecutively is optimal). However, they will be considered to have completed the regimen if they receive at least 11 doses (90%) during this 16-week study drug regimen window. Skipped doses should be taken late rather than missed.

If a woman will not complete the therapy in the allotted 16 weeks (e.g., misses four doses in a row), there will be no limit to the number of times she can restart the study drug regimen. That is, if a woman chooses to stop participating or is lost to follow-up per Section 8.3 and then returns to the clinic while still within the gestational age requirements of the protocol, she will be allowed to restart the study drug regimen if she wishes. In this situation, the woman would be enrolled as a new participant into the appropriate cohort based on the gestational age at the time of restarting. The above definition must be met for the regimen to be considered complete.

5.2 Study Drug Formulation

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

Isoniazid (INH) will be supplied through the study and must be stored in accordance with the manufacturer's instructions.

Pyridoxine (vitamin B_6) will not be supplied through the study and must be stored in accordance with the manufacturer's instructions.

5.3 Product Supply/Acquisition, Distribution and Accountability

5.3.1 Study Product Supply/Acquisition/Distribution

Rifapentine (RPT) will be supplied by Sanofi, and isoniazid (INH) will be supplied by Macleods Pharmaceuticals Limited. Both RPT and INH will be made available through the National Institute of Allergy and Infectious Diseases (NIAID) Clinical Research Products Management Center (CRPMC). The site pharmacist can obtain RPT and INH 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 B_6) will not be supplied through the study and must be obtained locally by the site. ARVs are not provided by the study and are not considered part of the study drug regimen.

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/Pages/Default.aspx

5.3.2 Study Product Accountability

The site pharmacist is required to maintain complete records of all study products received from the NIAID CRPMC and subsequently dispensed. At 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 Study Drug Adherence Counseling

Women will be counseled during the informed consent process at the Screening Visit on the study drug regimen and the importance of maintaining the study visits. All doses will be given under DOT.

5.5 Prohibited and Precautionary Medications

Special attention should be paid to medications known to be metabolized by cytochrome P450 enzyme 3A (CYP3A) because of potential drug interactions with rifapentine, which is an inducer of metabolizing enzymes. A list of prohibited and precautionary medications may be found on the IMPAACT 2001 webpage on the IMPAACT website: http://impaactnetwork.org/.

5.6 Concomitant Medications

All concomitant medications will be recorded on source documents. With the exception of vitamins, topical medications, alternative therapies, and vaccines, all concomitant medications (e.g., ARVs, contraceptives) will be recorded on CRFs. Whenever a concomitant medication or study agent is initiated or a dose changed, investigators must review the concomitant medication/study agent's most recent package insert, Investigator's Brochure, or updated information from Division of AIDS, NIAID (DAIDS) to obtain the most current information on drug interactions, contraindications, and precautions.

While on the study drug regimen, currently only EFV-based and reverse transcriptase inhibitor (NRTI) based antiretroviral therapy (ART) regimens are permitted. Nevirapine (NVP), etravirine, rilpivirine, and other ART regimens (e.g., PI-based, entry inhibitors) are prohibited. Of note, infants born to mothers taking the study drug regimen can continue to receive NVP for prevention of perinatal transmission of HIV, as maternal rifapentine, like rifampin, is unlikely to affect levels of NVP in the infant (59).

6 STUDY VISITS AND PROCEDURES

An overview of the study visit and evaluations schedule is provided in Appendix I; blood draw volumes for each visit are also detailed in Appendix I. Presented in this section is additional information on visit-specific study procedures. Sections 6.7 and 6.8 below further describe Clinical Evaluations and Laboratory Evaluations, respectively. Section 10 further describes the PK specimen collection schedule.

All visits and procedures must be performed at the clinical research site or associated facilities identified in each site's approved Study Implementation Plan and must be documented in accordance with the NIAID Division of AIDS (DAIDS) policies for source documentation; refer to Section 11 for more information on documentation requirements and completion of CRFs. Refer to Section 7 for information on expedited adverse event (EAE) reporting, which may be required at any time during follow-up. As indicated in Appendix I, women will complete Screening and Entry Visits; infants will be enrolled *in utero* and will not complete Screening or Entry Visits after birth. Women will complete follow-up visits during pregnancy and postpartum; infants will complete follow-up visits postpartum.

In addition to the protocol-specified procedures listed in this section, study staff may also complete other tasks consistent with site SOPs, including but not limited to collecting, reviewing, and updating demographic and locator information; reviewing elements of informed consent; scheduling visits; providing instructions for contacting study staff between visits; providing reminders for scheduled visits; and following up on missed visits. All such tasks should be documented consistent with site SOPs. Study staff should inform women of clinically meaningful physical exam findings and laboratory test results when available.

6.1 Mother Screening Visit

The Screening Visit may take place up to two weeks prior to the Entry Visit. Multiple visits may be conducted within this timeframe to complete all required procedures, if necessary. Written informed consent will be obtained before any study-specific screening procedures are performed. For potential participants who do not meet the eligibility criteria, screening may be discontinued once ineligibility is determined. A Screening Failure Results CRF must be completed for any mother-infant pair who screen but do not enroll for any reason. Ineligible women may rescreen for study participation at a later time.

Mother Screening Visit Procedures *(up to 2 weeks prior to enrollment)*	
Administrative and Regulatory	• Obtain written informed consent • Obtain screening number from SES • Assign PIDs to mother and infant • Assess eligibility
Behavioral and Counseling	• Provide HIV pre-/post-test counseling (if applicable) • Assess alcohol and drug use
Clinical	• Obtain medical and medications history • Perform complete physical examination • Perform obstetrical exam to assess fetal health • Assess TB symptoms, risk, and exposure • Gene Xpert, shielded chest x-ray, or sputum microscopy • Perform TST (if not available per medical record)
Laboratory	*Collect blood for:* • IGRA (if not available per medical record) • Complete blood count (CBC) • Liver Function Tests • HIV-1 test (confirmatory tests as needed) • Coagulation profile

6.2 Mother Entry/Intensive PK Visit

The Entry Visit will be conducted over multiple days as a split visit. The administrative, regulatory, and clinical procedures should be conducted on the first day of the split visit; procedures that may provide information relevant to eligibility for the study (e.g., medical and medications history, physical examination, assessment of fetal movement and heart sounds) should be performed first, prior to final eligibility determination. In the event that a woman is found to be ineligible on the day of enrollment, enrollment should not occur.

Additional requirements for sequencing of procedures at the Entry Visit are as follows:

- Before enrollment:
  - Confirm final eligibility determination
  - Confirm the woman's continued consent for study participation
- After enrollment:
  - Prescribe study drug regimen
  - Provide meal
  - Perform first intensive PK blood draw
  - Administer study drug regimen (within 30 minutes after providing meal)
  - Complete remaining blood draws for intensive PK

Mother Entry/Intensive PK Visit Procedures *(Day 0 and 72 hours following)*	
Administrative and Regulatory	• Review elements of informed consent and confirm woman's continued consent for study participation* • Complete final eligibility determination and confirmation* • Complete paper-based eligibility checklist*, enter checklist data into SES to enroll the mother-infant pair, print and file a copy of the confirmation file • Provide meal within 30 minutes prior to administering study drug
Behavioral and Counseling	• Signs and symptoms of active TB Counseling
Clinical	• Assess TB symptoms, risk and exposure* • Update medical and medications history* • Perform targeted physical examination* • Provide available findings/test results • Record baseline AEs* • Assess fetal movement and heart sounds*
Laboratory	*Collect blood for:* • Intensive PK sample collection • CD4 count (HIV-1-infected only) • HBsAG, HBsAb, HCV Ab
Study Product	• Prescribe (according to local guidelines) study drug and administer RPT, INH, and pyridoxine under DOT

*Perform prior to enrollment

The Intensive PK sampling must be initiated on the same day (ideally in the morning) as the first dose of the study drug regimen, and conducted over the course of 72 hours according to the following time points: just prior to the first dose (t0), then 0.5h, 1h, 2h, 4h, 5h, 8h, 12h, 24h, 48h and 72h after the observed dose. Depending on site capacity, women may stay at the clinical research facility overnight after day 1 of the Entry Visit or return to the clinic at a designated time in the morning for administration of study drug and initiation of PK sampling. The same procedure can be followed for obtaining the PK samples at 48 and 72 hours after dosing.

Women will be asked to refrain from eating for two hours prior to each PK sampling dose of study drug, except for the meal provided by the site, which is to be eaten within 30 minutes before study drug administration. Women will be asked to refrain from further intake (except water) until three to four hours after the dose. The food type and quantity prior to each PK sampling dose will be recorded on CRFs.

RPT PK testing will be performed on all Intensive PK samples, after which, the t0 and 2h (or 4h) samples will be stored for later INH PK testing (see LPC for further details).

Women will be counseled about the signs and symptoms of active TB and asked to come to the clinic for an interim visit should any of the symptoms develop during the course of the study.

6.3 Mother Weekly Visit (On Study Drug Regimen), Sparse PK Visit

Women will have weekly study visits while on the study drug regimen. Requirements for sequencing of procedures at the weekly visits are as follows:

- Before administering study drug regimen:
  - Prescribe study drug regimen per site SOP
  - Provide meal

The PK sampling visits are ideally conducted in the morning. The Sparse PK sample collection will be conducted on the visit of the woman's last dose of the study drug regimen over the course of 48 hours according to the following time points: 1h, 4h, 24h, and 48h after the observed dose. Women who are still taking study drug and breastfeeding postpartum will express breast milk, and plasma samples will also be drawn at the following time points:

- First weekly visit after delivery, three hours after the study drug dose
- Second weekly visit after delivery, six hours after the study drug dose
- Last dose visit, 24 hours after the study drug dose (breast milk collection only)

Women will be asked to refrain from eating for two hours prior to each PK sampling dose, except for the meal provided by the site, which is to be eaten within 30 minutes before study drug administration. Women will be asked to refrain from further intake (except water) until three to four hours after the dose. The food type and quantity prior to each PK sampling dose will be recorded on CRFs.

RPT PK testing will be performed on all Sparse PK samples, after which, the 1h and 4h samples will be stored for later INH PK testing (see LPC for further details).

Mother Weekly Visit Procedures *(7 ± 2 days apart)*		
Administrative and Regulatory		• Provide meal within 30 minutes prior to administering study drug
Behavioral and Counseling		• Signs and symptoms of active TB Counseling • Assess infant feeding methods (postpartum only)
Clinical		• Perform targeted physical exam • Record/update medical and medications history • Record/update AEs • Provide available test results • Assess TB symptoms, risk and exposure • Assess fetal movement and heart sounds (until delivery)
Laboratory	Blood	*Collect blood for:* • Sparse PK sample collection (during the visit of the last dose and 48 hours following) • Plasma sample collection (breast milk PK participants only, conducted first and second week postpartum) • Complete blood count (every four weeks) • Liver Function Test (every four weeks) • Coagulation profiles (at one visit at ≥34 weeks gestational age only)
	Breast milk	*Collect breast milk for:* • Breast milk PK sample collection (if eligible, conducted first and second week postpartum and on the visit of the last dose)
Study Product		• Prescribe (according to local guidelines) and administer RPT, INH, and pyridoxine under DOT

6.4 Mother Monthly Visits (Post-study drug regimen) and Study Exit Visit

The change from the weekly visit schedule (on study drug regimen) to the monthly visit schedule (post-study drug regimen) is independent of the woman's delivery date. It is possible that a woman enrolled in Cohort 1 could continue the study drug regimen postpartum (e.g., if she delivers her infant pre-term). Following the completed study drug regimen, all women will be followed once monthly (i.e., every four weeks counting from labor and delivery, ideally coinciding with infant monthly visits) until 24 weeks postpartum to assess for the development of active TB disease. At the final weekly visit, follow-up dates for the monthly visits will be provided to the woman. Contact information will also be obtained to improve retention if a visit is missed. A woman who does not present for a follow-up visit within two weeks of the scheduled visit will be considered as having missed that study visit.

There is no required sequencing of procedures at these visits.

The final study visit for women will occur 24 weeks postpartum and will ideally be scheduled to occur on the same day as the Infant Study Exit Visit.

Mother Monthly Visit and Study Exit Visit Procedures *(± 2 weeks)*	
Administrative and Regulatory	• None
Behavioral and Counseling	• Signs and symptoms of active TB Counseling • Assess infant feeding methods (postpartum only)
Clinical	• Complete physical exam • Record/update medical and medications history • Record/update AEs • Provide available test results • Assess TB symptoms, risk and exposure • Assess fetal movement and heart sounds (until delivery)
Laboratory	*Collect blood for (no blood is collected at the Study Exit Visit):* • Complete blood count • Liver Function Test • Coagulation profiles if clinically indicated (e.g., bleeding event)

6.5 Infant/Newborn Visit

The infant single PK sample collection will be conducted within three days of life, ideally in the morning. When a study participant is admitted for delivery, the research team should be notified (i.e., the medical records may indicate that the patient is enrolled in IMPAACT 2001, and the research staff's contact information may be available). The participants may also be asked to contact the research staff once they are in labor. The infant single PK sample will only be collected if the mother's most recent dose was taken within 72 hours of drawing the infant's blood.

At sites with capacity, cord blood PK sample collection will be offered to mothers to be conducted during labor and delivery. See Section 10 below for details and eligibility of the single PK sample and cord blood sample collections. Eligibility for single PK sampling must be confirmed prior to collection of this sample.

Infant/Newborn Visit Procedures *(within 3 days of life)*	
Administrative and Regulatory	• None
Clinical	• Assess eligibility for single PK sampling • Complete physical exam • Record medical and medications history • Record AEs • Provide available test results to mother
Laboratory	*Collect blood for:* • Single PK sample collection (if eligible) • Coagulation profile (if eligible) • Cord blood (optional if eligible, during mother's delivery)

6.6 Infant Monthly Visits and Study Exit Visit

Infants will be followed monthly for the first 24 weeks of life. Infants will be assessed at each visit for TB exposure and signs and symptoms suggestive of TB disease. The mother's visits and the infant's visits will ideally be scheduled to occur on the same day.

There is no required sequencing of procedures at these visits.

The final study visit for infants will occur at 24 weeks of life.

Infant Monthly Visit and Study Exit Visit Procedures *(± 2 weeks)*	
Administrative and Regulatory	• None
Clinical	• Limited physical exam • Record medical and medications history • Record/update AEs • Provide available test results to mother • Assess TB symptoms, risk and exposure
Laboratory	*Collect blood for (no blood is collected at the Study Exit Visit):* • Complete blood count (if clinically indicated) • Liver Function Test (if clinically indicated) • Coagulation profile (if clinically indicated)

6.7 Clinical Evaluations and Procedures

Additional clinical assessments may be performed at the discretion of the examining clinician in response to symptoms or illnesses present at the time of the exam.

6.7.1 Clinical assessment for development of TB disease

TB symptoms, risk, and exposure will be assessed for each participant (i.e., women and infants) at each study visit. A pulmonary and lymph node exam will be conducted for participants with suspected TB disease.

For women, the WHO TB symptom screen will be used. In addition, failure to have adequate weight gain in pregnancy will be recorded.

For infants, TB will be assessed by known exposure or with the following symptoms: cough, respiratory distress, failure to gain weight, weight loss, or fever.

See Section 8.1 for details regarding participant management of suspected and confirmed TB disease. The IoR/designee may conduct additional testing and confirmatory procedures per local standard of care for infants suspected of developing TB disease. Participants will remain on-study for follow-up visits.

All participants (i.e., women and infants) confirmed with active TB disease will be referred to local standard of care for treatment. Infants of mothers who develop active TB will also be referred for evaluation and initiation of TB preventive therapy as per local pediatric TB guidelines.

6.7.2 Physical Examination

Maternal complete physical examination:
For women, a complete physical exam will include the following: vital signs (temperature, pulse, blood pressure, and respiration), assessment of general appearance, cardiac exam, pulmonary exam, lymph node exam, and liver and spleen size per abdominal exam. Weight (so BMI and change in weight can be calculated) and mid-upper arm circumference (MUAC) will also be measured. Height will be assessed at the Entry Visit only.

Maternal targeted physical examination:
For women, a targeted physical exam during study follow-up will include vital signs (temperature, pulse, blood pressure, and respiration) and weight. Additional assessments should be driven by any previously identified or new signs or symptoms including diagnoses that the woman has experienced since the last visit.

Infant complete physical examination:
For infants, at the Newborn Visit, a complete physical exam will include the following: APGAR scores, birth weight and length, head circumference, gestational age, congenital abnormalities, demographics.

Infant limited physical examination:
For infants, at the monthly study visits, a limited physical exam will include the following: Weight (documented on a growth chart), length, head circumference, and vital signs (temperature, heart rate, and respirations). Additional assessments should be driven by any previously identified or new signs or symptoms including diagnoses that the infant has experienced since the last visit.

6.7.3 Obstetrical Exam to Assess Fetal Health: Mothers

At the Screening Visit, an obstetrical exam will be conducted to assess the following:

- Gestational age, presence of severe fetal abnormalities, and presence of multiple births, by ultrasound
- Fetal heart sounds confirmed on Doppler or fetal movements felt by mother

The Entry Visit and follow-up visits will include the following assessments until the mother delivers:

- Fetal heart sounds confirmed on Doppler or fetal movements reported by mother

6.8 Laboratory Evaluations and Procedures

Test results obtained from standard of care visits within 14 days of the participant's monthly study visit will be used. Lab evaluations must be performed in DAIDS-approved laboratories that are participating in an external quality assurance (EQA) program.

Note: NIH recommendations for maximum pediatric and adult blood draw volumes will be followed in this study. For women, the volume of blood drawn shall not exceed 10.5 mL/kg or 550 mL, whichever is smaller, over any eight week period. For infants, the volume of blood drawn at any study visit should not exceed 5 mL/kg in a single day and 9.5 mL/kg over any eight-week period. The priority order of sample collections will be as follows: samples needed for clinical safety assessments/AEs will be collected first (specific tests as determined by investigator), followed by samples needed for PK analysis.

6.8.1 Laboratory Evaluations

Normal laboratory ranges will be the institutional values at the clinical research site. If a site does not have normal laboratory ranges, per an IMPAACT memorandum dated 11 December 2009, the site laboratory may adopt established ranges from another study or laboratory without verification. The medical director of the laboratory is responsible for the adoption of external unverified ranges, and s/he must provide reasonable evidence that the ranges are appropriate. Documentation of "reasonable evidence" may include the opinions of one or two local pediatricians, pathologists, or other knowledgeable laboratory personnel.

For the maternal laboratory evaluations, the following will be recorded on the case report forms (CRFs):

- Complete blood count will include white blood count, hemoglobin and platelets.
- Liver function tests will include albumin, AST, ALT, and total bilirubin.
- Coagulation profile will assess Prothrombin Time (PT) only.

For women, blood will be collected at the Entry Visit for later testing of HBs AG, HBs Ab, HCV Ab, as determined by the Core Team.

For the infant laboratory evaluations, the following will be recorded on the case report forms (CRFs):

- A coagulation profile to assess PT will be collected at the Newborn Visit only if the mother is still on the study drug regimen.
- Complete blood count will include white blood count, hemoglobin and platelets, if indicated based on symptoms.
- Liver function tests will include albumin, AST, ALT, and total bilirubin, if indicated based on symptoms.

6.8.2 PK Specimen Collection

Details regarding the Intensive, Sparse, and breast milk PK specimen collections (and the optional cord blood collection) for women, as well as the single PK specimen collection for infants are included in Section 10.

6.8.3 Specimen Preparation, Testing, Storage, and Shipping

The IMPAACT 2001 Laboratory Processing Chart (LPC) provides instructions regarding the collection, processing, and shipping of specimens for this study and is available on the IMPAACT website.

6.8.4 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.

All infectious specimens will be sent using packaging that meets requirements specified by the International Air Transport Association Dangerous Goods Regulations for UN 3373, Biological Substance, Category B, and Packing Instruction 650. Refer to individual carrier guidelines (e.g., Federal Express or Airborne) as well as specific requirements of the host country for specific instructions required for ground transportation within that country.

Infection control for active TB cases and good laboratory practices for TB isolation will be according to WHO guidance and best practices locally to minimize TB transmission. Please refer to instructions detailed in the International Air Transport Association (IATA) Dangerous Goods Regulations.

6.9 Behavioral and Counseling Evaluations

Eligibility behavioral assessments conducted at the Screening Visit will assess a woman's alcohol and drug use to determine whether related inclusion/exclusion criteria are met.

Site staff will counsel enrolled women about the signs and symptoms of active TB at the enrollment visit and each study follow-up visit. Women will be asked to come to the clinic for an interim visit should any of the symptoms develop during the course of the study.

HIV pre-/post-test counseling will be offered per local standard of care in the event that HIV testing must be performed by the site in order to confirm HIV status. Participants requiring HIV testing and counseling during study participation will be referred to local providers.

6.10 Procedures for Premature Discontinuation of Study Drug Regimen/Study Participation

Women who permanently discontinue the study drug regimen (i.e., RPT, INH, and pyridoxine) prematurely will remain on-study and follow the visit schedule until 24 weeks postpartum. Infants of mothers who permanently discontinue study drug regimen will also remain on study per the visit schedule until 24 weeks of life.

Participants who must be withdrawn from study participation will be requested to complete their Study Exit Visit, if possible.

7 SAFETY MONITORING, ASSESSMENT AND REPORTING

An adverse event (AE) is defined as any untoward medical occurrence in a clinical research participant administered an investigational product and which does not necessarily have a causal relationship with the investigational product. As such, an AE can be an unfavorable or unintended sign (including an abnormal laboratory finding, for example), symptom or disease temporally associated with the use of an

investigational product, whether or not considered related to the product. This definition is applied at the time of enrollment (i.e., once a participant has successfully completed the SES). The term "investigational product" for this study refers to the study drug regimen.

Women will be provided instructions for contacting the study site to report any untoward medical occurrences they or their infants enrolled in the study may experience. In cases of potentially life-threatening events, participants will be instructed to seek immediate emergency care. Where feasible and medically appropriate, participants will be encouraged to seek evaluation at the hospital/clinic where a study clinician is based, and to request that the clinician be contacted upon their arrival.

7.1 Safety-Related Roles and Responsibilities

Routine monitoring will be done by the IMPAACT 2001 Core Team which consists of the Protocol Chair, Vice Chairs, NIAID and NICHD Medical Officers, Protocol Statisticians, Protocol Data Manager, and the Clinical Trials Specialist (impaact.core2001@fstrf.org) or their designees. Site IoRs/designees are responsible for continuous close safety monitoring of all study participants, and for alerting the Core Team if unexpected concerns arise. The IMPAACT SDMC prepares routine safety monitoring and clinical data reports for review by the Core Team, which meets via conference call approximately twice per month or as needed throughout the period of study implementation to review safety data, discuss product use management, and address any potential safety concerns.

An IMPAACT Study Monitoring Committee (SMC) will review the study regularly, at least twice annually, and on a more frequent or ad hoc basis for safety issues or any other concerns. Other study implementation issues, such as participant accrual, participant retention, and data quality, will also be monitored by the SMC. The protocol team may also request ad hoc SMC reviews if any potential safety concerns arise. For example, if a potential concern is identified during a routine protocol team review of safety data, the team may request an ad hoc SMC review to further evaluate that potential concern. Based on any of its reviews, the SMC may recommend that the study proceed as currently designed, proceed with design modifications, or be discontinued.

7.2 Safety-Related Recording on Case Report Forms

Study site staff will document in source documents all AEs reported by or observed in enrolled study participants regardless of severity and presumed relationship to study product.

Pre-existing conditions and AEs identified in this study will be recorded on CRFs as abnormal laboratory test results, signs, symptoms, and diagnoses, as follows:

Laboratory test results: The results of all protocol-specified screening, entry, and follow-up laboratory test results will be recorded on the relevant CRFs. In addition, throughout follow-up through the Study Exit Visit, Grade 2 or higher test results related to pregnancy complications, hepatotoxicity, hemorrhage, or peripheral neuropathy, all Grade 3 or higher test results, test results that result in discontinuation of study drug regimen, and test results that meet criteria for EAE reporting (included congenital anomalies) will be further evaluated, with additional data recorded on the relevant event evaluation CRF.

Signs and symptoms: All signs and symptoms occurring from the Screening Visit through immediately prior to the first administration of study drug regimen will be recorded as pre-existing conditions on the relevant CRF. While maternal participants are receiving study drug, all signs and symptoms will be recorded on the relevant CRF. Thereafter, Grade 2 or higher signs and symptoms related to pregnancy complications, hepatotoxicity, hemorrhage, or peripheral neuropathy, all Grade 3 or higher signs and symptoms, and signs and symptoms that meet EAE reporting criteria will be recorded on CRFs. In addition, throughout follow-up through the Study Exit Visit, Grade 3 or higher signs and symptoms, signs and symptoms that result in discontinuation of study drug regimen and signs and symptoms that meet

criteria for EAE reporting (included congenital anomalies) will be further evaluated, with additional data recorded on the relevant event evaluation CRF.

Diagnoses: All diagnoses identified from the Screening Visit through immediately prior to the first administration of study drug regimen, except Grade 1 and Grade 2 diagnoses listed on the IMPAACT Do Not Record list (available at www.fstrf.org), will be recorded as pre-existing conditions on the relevant CRF. During follow-up through the Study Exit Visit, all diagnoses since the last study visit except Grade 1 and Grade 2 diagnoses listed on the IMPAACT Do Not Record list will be recorded on the relevant CRF. In addition, throughout follow-up, Grade 2 or higher diagnoses related to pregnancy complications, hepatotoxicity, hemorrhage, or peripheral neuropathy, all Grade 3 or higher diagnoses, diagnoses that result in discontinuation of study drug regimen, and diagnoses that meet criteria for EAE reporting (including congenital anomalies) will be further evaluated, with additional data recorded on the relevant event evaluation CRF. All diagnoses recorded on CRFs should be recorded consistent with the specifications of the relevant diagnosis appendix (available at www.fstrf.org).

With appropriate permission of the participant/mother, whenever possible, records from all non-study medical providers related to untoward medical occurrences will be obtained and required data elements will be recorded on study CRFs.

7.3 Expedited Adverse Event (EAE) Reporting

7.3.1 Adverse Event Reporting to DAIDS

Requirements, definitions and methods for expedited reporting of adverse events (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 Experience Reporting System (DAERS), an internet-based reporting system, must be used for expedited AE reporting to DAIDS. In the event of system outages or technical difficulties, expedited AEs may be submitted via the DAIDS EAE Form. For questions about DAERS, please contact DAIDS-ES at DAIDS-ESSupport@niaid.nih.gov. Site queries may also be sent from within the DAERS application itself.

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

7.3.2 EAE Reporting Requirements for this Study

- EAEs will be reported for women and infants enrolled in this study.
- The SAE Reporting Category, as defined in Version 2.0 of the DAIDS EAE Manual, will be used for this study.
- The study agents for which expedited reporting is required are: rifapentine and isoniazid. Open-label pyridoxine (vitamin B_6) and prenatal multivitamins are not to be considered for EAE reporting.

7.3.3 Grading Severity of Events

Severity and laboratory tests will be graded per the DAIDS Table for Grading Adult and Pediatric Adverse Events, Version 2.0 (dated November 2014 available on the RSC website (http://rsc.tech-res.com/safetyandpharmacovigilance/), except for complications during pregnancy. Complications during pregnancy will be graded per the Complications of Pregnancy Section of the Female Genital Grading Table for Use in Microbicide Studies (Version 1.0, dated November 2007) found on the DAIDS RSC website (http://rsc.tech-res.com/safetyandpharmacovigilance/gradingtables.aspx).

For any serious or expedited AEs (SAEs/EAEs) that are continuing at a participant's study exit visit, the IoR/designee must establish a clinically appropriate follow-up plan for the AE, including referrals to local standard of care. The same approach must be taken for any AEs that are found to have increased in severity at the time of the study exit visit or continue requiring re-assessments beyond the study exit visit.

Serious adverse events (SAEs) will be defined by the Manual for Expedited Reporting of Adverse Events to DAIDS (Version 2.0, January 2010), as AEs occurring at any dose that:

- Results in death
- Is life-threatening
- Requires inpatient hospitalization or prolongation of existing hospitalization
- Results in persistent or significant disability/incapacity
- Is a congenital anomaly/birth defect
- Is an important medical event that may not result in death, be immediately life-threatening, or require hospitalization but may jeopardize the participant or require intervention to prevent one of the outcomes listed in the definition above

7.3.4 Expedited AE Reporting Period

- The expedited AE reporting period for this study begins once the participant is enrolled and continues through and including the participant's final study visit (Mother or Infant Study Exit).
- After the protocol-defined AE reporting period, unless otherwise noted, only suspected unexpected serious adverse reactions (SUSARs) as defined in Version 2.0 of the EAE Manual will be reported to DAIDS if the study staff become aware of the events on a passive basis (from publicly available information).

8 PARTICIPANT MANAGEMENT – MOTHERS AND INFANTS

Guidelines for clinical management and temporary hold/permanent discontinuation of the study drug regimen are outlined in this section. In general, the IoR/designee has the discretion to hold study drug regimen temporarily at any time if s/he feels that continued use would be harmful to the woman or interfere with treatment deemed clinically necessary, and s/he should notify the Core Team in such cases. Unless otherwise specified below, the IoR/designee should immediately consult the Core Team for further guidance on resuming study drug regimen, continuing the hold temporarily, or progressing to permanent discontinuation of study drug regimen. The IoR/designee will document all temporary study drug regimen holds and permanent discontinuations on applicable CRFs. When indicated, sites should notify the Core Team within 48 hours. Unless otherwise specified, study drug regimen refers to RPT, INH, and pyridoxine.

8.1 Management of Adverse Events

Management of adverse events will be according to the best clinical practice and the judgment of the site investigator. Enrolled infants of women participating in IMPAACT 2001 are not actively provided with the study drug regimen but may be exposed in utero or through breastfeeding. Infant management is the responsibility of the clinical care provider at the site. AEs involving these infants should be reported according to requirements in Section 7 as well as to the local Institutional Review Board/Ethics Committee according to prevailing local law and Good Clinical Practices. All protocol-specific reportable events and SAEs will be recorded on CRFs as per Section 7.2. Unless otherwise specified, participants will remain on-study for the duration of the scheduled follow-up visits.

All adverse events identified in infants in this study will be source documented consistent with the policies and procedures referenced in Section 11. Among other details, source documentation will include the severity of each event (graded as described in Section 7.3.3) and its relationship to study product, assessed by the site clinician according to the following categories and definitions:

- *Definitely Related*: The adverse event and administration of the medication are related in time, and a direct association can be demonstrated.
- *Probably Related*: The adverse event and administration of the medication are reasonably related in time, and the adverse event is more likely explained by the medication than other causes.
- *Possibly Related*: The adverse event and administration of the medication are reasonably related in time, and the adverse event can be explained equally well by causes other than the medication.
- *Probably Not Related*: A potential relationship between the medication and the adverse event could exist (i.e., the possibility cannot be excluded), but the adverse event is most likely explained by causes other than the medication.
- *Not Related*: The adverse event is clearly explained by another cause not related to the medication.

Note: The above classification applies for AE documentation (source documentation and CRF completion) and management but does not apply for expedited adverse event (EAE) reporting. EAEs will be reported, per the DAIDS EAE Manual, as related or not related. Please see Section 7.3 for more information on EAE reporting.

8.1.1 Suspected TB Disease

- Hold study drug regimen (i.e., RPT, INH, and pyridoxine) for suspected TB disease
- Perform confirmatory test (specific test as determined by site IoR/designee)
- If active TB disease is confirmed, permanently discontinue study drug regimen and notify the Core Team. Women and infants diagnosed with active TB during the study will be referred to local care for active TB management and treatment, where (if available) they will have a sputum sample (or other appropriate sample if extrapulmonary TB) sent for drug susceptibility testing (DST) to ensure susceptibility to first-line regimens. .
- If active TB disease is not confirmed and the IoR/designee suspects active TB based on clinical judgment, the IoR/designee may choose to permanently discontinue study drug regimen, refer participant to local care for TB management, and notify the Core Team.
- If active TB disease is not confirmed, the IoR/designee may resume the woman on the study drug regimen.

8.1.2 Rifamycin hypersensitivity syndrome (RHS)

For women who develop signs or symptoms suggestive of RHS (e.g., fever, myalgia, rash, hypotension, clinical hepatitis):

- Hold study drug regimen
- Assess the women for RHS (see note below for definition) through clinical evaluation and laboratory testing, including comprehensive metabolic panel, CBC with manual differential, and other tests that, at the discretion of the site IoR/designee, are necessary to exclude likely alternative diagnoses (e.g., should symptoms suggest influenza, a nasopharyngeal aspirate for viral testing could be sent).
- If $\geq$ Grade 2 AE or toxicity meets the case definition for RHS, permanently discontinue the study drug regimen and notify the Core Team.

  In the event of treatment discontinuation, participants will remain on-study and continue to be followed through 24 weeks postpartum.

Note: RHS is defined as follows:

- Hypotension, urticaria, angioedema, acute bronchospasm, conjunctivitis, thrombocytopenia, or neutropenia that occurred in relation to study drug regimen; *or*
- More than four of the following that occurred in relation to study drug (one of which must be assessed as having been > Grade 2): weakness, fatigue, muscle pain, nausea, vomiting, headache, fever, aches, sweats, dizziness, shortness of breath, flushing, rash, itching, syncope, cough, palpitations, chills, or eosinophilia.
- A complete listing of RHS symptoms reported by the woman should be recorded on the appropriate CRFs.

8.1.3 Gastrointestinal

For Grade 2 AE with symptoms not present at the previous visit, or for nausea/vomiting and/or diarrhea ≥ Grade 3:

- Hold study drug regimen until the symptoms have resolved. Antiemetic and antidiarrheal medication may be used at the site investigator's discretion

For nausea and vomiting occurring as a result of hepatitis (determined as unrelated to study drug regimen), hold study drug regimen until the symptoms return to baseline levels.

8.1.4 Cutaneous

For Grade 2 or 3 rash, or showing a significant increase over baseline, hold study drug regimen. When the AE resolves or returns to baseline, resume study drug regimen.

For Grade 4 cutaneous or Grade 4 mucocutaneous rash, hold study drug regimen. Study drug regimen may be interrupted and resumed at the discretion of the site investigator. If Grade 4 returns and is determined to be related, permanently discontinue study drug regimen.

8.1.5 Drug-Associated Fever

If ≥ Grade 3, hold the study drug regimen. When the temperature returns to normal, resume the study drug regimen. If symptoms recur, permanently discontinue and notify Core Team.

8.1.6 Peripheral Neuropathy

Peripheral neuropathy associated with INH is usually avoided by the concurrent administration of vitamin $B_{6,}$ and is expected to be rare given the once-weekly dosing and duration of the study drug regimen (12 weeks). In this study, all women will take vitamin B_6 as part of the complete study drug regimen. If peripheral neuropathy develops, every effort should be made to determine the etiology (i.e., to uncover other potential contributing factors such as alcohol use or concomitant drugs with this side effect). Women with Grade 1 peripheral neuropathy may be entered into the study, but should be monitored carefully for any progression of peripheral neuropathy.

Grade 1 or 2:
Continue the study drug regimen and assess the woman for progression of peripheral neuropathy.

Grade 3 or 4:

- Hold study drug regimen and assess weekly until toxicity resolves to Grade ≤2; then study drug regimen may be reintroduced at the site investigator's discretion.
- If peripheral neuropathy does not resolve to Grade ≤2, then the study drug regimen can be discontinued or reintroduced at the site investigator's discretion.

8.1.7 Asymptomatic Elevations in AST/ALT

Every effort should be made to determine the etiology (i.e., whether the elevated AST/ALT is due to RPT/INH toxicity, alcohol, or other factors) in instances of suspected hepatotoxicity. Reintroduction of potential hepatotoxic non-study concomitant medications is at the discretion of the site investigator and the study participant. If a participant becomes symptomatic, follow guidance for symptomatic hepatitis.

Grade 1:
- Continue study drug regimen.
- Repeat test as soon as possible and within seven days.
- If repeat assessment is Grade ≤ 1, continue study drug regimen.

Grade 2:
- Continue study drug regimen.
- Repeat test as soon as possible and within seven days.
  - Assess for alcohol use, non-study medication-related drug toxicity, lactic acidosis syndrome, pre-eclampsia, fatty liver of pregnancy, and viral hepatitis as the cause of the AST/ALT elevation. If the AST/ALT elevation is considered most likely to be due to concomitant illness or medication, standard management, including discontinuation of the likely causative agent, should be undertaken
- If repeat assessment is Grade ≤ 2, continue study drug regimen.

Grade 3:
- Continue study drug regimen.
- Repeat test within three working days.
  - Assess for alcohol use, non-study medication-related drug toxicity, lactic acidosis syndrome, pre-eclampsia, fatty liver of pregnancy, and viral hepatitis as the cause of the AST/ALT elevation.
- If repeat assessment is Grade ≤ 2, manage as per Grade 2.
- If repeat assessment is Grade 3 and is attributed to concomitant illness or medication (not related to study drug), study drug regimen may be continued at the discretion of the site investigator, and the Core Team notified. Treat the underlying illness or remove the likely causative agent.
- If the repeat assessment is Grade 3 and is assessed as related, hold study drug regimen.
  - Repeat testing weekly, and once the toxicity grade is Grade ≤ 2, resume study drug regimen and notify the Core Team.
- When study drug regimen is resumed following a hold for Grade 3 AST/ALT, repeat testing should be performed one week after resumption. If the result of this testing is Grade 3 or 4, consult the Core Team.

Grade 4:
- Hold study drug regimen.
- Repeat test within three working days, in addition to total bilirubin and INR if available at the site.
  - Assess for alcohol use, non-study medication-related drug toxicity, lactic acidosis syndrome, pre-eclampsia, fatty liver of pregnancy, and viral hepatitis as the cause of the AST/ALT elevation.
- If repeat assessment is Grade < 4, manage per the grade of the repeat assessment.
- If repeat assessment is Grade 4, continue to hold study drug regimen.
  - Repeat ALT/AST testing weekly, and consult the Core Team on study drug regimen and frequency of repeat assessments.
  - Once the repeat testing results in Grade ≤ 1, resume study drug regimen.
- When study drug regimen is resumed following a hold for Grade 4 AST/ALT, repeat testing should be performed one week after resumption. If the result of this testing is Grade 3 or 4, consult the Core Team.

8.1.8 Hepatotoxicity (Symptomatic Hepatitis)

Signs and symptoms of hepatitis include but are not limited to fatigue, malaise, anorexia, nausea, acholic stools, bilirubinuria, jaundice, liver tenderness, and/or hepatomegaly (icteric sclera in isolation without systemic complaints would not be considered symptomatic).

- Hold study drug regimen.
- Immediately perform AST and ALT tests, in addition to total bilirubin and INR if available at the site; stored assays for hepatitis B/C should be processed. Follow general management guidelines based on the highest grade sign or symptom.
- Consult the Core Team on study drug regimen and frequency of repeat assessments (in general, at least weekly re-assessment is recommended).

8.1.9 HIV-1 Infection

Participants (i.e., women or infants) who become infected with HIV during the course of the study will be referred to local care for treatment. HIV-1-infected women who are changed from an EFV + 2 NRTI regimen by their HIV treatment provider and are prescribed a triple or quadruple NRTI regimen can continue to take study drugs as planned.

- Continue on study drug regimen, as long as they are not initiated on contraindicated medications (e.g., protease inhibitors).
- If not taking an EFV-based regimen, permanently discontinue the study drug regimen. Such women and their infants will remain on-study for follow-up visits to complete follow-up through 24 weeks postpartum. Infant feeding, prevention and treatment of HIV and other co-morbidities will also be according to local standard of care.

8.1.10 Postpartum Hemorrhage

There are multiple causes of postpartum hemorrhage. Rifampin, another rifamycin product, may increase the risk for maternal postpartum hemorrhage and bleeding in the exposed neonate. This has not been reported in mothers on rifapentine or rifampin-containing active TB regimens. As a precautionary measure, mothers will have their prothrombin time (PT) monitored at baseline, in late third trimester, and as clinically indicated during monthly follow-up. Infants will be monitored for PT at birth and as clinically indicated during monthly follow-up. If there is an increase in PT with associated prolonged bleeding in the mother or infant, treatment with vitamin K may be indicted as per local standard of care. For maternal postpartum hemorrhage or bleeding in infants:

Grade 1 or 2:

- Continue study drug regimen.
- Follow local standard of care and monitor PT.

Grade 3 or 4:

- Hold study drug.
- Assess for signs and symptoms of active bleeding and other pregnancy-related etiologies.
- If no signs of active bleeding or other etiologies of elevated PT are found, administer vitamin K per local standard of care and repeat PT within three working days.
- If repeat PT is ≤ Grade 2, resume study drug regimen. Continue to monitor PT until it normalizes (i.e., returns to Grade 1 or lower).
- If repeat PT is ≥ Grade 3, permanently discontinue study drug regimen. Continue to monitor PT until it normalizes (i.e., returns to Grade 1 or lower).
- If signs of active bleeding are found, permanently discontinue study drug regimen. Administer vitamin K per local standard of care. Continue to monitor bleeding and repeat PT until it is resolved to Grade 1 or lower.

Note: Postpartum hemorrhage is defined as blood loss greater than 500 mL in vaginal delivery and 1,000 mL in caesarean section within 24 hours of birth, at the discretion of the site investigator.

8.1.11 Pregnancy

For women who become pregnant again (during study follow-up) while still on the study drug regimen, permanently discontinue study drug regimen and refer to local standard of care. They will remain on-study and complete the study procedures and evaluations per the schedule, with follow-up through 24 weeks postpartum from the initial pregnancy. For women who are HIV-1-infected, the new pregnancy will be reported on the ARV Pregnancy Registry (http://www.apregistry.com/). At the end of this new pregnancy, site staff will contact the woman so the pregnancy outcome can be recorded on a CRF.

8.1.12 General Management of Adverse Events (Not Otherwise Specified) - Mothers

Grades 1 and 2:
A woman who develops a Grade 1 or 2 AE (regardless of relatedness to study drug regimen) may continue the study drug regimen at the discretion of the site investigator.

Grades 3 and 4:
Study drug regimen should be temporarily held until the AE returns to baseline (enrollment visit levels) if baseline was > Grade 2, until ≤ Grade 2, or within normal limits if baseline was ≤ Grade 2. If the Grade 3 or 4 AE does not resolve within four weeks, then the study drug regimen may be permanently discontinued and the Core Team notified.

8.2 Criteria for Premature Permanent Discontinuation of Study Drug

In the event of treatment discontinuation, women and their infants will remain on-study but off study treatment to complete follow up for 24 weeks postpartum.

- Participant has been confirmed as having developed active pulmonary or extrapulmonary TB, per Gene Xpert, shielded chest x-ray, or AFB sputum smear microscopy, or other available TB diagnostics
- Drug toxicity requires permanent study drug discontinuation as defined in Section 8.1 above
- Repeat pregnancy during study follow-up
- For HIV-1-infected women, not taking an EFV-based HIV regimen
- If the woman chooses to discontinue the study drug regimen, the Core Team should be notified within 48 hours. The site should complete the evaluations specified in Section 6.10 within seven days after stopping the study drug regimen.

8.3 Criteria for Premature Discontinuation of Study Participation

A participant must be withdrawn from study participation if:

- The participant withdraws consent and/or does not wish to continue in the study.
- The site investigator determines further participation would be detrimental to the participant's health or well-being.
- The participant fails to comply with study requirements, so as to cause harm to self or seriously interfere with the validity of the study results.
- The study is cancelled at the discretion of IMPAACT, the Food and Drug Administration (FDA), NIAID, the Office for Human Research Protections (OHRP), the local and/or national IRB or EC, or a country-specific governmental agency.

Note: Lost to follow-up is defined as a participant having missed four or more consecutive study visits without contact with study staff.

See Section 6.10 for procedures to be conducted in the event of premature discontinuation of study participation.

9 STATISTICAL CONSIDERATIONS

9.1 General Design Issues

This study is a Phase I/II, open-label, multi-center, intensive PK study to evaluate the pharmacokinetics, safety, and tolerability of RPT and INH dosed once weekly for 12 doses in HIV-1-infected and HIV-1-uninfected pregnant women with latent TB infection at high risk for development of TB. Infants will also be enrolled, and breast milk samples from postpartum women who are still taking RPT/INH will be collected.

Two study cohorts are planned:
Cohort 1: Pregnant women ≥14 weeks gestation through <28 weeks gestation (second trimester)
Cohort 2: Pregnant women ≥28 weeks gestation through ≤34 weeks gestation (third trimester)

An interim analysis to assess the PK of RPT will be conducted, and a dose adjustment may be indicated for each cohort. Dose adjustments indicated for Cohort 2 will be implemented for Cohort 1 women as they enter their third trimester of pregnancy. See Section 3.4 for accrual into the cohorts, and Section 10 (Clinical Pharmacology Plan) for further details regarding the interim analysis and dose adjustment.

In this section, only analyses related to Objectives 2.1.2, 2.1.3, 2.2.4, 2.2.6, and 2.2.7 are described. All other analyses are described in Section 10, as they are pharmacology objectives.

Primary analyses in this study estimate pharmacokinetic parameters cross-sectionally and longitudinally. The fundamental concern is to assess maintenance of drug levels between second and third trimesters of pregnancy, along with assessment of postpartum drug levels in women and infants. Dose-exposure relationships will be modeled, concentrations in infant blood samples and breast milk will be quantified, and safety-related event rates will be estimated.

9.2 Outcome Measures

The primary outcome measures for pregnant women during the second trimester, third trimester, and postpartum period who are receiving a dose of RPT 900mg once weekly together with once-weekly INH (900mg) are detailed below. All outcome measures will be collected and recorded on the CRFs according to standard IMPAACT procedures and transmitted to the Data Management Center for inclusion in standard database tables. Standard quality assurance procedures will be followed throughout the data lifetime.

9.2.1 Primary Outcome Measures

9.2.1.1 Estimates of CL/F, absorption, and volume of distribution of RPT and its desacetyl-rifapentine metabolite (desRPT).

9.2.1.2 Safety (maternal)

- Incidence of related serious adverse events (SAEs) in pregnant and postpartum women taking once-weekly RPT + INH
- Grade 2 adverse events (AEs) judged to be related to study drug regimen
- All Grade 3 and 4 AEs
- All serious AEs
- All AEs leading to permanent discontinuation of study drug regimen (i.e., RPT, INH, and pyridoxine)

9.2.1.3 Safety (infant)

Incidence of related serious adverse events (AEs) in infants born to women taking once-weekly RPT + INH.

9.2.2 Secondary Outcome Measures

9.2.2.1 Vd, CL/F, Ka for pregnant women in their second or third trimester.

9.2.2.2 RPT and desRPT concentrations in infants born to women receiving once-weekly RPT + INH.

9.2.2.3 Tolerability

- Permanent discontinuation of study drug regimen (i.e., RPT, INH, and pyridoxine)
- All AEs leading to permanent discontinuation of study drug regimen (i.e., RPT, INH, and pyridoxine)

9.2.2.4 RPT and des-RPT concentrations in breast milk of postpartum women receiving once-weekly RPT + INH.

9.2.2.5 Incidence of active TB in mother-infant pairs up to 24 weeks postpartum.

9.2.2.6 Estimates of CL/F, absorption, and volume of distribution of INH.

9.3 Stratification

Pregnant women will be stratified by gestational age. Cohort 1 includes pregnant women ≥14 weeks gestation through <28 weeks gestation, and Cohort 2 includes pregnant women ≥28 weeks gestation through ≤34 weeks gestation. The eligibility determinations will guarantee enrollment of at least 10 HIV-1-infected women in each cohort, and the algorithm will endeavor to balance sites with respect to number of HIV-1-infected women per site.

9.4 Accrual and Participant Number

Up to 82 pregnant women will be accrued to yield 50 evaluable women (a minimum of 25 evaluable women in each cohort) and their infants. A target of at least 10 evaluable HIV-1-infected pregnant women will be enrolled in each cohort.

Women are considered evaluable if they meet any of the following criteria:

- Contribute any data to the Intensive PK or Sparse PK sampling collections
- Complete the study drug regimen (see Section 5.1.2 for adherence definition)

9.5 Sample Size Justification

9.5.1 Precision of RPT Clearance Estimation

The stochastic simulation-estimation (SSE) methodology for clinical trial simulation and re-estimation was employed to evaluate sample sizes required to evaluate key pharmacokinetic parameters with precision adequate for decision making on use of RPT + INH in pregnancy (60). This methodology simulates the data from a planned trial with proposed design (number of samples, patients), followed by the estimation of the parameters under the true and alternative model. This is repeated at least 1,000 times, and parameter estimates, relative standard error (RSE), and between subject variability (BSV) estimates are assessed. Table 3 below shows that the RSE of the estimated contrast between median clearance in second trimester and median clearance in third trimester (CL_3rd, column 3) reaches a desirable level of 18% for a total evaluable sample size of 50 women. Precision of estimation of other parameters (CL, V, ka) and BSV are seen to be very good for this sample size, and the estimation of between-participant variation achieves reasonable precision at N=50 as well. In general, RSE of 5% for a pharmacokinetic parameter (e.g. CL, V, ka), 10% for impact of covariate (e.g., impact of pregnancy on CL), and 20% for BSV is considered satisfactory. This is based on literature reviews where RSE associated with these parameters are often higher than proposed values here.

Table 3: Evaluation of sample sizes and power

Number of participants	RSE (CL) (%)	RSE, CL_3rd (%)	RSE (V) (%)	RSE (ka) (%)	RSE (BSV-CL) (%)	RSE (BSV-V) (%)	Power (%)
10	9	39	9	12	36	41	82.2
15	8	33	8	10	33	35	91
20	7	27	7	9	29	32	94.6
30	6	23	6	7	25	27	98.2
40	5	20	5	6	22	24	99.5
50	5	18	4	6	20	22	99.9
60	4	17	4	5	18	19	100
70	4	14	4	5	17	18	100

The power for an interim analysis sample of size 12 has been computed in comparison to a fixed historical value via a likelihood ratio test at the 0.01 level. Using the stochastic simulation and estimation methodology (60) and employing all available historical data, for Type I error rate of 1%, the power to detect an average 25% departure from mean historical value of CL with 12 individuals is 96%.

9.5.2 Precision of Estimation of Adverse Events Incidence

With a sample size of 50 evaluable subjects, there is 90% power to detect one or more safety events for which the true rate of occurrence is 5 per 100 women or infants treated (see Table 4**)**. The sample size of 25 per cohort is sufficient to rule out only very extreme safety incidence rates. For example, if zero safety events are noted for a cohort of size 25, the upper bound of a 95% confidence interval for the event rate is approximately 15%. If two events are observed for such a cohort, the upper bound is in the vicinity of 30%. Such statistics are, at best, marginally useful for decision making about the risk-benefit ratio for use of this regimen in pregnancy but should nevertheless contribute information on the tolerability and safety of the treatment. All women receiving any dose of study drug will be included in the safety analysis.

9.6 Study Monitoring: Statistical Aspects

Table 4: Power assessment for safety of protocol treatments

Cell entries are minimum sample size required to detect one or more safety events at the given rates			
	Safety Event Rates		
Power	0.05	0.1	0.15
0.8	33	17	11
0.9	47	24	16
Cell entries are minimum sample size required to detect two or more safety events at the given rates			
	Safety Event Rates		
Power	0.05	0.1	0.15
0.8	60	30	20
0.9	78	39	26

Sections 4.4 and 4.5 detail monitoring activities at the DMC concerning recruitment, enrollment, and retention. Section 7 describes procedures for safety monitoring, assessment, and reporting.

A monitoring plan will be developed for this study to ensure that the data collected are clean, complete, and of high quality and to make the team aware of the study's progress in an ongoing manner. Monthly conference calls will be held by the study team to assess study progress, and follow-up statistics will be reported to the team by the DMC on a monthly basis. Rate of enrollment will be closely monitored, with input provided from team members and participating sites on methods to speed enrollment if needed.

9.6.1 Study Monitoring Committee

The study will be monitored intensely by the protocol team, which will review safety and pharmacokinetic data approximately monthly. In addition, the study will be monitored by an SMC according to standard IMPAACT procedures. The committee will meet via conference call to review relevant data as described below and in Section 7.1 to ensure participant safety. The SMC could meet at least once annually and more frequently if indicated by the protocol team or the study sponsor.

9.6.2 Study Safety Monitoring

Since Phase I studies are not routinely reviewed by a Data and Safety Monitoring Board (DSMB), it is the responsibility of the Protocol Team to interpret safety data and make decisions regarding AEs that are needed to protect participants from undue risk. Per Section 7.1, the Core Team will review routine safety monitoring and clinical data reports. In addition, the Study Monitoring Committee described above is appointed to provide impartial reviews in situations where participant safety is in question.

The safety and tolerability of the study agent will be monitored by means of adverse events reports and toxicity reports presenting laboratory and clinical events. The data required for the toxicity reports must be entered into the database within 48 hours of the time at which the results of the laboratory tests or clinical examinations become available.

Reports compiled by the DMC will be reviewed and discussed by the Protocol Team on conference calls held approximately monthly. The attribution of relationship of ≥ Grade 3 AEs to RPT/INH will be determined by the protocol team, and any discrepancies of assessments between site investigators and the protocol team will be reconciled during the conference calls. For safety monitoring, a drug-related AE is an AE that is judged to be definitely, probably, or possibly related to study drug (RPT/INH).

Data on accrual, pharmacokinetics and toxicity will be reviewed by the study's Study Monitoring Committee:
1) When the consensus among the site investigator, the protocol team and the DAIDS medical officers regarding to relationship of AEs to the study drug cannot be established
2) When there is any specific safety concern.

Adverse events will be monitored from screening onward throughout the follow-up period. If any Grade 4 AEs that are possibly, probably, or definitely related to the study regimen or deaths occur, or if the protocol team identifies any potentially treatment-related toxicities that could compromise participant safety, the study may be paused, and the Study Monitoring Committee will review all relevant data and will determine whether, and under what conditions, the study will be allowed to proceed.

9.7 Analysis

9.7.1 Pharmacokinetic Outcomes

Analysis for objectives 2.1.1, 2.2.1, 2.2.2, 2.2.3, 2.2.4, 2.2.5, 2.2.8, and 2.3.1 is fully described in Section 10 below.

9.7.2 Safety Outcomes

The primary safety analysis will include all women who have been exposed to RPT/INH at any dose in the study. Women whose doses have been adjusted for inadequate PK will be included in the primary safety analysis. Women who have been removed from treatment due to toxicities while on the optimal dose will be included and treated as safety failures in the primary safety analysis. Additional analyses will look at the combined data from women whose doses failed and those who have been treated solely at the optimal doses determined for their cohorts. Each woman's safety data will be summarized as: the worst grade of adverse event experienced during study treatment and the worst grade of adverse event judged to be at least possibly related to study treatment during this time period.

Frequency distributions of these safety outcomes will be presented in the aggregate and broken down by cohort. Listings of all ≥ Grade 3 or ICH defined serious events will be provided,
The proportions of participants experiencing ≥ Grade 3 or ICH defined serious adverse events will be presented in aggregate and broken down by cohort, with these proportions bounded by exact 95% confidence intervals. Similar analyses will present the proportions of participants exhibiting ≥ Grade 3 or ICH defined serious events which have been judged to be at least possibly related to study medication, again bounded by exact 95% confidence intervals.

For objectives 2.1.2, 2.1.3, and 2.2.6, Poisson regression will be used to estimate the incidence of serious adverse events related to treatment, adjusting for important cofactors. Analyses of tolerability and safety for infants will employ standard descriptive techniques; events of intolerability or compromise to infant safety are expected to be rare.

10 CLINICAL PHARMACOLOGY PLAN

10.1 Pharmacology Overview and Objectives

The goal of this study is to assess the pharmacokinetics of RPT, des-RPT, and INH in pregnant women. Population pharmacokinetics will be estimated based on the sample, and exposure parameters will also be compared between the pregnant cohort and non-pregnant historical controls (58). Finally, this study will determine how stage of pregnancy impacts the pharmacokinetics of RPT and des-RPT and dosing.

The design and analysis plans for objectives 2.1.1, 2.2.1, 2.2.2, 2.2.3, 2.2.4, 2.2.5, 2.2.8, and 2.3.1 are described in this section.

10.2 Methods and Timing for PK Collections, Processing, Handling, and Storage

10.2.1 Intensive and Sparse PK collections: Mother

Both the Intensive and Sparse PK sampling are ideally conducted in the morning. The Intensive PK sampling must be initiated on the same day as the first dose of the study drug regimen per Section 6.2. As mentioned in Section 6.2 above, the Entry Visit may be conducted as a split visit. The Sparse PK sampling will be completed after the final study drug dose per Section 6.3. Depending on site capacity, women may stay at the clinical research site or affiliated health care facility the evening prior to and after the PK sampling dose in order for an early morning PK sampling to be initiated. Further operational details on these visits are found in Sections 6.2 and 6.3.

10.2.2 Breast Milk PK Collection: Mothers

Postpartum women who are breastfeeding while still on the study drug regimen will be eligible for the breast milk PK sample collection. Breast milk will be expressed by the woman, and a plasma sample collection will also be drawn per Section 6.3.

10.2.3 Cord Blood PK Collection: Mothers

At sites with capacity, women will be offered an option of also having a cord blood sample taken. Women must have received a study drug regimen dose within 72 hours prior to delivery to be eligible for the cord blood sample collection.

10.2.4 Single PK collection: Infant

For infants meeting PK sampling eligibility criteria described below, a single PK sample will be obtained within the first three days of life. Ideally, the single PK sample for the infants will be obtained prior to the mother being discharged from the hospital.

Infants must meet all of the criteria below to be eligible for the Infant PK Sample Collection:

- Infant birth weight > 1000 grams
- Infant NOT receiving disallowed medications described in Section 5.5
- Infant does not have any severe congenital malformation or other medical condition not compatible with life or that would interfere with study participation or interpretation, as judged by the site investigator
- The mother's most recent dose was taken within 72 hours of drawing the infant's blood

10.2.5 Processing, Handling, and Storage of PK Specimens

Detailed blood processing, handling, and storage procedures can be found in the IMPAACT 2001 Laboratory Processing Chart (LPC) and study-specific MOP.

10.3 Interim Analysis and Dose Adjustment

An interim analysis will be conducted for each cohort to determine whether a dose adjustment is indicated by comparing the median parameter estimates of clearance (CL/F) of RPT in the participants to those of non-pregnant historical controls.

For each cohort, the dose of RPT will be judged acceptable if:

- Median exposure following this dose is not altered > 25% compared to the exposures from non-pregnant historical controls

These guidelines will be reviewed by the Core Team and the SMC during an interim analysis (further described below and in Section 3.4). If these guidelines are not met, the Core Team will carefully assess whether a dose adjustment is needed (see Section 10.3.2).

Accrual into each cohort (including pausing for interim analysis) will proceed as described in Section 3.4. Follow-up of already-enrolled women will continue as planned during a pause for interim analysis. Any pause in accrual to allow for an interim analysis and any changes in the dosing of the study drug regimen will be communicated by the IMPAACT 2001 Core Team to all participating sites.

If there is an effect of pregnancy on drug disposition, those effects are likely to be most prominent late in pregnancy (i.e., in the third trimester). Therefore, a dose adjustment indicated for Cohort 2 will be implemented for Cohort 1 women as they enter their third trimester of pregnancy.

Based on the robust data on RPT PK in other populations including non-pregnant women, the current proposed design with intensive PK sampling provided during the second trimester (Cohort 1, visit 1) and third trimester (Cohort 2, visit 1) in this study will be sufficient to accurately estimate any required dose change that would be needed to achieve PK parameters similar to non-pregnant controls. To date, a dose change has not been indicated for RPT in any of the adult populations studied, including those who are HIV-1-infected. A similar approach was used to recommend dose change in children and adolescents, which was graded by developmental stage and weight (see Appendix II).

10.3.1 Timing of Interim Analysis

The timing of the interim analysis may differ between the two cohorts:

- The interim analysis will be conducted for Cohort 1 when the first 12 women of Cohort 1 have completed the Intensive PK sampling *or* after the first 12 women have enrolled into Cohort 2, whichever event occurs first. (If there are effects of pregnancy on drug disposition, those effects are likely to be most prominent late in pregnancy (i.e., in the third trimester)).

- The interim analysis for Cohort 2 will be conducted when 12 women have enrolled into Cohort 2 and completed the Intensive PK sampling.

10.3.2 Starting Dose and Dose Adjustment

Prior to the interim analysis, all women will be started at a 900mg rifapentine dose (see Section 1.3 for rationale for study design). If a dose adjustment is indicated by the interim analysis, all women enrolled thereafter will be started at the adjusted dose.

Based on the data reviewed during the interim analysis, if the median parameter estimates of CL/F differ more than 25% compared to CL/F in non-pregnant historical controls (2.07 L/h for 60.0 kg female if fasting and 1.47 L/h if tablet taken with any food), a dose adjustment will be discussed. There will be no intra-person dose adjustments done based on an individual's PK data during the course of the study.

- Clearance within 25% of clearance in non-pregnant controls: If the median clearance is similar to that of non-pregnant controls, then the remaining accrual target will be enrolled for a total of 25 evaluable women on the 900mg dosing in the respective cohort.

- Clearance decreased by >25% of clearance in non-pregnant controls: If the PK analysis suggests that a dose decrease is required, then the remaining accrual target in the respective cohort will be enrolled at the lower dose. The dose will be decreased to deliver the appropriate target AUC (defined as dose over clearance) in increments of available tablet size (e.g., 150mg): % change in CL/F corresponds to the % change in required dose (e.g., if CL/F is decreased 30%, that will require dose decrease of 30% (approximately 300mg) leading to a new dose of 600mg). Women enrolled into Cohort 1 after the interim analysis for Cohort 2 is completed will transition to the lower dose in their third trimester.

- Clearance increased by >25% of clearance in non-pregnant controls: If the PK analysis suggests that a dose increase is required, 25 evaluable women will be newly enrolled into the respective cohort at the higher dose, because safety will need to be adequately assessed at the higher dose. The dose will be increased to deliver the appropriate target AUC (defined as dose over clearance) in increments of available tablet size (e.g., 150mg): % change in CL/F corresponds to the % change in required dose (e.g., if CL/F is increased 30%, that will require dose increase of 30% (approximately 300mg) leading to a new dose of 1200mg). Women enrolled into Cohort 1 after the interim analysis for Cohort 2 is completed will transition to the higher dose in their third trimester.

10.4 Laboratory Performing the Assays

Plasma RPT and desRPT concentrations will be determined by a validated procedure performed according to written standard operating procedures. The intraday accuracy and intraday precision will be obtained with quality control samples, which will be analyzed concurrently with each set of volunteer samples. Quality control procedures will be in place to ensure stability of sample materials.

10.5 Primary and Secondary Data Analysis Plan

Primary: Pharmacokinetic data (concentration-time data) and safety data of rifapentine and desacetyl-rifapentine in pregnant women; safety outcomes in infants

Secondary: Pharmacokinetic data of rifapentine and desacetyl-rifapentine in postpartum women and infants; pharmacokinetic data of isoniazid in pregnant and postpartum women

Population-based estimates of RPT CL/F, absorption, and volume of distribution will be derived for pregnant women in second and third trimesters of pregnancy and in the postpartum period. Study data will provide a mix of longitudinal and cross-sectional observations, which will be combined using standard algorithms in wide use in pharmacology research. The pharmacokinetics of the desacetyl-rifapentine (des-RPT) metabolite of RPT and INH will be estimated based on the sample in like fashion. Rates of adverse events and other safety-related parameters will be computed and reported for study monitoring and regulatory use. Secondary objectives are: characterization of PK data of RPT and des-RPT in the postpartum period, description of adverse and safety outcomes in pregnant women, assessment of impact of covariates on primary PK parameters, comparison of RPT and des-RPT exposures between study participants and non-pregnant historical controls, estimation of effective RPT dose for pregnant women, estimation of RPT concentrations in newborns, description of pregnancy and infant safety outcomes, description of RPT + INH tolerability in pregnancy, and characterization of PK data of INH in pregnant and postpartum women.

The primary tool for estimation of parameters of interest is the single compartment model for RPT absorption and disposition kinetics:

$$\frac{dA(1)}{dt} = -ka \times A(1); \text{ Absorption compartment}$$

$$\frac{dA(2)}{dt} = ka \times A(1) - \frac{CL}{V} \times A(2); \text{ Central Plasma compartment}$$

The parameters CL and V will be elaborated upon to incorporate allometric scaling and effects of gestational age.

10.6 Anticipated Outcomes

The anticipated outcomes of the pharmacology evaluations are:

- Estimates of all PK parameters including CL (in relationship to the pregnancy stage), volume of distribution, model-based C_{max} and exposure (AUC) as well as estimates between participant variability associated with all these parameters.
- Absorption rate constant (ka) of RPT.
- Incidence of adverse safety events in pregnant women and their infants.

11 DATA HANDLING AND RECORD KEEPING

11.1 Data Management Responsibilities

As described in Section 4.4, data on screening and enrollment in this study will be collected using the DMC SES.

Study sites must maintain adequate and accurate research records containing all information pertinent to the study for all screened and enrolled participants, including CRFs and supporting source data. In maintaining these records, sites must comply with the standards of source documentation specified in the DAIDS policy on Requirements for Source Documentation in DAIDS Funded and/or Sponsored Clinical Trials (available on the web site referenced in Section 11.2).

CRFs are completed by site staff and, following quality control and quality assurance reviews, are keyed using a remote data entry system designated by the DMC and transferred electronically to the DMC. Selected laboratory data are transferred electronically to the DMC through the LDMS. At the DMC, computerized checks are applied to the transferred data and, when required, data queries are issued for resolution by site staff. All data must be transferred to the DMC within timeframes specified in the forms instructions; queries must also be resolved in a timely manner.

Further information on the study CRFs and IMPAACT data management procedures, including a Forms Manual: Policies and Procedures for Forms Completion for DAIDS-Sponsored Clinical Trials, a comprehensive Computing Manual, and a User Manual for the SES, is available on the DMC portal at www.fstrf.org.

11.2 Essential and Source Documents and Access to Source Data

All DAIDS policies referenced in this section are available at:
http://www.niaid.nih.gov/LabsAndResources/resources/DAIDSClinRsrch/Pages/ClinicalSite.aspx

Study sites must comply with the DAIDS policies on Requirements for Essential Documents at Clinical Research Sites Conducting DAIDS Funded and/or Sponsored Clinical Trials and Requirements for Source Documentation in DAIDS Funded and/or Sponsored Clinical Trials. In its policy on Requirements for Manual of Operational Procedures, DAIDS requires sites to establish SOPs for maintaining essential

and source documents in compliance with these policies. Site SOPs should be updated and/or supplemented as needed to describe roles, responsibilities, and procedures for this study, and site SOPs should be followed throughout the study.

Per the DAIDS policy on Storage and Retention of Clinical Research Records, study records must be stored in a manner that ensures privacy, confidentiality, security, and accessibility during the conduct of the study and after the study is completed. Records must be retained for a minimum of three years after the completion of the study. Per 21 CFR 312.62, records must be maintained for two years after the date a marketing application is approved for one or more of the study drugs for the indication for which it is evaluated in this study; or, if no application is filed, or if the application is not approved for this indication, records must be retained two years after the study is discontinued and the FDA is notified.

All study records must be accessible for inspection, monitoring, and/or auditing during and after the conduct of the study by authorized representatives of the study sponsors and their contracted monitors, the companies that provide the study products, IMPAACT, site IRBs/ECs, site IBCs, the FDA, OHRP, and other applicable regulatory entities. Participants' study information will not be released without their (or, if applicable, other authorized guardian's) written permission, except as necessary for the aforementioned inspection, monitoring, and/or auditing. Records must be kept on site throughout the period of study implementation; thereafter, instructions for off-site storage may be provided by NIAID or NICHD. No study records may be removed to an off-site location or destroyed prior to receiving approval from NIAID or NICHD.

11.3 Quality Control and Quality Assurance

Study sites must ensure that essential documents and participant research records are subject to continuous quality control and quality assurance procedures consistent with the DAIDS policy on Requirements for Clinical Quality Management Plans, which is available at:

http://www.niaid.nih.gov/labsandresources/resources/daidsclinrsrch/documents/qmppolicy.pdf

12 CLINICAL SITE MONITORING

Site monitors under contract to NIAID or NICHD will visit study sites to inspect study facilities and review participant study records including consent forms, CRFs, medical records, laboratory records, and pharmacy records to ensure protection of study participants, compliance with the IRB/EC approved protocol, and accuracy and completeness of records. The monitors also will review essential document files to ensure compliance with all applicable regulatory requirements. Site investigators will make study facilities and documents available for inspection by the monitors.

13 HUMAN SUBJECTS PROTECTIONS

13.1 IRB/EC Review and Approval

Prior to study initiation, site investigators must obtain IRB/EC review and approval of this protocol and site-specific ICFs in accordance with 45 CFR 46 and 21 CFR 56; subsequent to initial review and approval, IRBs/ECs must review the study at least annually. Site investigators must also promptly report to the IRB/EC any changes in the study and any unanticipated problems involving risks to participants or others.

All IRB/EC policies and procedures must be followed, and complete documentation of all correspondence to and from the IRBs/ECs must be maintained in site essential document files. Sites must submit documentation of both initial review and approval and continuing review to the DAIDS Protocol Registration Office (PRO) in accordance with the DAIDS Protocol Registration Manual (see also Section 14.2).

13.2 Vulnerable Participants

The NIH is mandated by law to ensure that pregnant women and children be included in clinical research when appropriate (61, 62). This study responds to that mandate and will provide clinical research data to inform TB treatment guidelines for pregnant women. Nonetheless, the pregnant women, fetuses, and children who take part in this study are considered vulnerable participants per the US Code of Federal Regulations, and site IRBs/ECs must consider the potential risks and benefits to maternal, fetal, and infant participants as described in 45 CFR 46 Subpart B (for pregnant women, fetuses, and neonates) and 45 CFR 46 Subpart D (for children).

With respect to 45 CFR 46 Subpart B, the specifications of 45 CFR 46.204 (d) are considered to apply; therefore, women will be asked to provide written informed consent for their own and their children's study participation.

With respect to 45 CFR 46 Subpart D, IRBs/ECs must determine the level of risk to children in the categories specified in 45 CFR 46.404-407. Documentation of this determination is required to complete the DAIDS protocol registration process described in Section 14.2, and the risk category assigned by the IRB/EC further determines the parental informed consent requirements for the study at each site. Per 45 CFR 46.408 (b), the IRB/EC may find that the consent of one parent is sufficient for research to be conducted under 46.404 or 46.405. If the IRB/EC finds that the research is covered by 46.406 or 46.407, both parents must give their consent, unless one parent is deceased, unknown, incompetent, or not reasonably available or when only one parent has legal responsibility for the care and custody of the child (as determined locally). IRBs/ECs must document their risk determination, and study sites should adapt the signature pages of their site-specific ICFs as needed to accommodate the parental consent requirements associated with the IRB/EC determination.

Study sites must comply with the requirements of the DAIDS policy on Enrolling Children (including Adolescents) in Clinical Research, which is available at: www.niaid.nih.gov/labsandresources/resources/daidsclinrsrch/Pages/ClinicalSite.aspx.

13.3 Informed Consent

Written informed consent for study participation will be obtained before any study-specific procedures are performed. It is generally expected that women will provide informed consent for their own and their children's participation in this study. However, parental consenting requirements at each site will depend on the IRB/EC risk determination described in Section 13.2, and all IRB/EC requirements will be followed. Refer to Section 4.4 and the study-specific MOP for further information on informed consent procedures for this study.

Should the consenting mother of an enrolled infant die or no longer be available for any reason, no further study-specific visits or procedures may be performed with her infant until informed consent for continued study participation is obtained from a locally authorized guardian. In accordance with the DAIDS policy on Enrolling Children (including Adolescents) in Clinical Research (available at the website referenced in Section 13.2), all study sites must establish and maintain written procedures describing the standards that will be followed to identify who may serve as guardian for an enrolled infant, reflective of applicable IRB/EC guidance for conduct of human subjects research within the context of available local law, regulation, or government policy.

13.4 Potential Benefits

There is a prospect of direct benefit to the participants, both mother and infant. Taking anti-TB medicine, as well as vitamin B_6, may provide a benefit to the mother and her infant. Furthermore, early detection of TB may be a benefit and would help prevent transmission of TB to the infant. Maternal TB is also associated with an increased risk of neonatal death, fetal distress, low birth weight, prematurity, and increased risk of perinatal transmission of HIV. Therefore, participation in this trial may provide a direct benefit to the infant as well by reducing these risks. Participants will receive clinical evaluations, laboratory testing, and TB signs and symptoms counseling. For other medical conditions identified as part of the study screening and/or follow-up procedures, participants will be referred to other sources of care available in their community. Some participants may have the opportunity to access expedient treatment and decreased morbidity due to early diagnosis and treatment of abnormalities identified during tests, examinations and referrals.

Participants in this study may experience no direct benefit. Participants and others may benefit in the future from information learned from this study. Specifically, information learned in this study may lead to the development of treatment guidelines tailored for pregnant women with latent TB infection. Participants also may appreciate the opportunity to contribute to the field of TB research.

13.5 Potential Risks

The potential risks of this study are those associated with having blood drawn, treatment failure, resistance to TB medications, suboptimal dosing for latent TB, possible reactions to the RPT + INH investigational product and breach of confidentiality.

Drawing blood may cause transient discomfort and fainting. Fainting is typically transient and managed by having the participant lie down. Bruising at the blood draw site may occur, but can be prevented or lessened by applying pressure to the draw site for several minutes. There is a slight risk of infection associated with drawing blood.

A chest x-ray may be indicated to confirm active TB disease. The radiographic exposure required is minimal and is far below the maximum allowed, even for pregnant women. Therefore, this procedure is associated with minimal risk.

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

- Rash
- 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
    - Pale-colored stools
    - Yellowing of the eyes or skin
    - Pain in the upper abdomen
    - Dark urine
    - Loss of appetite
    - Low blood counts (for example, for the blood cells that help your body fight infection)
    - Dizziness
    - Hypertension
    - Headache
    - Low blood sugar
    - Upset stomach or vomiting

- Decreased effectiveness of hormonal contraceptives and other medications. Tell your doctor about all medications that you are taking.

Women taking rifapentine may have a serious allergic reaction called Rifamycin Hypersensitivity Syndrome (RHS) that can be dangerous if not caught right away. Women will be told to report to the study clinic as soon as possible for an evaluation if they report any of the symptoms (defined in Section 8).

When administered during the last few weeks of pregnancy, rifampin, another rifamycin product, has been shown (in rare cases) to increase the risk of maternal postpartum hemorrhage and bleeding in the exposed neonate (see Section 8.1.10).

13.6 Potential Social Impacts

Participation in clinical research includes the risk of loss of confidentiality. Although study sites make every effort to protect participant privacy and confidentiality, it is possible that participants' involvement in the study could become known to others, and that social harms may result (e.g., because participants could become known as having LTBI). For example, participants could be treated unfairly or discriminated against or could have problems being accepted by their families and/or communities.

13.7 Reimbursement/Compensation

Pending IRB/EC approval, women will be reimbursed for costs associated with completing study visits (e.g., transport costs). Reimbursement amounts will be specified in site-specific ICFs or other materials if applicable per IRC/EC policies and procedures.

13.8 Privacy and Confidentiality

All study procedures will be conducted in private, and every effort will be made to protect participant privacy and confidentiality to the extent possible. Each study site will implement confidentiality protections that reflect the local study implementation plan and seek the input of study staff and community representatives to identify potential confidentiality issues and strategies to address them. In addition to local considerations, the protections described below will be implemented at all sites.

All study-related information will be stored securely. All participant information will be stored in locked areas with access limited to study staff. All laboratory specimens, study data collection, and administrative forms will be identified by coded number only to maintain participant confidentiality. All records that contain names or other personal identifiers, such as locator forms and informed consent forms, will be stored separately from study records identified by code number. All local databases will be secured with password protected access systems. Forms, lists, logbooks, appointment books, and any other listings that link participants' ID numbers to identifying information will be stored in a separate, locked file in an area with limited access. After receiving appropriate approval, all study documents/data will be properly disposed of, including the proper destruction and/or deletion of paper files, electronic study data, and electronic documents. If used, audio files will be transcribed and destroyed as soon as transcription and analyses are completed.

Study sites are encouraged but not required by DAIDS policies to store study records that bear participant names or other personal identifiers separately from records identified by PID. All local databases must be secured with password protected access systems. Lists, logbooks, appointment books, and any other documents that link PID numbers to personal identifying information should be stored in a separate, locked location in an area with limited access.

13.9 Communicable Disease Reporting

Study staff will comply with local requirements to report communicable diseases including HIV-1 identified among study participants to health authorities. Participants (or other authorized guardians if applicable) will be made aware of reporting requirements during the informed consent process.

13.10 Management of Incidental Findings

Site clinicians will inform participants (or other authorized guardians if applicable) of clinically meaningful physical exam findings and laboratory test results, including results of HIV tests. Participants will not receive PK test results. When applicable, site clinicians will provide referrals to non-study sources of medical care for further evaluation and/or treatment of these findings.

13.11 Management of New Information Pertinent to Study Participation

Participants (or other authorized guardians if applicable) will be provided any new information learned over the course of the study that may affect their willingness to participate and/or remain in the study or their willingness to allow their children to participate and/or remain in the study.

13.12 Post-Study Access to Study Drug

Participants will complete the study drug regimen prior to exiting the study. Therefore, post-study access to study drug is not applicable.

14 ADMINISTRATIVE PROCEDURES

14.1 Regulatory Oversight

This study is sponsored by the National Institute of Allergy and Infectious Diseases (NIAID), *Eunice Kennedy Shriver* National Institute of Child Health and Development (NICHD), and National Institute of Mental Health (NIMH), which are part of the United States National Institutes of Health (NIH). The study drug rifapentine (RPT) is provided by Sanofi; however, this organization is not involved in sponsorship or regulatory oversight of this study.

The Division of AIDS (DAIDS) within the NIAID is responsible for regulatory oversight of this study and holds the Investigational New Drug (IND) application under which the study will be conducted. DAIDS will distribute safety-related information pertaining to the study products prior to and during the conduct of the study in accordance with its sponsor obligations.

NIAID and NICHD provide funding to the clinical research sites at which this study will be conducted. Each institute contracts with independent clinical site monitors who will perform monitoring visits as described in Section 12. As part of these visits, monitors will inspect study-related documentation to ensure compliance with all applicable US and local regulatory requirements.

14.2 Protocol Registration

Prior to implementation of this protocol and prior to any subsequent full version amendments, each site must have the protocol and the protocol informed consent form approved, as appropriate, by their local IRB/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 (DAIDS 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.

Site-specific 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.

For any future protocol amendments, upon receiving final IRB/EC and any other applicable regulatory entity approvals, sites should implement the amendment immediately. Sites are required to submit an amendment registration packet to the DAIDS PRO at the RSC. Site-specific ICFs will not be reviewed and approved by the DAIDS PRO, and sites will receive an Amendment Registration Notification from the DAIDS PRO that indicates successful completion of the amendment protocol registration process. A copy of the final amendment Registration Notification issued by the DAIDS PRO 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, which is available on the RSC website: http://rsc.tech-res.com/protocolregistration/.

14.3 Study Implementation

This study will be conducted in accordance with the protocol, international good clinical practice guidelines, and all applicable US and local regulations. Study implementation will also be guided by the study-specific MOP, LPC, and other study implementation materials, which will be available on the IMPAACT web site: www.impaactnetwork.org.

Study implementation at each site will also be guided site SOPs. The DAIDS policy on Requirements for Manual of Operational specifies the minimum set of SOPs that must be established at sites conducting DAIDS-funded and/or -sponsored clinical trials (available on the website referenced in Section 11.2). These SOPs should be updated and/or supplemented as needed to describe roles, responsibilities, and procedures for this study.

14.4 Protocol Deviation Reporting

Per the policy for Requirements for Source Documentation in DAIDS Funded and/or Sponsored Clinical Trials (available at the website referenced in Section 11.2), all protocol deviations must be documented in participant research records. Reasons for the deviations and corrective and preventive actions taken in response to the deviations should also be documented.

Deviations should be reported to site IRBs/ECs and other applicable review bodies in accordance with the policies and procedures of these review bodies. Serious deviations that are associated with increased risk to one or more study participants and/or significant impacts on the integrity of study data must also be reported within IMPAACT, following procedures specified in the IMPAACT Manual of Procedures.

14.5 Critical Events Reporting

Per the DAIDS policy on Identification and Classification of Critical Events, a critical event is defined as an unanticipated study-related incident that is likely to cause harm or increase the risk of harm to participants or others or has a significant adverse impact on study outcomes or integrity. All such events must be reported following procedures specified in the DAIDS Critical Events Manual, which is available at:
http://www.niaid.nih.gov/LabsAndResources/resources/DAIDSClinRsrch/Pages/Safety.aspx

14.6 ClinicalTrials.gov

This protocol is not subject to the Food and Drug Administration Amendments Act of 2007 (FDAAA); however, it will be registered in https://clinicaltrials.gov/ to meet International Committee of Medical Journal Editors (ICMJE) requirements.

15 PUBLICATIONS

All presentations and publications of data collected in this study are governed by IMPAACT policies, which are available in the IMPAACT Manual of Procedures.

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APPENDICES

Appendix I-A: Mother Schedule of Evaluations

	SCR (*up to 2 weeks prior to entry*)	Entry/Intensive PK Sampling (*Days 0-3*)	Weekly (7 ± 2 days apart) (*weeks 1-12*)	Monthly (Every 4 weeks ±2 weeks) (*until 24 weeks after delivery*)	Study Exit/ Early Discontinuation
Administrative and Regulatory					
Obtain written informed consent	X				
Assign participant identification numbers (PIDs) to mother and infant	X				
Obtain screening number from SES	X				
Complete eligibility checklist and enter into SES		X			
Assign separate study identification numbers to mother and infant		X			
Assess eligibility	X	X			
Provide meal prior to administering study drug		X	X		
Behavioral and Counseling					
Provide HIV pre-/post-test counseling if applicable	X				
Assess alcohol and drug use	X				
Signs and symptoms of active TB Counseling		X	X	X	X
Assess infant feeding methods (postpartum only)			X	X	
Clinical					
Obtain/update medical and medications history	X	X	X	X	X
Perform physical examination	X	X	X	X	X
Perform obstetrical exam/assess fetal movement and heart sounds (until delivery)	X	X	X	X	
Perform ultrasound	X				
Provide available findings/test results		X	X	X	X
Assess TB symptoms, risk, and exposure	X	X	X	X	X
Gene Xpert, shielded chest x-ray, or sputum microscopy	X				
Record/update AEs		X	X	X	X
TST (if not available per medical record)	X				
Study Product					
Prescribe and administer DOT of study drug regimen		X	X		

Laboratory					
IGRA (3mL) (if not available per medical record)	3mL				
Complete blood count (CBC)	3mL		3mL (every 4 weeks)	3mL	
Liver Function tests	3mL		3mL (every 4 weeks)	3mL	
HIV-1 test (confirmatory tests as needed)	6mL				
CD4 count (HIV-1-infected only)		3mL			
Coagulation profile	5mL		5mL (at one visit at ≥34 weeks gestational age only)	5mL (if clinically indicated)	
HBsAG, HBsAb, HCV Ab		6mL			
Intensive PK sample collection		22mL			
Sparse PK sample collection			8mL (last dose)		
Plasma sample collection (breast milk PK eligible only)			24mL (first and second week postpartum)		
Breast milk PK sample collection (if eligible)			X (first and second week postpartum and last dose)		
TOTAL BLOOD	17-20mL	28-31mL	11-43mL	6-11mL	

Appendix I-B: Infant Schedule of Evaluations

	Newborn Visit (*within 3 days of life*)	Monthly (Every 4 weeks ± 2 weeks) (*until 24 weeks after delivery*)	Study Exit/Early Discontinuation
Clinical			
Assess eligibility for single PK sampling	X		
Physical exam	X	X	X
Record/update medical and medications history	X	X	X
Record/update AEs	X	X	X
Provide available test results to mother	X	X	X
Assess TB symptoms, risk and exposure		X	X
Laboratory			
Single PK sample collection (if eligible)	2mL		
Coagulation profile (if eligible)	2mL	2 mL (if clinically indicated)	
Complete blood count (if clinically indicated)		1mL	
Liver Function Test (if clinically indicated)		2mL	
Cord blood (optional if eligible, during mother's delivery)	X		
TOTAL BLOOD	2-4mL	1-5mL	

Appendix II: Modeling and Simulation Population Analysis Report – Rifapentine

This population pharmacokinetic (PK) analysis estimates the pharmacokinetics of rifapentine (RPT) and its main metabolite 25-desacetyl-rifapentine (25-des-RPT) based on the combined dataset from 4 clinical studies in children, healthy adolescents and adult patients with active or latent tuberculosis infection (LTBI) where rifapentine was administered either as a single dose or weekly: two Phase I clinical studies (children, adolescents) (63, 64), one Phase I/II clinical study (TBTC Study 25) (65) and one Phase III clinical study (TBTC Study 26) (25).

The population PK analysis comprised a total of 1634 rifapentine and 25-desacetyl-rifapentine serum concentrations from 227 children, adolescents and patients with active or latent tuberculosis who received a range of 300-1200 mg oral doses of rifapentine as a single agent (children, adolescents), or in combination with isoniazid (INH) in TBTC Study 25 and TBTC Study 26. Serum concentration data of RPT and 25-des-RPT were modeled simultaneously using a population analysis approach to estimate RPT and 25-des-RPT population PK parameters (mean and inter-patient variability) as well as the relationship between PK parameters and covariates.

The structural model that best described the pharmacokinetics of rifapentine was a 1-compartment model with a transit compartment chain for description of the absorption delay. All clearance and volume of distribution parameters were allometrically scaled using standard exponents (e.g. 0.75 for clearance and 1 for volume). The following typical population estimates (%RSE) of rifapentine pharmacokinetics were obtained: oral clearance (CL/F) for 70kg patient 2.32 L/h (11 %); central volume of distribution (Vc/F) for 70 kg patient 51.7 L (10 %); absorption rate constant (ka) 1.69 (34) h-1, mean transit time (MTT) 0.62 h (27) and number of transit compartments (n) 1.8 (76). The inter-patient variability was 40% (13 %) for CL/F, 47% (15 %) for V/F and 90% (47 %) for MTT.

The structural model that best described the pharmacokinetics of 25-des-RPT was a 1-compartment model. The typical population estimates (%RSE) of 25-des-RPT apparent clearance (CLm/Fm) and apparent volume (Vm/Fm) for 70kg patient were 2.05 L/h (10 %) and 21.9 L (7 %), respectively. The inter-patient variability was 64% (18 %) for CLm/Fm.

Apparent clearance per kilogram body weight was significantly higher in children than adults. This relation was described by a maturation function, where clearance for the youngest child (age, 2 y) was 0.052 L/h/kg, decreasing to the fully matured value of 0.026 L/h/kg by older age (half-life, 1.5 y (38% RSE), resulting with fully matured value by approximately age 10). Relative bioavailability of rifapentine in fasting condition for higher doses, 900 mg and 1200mg compared to the lowest available dose in adults (600 mg) was found to be 0.96 (19% RSE) and 0.76 (16% RSE) respectively. Food increased relative bioavailability by 40% (8% RSE). Children who received crushed tablets had 26% (36% RSE) decreased relative bioavailability. There was no autoinduction with once-weekly dosing. Gender and race have also been investigated, and were not associated with rifapentine pharmacokinetics.

SUMMARY OF STUDY FEATURES

This population PK analysis evaluated data obtained from 4 clinical studies of rifapentine (TBTC Study 25, TBTC Study 26, children and adolescent study) (25, 63-65). A summary of the studies is provided in Table 1. PK profiles from a total of 227 subjects were used in this analysis.

Table 1. Summary of Studies Included in the Population PK Analysis

Study	Phase	n[a]	Population	Treatment	DrugX Dose
TBTC 25	I/II	35	Adult Patients with TB	RPT+INH	600mg, 900mg, 1200mg weekly
TBTC 26	III	157	Children and Adults with LTBI	RPT + INH	300- 900mg weekly
children	I	23	Children w/o TB	RPT	150mg, 300mg single dose
adolescent	I	12	Healthy Adolescents	RPT	450mg, 600mg single dose

[a] Number of subjects receiving RPT included in the population PK analysis

TBTC Study 25
TBTC Study 25 was a prospective, double-blind, randomized Phase II trial to evaluate the tolerability of once-weekly, continuation phase, directly observed therapy with rifapentine at three doses (600, 900, and 1,200 mg) and of isoniazid in 150 HIV-seronegative patients with drug susceptible tuberculosis. The pharmacokinetic substudy included 35 adult patients with tuberculosis (continuation phase therapy) who received commercial formulation of rifapentine (600, 900, or 1200 mg once weekly), usually without food. Pharmacokinetic data were collected after ≥ 3 weeks of once-weekly treatment. Plasma samples for rifapentine and metabolite concentrations were collected (11 samples: baseline, 2, 4, 6, 8, 10, 12, 18, 24, 48, and 72 h after the dose) (65, 66).

TBTC Study 26 (PREVENT-TB Study)
TBTC Study 26 was a Phase 3, randomized treatment trial of 8,053 patients with LTBI, comparing a 12-dose, once-weekly rifapentine and isoniazid regimen (3HP) to nine months of daily isoniazid (25). 161 patients were recruited into PK substudy from the Phase 3, PREVENT TB trial, of whom 157 had evaluable PK samples (80 children and 77 adults). Risk groups in the treatment trial were recent close contacts of pulmonary tuberculosis cases, HIV-infected persons, those with a recent tuberculin skin test conversion, or those with fibrotic or fibronodular abnormalities consistent with old, healed tuberculosis on chest radiograph. All patients had evidence of latent tuberculosis infection (e.g. positive tuberculin skin test) and no evidence of active tuberculosis. Children enrolled in this substudy were age 2 to 11 years and all children and adults in the PK substudy were treated with 3HP. Rifapentine was administered as 150 mg tablets. Rifapentine doses in children ranged from 300 to 900 mg based on weight and dosage (Table 2) and the rifapentine dose in adults was 900 mg (all patients weighed more than 45 kg). Children who could not swallow tablets were administered a suspension of crushed rifapentine and isoniazid tablets in either a soft food or liquid. Other foods consumed within two hours of drug administration were documented. For children, the once-weekly dosage of isoniazid was 25 mg/kg, (900 mg maximum), and adults were administered isoniazid 15 mg/kg (900 mg maximum) (25).

Table 2. Rifapentine dosing algorithm used for children in the PREVENT-TB study

Weight (kg)	Rifapentine dose (mg)	Rifapentine dosage (mg/kg)	Number of children in each group	Age of study patients (mean +SD in years)
10-14	300	21-30	34	2.6 ± 0.8
>14-25	450	18-32	40	4.5 ± 1.6
>25-32	600	19-24	7	7.4 ± 2.2
>32-50	750	15-23	16	9.7 ± 2.4
>50	900	<18	3	10.0 ± 1.0

After at least three once-weekly doses of rifapentine and isoniazid, a single plasma sample collected 24-hours after administration of study drugs (C24) was used in the sampling protocol. A 2 mL venous blood sample for PK analysis was obtained 23 to 25 hours after drug administration and was processed according to standard procedures (67). Plasma concentrations of rifapentine and 25-des-RPT were determined using a validated high-pressure liquid chromatography assay (66).

Children study
The pharmacokinetic study in children included 23 children (age, 2 to 12 y) without tuberculosis. The children received rifapentine tablets (150 or 300 mg) without food. If a child had difficulty swallowing tablets, the tablets were crushed before administration (that was the case in 9 out of 23 children). Plasma samples for rifapentine and metabolite concentrations were collected (11 samples: before the dose and 0.5, 1, 2, 3, 4, 6, 10, 12, 24, and 32 h after the dose) (64).

Adolescent study
The pharmacokinetic study in adolescents included 12 healthy subjects (age, 12 to 15 y) who received rifapentine (1 dose; 450 mg for adolescents weighing < 45kg or 600 mg for adolescents weighing >45 kg) without food. Plasma samples for rifapentine and metabolite concentrations were collected (11 samples: before the dose and 2, 3, 4, 5, 6, 8, 12, 24, 48, and 72 h after the dose) (63).

Appendix III: Sample Informed Consent Form

IMPAACT 2001
A Phase I/II Trial of the Pharmacokinetics, Tolerability, and Safety of Once-Weekly Rifapentine and Isoniazid in HIV-1-infected and HIV-1-uninfected Pregnant and Postpartum Women with Latent Tuberculosis Infection

VERSION 1.0, DATED 10 NOVEMBER 2015

INTRODUCTION
You are being asked to take part in this research study with your baby because you are pregnant and may be at risk for developing tuberculosis (TB). This study is sponsored by the National Institutes of Health (NIH) in the United States. The person in charge of this study at this site is: [*insert name of Investigator of Record*]. Before you decide if you want to take part in this study with your baby, we want you to know about the study.

This is a consent form. It provides you with 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 form. You will be given a copy to keep.

WHY IS THIS STUDY BEING DONE?
Tuberculosis (TB) is a major cause of illness and death in women of reproductive age. In countries where TB is common, up to half of all women are infected with TB.

There are two types of TB that you should know about. When exposed to TB, there are two types of TB that may occur. In one type, people may become sick with symptoms such as cough and fever. These people are also contagious, meaning they can pass TB to other people. This type of TB is known as active TB disease. In the other type, people do not become sick or contagious, but they still have TB in an inactive form. This inactive form is known as latent TB.

If latent TB is not treated, it can become active TB, and this often happens for women around the time of pregnancy. There are medicines that help prevent latent TB from becoming active TB. These medicines are widely used by people who are not pregnant. The purpose of this study is to test the use of these medicines during pregnancy and soon after delivery. The study will look at the safety of the medicines for pregnant women and their unborn babies. It will also look at how the medicines are taken up in the bodies of pregnant women and their babies. The tests that are done to look at how the medicines are taken up in the body are called “pharmacokinetic” or “PK” tests.

The medicines tested in this study are rifapentine (RPT), isoniazid (INH), and pyridoxine (vitamin B_6). If you are taking antiretroviral medicines for HIV (ARVs), you will continue to receive these the way you usually do, but they will not be provided through the study. RPT and INH help prevent latent TB from becoming active TB. Vitamin B_6 is being given to help prevent numbness and tingling that may be caused by INH. The medicines will be taken in the study clinic once per week for 12 weeks. Women with latent TB are asked to take part in the study while they are pregnant and for six months after delivery, with their babies. The purpose of the study is to find out how the medicines are processed and tolerated in pregnant women and to test their safety for pregnant women and their babies.

WHAT DO MY BABY AND I HAVE TO DO AS PART OF THIS STUDY?

Screening
After having learned about this study, if you decide that you would like to take part, you will first have some screening tests to see if you are eligible. These tests will be done on the same day, after you have read and signed this form. [*Sites: add local information regarding how long the Screening Visit will take*].

The screening tests will include:

- Medical history: You will be asked questions about your health, your pregnancy, medications you are taking now and have taken in the past, and contacts with other people who have had TB. You will be asked about your drug and alcohol use.
- Physical exam: You will have an examination that includes measuring your height and weight. A machine will be used to listen to your baby's heartbeat, determine how long you have been pregnant, and check for any abnormalities.
- TB test: You may have a skin or blood test for TB, if you have not had one done recently. If a skin test is done, you will have a small injection under your skin that study staff will check in two to three days for evidence of exposure to TB. If a blood test is done, about 3 mL (about ½ teaspoon) will be drawn from a vein for the test. If you have symptoms of TB, you may also have other TB tests, including a Gene Xpert test, chest x-ray, or test of your sputum.
- Blood tests: You will have about 17-20 mL (about 3-4 teaspoons) of blood taken from a vein for:
    - HIV tests. These tests may be needed depending on the types of tests you had in the past and whether the results are available in medical records. [*Sites: add local information regarding HIV pre-/post-test counseling.]*
    - Routine safety tests. These tests check on your overall health, your liver, your blood cells, and how your blood clots.

You will be asked to return to the clinic within two weeks to receive your screening test results and find out if you are eligible for the study. If the test shows that you have active TB or other abnormalities, you will not be eligible for the study. However, the study staff will refer you to other sources of care and treatment that you may need.

If you do not join the study:
If you are not eligible for the study, or do not take part for any reason, we will still use the information from your screening tests. For example, your information may help us learn more about the reasons why people do not join the study.

If you join the study:
You will have an Entry Visit within two weeks after screening. You will then have study visits while you are pregnant and for six months after delivery of your baby. Depending on when you join the study and when your baby is born, you may have 18-24 study visits. The Entry Visit will require 3 days of your time. The next 12 visits will be weekly visits; that is, you will come to the clinic once a week for 12 weeks in a row. The last weekly visit will require 2 days of your time. After that, the visits will be monthly. More information about each of the visits and visits for your baby is given below.

At the Entry Visit you will:

- Answer questions about your health and medicines
- Have a physical exam, including assessments of your baby's health
- Have counseling for signs and symptoms of active TB
- Be given a meal and the first dose of study medicines
- Have blood collected for the first pharmacokinetic (PK) visit (see below)
- Have about 6-9mL (about 1-2 teaspoons) of blood collected for future testing for hepatitis (if you become sick later) and CD4 cell count (if you are HIV-infected). CD4 cells fight HIV and other infections.

First PK Visit
There are two PK visits for women in this study, on the day of the first dose of study medicines and on the day of the last dose of study medicines.

The first PK visit will begin the morning you take the first dose of the study medicines. If the study clinic is able, you may be allowed to stay at the clinic the night before and during your first PK visit. You will

be asked not to eat or drink (except water) for two hours before and four hours after taking the study medicines, other than the meal given to you at the clinic. You will stay at the clinic for 12 hours after you take the study medicines. Then you will need to return to the clinic 24, 48, and 72 hours after you took the medicines. Samples of your blood will be collected at 11 times during this period, for a total of 22 mL (about 5 teaspoons) over three days. [*Sites: add local information explaining if there will be a new needle stick for each blood draw or if a line/port will be established.]* These samples will be used to test the amount of RPT in your blood, and some of the samples will be stored to test the amount of INH in your blood at a later time.

At weekly visits while taking study medicines, you will:

- Answer questions about your health and medicines
- Have a physical exam, including assessment of your baby's health
- Have counseling for signs and symptoms of active TB
- Be given a meal and weekly doses of study medicines provided by the clinic staff
- Have blood collected every four weeks for tests that check on your overall health, your liver, your blood cells (11mL or a little more than 2 teaspoons).
- Have blood collected once during your 12 weekly visits to test how your blood clots (5 mL or 1 teaspoon)
- Have breast milk and additional blood (24mL or about 5 teaspoons) collected at the first two visits after delivery if you are still receiving study medicines at these visits. You will also have breast milk collected 24 hours after you receive the last dose of study medicines. These samples will be used to test the amount of study medicines in the blood and breast milk at these time points.

Second PK Visit

The second PK visit will begin the morning you take your last dose of the study medicine. If the study clinic is able, you may be allowed to stay at the clinic the night before and during your second PK visit. You will be asked not to eat or drink (except water) for two hours before and four hours after taking the study medicines, other than the meal given to you at the clinic. You will stay at the clinic for four hours after you take the study medicines. Then you will need to return to the clinic 24 and 48 hours after you took the medicines. Samples of your blood will be collected at four times during this period, for a total of 8 mL (about 2 teaspoons) over two days. [*Sites: add local information explaining if there will be a new needle stick for each blood draw or if a line/port will be established.]* These samples will be used to test the amount of RPT in your blood, and some of the samples will be stored to test the amount of INH in your blood at a later time.

At monthly visits (every four weeks) after you have finished taking study medicines, you will:

- Answer questions about your health and medicines
- Have a physical exam, including assessments of your baby's health (while you are pregnant)
- Have counseling for signs and symptoms of active TB
- Have blood collected for tests that check on your overall health, your liver, your blood cells, and how your blood clots (6-11mL or 1-2 teaspoons) except at the last visit, when no more tests will be done.

The procedures listed above will also be done, if possible, if you end study participation early.

Study visits for your baby:

- Once your baby is born, a PK visit will be done within the first three days of life. You may be asked to contact the research staff once you are in labor. Two mL (about ½ teaspoon) of blood will be collected to test the amount of RPT in the baby's blood. This visit will only be done if you received study medicines within 3 days before you delivered. Two mL (about ½ teaspoon) of blood may also be collected from your baby to test for clotting.

- If the study clinic is able, and you are still taking the study drug when you deliver, blood may be taken from the umbilical cord to test for the amount of RPT and INH.
- Your baby will then have monthly visits (with you) for six months. At these visits, you will be asked questions about your baby's health and medicines. The baby will have a physical exam. Blood (about 1-3 mL, or less than 1 teaspoon) may be collected to test the baby's overall health, liver, and blood cells.

The procedures listed above will also be done, if possible, if your baby ends study participation early.

OTHER INFORMATION

You will receive results from blood tests done on study visits at the next study visit following your blood draw or within two weeks. All blood samples for the first and second PK tests, and the blood samples from your baby's single PK test, will be shipped to a laboratory in South Africa where the tests will be performed. You or the site doctor will not be told the results of the PK tests, because the tests are for investigation only and will be done after the study is completed.

Any leftover blood samples after testing is completed for this study will be destroyed.

HOW MANY PEOPLE WILL TAKE PART IN THIS STUDY?

At least 50 and up to 82 pregnant women and their babies will take part in this study.

HOW LONG WILL I/MY BABY BE IN THIS STUDY?

You will be in this study from the time that you enter the study until 24 weeks after you have your baby. Depending on when you enroll, this could be for about six months or up to about one year.

Your baby will be in this study for about six months.

WHY WOULD I OR MY BABY BE TAKEN OFF THIS STUDY EARLY?

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

- Staying in the study would be harmful to your/your baby's health or well-being.
- The study is cancelled by the National Institutes of Health (NIH), U.S. Food and Drug Administration (FDA), IMPAACT, Sanofi, Office for Human Research Protections (OHRP), the site's Institutional Review Board (IRB) or Ethics Committee (EC), or other country-specific governmental agencies as part of their duties to ensure that research participants are protected. An IRB or EC is a committee that watches over the safety and rights of research participants.
- You are/your baby is not able to attend the study visits as required by the study.

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

- You are diagnosed with active TB.
- Continuing the study medicines may be harmful to you/your baby.
- You/your baby need(s) a treatment that you/your baby may not take while on the study medicines.
- You are not able to take the study medication as required by the study.
- You become pregnant again.

If you become pregnant again during the study, the site staff will contact you at the end of your pregnancy to record information about the outcome of your pregnancy. If you become pregnant again and you are HIV-1-infected, your new pregnancy will be reported to the ARV Pregnancy Registry. If you are taken off the study medicines, you and your baby will still stay in the study and have all of the visits described in this form.

WHAT IF I DEVELOP ACTIVE TB?

If you develop active TB, you will stop taking the study medicines and be referred to local sources of TB care and treatment.

It is possible that taking the study medicines while you have active TB could cause resistance. When resistance occurs, a medicine no longer works against TB, and different medicines may need to be taken. This is why you will stop taking study medicines if you develop active TB – to avoid resistance.

Tests for TB are done as part of your or your baby's clinical care, and no additional research tests, except for blood draws, are done only for the purpose of this study. These tests will only be done if the site investigator thinks the tests will help you and your baby. The site investigator will discuss any risks that may occur, at the time the tests are needed and the appropriate plan of care, depending on the results.

WHAT ARE THE RISKS OF THE STUDY?

Taking part in this study may involve some risks and discomfort. These include risks of blood draws, risks of study medicine and risks to your/your baby's privacy.

Risks of Blood Draws:

Drawing blood can cause pain, bruising or bleeding at the place where the needle goes into the skin. There is also a small risk of swelling or infection of the vein. These risks are greater for babies than for adults. In rare cases lightheadedness or fainting can occur.

Risks of Study Medicines:

There have not been many studies of the medicines used in this study in pregnant women. Studies of the study medicines in animals have shown some negative effects, but the benefits of the medicines for pregnant women are thought to be greater than the risks. These medicines 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 medicines. These lists include the more serious or common side effects with a known or possible relationship. If you have questions concerning additional study drug side effects please ask the medical staff at your site.

There are no known side effects associated with the study dose of vitamin B_6.

Both RPT and INH can cause damage to the liver, which may be seen in abnormal liver test results and other symptoms such as rash, changes in the color of urine, pale-colored stools, yellowing of the eyes or skin, pain in the upper abdomen, loss of appetite, upset stomach or vomiting, and low blood counts. RPT and INH may also cause diarrhea (loose or watery stools), including bloody diarrhea, which may be serious. These side effects may be worsened during pregnancy and when taking antiretroviral medicines for HIV (ARVs). These side effects can also be worsened when taking alcohol. The study staff will give you information and counseling about the risks of alcohol during pregnancy and while in this study.

Risk of TB Resistance:

If you are diagnosed with active TB while on the study medicines, there is a risk that you may have developed resistance to these medicines. If you develop active TB, you will be treated with other medicines for TB.

Risk of a Receiving Too Low a Dose of TB Medicine:

There is a risk that the dose of study medicines you receive for your latent TB may be too low. The dosing we are using has been used in many other clinical trials. The best dose during pregnancy is not known.

Rifapentine (RPT, Priftin®)

Other side effects of RPT may include: reddish coloring of urine, sweat, sputum, saliva, tears, and breast milk (contact lenses and dentures may be permanently stained); dizziness; hypertension; headache; low blood sugar; decreased effectiveness of hormonal contraceptives and other medications (tell your doctor about all medications that you are taking). In general, these side effects are temporary.

People taking RPT or drugs like it may have a serious allergic reaction called Rifamycin Hypersensitivity Syndrome (RHS). If you have any of the following reactions while taking RPT, call the study doctor right away: rash; fever; yellow eyes or skin or dark urine; achiness, general or extreme tiredness; dizziness or confusion; or easy bruising or bleeding. If you develop signs or symptoms of RHS, you will come to (or stay in) the clinic to be evaluated and have tests for this condition.

When given during the last few weeks of pregnancy, a drug similar to RPT may (in rare cases) increase the risk of bleeding in the mother and the baby. If you or your baby have increased bleeding, you will come to (or stay in) the clinic to be evaluated and treated for this condition.

Isoniazid (INH)

Other side effects of INH may include: changes in vision; clumsiness or unsteadiness; memory loss; confusion; trouble sleeping; changes in behavior or mood; seizures; high blood sugar; joint pain; weight loss, fever; tingling and numbness in the hands and feet which is the most common side effect; weakness and fatigue. In general, these side effects are temporary.

Other risks

There may be other risks to taking part in this study that are not known at this time. It is possible that others may learn of your participation in this study, and because of this, may treat you unfairly or discriminate against you. For your and your baby's safety, you must tell the study staff about all medications you/your baby are taking before starting the study and also before starting any new medications while on study, including medicines bought from the store or pharmacy and herbal or natural remedies. In addition, you must tell the study staff before you or your baby enrolls in any other clinical trials while on this study.

Breastfeeding

If you are breastfeeding your baby, he or she may get some of study medicines that you are taking from the breast milk. It is unknown whether the anti-TB medication may cause harm to your baby. Information learned from this study may show how safe the medication is for pregnant women and their babies.

WHAT ABOUT CONFIDENTIALITY?

Efforts will be made to keep personal information about you and your baby confidential. Your and your baby's personal information may be disclosed if required by law. Any publication of this study will not use your/your baby's name or identify you/your baby personally.

The outreach workers may contact you so we need to know the best way to reach you (such as home visit or phone call). Your records and those of your baby may be reviewed by the IMPAACT, the U.S. Food and Drug Administration (FDA), [*insert name of site*] Institutional Review Board (IRB) or Ethics Committee (EC), National Institutes of Health (NIH), Office for Human Research Protections (OHRP), study staff, study monitors, host country regulatory authorities, and drug companies supporting this study or their designees.

[U.S. sites only should include the following: In addition to the efforts of the study staff to help keep your personal information private, we have obtained a Certificate of Confidentiality from the US Federal Government. This certificate protects study staff from being forced to tell people who are not connected with this study, such as the court system, about your participation or information you give for study purposes. However, if the study staff learns of possible child abuse and/or neglect or a risk of harm to you or others, they will be required to tell the proper authorities. This certificate does not prevent you from releasing information about yourself and your participation in the study.]

ARE THERE BENEFITS TO TAKING PART IN THIS STUDY?

If you and your baby take part in this study, there may be a direct benefit to you and your baby, but no guarantee can be made. Taking anti-TB medicines such as INH and RFP may be of benefit to you and your baby. Taking vitamin B_6 may be of benefit to you and your baby. Having TB detected early may be of benefit to you and your baby.

It is also possible that there may be no direct benefit to you or your baby from taking part in this study. Information learned from this study may reduce women's risk of getting active TB after having a baby, and it may help others who have TB or others who do not have TB but live with someone who does.

WHAT OTHER CHOICES DO MY BABY AND I HAVE BESIDES THIS STUDY?

Instead of being in this study you have the choice of not being in the study. *[Sites: Please fill in information about available alternatives at the site]*.

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

WHAT ARE THE COSTS TO ME?

There is no cost to you or your baby for the study visits, examinations, or blood tests. 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/your baby is taking part in a research study. *[Sites: Modify or delete language regarding insurance as appropriate for your site.]*

WILL I RECEIVE ANY PAYMENT?

You may receive reimbursement for some expenses for this study (for example, for transportation or meals). *[Sites: This statement can be modified or deleted as needed for your site.]*

WHAT HAPPENS IF I AM/MY BABY IS INJURED?

If you are and/or your baby is injured as a result of being in this study, the study doctor will give or will refer you and/or your baby for immediate medical treatment. The cost for this treatment may be charged to you or your insurance company. There is no program for compensation either through this institution or the National Institutes of Health (NIH). You will not be giving up any of your legal rights by signing this consent form.
[Sites: modify or delete language regarding insurance as appropriate for your site and insert appropriate language for local costs].

WHAT ARE MY/MY BABY'S RIGHTS AS A RESEARCH PARTICIPANT?

Taking part in this study is completely voluntary. You may choose not to participate or to allow your baby to participate in this study or take yourself/your baby out of this study at any time. You/your baby will be treated the same no matter what you decide. Your decision will not have any impact on your/your baby's participation in other studies conducted by NIH and will not result in any penalty or loss of benefits to which you/your baby is otherwise entitled.

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

[Sites: include local information about how participants can find out about study results if applicable].

WHAT DO I DO IF I HAVE QUESTIONS OR PROBLEMS?

For questions about this study or a research-related injury, contact:
- *[Site name of the investigator or other study staff]*
- *[telephone number of above]*

For questions about your/your baby's rights as a research participant, contact:
- [*Name or title of person on the Institutional Review Board (IRB) or other organization appropriate for the site]*
- *[telephone number of above*]

SIGNATURE PAGE

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

_____	_____
Maternal Participant's Name (print)	Maternal Participant'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