IMPAACT P1078

A PHASE IV RANDOMIZED DOUBLE-BLIND PLACEBO-CONTROLLED TRIAL TO EVALUATE THE SAFETY OF IMMEDIATE (ANTEPARTUM-INITIATED) VERSUS DEFERRED (POSTPARTUM-INITIATED) ISONIAZID PREVENTIVE THERAPY AMONG HIV-INFECTED WOMEN IN HIGH TB INCIDENCE SETTINGS

"TB APPRISE" Stands for TB Ante vs. Postpartum Prevention with INH in HIV Seropositive mothers and their Exposed infants

A Multicenter International Trial of the International Maternal Pediatric Adolescent AIDS Clinical Trials Group (IMPAACT)

Sponsored by:
The National Institute of Allergy and Infectious Diseases (NIAID);
The Eunice Kennedy Shriver
National Institute of Child Health and Human Development (NICHD);
Scientific Collaboration with the Tuberculosis Trials Consortium (TBTC)
of the Centers for Disease Control and Prevention

DAIDS ES # 10732
IND # 113,835

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IMPAACT P1078 SITE REQUIREMENTS

An approved Site Implementation Plan (SIP) is required, for sites to be eligible to enroll. Please see Section 4.5 for additional information. P1078 protocol documents are available to download from the study webpage on the IMPAACT website: www.impaactnetwork.org. For the pharmacokinetic subset (see Section 9.0) planned in P1078, certain laboratory capabilities and training will also be required.

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STUDY MANAGEMENT

For additional guidance on study management questions and communications, please see the IMPAACT P1078 Manual of Procedures (MOP).

Protocol Registration Questions: Email protocol@tech-res.com or call (301) 897-1707. Protocol registration material can be sent electronically to epr@tech-res.com or via FAX at 1-800-418-3544 or (301) 897-1701.

Email the Computer Support Group at the Data Management Center (DMC) (user.support@fstrf.org) to have relevant site personnel added to the protocol email group (impaact.protp1078@fstrf.org). Inclusion in the protocol email group will ensure that sites receive important information about the study during its implementation and conduct.

General Questions: Email questions concerning any aspect of protocol interpretation and/or study implementation not listed below, including administrative, ethical, regulatory, counseling, data, and laboratory operations, to impaact.teamp1078@fstrf.org. See Section 1 of the P1078 MOP for more information on communication with the P1078 protocol team.

Clinical and Toxicity Management Questions and Notifications: Email questions concerning clinical management of study participants and adverse experiences to the study Clinical Management Committee (CMC) at impaact.p1078cmc@fstrf.org. See the P1078 MOP for more information on communication with the P1078 CMC.

Questions related to participant eligibility, potential enrollment of an ineligible participant, and/or deviation from other protocol requirements for screening and enrollment should be directed to the Core team (impaact.corep1078@fstrf.org). Email questions related to co-enrollment in P1078 and other studies to the Core team. See the P1078 MOP for more information on communication with the Core team.

Randomization: For randomization questions or problems and study identification number (SID) lists, email rando.support@fstrf.org or call the DMC Randomization Desk at (716) 834-0900 x7302.

Computer and Screen Problems: For computer and screen problems, email user.support@fstrf.org or call the DMC at (716) 834-0900 x7302.

Product Package Inserts or Investigator Brochures: Product package inserts or investigator brochures may be accessed on the DAIDS Regulatory Support Center (RSC) website: http://rsc.tech-res.com.

Study Drug: For questions or problems regarding study drug, dose, supplies, records, and returns, contact the DAIDS Protocol Pharmacist at Kashin@niaid.nih.gov or call (240) 627-3047.

Study Drug Orders: Email the Clinical Research Products Management Center (bio.crpmc.ph@thermofisher.com) or call (301) 294-0741.

Expedited Adverse Event (EAE) Reporting/Questions: Contact the DAIDS RSC Safety Office via email (RSCSafetyOffice@tech-res.com) or phone (1-800-537-9979 or +1-301-897-1709) or fax (1-800-275-7619 or +1-301-897-1710). For questions about the DAIDS Adverse Experience Reporting System (DAERS), email DAIDS-ESSupport@niaid.nih.gov. Questions may also be sent within the DAERS application.

TABLE OF CONTENTS

Glossary

ACTN	AIDS Clinical Trials Network
AE/EAE	Adverse Event / Expedited Adverse Event
AFB	Acid-fast bacillus
ALT (SGPT)	Amino Alanine Transferase (Serum Glutamate Pyruvate Transaminase)
ART/ARV	Antiretroviral Therapy / Antiretroviral
AST (SGOT)	Aspartate Amino Transferase (Serum Glutamic Oxalacetic Transaminase)
ATS	American Thoracic Society
AUC	Area Under the Curve
BCG	Bacille Calmette-Guérin
BPNS	Brief Peripheral Neuropathy Screen
CAP	College of American Pathologists
CDC	Centers for Disease Control and Prevention
CI	Confidence Interval
CL/F	Clearance
CLIA	Clinical Laboratory Improvement Amendments
CMC	Clinical Management Committee
CMI	Cell-Mediated Immunity
CONSORT	Consolidated Standards for Reporting Trials
CPQA	Clinical Pharmacology Quality Assurance
CRC	Clinical Research Center
CRF	Case Report Form
CRPMC	Clinical Research Products Management Center
CRS	Clinical Research Site
DAERS	DAIDS Adverse Experience Reporting System
DAIDS	Division of AIDS, NIAID
DAIDS PRO	DAIDS Protocol Registration Office
DMC	Data Management Center
DNA	Deoxyribonucleic Acid
DSMB	Data and Safety Monitoring Board
EC	Ethics Committee
EFV	Efavirenz
ELISPOT	Enzyme-linked Immunosorbent Spot
ERC	Endpoint Review Committee
FDA	Food and Drug Administration
GCLP	Good Clinical Laboratory Practice
HAART	Highly Active Antiretroviral Therapy
HBsAg	Hepatitis B Surface Antigen
HHS	(US Department of) Health and Human Services
HIV/AIDS	Human Immunodeficiency Virus / Acquired Immunodeficiency Syndrome
ICF	Informed Consent Form
IGRA	Interferon Gamma Release Assay
IMPAACT	International Maternal Pediatric Adolescent AIDS Clinical Trials Network
IND	Investigational New Drug
INH	Isoniazid
IPT	INH-Preventive Therapy
IRB	Institutional Review Board

ITT	Intent-To-Treat
IUGR	Intrauterine Growth Restriction
LAR	Legally Authorized Representative
LFT	Liver Function Test
LPC	Laboratory Processing Chart
LTBI	Latent Tuberculosis Infection
MMWR	Morbidity and Mortality Weekly Report
MOH	Ministry of Health
MOP	Manual Of Procedures
M.tb.	Mycobacterium tuberculosis
MVI	Multivitamins
NAT2	N-acetyltransferase 2
NIAID	National Institute of Allergy and Infectious Diseases
NICHD	National Institute of Child Health and Human Development
NIH	National Institutes of Health
OHRP	Office for Human Research Protections
PBMC	Peripheral Blood Mononuclear Cell
PCP	*Pneumocystis jiroveci* (previously *Pneumocystis carinii*) Pneumonia
PCR	Polymerase Chain Reaction
PEPFAR	President's Emergency Plan for AIDS Relief
PHQ	Patient Health Questionnaire
PI	Predicted Interval
PID/SID	Patient Identification Number / Study Identification Number
PK	Pharmacokinetics
PMTCT	Prevention of Mother To Child Transmission
PN	Peripheral Neuropathy
QGIT	QuantiFERON Gold-In Tube
RE	Regulatory Entity
RNA	Ribonucleic Acid
RSC	Regulatory Support Center
SAE	Serious Adverse Event
SDAC/SDMC	Statistical Data Analysis Center / Statistical and Data Management Center
SERC	Secondary Endpoint Review Committee
SES	Subject Enrollment System
SIP	Study or Site Implementation Plan
SOE	Schedule of Evaluations
SOP	Standard Operating Procedure
SUSAR	Suspected Unexpected Serious Adverse Reaction
TB	Tuberculosis
TST	Tuberculin Skin Test
UCSF	University of San Francisco
ULN	Upper Limit of Normal
USA	United States of America
WHO	World Health Organization

For this protocol, QGIT and TB ELISPOT are both included under the term IGRA. IGRA will be the term used for those tests except where a more specific test is noted.

Schema, P1078 TB APPRISE

A Phase IV Randomized Double-Blind Placebo-Controlled Trial to Evaluate the Safety of Immediate (Antepartum-Initiated) Versus Deferred (Postpartum-Initiated) Isoniazid Preventive Therapy Among HIV-Infected Women in High TB Incidence Settings

"TB APPRISE" Stands for TB Ante vs. Postpartum Prevention with INH in HIV Seropositive mothers and their Exposed infants

Design: Phase IV, randomized, double-blind, placebo-controlled study

Sample Size: 950 women and their infants (475 women per study arm)

Population: Mother-infant pairs; HIV-infected pregnant women ≥ 14 weeks through ≤ 34 weeks (34 weeks, 6 days) gestation

Randomization: At study entry, randomization will be in a 1:1 ratio to Arm A (immediate INH treatment) OR Arm B (deferred INH treatment)

Randomization will be balanced at each clinical research site (CRS).

Stratification: Pregnant women will be stratified by gestational age in each arm as follows:
Stratum a: ≥ 14 to < 24 weeks gestational age at study entry
Stratum b: ≥ 24 through ≤ 34 weeks (34 weeks, 6 days) gestational age at study entry

There will be no limits on the number of women in each stratum.

Regimen: Women in *Arm A (Immediate INH)* will be given:

- INH 300 mg – initiated at study entry and continued for 28 weeks
  THEN
- Placebo for INH – initiated after 28 weeks of INH treatment and continued until 40 weeks postpartum

Women in *Arm B (Deferred INH)* will be given:

- Placebo for INH – initiated at study entry and continued until 12 weeks postpartum
  THEN
- INH 300 mg – initiated at 12 weeks postpartum and continued until 40 weeks postpartum

Women in *Arm A and Arm B* will be given:
Open-label Pyridoxine (vitamin B_6) and prenatal multivitamins from study entry until 40 weeks postpartum. Pyridoxine and prenatal multivitamins will be obtained locally by the site.

Study Duration: From enrollment through 48 weeks post-delivery

Pharmacokinetic Studies: An intensive pharmacokinetic (PK) subset analysis will be performed on a limited number of women who are receiving both INH/placebo for INH plus HAART. Population PK will be done on all women, except those who participate in the intensive PK study. As a biomarker of adherence and exposure, small hair samples for the measurement of ART and INH concentrations will be collected and analyzed at relevant study visits.

Immunology Studies: Immunology studies, including IGRA (QGIT and TB ELISPOT) and TST, will be performed on women and infants throughout the study; sera, plasma, and PBMCs will also be collected and stored on a subset of women and infants to be used for future TB/HIV-related testing. QGIT results will be blinded to the clinical site staff.

For this protocol, QGIT and TB ELISPOT are both included under the term IGRA. IGRA will be the term used for those tests except where a more specific test is noted.

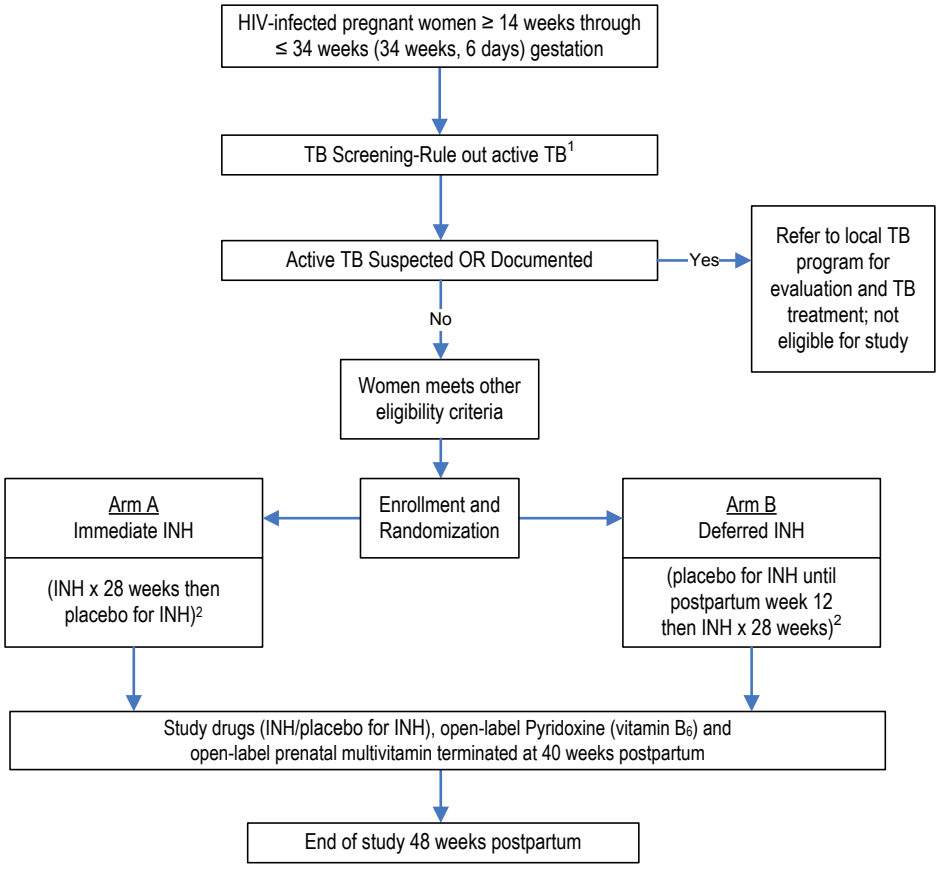
Primary Objective: To compare overall safety and toxicity of immediate versus deferred INH preventive therapy in HIV-infected pregnant women enrolled at ≥ 14 through ≤ 34 weeks gestation (34 weeks, 6 days)

Secondary Objectives:
1. To compare safety and toxicity of INH *in utero* exposure and on infants on study
2. To compare TB incidence and all-cause mortality in HIV-infected women and their infants enrolled on study
3. To compare overall safety and hepatotoxicity, as well as evaluate risk factors for these outcomes, during pregnancy and immediate postpartum in women on immediate versus deferred INH therapy
4. To evaluate for INH resistance among *M.tb.* isolates from HIV-infected women and infants who develop TB while on study
5. To evaluate the intensive pharmacokinetics of INH and selected ARV drugs in a subset of HIV-infected pregnant and postpartum women receiving HAART
6. To evaluate and compare the performance characteristics of IGRA (TB ELISPOT and QGIT) with TST in HIV-infected women and their infants
7. To compare adherence in women initiating immediate versus deferred INH preventive therapy via self-report and pill counts

Exploratory Objectives:
1. To evaluate population pharmacokinetics and pharmacogenomics of INH and efavirenz (EFV) in HIV-infected pregnant and postpartum women
2. To assess the effects of INH preventive therapy on the functional characteristics of TB specific T-cell responses measured by TB ELISPOT in HIV-infected women and their infants on study
3. To evaluate adherence and exposure to INH and EFV using drug levels in hair and analyze the association between these drug levels and adverse effects
4. To compare the two arms with respect to the overall (risk:benefit) clinical outcomes of the mother-infant pairs

5. To explore associations of maternal and infant specific TB responses and novel biomarkers with risk of maternal and infant TB infection and disease
6. To explore the neurotoxicity of INH in combination with EFV in a subset of women

Study Schema



[1]All women will receive a TB exposure history, World Health Organization (WHO) TB symptom screen, any available TB screening procedures as per local standard of care and complete physical exam at screening.

[2]All women will receive standard of care + prenatal multivitamin + Pyridoxine (vitamin B_6) from study entry to 40 weeks postpartum in addition to INH/Placebo for INH. All women will also receive a TB exposure history, WHO TB symptom screen and targeted physical exam at each study visit. All infants will also receive standard of care.

1.0 Introduction

1.1 Background

Tuberculosis (TB) is the most important cause of morbidity and mortality among HIV-infected persons residing in high TB burden settings such as sub-Saharan Africa and India. TB predominantly affects women of reproductive age, and when it occurs during pregnancy or early postpartum, it can result in adverse maternal outcomes and infant TB and death. Infant TB is very challenging to diagnose. It is estimated that up to a half of infant TB cases are due to maternal TB disease. While there is no controversy about the need and benefit of treating active TB during pregnancy or benefit of isoniazid (INH) preventive therapy (IPT) to HIV-infected adults, particularly those who are tuberculin skin test (TST) positive, data on the safety and efficacy of administering IPT to HIV-infected pregnant women in the era of antiretroviral therapy (ART) are not available.

There have been a number of clinical trials involving IPT in HIV-infected adults and HIV-infected or HIV-exposed children. Current guidelines from the World Health Organization (WHO) recommend that all HIV-infected persons residing in low- and middle-income regions where TB is endemic receive at least 6 months of IPT [1]. The guidelines have removed the prior requirement of a positive TST due to difficulties in implementation and have now included a recommendation of IPT to pregnant women and children. However, none of the more than 13 adult IPT trials has included HIV-infected pregnant women, a population that may have a higher risk of adverse events (AEs) and drug-induced liver injury. There remains limited data regarding highly active antiretroviral therapy (HAART) initiation in close approximation with INH but a pragmatic trial conducted in South Africa suggested IPT + HAART was beneficial irrespective of TST status. Pregnant women, however, were excluded from this trial as well. [2]

The optimal timing of IPT in pregnancy remains unknown and this knowledge gap is acknowledged in the WHO guidelines. The US Centers for Disease Control and Prevention (CDC) guidelines and literature to date acknowledge that there is increased toxicity risk of IPT in pregnancy and within 3 months postpartum. Pregnant women also have increased risk of adverse antiretroviral drug toxicity and increased risk of hepatic dysfunction from pregnancy itself. Currently the US Food and Drug Administration (FDA) categorizes INH as category C, meaning that animal reproduction studies have shown an adverse effect on the fetus and there are no adequate and well-controlled studies in humans, but potential benefits may warrant use of the drug in pregnant women despite potential risks. Although the WHO guidelines recommend use of IPT in HIV-infected pregnant women, in the absence of safety data, it is unclear if this recommendation will be followed. Furthermore, safety data specific to IPT initiation among pregnant women also initiating HAART are lacking but needed. Small studies have observed that continuing IPT when women become pregnant or initiating IPT in pregnancy is not associated with severe adverse events. [3, 4] However, the Lesotho study, for example, had only liver function test data for 20 of 160 women of whom only a small number were on HAART. HAART is known to have an independent effect on reducing TB incidence but prospective data on the risks and benefits of combining IPT with HAART in pregnancy is unknown. Since some HIV-infected pregnant women may not have latent TB infection (LTBI) and, therefore, may not

have significant benefit from IPT, it is important to evaluate the safety of IPT in pregnancy, the optimal timing of IPT in this population, as well as overall efficacy, risk and benefits.

The goal of IMPAACT P1078 is to evaluate whether initiating IPT is safe in HIV-infected pregnant women who may be receiving HAART. This study will also assess the tolerability of IPT in the context of HAART during pregnancy and as secondary objectives include assessment of efficacy of INH, pregnancy and infant outcomes, adherence to INH and ART via hair sampling, pharmacology of INH/HAART and performance of latent TB diagnostics. In addition, the data and samples from this study may allow for novel and important immunologic studies that will provide insights into *Mycobacterium tuberculosis (M.tb)*-specific responses, LTBI, risk of maternal disease, and risk of infection and disease among infants born to women who have received INH antepartum versus postpartum.

1.2 Rationale

TB: Major Cause of Morbidity and Mortality in HIV-infected Women in Low-income Countries

An estimated 2 billion individuals are latently infected with *Mycobacterium tuberculosis* (*M.tb.*) and over 9 million cases of active TB occur each year globally with an estimated 3.8 million cases occurring in women [5]. HIV is an important contributor to the TB epidemic, most notably in sub-Saharan Africa. TB disease is the most common HIV-related opportunistic infection and is the most important cause of morbidity and mortality in HIV-infected adults in low-income settings [6]. Even in the era of HAART, significant rates of TB disease persist [7, 8]. The greatest burden of HIV and TB among women occurs during the childbearing years (15-49 years). Active TB seems particularly prevalent during pregnancy, delivery, and the postpartum period [9-14]. Active TB in women with HIV co-infection is an independent factor for non-obstetric maternal mortality. In a study of maternal mortality in South African teaching hospitals, mothers with TB and HIV had a 3.2 fold increased risk of death compared to mothers with TB without HIV; 54% of maternal deaths due to TB disease were attributable to HIV co-infection [15]. In a study in Zambia, TB accounted for 25% of non-obstetric deaths and most of these deaths occurred in HIV/TB co-infected women [16]. Similar studies in Zimbabwe, India, and Tanzania have identified TB as a major cause of maternal non-obstetric deaths (within first 1-2 years postpartum) in HIV-infected women [13, 17, 18].

Maternal TB has Negative Impact on Young Infants

Data indicate that infants born to HIV-infected mothers with active TB have higher rates of prematurity, low birth weight, and intrauterine growth retardation (IUGR) [10]. Furthermore, newborn and young infants exposed to HIV-infected mothers with active TB are at high risk for tuberculosis morbidity, all-cause mortality, and HIV infection [17, 19]. In IMPAACT P1041, A Randomized Double Blind Placebo Controlled Trial to Determine the Efficacy of Isoniazid in Preventing Tuberculosis Disease and Latent Tuberculosis Infection Among Infants with Perinatal Exposure to HIV, infants experienced very high rates of TB exposure (nearly 10% during the first 3-4 months of life); HIV-infected mothers accounted for the majority of this exposure [20]. Similarly high prevalence of TB infection has been reported in Kenyan infants [21]. It is well documented in natural history studies conducted prior to the 1950's (when INH became widely

available) and more recent observational studies [22] that infants are likely to develop progressive TB disease following primary infection.

IPT in HIV-infected Individuals

Strategies to reduce TB burden are critical to ensuring successful clinical management of HIV-infected individuals. IPT reduces incident TB in HIV-infected adults by 33% and in those with a positive TST by 62% as well as in HIV-infected children [23, 24]. IPT has also been associated with a mortality benefit in HIV-infected infants and there may be a reduction in mortality among adults particularly if they are TST-positive (20% reduction, 4 trials pooled). None of these studies included pregnant women.

A study of IPT in HIV-exposed infants 3 months of age or older, was conducted as IMPAACT P1041. This study was stopped early because no benefit was identified [25-27]. P1041 excluded infants whose mothers had TB disease or any other documented TB exposure. It also excluded infants less than 3 months of age, a population at particularly high risk for active TB. P1041 identified maternal TB as the major source of TB exposure in infants and a risk factor for infant TB in at least 50% of cases [20]. Given that an important risk factor for infant TB and all-cause mortality is incident TB in the mother, a strategy that targets IPT in infants does not appear to be effective and does not address TB risk in the mother. Therefore, it is important to demonstrate that IPT given during pregnancy is a safe and effective maternal-child health intervention in the HAART era.

INH Resistance

A concern that has been raised with use of INH to HIV-infected persons residing in low- and middle-income countries with high TB burden is the risk of INH resistance. A review of 13 IPT trials in non-pregnant, HIV-infected and uninfected populations with approximately 35,000 participants showed low risk of selecting for INH resistance [28].

To avoid INH resistance, cases of active TB will be excluded using best available approaches. Studies have shown that the absence of cough, fever, weight loss, or night sweats have the highest negative predictive value for TB (>98%) [29-31]. Sites will also be encouraged to use additional diagnostics, such as Xpert (Xpert MTB RIF Assay or similar rapid NAAT-based test) and shielded chest radiograph, when readily available. The current WHO guidelines also recommend this approach to rule out TB and initiate IPT.

As a secondary objective, INH resistance will be assessed in participants who develop active TB while on the study. Furthermore, women and infants will be screened for active TB at each visit. Those with a positive symptom screen will be further assessed with sputa for AFB smear, radiography, AFB cultures, and/or additional TB diagnostics, as recommended by local and WHO guidelines. *M.tb.* isolates will be tested for INH resistance.

INH and Highly Active Antiretroviral Therapy (HAART)

In adults, HAART without INH has been associated with a 60% reduction in TB incidence and HAART after INH receipt was found to reduce TB incidence by 80% in one retrospective cohort in Brazil and by 89% in a prospective cohort in South Africa [32, 33]. However, these studies did not prospectively assess the combination of HAART and IPT given around the same time. A recent pragmatic study of IPT and HAART in South Africa found reduction in TB incidence irrespective of LTBI test status [2]. Being female, pregnant and obese are risk factors associated with increased drug-induced hepatotoxicity [34]. Nevirapine-containing HAART, which is sometimes used in pregnant and postpartum women, carries an additional risk of hepatotoxicity; therefore, it is imperative to assess the risks and benefits of combining INH with HAART whether used for PMTCT or maternal HIV treatment.

Another IPT and HAART consideration is recent PK data from South African HIV-infected pregnant women found that INH for prophylaxis or for treatment reduced EFV clearance, especially among those with slow NAT2 acetylator status. INH influences EFV concentrations via inhibition of CYP-2A6 [35, 36]. Whether this INH/EFV interaction results in increased EFV toxicity in pregnancy needs further study. Several assessments will be used to inform this exploratory analysis. A nine-item assessment tool (Patient Health Questionnaire 9, PHQ-9) that has been internationally validated and is available in most languages will be used as a tool to capture depression in pregnancy or postpartum that may or may not be related to slow INH and slow efavirenz (EFV) metabolism [37]. A three-item neurocognitive impairment tool [38] as well as several questions from the Pittsburgh Sleep Quality Index [39] will also be assessed. Depression and other neuropsychiatric toxicities are also captured by the DAIDS AE toxicity reporting requirements.

INH Safety Data

Hepatotoxicity

INH is cleared predominantly by the liver, primarily by acetylation of N-acetyl transferase 2 (NAT2) as discussed below. Hepatotoxicity due to IPT in US settings has been summarized in the American Thoracic Society (ATS) 2006 guidelines [40] and by a recent MMWR which assessed severe INH-associated liver injuries for LTBI treatment in the US from 2004-2008 [41]. Up to 20% of persons who receive IPT may experience low-grade, transient, asymptomatic transaminase elevations, much of which is attributed to "hepatic adaptation," a nonprogressive injury to hepatocyte cell structures. INH hepatotoxicity is mostly asymptomatic, but symptomatic hepatotoxicity can occur at varying transaminase levels. Generally, INH hepatotoxicity occurs within weeks to months (60% in first 3 months). The ATS recommends defining hepatotoxicity as one of the following: 1) amino alanine transferase (ALT) that are three times the upper limit of normal (ULN) or greater with clinical symptoms compatible with hepatitis (e.g., nausea, vomiting, abdominal pain, jaundice or unexplained fatigue); or 2) ALT that is at least five times the ULN in the absence of symptoms. The FDA definition of drug-induced hepatotoxicity for pre-market evaluation of new drugs consists of the following: ALT of 8 X ULN or ALT > 3 X ULN with a total bilirubin > 2 X ULN; as well as 1) the liver injury is hepatocellular in nature and there is no prominent cholestatic component; 2) there are no other

causes of hepatotoxicity, such as acute viral hepatitis A or B, or other acute liver disease; and 3) the drug causes more frequent hepatocellular injury as shown by ALT elevations > 3 X ULN in the treated group relative to the group on control treatment. In P1078, both of these hepatotoxicity definitions will be assessed as secondary analyses.

Risk factors for hepatotoxicity include pregnancy and being within 3 months postpartum among others. The data come from two US studies conducted in the pre-HIV era. Both studies were retrospective and had problems such that their results have to be interpreted with caution. One study found a non-significant 2.5-fold increased risk of hepatotoxicity and a 4-fold increased risk of death in pregnant women. However, there was significant loss to follow up (1,030 of 3,681 women who began IPT never returned and only 46% completed 6 months of IPT). Also, the numbers of events were small (5 pregnant women developed INH hepatitis and 2 died) [42]. A second study described 20 deaths in California over 14 years from INH-induced hepatitis; four were women who started IPT in pregnancy [43]. Supporting the notion that INH may have increased toxicity during pregnancy and early postpartum is the fact that both periods are independently associated with increased risk of hepatotoxicity due to other drugs, including ARVs [44].

Rates of grade 3 or higher hepatotoxicity in persons receiving IPT in US range from 0.1% to 4% but varying definitions of hepatotoxicity have been used as well as varying degrees of adherence to INH. All IPT trials in HIV-infected persons done to date have excluded pregnant women. One South African trial assessing novel latent TB regimens compared with INH was predominantly among HIV-infected women (83%) and 99.5% were Black African. The overall rate of Grade 3 or 4 events was 9% in the INH arm (hepatotoxicity not specifically reported). Twenty six women became pregnant on IPT and 10 chose to continue IPT and no specific toxicity concerns were noted but numbers were small [45].

Other Toxicities of IPT

Peripheral neuropathy is the most common side effect of INH, occurring in about 20% of patients receiving 300 mg per day without supplemental pyridoxine (vitamin B_6). The side effects appear to be dose related and may be prevented with concomitant pyridoxine therapy. Patients with alcoholism, cancer, uremia, chronic liver disease, advanced age, or pregnancy may be predisposed to neurotoxicity from INH because they often have subclinical deficiencies of pyridoxine. Neuropathy also occurs most often in "slow-acetylators," malnourished patients, and diabetics [46].

Toxicities other than drug-induced liver injury and peripheral neuropathy are rare. Cutaneous hypersensitivity occurs in less than 1% and hematologic abnormalities are rare. The incidence of INH-induced toxic fever is estimated at 1%. Fever usually occurs within 6 to 47 days after starting INH therapy; upon re-challenge fever usually reappears within 2 to 5 hours [46].

Use of INH in Pregnant and Breastfeeding Mothers and Data from Animal Reproductive Toxicology Studies

INH is a FDA category C drug due to limited information in pregnant women. INH is used in pregnancy to treat active TB, where its benefit clearly exceeds the risk. INH is known to cross 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 [47-49].

Animal studies show an increased rate of growth retardation in rats thought to be secondary to an insult to the yolk sac blood vessel walls [50, 51]. No increase in malformations was observed in mice pups or rabbits whose mothers received as much as 60 times the dose used in humans. There, however, was a modest increase in skeletal malformations in rats [52-54]. Chick embryo studies observed demyelination and degeneration of the central nervous system after a single dose of INH at different days of incubation however supplementation with vitamin B_6 reversed these effects completely [55, 56]. Doses 30 times the usual human dose during pregnancy and lactation increased frequency of pulmonary adenocarcinomas in murine offspring, although a large case-control study of 11,169 children with cancer found no association with maternal INH during pregnancy (only a small number of mothers in either group took INH). No neoplasms were noted in 660 children 1 to 13 years of age born to women who received INH during pregnancy [57-59]. An association between INH and hemorrhagic disease of the newborn was seen in one study but not confirmed in others; some recommend prophylactic administration of vitamin K at birth but this is not commonly done in practice [50].

Safety 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 100 mg [60]. It can reduce pregnancy-associated nausea and in combination with other vitamins in B complex, C and E, it has been associated with reduced HIV disease progression in pregnant women in Tanzania [61]. In P1078, open-label vitamin B_6 from study Entry until Week 40 postpartum will be administered. In addition, the study will provide open-label prenatal multivitamins (MVI) to all women during pregnancy and until 40 weeks postpartum as part of standard of care. Prenatal MVI will contain less than 5 mg of vitamin B_6; therefore, the doses of vitamin B_6 to be used in our study will be well within the safe range.

Hair Concentrations of INH and ART as Markers of Adherence and Cumulative Exposure

In a manner analogous to glycosylated hemoglobin A1C (HbA1C) providing information on average glucose levels over long periods of time [62], the concentration of medications in hair reflects drug uptake from the systemic circulation over weeks to months [63]. Drug levels in hair provide an advantage over single plasma ARV concentrations – where marked day-to-day variation limits their utility in therapeutic drug monitoring [64, 65] – in estimating an average or long-term measure of medication exposure [63]. Moreover, average adherence to ARVs may be

a better predictor of virologic suppression than duration or frequency of missed doses (captured by single plasma levels) [66].

The PROMISE 1077BF and 1077FF protocols have collaborated with a group at the University of California, San Francisco (UCSF) to incorporate a novel measure of assessing long-term adherence and exposure to ART in the study using hair samples. Methods have been developed to extract and analyze tenofovir and emtricitabine, lopinavir/ritonavir, atazanavir, darunavir, nevirapine, efavirenz, and raltegravir from small scalp hair samples [67-71]. Hair concentrations of ARVs have been demonstrated to be the strongest independent predictor of virologic success in large prospective cohorts of HIV-infected patients [68, 69, 72-78], serving as stronger predictors of treatment outcomes than self-reported adherence [69, 73, 79, 80] or single plasma ARV concentrations [72]. Given concerns about waning adherence to ARVs in the postpartum period, incorporating an objective biomarker of ART adherence for participants in Arm A and Arm B of the study will further investigate this finding.

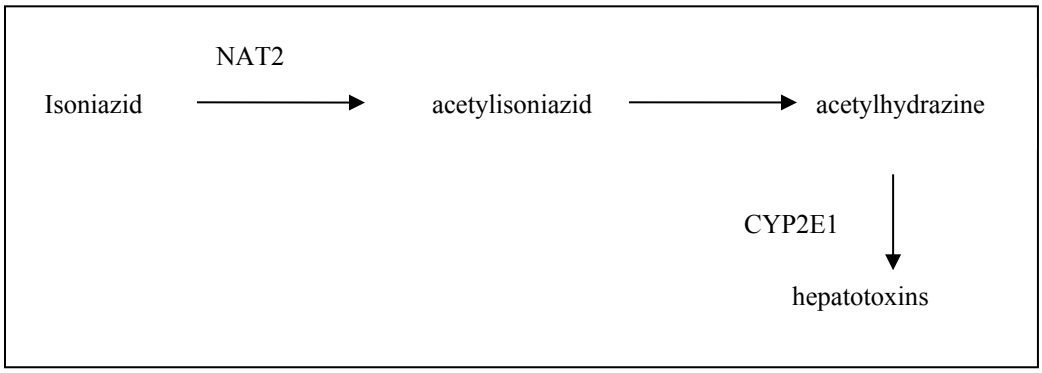
The UCSF Drug Studies Unit has also recently developed a method to analyze INH in small hair samples as a biomarker of adherence/exposure and this study will similarly incorporate hair collection into P1078 to assess INH adherence among participants randomized to Arm A or B of the study.

Pharmacology

Pharmacokinetics, Pharmacogenetics, and Hepatotoxicity of INH

INH is metabolized via hepatic acetylation to the N-acetyl transferase-2 (NAT2) enzyme to acetylisoniazid, which is further converted via oxidation by cytochrome P450 2E1 to hepatotoxic metabolites [81, 82]. Genetic polymorphisms of NAT2 correlate with fast, slow, and intermediate acetylation phenotypes. Rapid acetylators convert 90% to acetylisoniazid while slow acetylators convert 67% to acetylisoniazid. The remaining portion is excreted in urine as unchanged drug. The influence of acetylation rate on INH hepatotoxicity remains controversial. Although it has been expected that rapid acetylators may exhibit more toxicity (greater conversion to hepatotoxic metabolites), studies have suggested slow acetylators have higher rates of hepatotoxicity than fast acetylators (26 vs. 11%). A paper by Possuelo et al. reported that 5.5% of 254 INH treated TB patients developed hepatotoxicity. Of these 14 patients, nine (64.3%) were slow acetylators and five (35.7%) were fast acetylators indicating that slow acetylator status seems to be a risk factor for hepatotoxicity [83], although the mechanism remains obscure. For NAT2, the rate of slow acetylation (as per diminished NAT2 activity) has been reported to range from 10 to 62% and there is substantial inter- and intraethnic variability in NAT2 polymorphisms with higher rates observed in Indian and Caucasians, moderate rates in South African blacks, Hispanics and lower rates in East Asians [84, 85]. However, these observations depend on which NAT2 polymorphisms are assessed, what method is used, and how ethnicity is classified. The frequency of 2E1 variants, (including the CYP2E1*1 variant associated with altered 2E1 function) have been reported to be as high as 20%, but its impact on a population level has not been well studied [86].

Figure 1: Schematic of INH metabolism



INH and ART Pharmacokinetics in Pregnancy and Breastfeeding

Data on INH pharmacokinetics in pregnancy is largely from the 1950's and 1960's, prior to the HIV epidemic. There is a potential effect of pregnancy on NAT2 activity, using the urinary ratio of metabolites to caffeine suggests a slight decrease in NAT2 activity during pregnancy. There are also ethnic/geographic variations in the prevalence of fast and slow acetylator status. Given the potential increased toxicity risk there is a need to evaluate the pharmacokinetics of INH among HIV-infected women, especially in those areas where TB is endemic. INH penetrates into breast milk but the concentrations achieved in infants are very low and below any level of concern based on available data. The potential dose that an infant would be exposed to from breast milk is reported to be around 2 mg/kg/day [87]; roughly 10-20% of the usual therapeutic dose of 10-20 mg/kg/day advised in infants.

In addition, limited information is available on ART pharmacokinetics in pregnant women at risk for TB in resource-limited settings. ART exposure in the context of INH therapy may also contribute to the overall risk of toxicity. As described above, INH may also impact levels of ART, for example, EFV [36]. In a subset of pregnant women on EFV and INH, higher levels of EFV were measured compared to those on EFV alone. These women were both slow metabolizers of EFV and INH. This study, however, did not capture any data on these interactions that were clinically significant. In P1078, the study will capture whether any clinical evidence of increased EFV or INH toxicity, including the assessment of neurotoxicity through the use of the PHQ-9 instrument, a neurocognitive impairment assessment, several modified questions from the Pittsburgh Sleep Quality Index, and AE reports. In P1078, both an intensive PK and a population PK study are included to assess variation between third trimester and early postpartum periods. Moreover, as summarized above, ARV and INH exposure will be assessed when relevant via the analysis of concentrations in small hair samples.

Diagnosis of LTBI in Women and Children

TST screening is unreliable in patients with HIV/AIDS. In addition to its suboptimal sensitivity, TST has other limitations: 1) it requires a return visit ideally within 2-3 days for interpretation [9, 88]; and 2) it has reduced specificity in settings where atypical mycobacterial infections are common and where Bacille Calmette-Guérin (BCG) vaccine is routinely given. Due to these limitations and the fact that LTBI (as measured by a positive TST) is difficult to diagnose, the

current WHO guidelines do not require TST screening prior to initiation of IPT in HIV-infected individuals. The 2011 WHO Guidelines for TB conditionally recommended the use of at least 36 months of IPT for people living with HIV in high TB-prevalence and transmission settings, based on unpublished studies [1]; in 2015, the WHO provided an update to this recommendation, which provided a conditional recommendation to provide IPT to people living with HIV, with unknown or positive TST status. However, the quality of evidence was rated as low [89].

Novel tests such as interferon gamma release assays (IGRAs) have been developed which may aid in the diagnosis of LTBI in pregnancy. In non-pregnant HIV-infected populations, IGRAs (e.g., QuantiFERON Gold in Tube [QGIT] and TB ELISPOT) are associated with increased specificity (and possibly sensitivity) to identify LTBI, although they fail to make the crucial distinction between LTBI and active disease [90]. There are some data to suggest that IGRA may be more sensitive than TST in pregnancy [91]. IGRAs may have better predictive value than TST in HIV-infected individuals [92]. These tests are not standard of care in developing countries and further evaluation of IGRAs in the context of HIV infection and pregnancy is needed and will be done in this study.

In P1078, there are other areas of uncertainty with respect to QGIT and TB ELISPOT in HIV-infected pregnant and postpartum women that need to be addressed with high priority [8, 9, 90], including the cell type that mediates the response measured by IGRA and the effect of TST and of IPT on IGRA. IFNγ is a relatively ubiquitous cytokine produced by multiple cells of the immune system including memory and effector T-cells. TB-specific effector cells, which have a limited life span, may become undetectable after eradication of latent TB. Conversely, memory T-cells typically persist after eradication of the antigen that originally elicited a response. It is unclear whether IGRAs measure memory or effector cell-mediated immunity (CMI) and how to interpret their results after TST or IPT. In this study, there is a unique opportunity to address these questions by performing TB ELISPOT before and after TST; before and after IPT; and by assessing the CD4- and CD8-mediated production of IFNγ and IL2 in response to *M.tb.* antigenic stimulation.

The study will also compare IGRA with TST in infants born to HIV-infected mothers enrolled in P1078. This will be of particular interest, because precise diagnosis of *M.tb.* infection in infants is very difficult in the absence of an accepted gold standard [22]. Several investigators have noted high discordance rates between IGRAs and TST in infants and young children. Many children with strongly positive TST have been reported with negative IGRAs and vice versa, even in the absence of BCG vaccination [93-95]. Whether this is due to increased specificity of the IGRAs or increased sensitivity of TST remains uncertain.

The study design of P1078 involves following a cohort of HIV-exposed infants from birth with careful assessment for TB disease in the first year of life. Testing of infants with both IGRA and TST combined with the clinical endpoints of TB disease and/or documented TB exposure will allow a comparison of the total infant TB infection and/or disease burden by one year of life and determine if there is any difference between infants whose mothers received antepartum versus postpartum IPT. In addition, because both TST and IGRA testing will be performed, concordance and clinical relevance of these tests results will be assessed.

The study will compare responses to mycobacterial antigens by TB ELISPOT measuring IFN-γ and IL-2 at 12 weeks for approximately 460 infants. The response by TST and IGRA (QGIT) will also be compared for all infants at 44 weeks and retest the subset of 460 infants by TB ELISPOT. The paucity of IGRA data in infants and lack of comparative studies with TST have limited the understanding of the utility of these tests. Additionally, there is no information regarding the cell type that mediates the response detected by IGRA in infants. Understanding the immune basis for these tests in infants is a high priority. Lastly, storage of samples from infants will also allow for future exploration of the relationships between maternal immune responses to LTBI, INH, infant BCG responses, and infant TB responses, some of which have been recently shown to be important [96].

TB Disease Diagnosis and Outcomes in HIV-exposed Young Children

The natural history of disease demonstrates that age and immune status are the most important variables that determine a child's risk to develop TB following primary *M. tuberculosis* infection [22]. Infants are at highest risk with up to 50% progressing to active disease following documented TB exposure/infection, with a significant number developing disseminated disease [97, 98]. HIV infection dramatically increases a child's risk to develop TB in TB endemic areas [99, 100]. HIV-exposed uninfected children, who should form the vast majority of children in the study given the provision of optimal PMTCT, also seem vulnerable to multiple pathogens [101, 102]. A secondary objective of P1078 is to compare infant TB and outcomes between those born to HIV-infected mothers who initiated INH during pregnancy and those who initiated it at 3 months postpartum.

Diagnosis of TB in infants is challenging because sputum specimens for smear and/or culture, the "gold standard" used in adults, is hampered by 1) the inability of young children to expectorate and 2) the poor bacteriological yield in children with pauci-bacillary TB [103], therefore, P1078 will use the IMPAACT Network's pediatric TB case definition that includes a combination of symptomatic presentation and either bacteriologic confirmation or radiographic certainty.

Specific Study Design Issues

All women and their infants will receive standard of care for HIV infection, PMTCT, and co-infection treatment according to WHO guidelines. More information on WHO guidelines and in-country standard of care can be found at:

http://www.who.int/hiv/pub/mtct/advice/en/index.html

As standard of care may vary between sites, provided care will be recorded as standard of care for study purposes.

For this study, at least 6 months (WHO guidelines) has been translated into 28 weeks ± 2 weeks of INH prophylactic therapy. As women are coming every 4 weeks for clinic visits, a 28-week duration will be most feasible to implement.

Rationale for Deferring IPT to Three Months Postpartum

HIV-infected pregnant and early postpartum women have a higher risk of hepatotoxicity and it is thought that beyond 12 weeks (3 months) postpartum this risk returns to the non-pregnant baseline risk (30). Recognizing that women may be at increased risk for active TB in pregnancy and early postpartum, it is important to balance the risks of drug toxicity with the benefits of earlier INH initiation. This study will compare the INH toxicity initiated in HIV-infected women during pregnancy versus at 12 weeks after delivery to determine the risk of earlier initiation of INH in the era of HAART. The study will also measure the effectiveness (e.g., incidence of maternal-infant TB or death) as a secondary objective.

Equipoise for Study and for Use of Placebo

Pregnancy, delivery, and the postpartum period are important entry points into the healthcare system for HIV-infected women and may provide the best opportunity to educate and screen for TB and initiate IPT [9, 104, 105]. The current WHO guidelines for IPT in HIV-infected persons recommend IPT to all HIV-infected persons, including pregnant women. The guidance for pregnant women has been based on expert opinion and not on any clinical trial evidence as none of the IPT trials included HIV-infected pregnant women. The WHO also issued further guidance in 2015 to clarify that IPT should be provided for individuals with HIV-infection, with an unknown or positive TST; this guidance is noted to have a low quality of evidence [89]. Furthermore, the WHO guidelines to provide IPT to HIV-infected persons has been in place since 1998 and < 0.01% of HIV-infected adults have been receiving it, largely because of safety and lack of effectiveness concerns on part of providers. In an IMPAACT site survey, none of the 12 interested sites in Africa or India were routinely providing IPT to pregnant or postpartum women. The lack of IPT data specific to HIV-infected pregnant women in the HAART era will likely continue to be a deterrent to initiation of IPT during pregnancy. The goal of this study is to provide the necessary safety information that supports the premise that IPT can be safely initiated in HIV-infected women during pregnancy. It will also address the question of optimal timing of IPT, an issue the WHO guidelines acknowledge remains unanswered. In light of this, the study is designed primarily as a non-inferiority study to show that providing IPT during pregnancy does not result in significantly more drug-related toxicities than delaying initiation to 12 weeks postpartum. The study will assess the risk of hepatotoxicity, the possible additive/synergistic toxicities of HAART with IPT, and model the estimated incremental risks/benefits in TB prevention afforded by HAART plus IPT. In this study, all women will receive IPT, be counseled about adherence to IPT and other important health measures, and be provided prenatal MVI. Furthermore, both the women and their infants will be closely monitored and will be actively screened for signs and symptoms of TB at each visit. It is therefore anticipated that women and their infants in the study will be receiving significantly enhanced standard of care than what they would be receiving outside the study.

To best assess whether IPT initiation in pregnancy is safe the study will compare adverse effects with those of IPT initiated 12 weeks postpartum. Since many women will be on various types of ART as well as treatment and/or prophylaxis for *Pneumocystis jiroveci* [previously *Pneumocystis carinii* Pneumonia (PCP)], malaria and possibly other illnesses, these therapies could impact safety and toxicity. The use of a placebo is therefore critical to understand the true incidence of

AEs associated with IPT. Furthermore, it is not anticipated that women with CD4 < 200 or < 350 cells/mm^3 will be at substantial increased risk if they are randomized to early receipt of placebo as they will be on HAART or will be initiated on HAART. As discussed earlier, HAART has a significant impact on reducing TB incidence and mortality. There has been a call for research to see the relative risks and benefits of initiating HAART + IPT in patients with advanced HIV [106]. The protocol investigators therefore feel justified for randomizing this group to early receipt of placebo.

Study data will address the research gap for HIV/TB care for pregnant women and their infants in TB endemic areas and provide much needed evidence to optimize policies and programs for these vulnerable populations.

In light of the current WHO INH preventive therapy guidelines for HIV-infected persons, in which INH has been recommended for all HIV-infected persons, including pregnant women, the P1078 team resurveyed the IMPAACT sites that expressed strong interest in P1078. All sites remain very interested in the study.

2.0 Study Objectives

2.1 Primary Objective

To compare overall safety and toxicity of immediate versus deferred INH preventive therapy in HIV-infected pregnant women enrolled at ≥ 14 through ≤ 34 weeks gestation (34 weeks, 6 days)

2.2 Secondary Objectives

- To compare safety and toxicity of INH *in utero* exposure and on infants on study
- To compare TB incidence and all-cause mortality in HIV-infected women and their infants enrolled on study
- To compare overall safety and hepatotoxicity, as well as evaluate risk factors for these outcomes, during pregnancy and immediate postpartum in women on immediate versus deferred INH therapy
- To evaluate for INH resistance among *M.tb.* isolates from HIV-infected women and infants who develop TB while on study
- To evaluate the intensive pharmacokinetics of INH and selected ARV drugs in a subset of HIV-infected pregnant and postpartum women receiving HAART
- To evaluate and compare the performance characteristics of IGRA (TB ELISPOT and QGIT) with TST in HIV-infected women and their infants
- To compare adherence in women initiating immediate versus deferred INH preventive therapy via self-report and pill counts

2.3 Exploratory Objectives

- To evaluate population pharmacokinetics and pharmacogenomics of INH and EFV in HIV-infected pregnant and postpartum women
- To assess the effects of INH preventive therapy on the functional characteristics of TB specific T-cell responses measured by TB ELISPOT in HIV-infected women and their infants on study
- To evaluate adherence and exposure to INH and EFV using drug levels in hair and analyze the association between these drug levels and adverse effects
- To compare the two arms with respect to the overall (risk:benefit) clinical outcomes of the mother-infant pairs
- To explore associations of maternal and infant specific TB responses and novel biomarkers with risk of maternal and infant TB infection and disease
- To explore the neurotoxicity of INH in combination with EFV in a subset of women

3.0 Study Design

P1078 is a Phase IV, randomized, double-blind, placebo-controlled non-inferiority study to determine overall safety as well as the other risks and benefits of immediate versus deferred INH in HIV-infected pregnant women and their infants, enrolled at ≥ 14 through ≤ 34 weeks (34 weeks, 6 days) gestation, at high risk for TB (i.e., reside in high TB prevalence area defined as having 60 TB cases per 100,000 population in the WHO TB annual report or documented local burden) infection and disease.

Enrollment	Week 28 Post-Entry Visit	Week 12 Postpartum Visit
ARM A INH 300 mg until Week 28 Post-Entry visit	ARM A Placebo for INH until Week 40 Postpartum visit	ARM A Continue current therapy
OR		
ARM B Placebo for INH until Week 12 Postpartum visit	ARM B Continue current therapy	ARM B INH 300 mg until Week 40 Postpartum visit
NOTE: - Week 12 Postpartum visit can occur at the same time, before, or after the Week 28 Post-Entry visit, depending on the gestational age at enrollment and delivery week. - Both arms will receive 28 weeks of INH 300 mg.		

- The basis for the non-inferiority design is the hypothesis that IPT can be safely initiated in HIV-infected women during pregnancy.
- The information on the treatment regimen assigned at each of the visits shown above for each participant will be in a Pharmacist Prescription List generated by the DMC. See Section 5.1.1 for details regarding the Pharmacist Prescription List.

- For some participants in both arms, the study Week 28 Post-Entry visit and the Week 12 postpartum visit will coincide. When this occurs, mothers in both arms will have their therapy switched in a blinded fashion (i.e., mothers in Arm A will switch to Placebo for INH and mothers in Arm B will switch to INH 300 mg).
- In addition, all women (Arm A and Arm B) will receive:
  - Intensified TB case finding defined as eliciting a TB exposure history, WHO TB symptom screen (see P1078 MOP), and targeted physical exam at each study visit.
  - Open-label Pyridoxine (vitamin B_6) and prenatal multivitamin from study entry until postpartum Week 40
  - Standard of care (defined as PMTCT and standard of care for HIV-infected pregnant women according to WHO guidelines)
- All study-provided medications (INH or Placebo for INH) will be initiated at study entry within 72 hours of randomization. Locally-obtained Pyridoxine (vitamin B_6) and prenatal multivitamin will also be started in close proximity to INH/Placebo for INH.
- Mother-infant pairs will be followed for 48 weeks post-delivery.
- Infants of enrolled women will also receive standard of care according to WHO guidelines for HIV infection, PMTCT, and other maternal-child health measures.

Sites should refer to Appendix I for a complete description of clinical and laboratory evaluations to be performed.

3.1 Pharmacokinetic Testing

- Samples for intensive PK will be obtained at two time points in 36 women who are on HAART. Only women who are at ≥ 28 weeks age of gestation at entry into the study will be eligible to participate in the intensive PK. The samples will be collected from the same group of 36 women during the third trimester of pregnancy ≥ 2 weeks after start of INH/Placebo for INH and at the Week 16 postpartum visit.
- Samples for population PK will be obtained at two time points on all women except those who participate in the intensive PK study. These population PK samples will be collected during the third trimester of pregnancy and at the Week 16 postpartum visit.

See Section 9.0 for the intensive PK substudy and population PK assessments.

3.2 Immunologic Testing

Throughout the study, women and their infants will have several types of immunologic testing, including TST and IGRA (QGIT and TB ELISPOT). Specimens will be collected, tested, and/or stored, as follows below. Also note that PBMCs will be cryopreserved at selected sites and all QGIT will be performed in a blinded fashion (i.e., results will not be disclosed to the study clinical staff). QGIT testing may be performed in real time or batch tested within 90 days of collection, per the QGIT manufacturer's instructions, the P1078 MOP, and the P1078 LPC.

- At entry, all women will have IGRA (QGIT) done and plasma stored for future tests. QGIT supernatants will also be stored. Approximately 700 women will have PBMCs stored. IGRA (TB ELISPOT) will be done in 460 women and the remaining samples will be stored for future testing.

- At delivery, all women will have TST performed and IGRA (QGIT) done; QGIT supernatants will also be stored in the first 260 women. If TST is not obtained at the Labor and Delivery visit, sites may administer at the Week 4 postpartum visit.
- At postpartum Week 12, approximately 460 women and their infants will have PBMCs stored for IGRA (TB ELISPOT) and will also have plasma stored for future tests. Ideally, these will be the same women and infants who contributed PBMC for IGRA at entry and their infants, if feasible.
- At postpartum Week 44, all women and their infants will have TST and IGRA (QGIT) performed and plasma stored for future tests. QGIT supernatants will also be stored in the first 260 women. Approximately 460 women and their infants will have PBMCs stored for IGRA (TB ELISPOT). Ideally, these will be the same 460 women and infants who contributed PBMC for IGRA at entry and postpartum Week 12.
- At postpartum Week 48, approximately 260 women will have PBMCs stored for IGRA (TB ELISPOT) and will also have plasma stored for future tests. Ideally, these will be the same women who contributed PBMC for IGRA at entry, postpartum Week 12, and postpartum Week 44.
- At the suspected active TB visit for women, IGRA (QGIT) will be performed and additional plasma, QGIT supernatants, and PBMCs will be obtained and stored for IGRA (TB ELISPOT). At the suspected active TB visit for infants, TST will be done, as well as plasma and PBMC stored for future TB/HIV-related studies, for example, IGRA (TB ELISPOT).

Ideally, TST should be read 2-3 days after placement. However, it can be read by a trained observer up to 7 days from administration.

Assays will be performed on cryopreserved PBMCs obtained from the mothers including IFNγ/IL2 ELISPOT using whole and CD8-depleted PBMC. These assays will determine the relative participation of CD4 and CD8 cells and of memory cells in the IGRA result. T cell activation and inflammatory biomarkers will also be studied. Infants will have IFNγ/IL2 ELISPOT performed in PBMC only.

3.3 Screening for Active TB at the Screening Visit

All women will be screened for active TB using the current WHO recommended standardized TB symptom screen (see P1078 MOP) for any cough, fever, self-reported weight loss, or night sweats. Additional questions will include failure to have adequate weight gain in pregnancy and duration of symptoms. They will also have a standardized TB risk and exposure questionnaire administered and undergo a complete physical exam. Any additional TB diagnostics, such as shielded chest radiograph, AFB culture, and/or Xpert, will be performed as per local standard of care or as indicated by the site investigator. A woman who has a positive finding on the TB symptom screening evaluation, or is suspected or diagnosed with active TB, will be excluded from the study.

3.4 Enrollment and Randomization Phase

All women with a negative TB screening assessment who meet the inclusion criteria (Section 4.1) and do not meet any exclusion criteria (Section 4.2) will be randomized either to receive INH within 72 hours of randomization (Arm A) or to have INH deferred to start at Week 12 postpartum (Arm B).

3.5 Intensified TB Case Finding

At every scheduled visit, a standardized TB exposure history to determine if any new known TB exposure has occurred since the last visit will be done. In addition, the WHO-recommended TB symptom screen, other symptom assessment, and targeted physical examination will also be performed. Women will be educated about the signs and symptoms of active TB and be asked to come to the clinic should any of the symptoms develop during the course of the study. Infants born to these women will also be assessed at each visit for TB exposure and signs and symptoms suggestive of TB disease. Infants may also have TST done at a suspected active TB visit. Ideally, TST should be read 2-3 days after placement. However, it can be read by a trained observer up to 7 days from administration.

3.6 Standard of Care for Women and Infants Enrolled in the Study

The best available local standard of care will be provided to women and their infants. For women who develop TB, they will be referred for TB treatment according to local standard of care. Infants of these mothers who develop TB will also be referred for initiation of TB preventive therapy as per local pediatric TB guidelines. Infants who are suspected to have or who are diagnosed with TB will also be referred for TB treatment per local guidelines. Infant feeding, prevention and treatment of HIV, and other co-morbidities will also be according to local standard of care.

3.7 Unblinding Participants

Participants will be unblinded after follow-up is complete on all enrolled participants and the clinical and laboratory databases have been reviewed and finalized for analysis. Once this date has been determined by the Protocol Team, unblinding lists for each site will be distributed as outlined in IMPAACT network policies. See Section 6.1 for details on unblinding participants during the study.

4.0 Selection and Enrollment of Participants

4.1 Inclusion Criteria

4.1.1 Documented HIV-1 Infection

Documentation of HIV-1 infection is defined as positive results from two samples collected at different 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.

- 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 charts. Source documentation (participant's medical record/chart, Ministry of Health (MOH) registers, laboratory results, etc.) must be available if requested.
- Sample #2 must be performed in a CAP/CLIA-approved laboratory or in a laboratory that operates according to GCLP guidelines, participates in appropriate external quality assurance program, and is approved by the IMPAACT Laboratory Center.

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

If Sample #1 is positive, then collect and test Sample #2.

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)
- One qualitative HIV RNA PCR
- One total HIV nucleic acid test

4.1.2 Documented HIV treatment, according to WHO guidelines, for PMTCT and standard of care for HIV infection

4.1.3 Pregnant females age $\geq$ 18 years

4.1.4 Pregnant females between ≥ 13 and < 18 years who are able and willing to provide signed informed consent under local law, or pregnant females unable to consent under local law whose parents/legal guardians provide consent or "minimum age of consent according to locally applicable laws or regulations."

4.1.5 Pregnancy gestational age confirmed by best available method at site to be ≥ 14 weeks through ≤ 34 weeks (34 weeks, 6 days)

4.1.6 Weight ≥ 35 kg at screening

4.1.7 The following laboratory values obtained within 30 days prior to study entry:

- Absolute neutrophil count (ANC) ≥ 750 cells/mm^3
- Hemoglobin ≥ 7.5 g/dL
- Platelet count ≥ 50,000/mm^3
- AST (SGOT), ALT (SGPT), and total bilirubin ≤ 1.25 times the upper limit of normal (ULN) (Note: If participant is taking atazanavir, direct bilirubin may be used to determine eligibility.)

4.1.8 Intent to remain in current geographical area of residence for the duration of the study

4.2 Exclusion Criteria

4.2.1 Any woman with a positive TB symptom screen per WHO guidelines, including any one or more of the following: any cough, fever, self-reported weight loss, or night sweats (Note: If a potential participant is found to be negative for TB upon further testing, the participant may be re-screened for the study.)

4.2.2 Any positive AFB smear, Xpert, or any other rapid TB screening test or culture from any site within the past 12 weeks, or chest radiograph (x-ray) with findings suggestive of active TB, or clinician suspects active TB

4.2.3 Known exposure to AFB smear-positive active TB case within past 12 weeks prior to study entry

4.2.4 Reported INH exposure (> 30 days) in the past year prior to study entry

4.2.5 Receipt of any TB or atypical mycobacteria therapy for > 30 days in the past year

4.2.6 Evidence of acute hepatitis, such as jaundice, dark urine (not concentrated urine), and/or acholic stools sustained for > 3 days within 90 days prior to entry (Note: A positive HBsAg does not exclude a participant from joining the study.)

4.2.7 ≥ Grade 1 peripheral neuropathy (Note: Grading of peripheral neuropathy will be determined using the Brief Peripheral Neuropathy Screen (BPNS), discussed in Section 6.1.3, Appendix II and the P1078 MOP.)

4.2.8 History of acute systemic adverse reaction or allergy to INH

4.2.9 Known current heavy alcohol use (> 2 drinks per week) or alcohol exposure that, in the investigator's opinion, would compromise participation and the outcome of this study

4.2.10 Presence of new AIDS-defining opportunistic infection that has been treated less than 30 days prior to study entry

4.2.11 Receipt of an investigational agent or chemotherapy for active malignancy within 30 days prior to study entry

4.2.12 Any clinically significant diseases (other than HIV infection) or clinically significant findings during the screening medical history or physical examination that, in the investigator's opinion, would compromise participation and the outcome of this study

4.3 Concomitant Medication Guidelines

To avoid adverse drug interactions, package inserts of anti-TB agents, ARTs, and other concomitant medications should be referred to whenever a concomitant medication is initiated or dose changed. The following medications should be avoided, if possible, and alternative treatments sought:

- Chronic acetaminophen (such as paracetamol) use defined as > 1 gram per day for ≥ 4 weeks
- Chronic aminosalicyclic acid (aspirin) use defined as a dosage of ≥ 1 tablet per day for ≥ 4 weeks
- Stavudine (d4T) or Didanosine (ddI)
- Carbamazepine
- Chlorzoxazone
- Disulfiram
- Ketoconazole
- Phenytoin

The list above is not exhaustive. Participants may be on other medications not included in the list that may be known to result in AEs and toxicity in pregnant women.

4.4 Screening Procedures

All participants who sign the informed consent form must have a Screening Checklist entered and must obtain a screening number through the Data Management Center (DMC) Subject Enrollment System (SES).

Participants who meet eligibility criteria will be randomized to the study according to standard data management procedures. For all participants from whom informed consent is obtained, but who are deemed ineligible or who do not enroll into the protocol for any reason, a Screening Failure Results case report form must be completed and keyed into the database. The screening failure data will be collected in accordance with the Consolidated Standards for Reporting Trials (CONSORT) 2010 Statement, which provides guidelines for reporting randomized controlled trials [107].

4.5 Enrollment Procedures

4.5.1 A Study/Site Implementation Plan (SIP) will be required from each site participating in the study. The SIP will be reviewed and approved by members of the protocol team and sites will be notified that authorization to participate has been granted. The SIP will collect data on the following issues:

- Laboratory capacity including TB diagnostics
- Enrollment and retention plans
- Willingness to participate in PK study
- Local standard of care for HIV-infected women and infants
- Local standard of care for active TB treatment and infant TB prophylaxis
- Pharmacy procedures for study drug

4.5.2 Prior to implementation of this protocol, and any subsequent full version amendments, each site must have the protocol and the protocol consent form(s) approved, as appropriate, by their local institutional review board (IRB)/ethics committee (EC) and any other applicable regulatory entity (RE). Upon receiving final approval, sites will submit all required protocol registration documents to the DAIDS Protocol Registration Office (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 informed consent forms (ICFs) *WILL* be reviewed and approved by the DAIDS PRO and sites will receive an Initial Registration notification from the DAIDS PRO that indicates successful completion of the protocol registration process. A copy of the Initial Registration Notification should be retained in the site's regulatory files.

Upon receiving final IRB/EC and any other applicable RE approval(s) for an amendment, sites should implement the amendment immediately. Sites are required to submit an amendment registration packet to the DAIDS PRO at the RSC. The DAIDS PRO will review the submitted protocol registration packet to ensure that all the required documents have been received. Site-specific ICF(s) *WILL NOT* be reviewed and

approved by the DAIDS PRO and sites will receive an Amendment Registration Notification when the DAIDS PRO receives a complete registration packet. A copy of the Amendment Registration Notification should be retained in the site's regulatory files.

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

Written informed consent must be obtained before any study-specific screening or enrollment procedures are performed. The woman will be asked to read and sign the consent forms. If the woman is unable to read, the process for consenting illiterate participants, as defined or approved by the local IRB/EC, should be followed. After screening is completed and if eligibility criteria are met, the woman (and her unborn infant) will be enrolled and randomized into P1078.

Subject enrollment is done through the DMC's SES. The appropriate enrollment screen for this component is identified as P1078. Screening laboratory tests can be performed as early as 10 weeks gestation; however, where noted above in the inclusion and exclusion criteria, the specimens/assessments on which eligibility determination is based must be obtained within 30 days prior to study entry (earliest study entry is 14 weeks gestation). Re-assessment may be required, for example, if too much time (> 30 days) passes after the initial specimens/assessments were obtained.

Note: Mothers and their infants are randomized at the same time, to the same study arm. In the case of a multiple birth, the additional infants will be manually assigned to the same study arm. All infants will be followed in the same manner.

4.6 Co-enrollment Procedures

Co-enrollment will be considered on a case-by-case basis. Please contact the Core protocol team, impaact.corep1078@fstrf.org, for co-enrollment questions.

5.0 Study Treatment

Study treatment is defined as isoniazid (INH) and Placebo for isoniazid (INH). Both will be provided through the study.

Pyridoxine (vitamin B_6) and prenatal MVI will not be provided through the study and will be obtained locally by the site.

5.1 Regimens, Administration, and Duration of Regimen

Women will be randomized in a 1:1 ratio to Arm A (immediate INH then Placebo for INH) OR Arm B (Placebo for INH then deferred INH).

- Arm A
  Women in Arm A will initiate INH once daily by mouth at study entry. After receiving 28 (± 2) weeks of INH (i.e., Week 28 Post-Entry), women in Arm A will be switched to Placebo for INH. The women in this arm will take Placebo for INH until the Week 40 postpartum visit (± 2 weeks).

- Arm B
  Women in Arm B will initiate Placebo for INH once daily by mouth at study entry and continue until the Week 12 postpartum visit (± 2 weeks). At the Week 12 postpartum visit, women in Arm B will be switched to INH. The women in this arm will take INH for 28 weeks until the Week 40 postpartum visit (± 2 weeks).

Along with either INH or Placebo for INH, all women will be on the open-label prenatal multivitamin once daily by mouth and pyridoxine (vitamin B_6) 25 to 50 mg orally once daily, self-administered from entry until the Week 40 postpartum visit. The pyridoxine dose (vitamin B_6) may be increased up to 100 mg once daily for management of peripheral neuropathy by the site investigator, as described in Section 6.1.3.

5.1.1 Regimen

Upon randomization, a participant SID will be provided to the site (clinic) as well as the information necessary for the clinic to send an Entry Prescription to the Pharmacy in the P1078 Pharmacist Prescription List.

ENTRY

Women in both arms will receive:

- Prenatal multivitamins once daily by mouth until the Week 40 postpartum visit.
- Pyridoxine (vitamin B_6) 25 to 50 mg tablet orally once daily until the Week 40 postpartum visit.

Women will be randomized (1:1) to one of the following two arms:

- Arm A – Immediate INH
  Women will start INH ≤ 72 hours after randomization to maintain blinding.

  Isoniazid (INH) 300 mg tablet once daily by mouth, self-administered for 28 (± 2) weeks (until the Week 28 Post-Entry visit).

- Arm B – Deferred INH
  Women will start Placebo for INH ≤ 72 hours after randomization to maintain blinding.

  Placebo for INH tablet once daily by mouth, self-administered until the Week 12 postpartum visit (± 2 weeks).

WEEK 28 POST-ENTRY VISIT

All women (Arms A and B) must receive a new written prescription indicating "Week 28 Post-Entry Visit" for the pharmacist to dispense the Week 28 Post-Entry visit study drugs. Upon receipt of the new prescription, the site pharmacist should refer to the P1078 Pharmacist Prescription List to determine whether the participant should remain on the current treatment regimen or switch. This P1078 Pharmacist Prescription List will be generated by the DMC in such a fashion as to instruct the pharmacist on the treatment regimen to dispense while at the same time maintaining the blinding of the clinic staff and participant.

- Arm A
  Women will receive Placebo for INH 300 mg tablet once daily by mouth, self-administered until the Week 40 postpartum visit.

- Arm B
  Women will not change study therapy at their Week 28 Post-Entry visit; however, to maintain blinding, a new prescription will be required.

WEEK 12 POSTPARTUM VISIT

All women (Arms A and B) must receive a new written prescription indicating "Week 12 Postpartum Visit" for the pharmacist to dispense the Week 12 postpartum visit study drugs. Upon receipt of the new prescription, the site pharmacist should refer to the P1078 Pharmacist Prescription List to determine whether the participant should remain on the current treatment regimen or switch.

- Arm A
  Women will not change study therapy at their Week 12 postpartum visit, unless Week 12 postpartum visit is the same as the Week 28 Post-Entry visit (see note below). To maintain blinding, a new prescription will be required.

- Arm B
  Women will receive INH 300 mg tablet once daily by mouth, self-administered for 28 (± 2) weeks (until the Week 40 postpartum visit).

Note: The Week 28 Post-Entry visit and the Week 12 postpartum visit may not necessarily occur in that order for each woman. In the event that the Week 12 postpartum visit and the Week 28 Post-Entry visit occur at the same time, the P1078 Pharmacist Prescription List will provide the correct instructions for the pharmacist. The prescription list will contain the treatment regimen associated with the assigned SID for each woman at the following time points: Entry, Week 28 Post-Entry visit, and Week 12 postpartum visit.

It is left up to the pharmacy SOP whether a new prescription will be sent to the pharmacist at all other study visits except those at Entry, Week 28 Post-Entry and Week 12 postpartum. If Week 28 Post-Entry and Week 12 postpartum occur at the same time, both prescriptions should be sent to the pharmacist.

Sites (clinic) will complete a multi-part case report form (CRF) that will include the following information:

- Entry date (new prescription required)
- Delivery date
- Week 28 Post-Entry date (new prescription required)
- Week 12 postpartum date (new prescription required)

This CRF will be completed at the Entry visit, the Week 28 Post-Entry visit, and the Week 12 postpartum visit. A copy of this CRF will be provided to the pharmacy along with the new prescription at Entry, Week 28 Post-Entry, and Week 12 postpartum.

5.1.2 Administration

INH 300 mg one tablet or matching Placebo for INH one tablet will be administered orally once daily without food (1 hour before or 2 hours after meals).

Pyridoxine (vitamin B_6) 25 to 50 mg will be administered orally once daily with or without food. The pyridoxine dose (vitamin B_6) may be increased up to 100 mg once daily for management of peripheral neuropathy by the site investigator, as described in Section 6.1.3.

Prenatal multivitamins will be administered orally once daily with or without food.

5.1.3 Duration

Women randomized to Arm A (immediate INH) will receive INH for 28 (± 2) weeks and then will receive Placebo for INH until Week 40 postpartum visit (± 2 weeks).

Women randomized to Arm B (deferred INH) will receive Placebo for INH until the Week 12 postpartum visit (± 2 weeks) and then receive INH until Week 40 postpartum visit (± 2 weeks).

All women in both Arm A and Arm B will receive pyridoxine (vitamin B_6) and prenatal multivitamin until Week 40 (± 2 weeks) postpartum visit.

5.2 Product Formulation

- INH 300 mg tablets: store at room temperature below 30°C (86°F). Store in the original container.
- Placebo for INH tablets: store at room temperature below 30°C (86°F). Store in the original container.
- Pyridoxine (vitamin B_6) tablets must be purchased by the site locally and stored as directed by the manufacturer.
- Prenatal multivitamins must not have more than 5 mg of vitamin B_6 and 400 IU of vitamin D. Prenatal MVI will be prescribed to women as part of standard of care and must be purchased by the site locally and stored as directed by the manufacturer. All oral formulations of prenatal multivitamins (e.g., tablet, capsule, chewable tablet, or liquid) are acceptable for use in this study as long as they meet the above requirements.

5.3 Product Supply, Distribution, and Pharmacy

5.3.1 Study Product Supply

INH and Placebo for INH are manufactured by Macleods Pharmaceuticals Limited.

Pyridoxine (vitamin B_6) and prenatal multivitamins will be obtained locally by the site as part of standard of care.

5.3.2 Study Product Acquisition and Distribution

INH 300 mg and Placebo for INH tablets will be available through the NIAID Clinical Research Products Management Center (CRPMC). The IMPAACT site pharmacist can obtain the study products for this protocol by following the instructions in the manual, *Pharmacy Guidelines and Instructions for DAIDS Clinical Trials Networks,* in the section Study Product Control.

Women will come to the clinic every four weeks and be provided sufficient number of doses of INH or Placebo for INH to last until the next scheduled visit. No study products will be supplied after the Week 40 postpartum visit.

BCG vaccination for the infant follow-up will not be provided through the study.

Cotrimoxazole or ART drugs will not be provided by the study.

5.3.3 Study Product Accountability

The IMPAACT site pharmacists are required to maintain complete records of all study products received from the CRPMC and dispensed. Non-US sites will receive instructions regarding the final disposition of any remaining study products. The procedures to follow for accountability can be found in the manual, *Pharmacy Guidelines and Instructions for DAIDS Clinical Trials Networks*, in the section, Study Product Management Responsibilities.

6.0 Participant Management

6.1 Toxicity Management, Mothers

Except for peripheral neuropathy and hepatotoxicity grading, which are provided in Appendix II and III and discussed in Sections 6.1.3 and 6.1.4, respectively, the Division of AIDS Table for Grading the Severity of Adult and Pediatric Adverse Events (DAIDS AE Grading Table), Version 1.0, dated December 2004, Clarification August 2009, must be used for all AE grading and is available on the RSC website (http://rsc.tech-res.com). Management of adverse experiences will be according to the local standard of care and the judgment of the site investigator, except when noted below.

INH or Placebo for INH dose will not be reduced for toxicity; it will be continued at protocol specified dose, held, or discontinued. The site investigator should attempt to confirm any Grade 3 or greater clinical or laboratory findings as soon as possible. Abnormal clinical and laboratory findings should be followed until resolution to < Grade 2.

Women discontinuing study treatment will not be unblinded to their treatment unless the information is critical for making immediate therapeutic decisions for the participant (e.g., if withholding the treatment information would put the participant at risk of serious adverse events (SAEs) or death). If a participant does need to be unblinded, then the site should notify the study Chairs and Medical Officers and, with their approval, submit a request to the DMC using the Unblinding Request Program on the DMC website, as outlined in IMPAACT network policies. See Section 3.7 for details on unblinding participants after completion of follow-up.

All toxicity management questions and notifications should be emailed to the study Clinical Management Committee (CMC): impaact.p1078cmc@fstrf.org.

All AEs identified in this study will be source documented. Among other details, source documentation will include the severity of each event and its relationship to study drug (INH/Placebo for INH), 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 7.0 for more information on EAE reporting.

6.1.1 General Toxicity Management, Mothers

Clinical or laboratory AEs that are definitely unrelated to INH/Placebo for INH will generally not result in INH/Placebo for INH interruption, except as when defined below. For women who are not receiving study-provided INH/Placebo for INH at the time of the event, toxicity management including decision about non-study drug discontinuation should be at the discretion of the site investigator and should be according to local standard of care. Site investigators must report all SAEs to their local IRB/EC as per their guidelines.

Toxicity management of Pyridoxine (vitamin B_6), prenatal MVI, and/or concomitant medications should be managed at the discretion of the site investigator and should be according to the local standard of care. As vitamin B_6 is being provided to decrease the risk of peripheral neuropathy, potentially due to INH, it is typically expected that vitamin B_6 will be held/discontinued if INH/Placebo for INH is held/discontinued. Consultation with the P1078 Clinical Management Committee (CMC) is available but not required for questions related to vitamin B_6, prenatal multivitamins, or concomitant medications, including ARVs.

Toxicity management will be as outlined below (Section 6.1.2) for all qualifying events EXCEPT for the following toxicities:

- Peripheral neuropathy (see Section 6.1.3)
- Hepatic toxicity, with directions for asymptomatic elevations in liver enzymes and for symptomatic hepatitis (see Section 6.1.4)

Whenever a repeat assessment reveals a toxicity of a different grade than the initial toxicity, the management outlined for that toxicity grade will apply unless otherwise specified. If INH/Placebo for INH are restarted following a temporary hold, a repeat assessment should generally be done within one week, except as when defined below.

Participants should be counseled and educated on side effects and risks of INH at each study visit, particularly related to non-specific signs or symptoms of hepatotoxicity, per site procedures. (See Appendix I-A) These symptoms include new or worsening loss of appetite, nausea, vomiting, fatigue, yellowing of skin or eyes, and/or right upper quadrant tenderness.

Inform the CMC of any maternal death while on study, regardless of attribution to INH/Placebo for INH, as soon as possible and within 3 days of site awareness.

6.1.2 Adverse events other than elevated liver enzymes (AST, ALT, total bilirubin), symptomatic hepatitis or peripheral neuropathy for women receiving INH/Placebo for INH

GENERAL ADVERSE EVENTS		
CONDITION AND SEVERITY	**USE of INH/PLACEBO FOR INH**	**FOLLOW-UP AND MANAGEMENT**
Grade 1 and 2	Continue INH/Placebo for INH	Follow SoE.
Grade 3 (probably not or definitely not related to INH/Placebo for INH)	Continue INH/Placebo for INH	Confirm assessment generally within 3 working days of site awareness or as soon as possible. Consultation with the CMC is available but not required.
Grade 3 (possibly, probably, or definitely related to INH/Placebo for INH)	Continue or hold INH/Placebo for INH at discretion of site investigator	Confirm assessment generally within 3 working days of site awareness or as soon as possible. Inform the CMC if repeat assessment confirms initial ≥ Grade 3. If confirmed, follow condition weekly for 21 days and then at regular intervals at the discretion of the site investigator until resolved. If INH/Placebo for INH was held and condition recurs after restarting INH/Placebo for INH, permanently discontinue INH/Placebo for INH.
Grade 4 (probably not or definitely not related to INH/Placebo for INH)	Continue or hold INH/Placebo for INH at discretion of site investigator	Confirm assessment generally within 3 working days of site awareness or as soon as possible. Inform the CMC if repeat assessment confirms initial ≥ Grade 4.
Grade 4 (possibly, probably, or definitely related to INH/Placebo for INH)	Hold INH/Placebo for INH	Confirm assessment generally within 3 working days of site awareness or as soon as possible. Inform the CMC if repeat assessment confirms initial ≥ Grade 4. If confirmed, permanently discontinue INH/Placebo for INH.

6.1.3 Peripheral Neuropathy (PN), Mothers

Peripheral neuropathy is associated with the use of INH although it is uncommon at doses of 300 mg per day. To decrease the risk of peripheral neuropathy, pyridoxine (vitamin B_6) 25 – 50 mg will be given with each dose of INH. Site investigators may increase dosing of pyridoxine (vitamin B_6) up to 100 mg for management of peripheral neuropathy, as described below. As study clinicians will be blinded to whether women are on INH or Placebo for INH, pyridoxine (vitamin B_6) will be provided from study entry through the Week 40 postpartum visit to all women. It is also recommended that concomitant stavudine (d4T) or didanosine (ddI) be avoided as they increase the risk of PN and are associated with other complications. Women who are prescribed d4T or ddI should be closely monitored.

In P1078, the Brief Peripheral Neuropathy Screen (BPNS) grading system will be used instead of the DAIDS neuropathy grading system; signs/symptoms should be present for at least two weeks to be considered peripheral neuropathy (see Appendix II and P1078 MOP for additional details on how to perform the BPNS).

PERIPHERAL NEUROPATHY		
CONDITION AND SEVERITY	**USE of INH/PLACEBO FOR INH**	**FOLLOW-UP AND MANAGEMENT**
Grade 1	Continue INH/Placebo for INH	Assess for other causes and follow SOE.
Grade 2	Hold INH/Placebo for INH	Confirm assessment within 14 days. If confirmed, continue hold and follow condition as clinically indicated until resolved. If condition resolves to ≤ Grade 1 within 4 weeks, INH/Placebo for INH may be restarted. Continuation of vitamin B_6 or increase to up to 100 mg once daily, and the duration, is at the discretion of the site investigator. If condition does not resolve to ≤ Grade 1 within 4 weeks, permanently discontinue INH/Placebo for INH and follow condition as clinically indicated until resolved.
Grade 3	Hold INH/Placebo for INH	Confirm assessment within 14 days. Inform the CMC if repeat assessment confirms initial ≥ Grade 3. If confirmed, permanently discontinue INH/Placebo for INH and follow condition as clinically indicated until resolved. Continuation of vitamin B_6 or increase to up to 100 mg once daily, and the duration, is at the discretion of the site investigator.

6.1.4 Hepatotoxicity, Mothers

Women should be monitored for the development of non-specific prodromal signs and symptoms of hepatitis, which include *unexplained* anorexia, nausea or vomiting, right upper quadrant tenderness (i.e., liver tenderness or hepatomegaly), acholic stools, bilirubinuria, or jaundice, with or without initially abnormal ALT, AST, or total bilirubin. Malaise and new or worsening fatigue are often common in pregnancy but should also be assessed in relation to potential acute hepatotoxicity.

Clinical history and assessment for causality and confounding causes, such as concomitant prescribed medications, herbal and other complementary medications, alcohol, illicit drugs, over-the-counter medications, lactic acidosis syndrome, pre-eclampsia, acute fatty liver of pregnancy, and viral hepatitis should be undertaken in instances of suspected hepatotoxicity. If the suspected hepatotoxicity is considered more likely to be due to one of these factors, standard management should be undertaken and INH/Placebo for INH may be restarted once the adverse events have resolved to ≤ Grade 1, in consultation with the CMC. Reintroduction of potential hepatotoxic non-study concomitant medications, including ARVs, is at the discretion of the site investigator and the study participant.

Management instructions for INH/Placebo for INH and for continued follow-up of adverse events related to hepatotoxicity are described below in the tables as follows:

- Asymptomatic elevations in ALT, AST, and total bilirubin
- Symptomatic hepatitis

If a participant develops any signs or symptoms of hepatitis, management should follow the table for symptomatic hepatitis, regardless of ALT, AST, or total bilirubin levels.

The grading criteria for hepatotoxicity assessment (i.e., AST, ALT, total bilirubin, symptoms) are shown in Appendix III and all abnormal liver enzymes (AST, ALT, or total bilirubin) should be followed until resolution to < Grade 1.

NOTE: If a woman is on Atazanavir, then the total bilirubin thresholds described below are not diagnostic. In lieu of total bilirubin, a direct bilirubin measurement will be used to assess and grade toxicity in women using Atazanavir. Toxicity grading using direct bilirubin will follow the grading levels for total bilirubin in the Modified Grading Table for Hepatotoxicity (Appendix III).

NOTE: For any other scenarios not described below, consult the CMC on management of INH/Placebo for INH and frequency of repeat assessments.

ASYMPTOMATIC ELEVATIONS in ALT, AST, and Total Bilirubin		
CONDITION AND SEVERITY	**USE of INH/ PLACEBO FOR INH**	**FOLLOW-UP AND MANAGEMENT**
Grade 1 Asymptomatic	Continue INH/ Placebo for INH	Assess ALT, AST, and total bilirubin and clinical assessment within 14 working days of site awareness. Reinforce participant awareness and knowledge about signs and symptoms of hepatotoxicity. If confirmed, follow SoE. *If a participant develops any signs or symptoms of hepatitis, management should follow the table for symptomatic hepatitis, regardless of ALT, AST, or total bilirubin levels.
Grade 2 Asymptomatic	Continue INH/ Placebo for INH	Assess ALT, AST, and total bilirubin and clinical assessment as soon as possible and within 14 working days of site awareness. Reinforce participant awareness and knowledge about signs and symptoms of hepatotoxicity. If confirmed, management is at the discretion of the site investigator and should generally follow SoE. *If a participant develops any signs or symptoms of hepatitis, management should follow the table for symptomatic hepatitis, regardless of ALT, AST, or total bilirubin levels.

ASYMPTOMATIC ELEVATIONS in ALT, AST, and Total Bilirubin		
CONDITION AND SEVERITY	**USE of INH/ PLACEBO FOR INH**	**FOLLOW-UP AND MANAGEMENT**
Grade 3 Asymptomatic	Hold INH/ Placebo for INH	Assess ALT, AST, and total bilirubin and clinical assessment as soon as possible and within 3 working days of site awareness. Inform the CMC if repeat assessment confirms initial ≥ Grade 3. Reinforce participant awareness and knowledge about signs and symptoms of hepatotoxicity. If confirmed, continue to hold INH/Placebo for INH. Repeat testing weekly. If resolves to Grade ≤ 2 in ≤ 21 days, INH/Placebo for INH may be restarted and repeat testing should be done one week after resumption. If ≥ Grade 3 recurs after restarting INH/Placebo for INH, permanently discontinue INH/Placebo for INH and follow condition as clinically indicated until resolved. If condition does not resolve to Grade ≤ 2 in ≤ 21 days, permanently discontinue INH/Placebo for INH and follow condition as clinically indicated until resolved. * If a participant develops any signs or symptoms of hepatitis, management should follow the table for symptomatic hepatitis, regardless of ALT, AST, or total bilirubin levels.
Grade 4 Asymptomatic	Hold INH/ Placebo for INH	Assess ALT, AST, and total bilirubin and clinical assessment as soon as possible and within 3 working days of site awareness. Inform the CMC if repeat assessment confirms initial ≥ Grade 4. Reinforce participant awareness and knowledge about signs and symptoms of hepatotoxicity. If confirmed, permanently discontinue INH/Placebo for INH and follow condition as clinically indicated until resolved. *If a participant develops any signs or symptoms of hepatitis, management should follow the table for symptomatic hepatitis, regardless of ALT, AST, or total bilirubin levels.

SYMPTOMATIC HEPATITIS		
CONDITION AND SEVERITY	**USE of INH/ PLACEBO FOR INH**	**FOLLOW-UP AND MANAGEMENT**
Signs and symptoms of hepatitis	Hold INH/ Placebo for INH	Participants should be advised to immediately hold study drugs if they develop any signs or symptoms concerning for hepatitis: new or worsening nausea, vomiting, unexplained loss of appetite; yellowing of the skin or eyes; increased weakness or fatigue; pain in the upper abdomen (liver tenderness or hepatomegaly); pale or clay-colored stools; and/or unexplained weight loss. Participants should be advised to seek immediate medical attention and contact the site as soon as possible. Immediately assess ALT, AST and total bilirubin; assess INR if available at the site. Follow weekly until symptoms resolve. Inform the CMC if any signs or symptoms are confirmed ≥ Grade 3. - If ALT, AST, and total bilirubin are ≤ Grade 1, seek alternate causes of symptoms; INH/Placebo for INH may be restarted at discretion of site investigator. - If ALT, AST, or total bilirubin is ≥ Grade 2, permanently discontinue INH/Placebo for INH.

6.2 Toxicity Management, Infants

Infants of women participating in P1078 are not actively provided with study drugs but may be exposed to INH *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 7.0 as well as to the local IRBs/ECs, according to prevailing local law and Good Clinical Practices. All protocol-specific reportable events and SAE will be recorded on CRFs.

Laboratory normal ranges will be the institutional values. However, if a site does not have an age-specific normal range/value for a particular laboratory evaluation, the site should use the latest edition of the *Harriet Lane Handbook: a manual for pediatric house officers* by Jason W. Custer and Rachel E. Rau-Mosby for normal ranges/values and document this for monitoring purposes. Clinical management of toxicities in the infant should follow local standard of care.

6.3 Criteria for INH/Placebo for INH Treatment Discontinuation

- Woman has developed active TB.
- Woman is started on open-label INH for any reason.
- Drug toxicity that requires permanent study drug discontinuation as defined in Section 6.1.
- Repeat pregnancy during study follow-up, at site investigator's discretion.

In the event of treatment discontinuation, women and their infants will remain on-study but off study treatment for follow-up visits to complete follow-up through 48 weeks postpartum. Sites should refer to Appendix I-A for a complete description of clinical and laboratory evaluations to be performed for participants who are off study treatment but remain on study.

6.4 Criteria for INH/Placebo for INH Treatment Re-initiation

If a woman had her INH/Placebo for INH study drug discontinued because active TB was suspected but was subsequently determined to not have active TB, the woman will be allowed to have her INH/Placebo for INH study drug re-initiated if the duration of anti-tubercular therapy (e.g., 4-drug anti-TB treatment) is < 21 days.

6.5 Criteria for Study Discontinuation

- The participant or legal guardian refuses further treatment and/or follow-up evaluations.
- The investigator determines that further participation would be detrimental to the participant's health or well-being.
- The participant fails to comply with the study requirements so as to cause harm to him/herself or seriously interfere with the validity of the study results.
- Study is cancelled at the discretion of the FDA, IMPAACT, the IRB or EC, OHRP, NIAID, NICHD, or other country-specific governmental agencies.

7.0 Expedited Adverse Event Reporting

7.1 Adverse Event Reporting to DAIDS

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

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

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

7.2 Reporting Requirements for This Study

- The SAE Reporting Category, as defined in Version 2.0 of the DAIDS EAE Manual, will be used for this study.
- The study agents for which expedited reporting is required are: INH/Placebo for INH. Open-label Pyridoxine (vitamin B_6) and prenatal multivitamin are not to be considered for EAE reporting.
- In addition to the SAE Reporting Category identified above, other AEs that must be reported in an expedited manner are: fetal deaths (of any gestational age).

7.3 Grading Severity of Events

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

The Supplemental Toxicity Table for Grading Severity of ALT/AST/Total Bilirubin (Appendix III) and the Supplemental Toxicity Table for Grading Severity of Peripheral Neuropathy Adverse Events (Appendix II) will also be used. The parameters specified in these tables supersede the DAIDS Toxicity Table when grading these events.

7.4 Expedited AE Reporting Period

- The expedited AE reporting period for this study is the entire study duration for an individual participant (from study enrollment until study completion or discontinuation of the participant from study participation for any reason).
- After the protocol-defined AE reporting period, unless otherwise noted, only suspected unexpected serious adverse reactions (SUSARs) as defined in Version 2.0 of the EAE Manual will be reported to DAIDS if the study staff become aware of the events on a passive basis (from publicly available information).

8.0 Statistical Considerations

8.1 General Design Issues

This is a double-blind, placebo-controlled, randomized study designed to determine the safety of immediate (antepartum) initiation of INH compared to deferred (postpartum) initiation of INH. Secondary objectives include comparisons of these two strategies with respect to maternal as well as infant TB incidence, mortality, and morbidity (i.e., efficacy). Nine hundred and fifty mother/infant pairs will be followed from study entry during pregnancy until 48 weeks postpartum. Women will be stratified by gestational age (≥ 14 - < 24 weeks versus ≥ 24 through ≤ 34 weeks [34 weeks, 6 days]). Due to the developing changes in WHO guidelines since approval of protocol Version 1.0, HAART use among HIV-infected pregnant women has increased over the years regardless of CD4 count status. It is thus expected that almost all women enrolled in this study will be on HAART at study entry. In light of this, HAART use has been removed as a stratification factor during randomization in this protocol version (Version 2.0), but post-stratification analysis by HAART use will be performed, if feasible. The study will be opened at sites in high TB prevalence (≥ 60 cases per 100,000 population/year) settings, as defined by the WHO TB annual report or documented local burden.

The primary safety endpoint as defined in this study is the common basis for assessment of safety of INH preventive therapy in published studies [23]. It should be noted that since it depends on subjective attribution to INH/Placebo for INH, then potential bias may occur in the estimation of the event rates. The use of a double-blind, placebo-controlled design will minimize potential bias in the comparison of rates between these arms. Additionally, to check for bias in the analysis of the primary safety endpoint, a parallel analysis will be performed based on all Grade ≥ 3 AEs (regardless of attribution to INH/Placebo for INH).

Blood samples will be obtained for IGRA (QGIT and/or TB ELISPOT) to determine latent TB status at entry. Results will not be made available until the end of study to avoid introducing any biases into the clinical management. However, results will be used in a supplementary analysis that will compare the different strategies in INH prophylaxis (pregnancy versus postpartum) on incident TB in IGRA-positive (strong evidence of latent TB infection) versus IGRA-negative (no evidence of latent TB infection) women. TST and IGRA (QGIT) will be performed on all enrolled women at delivery. The study team suspects only a negligible number of crossovers (if ever) among women in the deferred arm who test TST-positive at this point since everyone

enrolled would either already be on active INH therapy at delivery or expect to start active INH in 12 weeks.

Sites will complete a Screening Failure Results CRF for all participants for whom informed consent was obtained, but who are deemed ineligible or who do not enroll into the protocol for any reason. The screening failure data will be collected in accordance with the Consolidated Standards for Reporting Trials (CONSORT) 2010 Statement, which provides guidelines for reporting randomized controlled trials.

8.2 Outcome Measures

8.2.1 Primary Endpoint

Grade ≥ 3 AEs possibly, probably, or definitely associated with INH/Placebo for INH or permanent discontinuation of INH/Placebo for INH due to an adverse reaction in women after randomization until 48 weeks postpartum.

8.2.2 Secondary Endpoints and Outcome Measures:

8.2.2.1 *In utero* exposure and infant outcomes:

- Fetal death
- Small for gestational age
- Premature birth (< 37 weeks gestation)
- Low birth weight (< 2500 mg)
- Congenital anomalies
- Grade 3 or higher clinical or laboratory AEs (all AEs and possibly, probably, or definitely related to INH/Placebo for INH)
- HIV infection
- Hospitalization

8.2.2.2 Any of the following endpoints:

- Maternal TB (probable or confirmed – see Appendix 100 for definitions)
- Infant TB (probable or confirmed, as defined in Appendix 100, and congenital TB, as defined using the Cantwell criteria)
- Death of infant
- Death of mother
- Combined endpoint of maternal TB or maternal death
- Combined endpoint of infant TB or infant death
- Combined endpoint of maternal TB, maternal death, infant TB, or infant death

NOTE: Appendix 100 will be the basis for adjudication of the TB endpoint by the Secondary Endpoint Review Committee (SERC). Appendix 100 is available in the CRF Appendix Codes section of the Frontier Science IMPAACT Portal; the web link to portal is in the MOP. Cantwell criteria for Congenital TB are in the MOP and will be collected on the P1078 CRF. Separate

secondary analysis can be performed to evaluate alternate definitions/classifications of TB and will be defined prospectively if available or applied retrospectively, as far as the study data collection strategy allows. (In special circumstance, a particular TB definition/classification introduced after the first SERC meeting could be used as the primary definition if concurred by the Core study team, the SERC and the DSMB and supported by existing data collection). In addition, changes to the data collection form when needed to enhance data collection of a predefined endpoint may not require formal protocol changes.

8.2.2.3 Occurrence of each of the following safety outcomes in HIV-infected women during pregnancy up to: (i) delivery (antepartum) and (ii) 12 weeks postpartum

- Grade ≥ 3 AEs possibly, probably, or definitely related to INH/Placebo for INH or permanent discontinuation of INH/Placebo for INH due to an adverse event
- Grade ≥ 3 AEs (all-cause)
- Hepatotoxicity possibly, probably, or definitely related to INH/Placebo for INH
- Hepatotoxicity (all-cause)

Each of the definitions of hepatotoxicity will be studied: (i) having ≥ Grade 3 LFTs (ALT > 5 X ULN or ALT > 3 X ULN with bilirubin > 2 X ULN) or ALT > 3 X ULN with persistent, symptomatic clinical hepatitis); and (ii) using DAIDS grading.

8.2.2.4 Resistance outcomes:

- Resistance to INH in isolates of *M.tb* from mothers who develop culture-confirmed TB
- Resistance to INH in isolates of *M.tb* from infants who develop culture-confirmed TB

8.2.2.5 Intensive pharmacokinetic outcomes as specified in Section 9.2

8.2.2.6 Latent TB Diagnostic Outcome Measures:

- IGRA assay result (positive, negative, indeterminate) in women
- IGRA assay result (positive, negative, indeterminate) in infants
- TST result (positive or negative) in women; TST positive if ≥ 5 mm
- TST result (positive or negative) in infants; TST positive if ≥ 10 mm in HIV-negative infants and if ≥ 5 mm in HIV-positive infants

8.2.2.7 Adherence to INH/Placebo for INH among women, assessed by self-report and pill count

For the self-report and pill counts, adherence will be considered as a continuous, ordinal categorical, or a binary variable. When presented as a continuous variable, adherence is defined as the percentage of expected doses/pills taken during the entire treatment period (28 weeks). When presented as an ordinal variable, excellent adherence is defined as taking at least 90% of doses/pills during the entire treatment period; good adherence as ≥ 80% to < 90%; reasonable adherence as ≥ 60% to < 80%; and poor adherence as < 60% of doses, as reported in any of the scheduled adherence evaluations. When presented as a binary variable (completer versus non-completer), a completer is defined as having excellent adherence.

8.2.3 Exploratory Outcome Measures

8.2.3.1 Population Pharmacokinetics

- Primary: Area under the plasma versus time curve (AUC) at each of two time points (antepartum and postpartum) in women.
- Secondary: C_{peak}, half-life ($t_{1/2}$), volume of distribution (V_d) and apparent clearance (CL/F)

Pharmacogenetics
- Presence of genetic variants to NAT2 and 2E1, PK of INH and EFV based on sparse sampling during pregnancy and postpartum

8.2.3.2 Immunologic Outcome Measures

- Functional and phenotypic characteristics of TB specific T-cell responses in women
- Functional characteristics of TB specific T-cell responses in infants

8.2.3.3 INH and EFV drugs levels in women's hair samples; adverse events are as defined Grade 3 or higher adverse events in women until 48 weeks postpartum

8.2.3.4 An overall ordinal measure of clinical outcomes in the mother-infant pair, which assigns a score to the mother-infant pair according to severity of totality of clinical outcomes (clinical outcomes include maternal death, maternal TB, maternal safety events, infant death, infant TB, infant safety events); the measure will be formulated in consultation with the study team and details will be included in the statistical analysis plan (SAP).

8.2.3.5 Maternal and infant specific TB responses and novel biomarkers

- Anti-mycobacterial antibody responses in maternal plasma at all weeks when samples are collected
- Anti-mycobacterial antibody responses in infant plasma at all weeks when samples are collected
- Inflammation and immune activation markers (and other potential biomarkers) measured from maternal plasma/PBMC samples at all available time points
- Inflammation and immune activation markers (and other potential biomarkers) measured from infant plasma/PBMC samples at all available time points

8.2.3.6 Depression scores determined from the PHQ-9 instrument; responses to neurocognitive impairment questions and Pittsburgh Sleep Quality Index subset questions

8.3 Randomization and Stratification

Pregnant women who meet the eligibility criteria will be randomized 1:1 to either Arm A: immediate INH therapy or Arm B: deferred INH therapy. Randomization will be done using a dynamic permuted block system and will be balanced by treatment arm at each site.

In order to balance factors thought to be strongly associated with the primary outcome, HIV-infected pregnant women will be stratified by gestational age in each arm as follows:

Stratification Factor: Gestational age
- Stratum a: ≥ 14 to < 24 weeks gestational age at study entry
- Stratum b: ≥ 24 through ≤ 34 weeks (34 weeks, 6 days) gestational age at study entry

There will be no limits on the numbers of women enrolled in each stratum.

8.4 Sample Size and Accrual

The study plans to enroll 950 women-infant pairs (approximately 475 women per arm) over a period of 96 weeks. The primary objective is to compare the safety of using an immediate INH strategy versus deferred INH in HIV-infected pregnant women by estimating the absolute difference in the rates of the primary endpoint (Grade ≥ 3 AEs possibly, probably or definitely associated with INH/Placebo for INH or permanent discontinuation of INH/Placebo for INH due to adverse reactions) between women in the two arms of the study from the time of randomization to 48 weeks postpartum. Determination of study sample size is based on absolute differences in rates, based on simple estimates for proportions using the normal approximation as shown below:

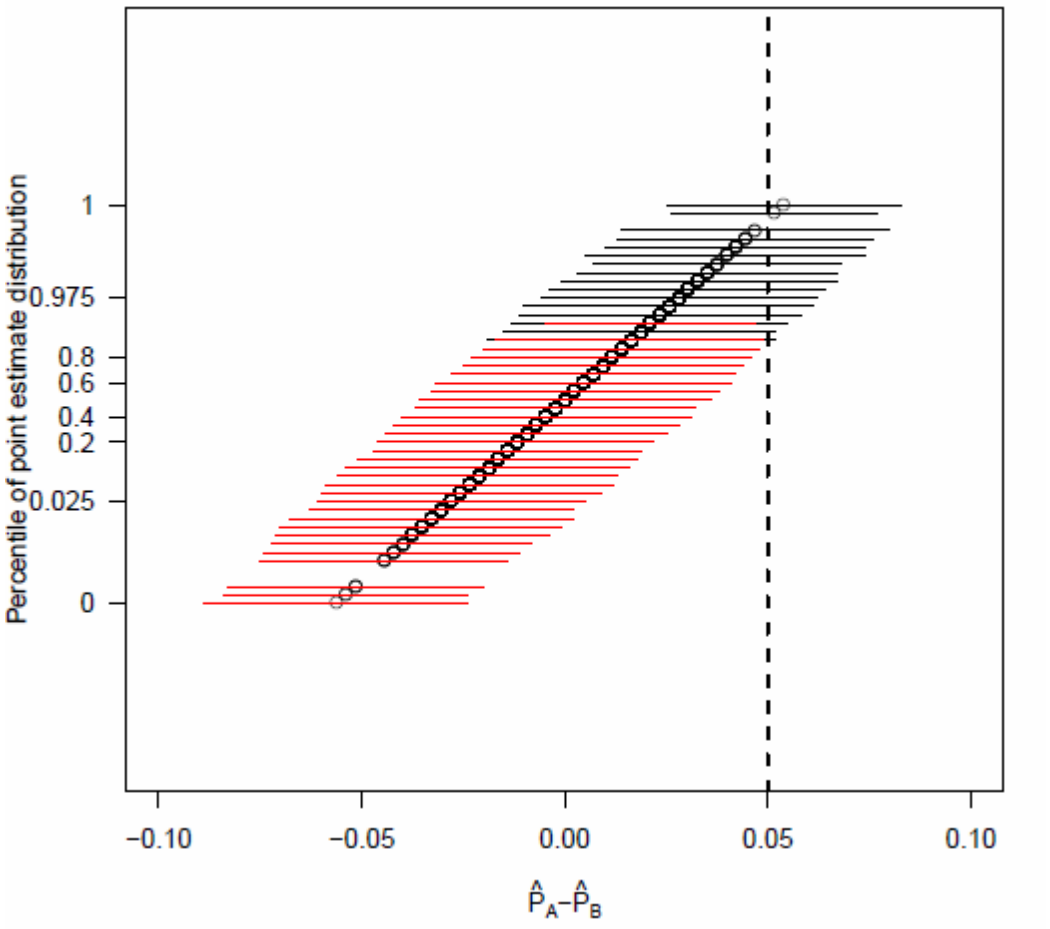
$$\left[\left(\hat{p}_1-\hat{p}_2\right)-z_{\alpha/2}\sqrt{\frac{\hat{p}_1(1-\hat{p}_1)}{n_1}+\frac{\hat{p}_2(1-\hat{p}_2)}{n_2}},\left(\hat{p}_1-\hat{p}_2\right)+z_{\alpha/2}\sqrt{\frac{\hat{p}_1(1-\hat{p}_1)}{n_1}+\frac{\hat{p}_2(1-\hat{p}_2)}{n_2}}\right]$$

It is anticipated that 90-100% of women enrolled will be on HAART at least during their pregnancy and this could contribute to the primary safety outcome measure. Based on AEs and effect size information found in the literature [23, 45, 108-110], it is estimated that the true primary endpoint rate in the deferred INH arm (control arm) would range from about 3%-12%. The team agreed that non-inferiority of the immediate arm (no excess toxicity) will be concluded if the upper boundary of the 95% CI of the difference in rates (immediate arm rate – deferred arm rate) is lower than 5%. A total sample size of 950 provides at least 90% power to conclude non-inferiority in an intent-to-treat analysis, assuming the true primary endpoint rate in the deferred arm (the control arm) is 5% and after adjusting for one interim analysis and a 10% loss to follow-up rate.

Simulations were used to investigate power to conclude non-inferiority under varied true conditions of the safety parameters of interest. 5000 simulations were run with 427 (475 minus 10% expected lost to follow-up) participants in each arm and a variety of true rates assumed for both the immediate and deferred arms, selected non-inferiority margins and with a type I error set as 100.0% - 95.0% = 5.0%. For example, 5000 simulations were performed with the true rate

set to 5.0% in both arms, and with a non-inferiority margin of 5%. From these, 5000 CIs were computed, with 91.6% of them having upper confidence limits below 5% (highlighted in red in Figure 2). With available information on the 10% expected lost to follow-up included in the primary analysis (as censored data), 91.6% would be the estimated minimum power to conclude non-inferiority under this set of conditions.

Figure 2: Predicted interval plot $P_A = 0.05$, $P_B = 0.05$



Using the simulation method described above, Table 1 shows the estimated power to conclude non-inferiority for varying true primary endpoint rates in the immediate and deferred arms, and for varying non-inferiority margins (expressed in terms of absolute difference in rates, which is the main parameter of interest).

Table 1: Power Calculations* for Non-inferiority (no excess toxicity) in Primary Safety Endpoint

True Safety Endpoint** Rate In Deferred Arm	Maximum Acceptable True Safety Endpoint** Rate in Immediate Arm	Margin for Non-inferiority (in terms of absolute difference in rates)***	Power for N=950
3.0%	3.6%	0.6%	8.3%
	4.5%	1.5%	26.7%
	5.4%	2.4%	54.4%
	6.0%	3.0%	72.1%
5.0%	6.0%	1.0%	10.2%
	7.5%	2.5%	40.0%
	9.0%	4.0%	75.3%
	10.0%	5.0%	91.6%
7.5%	10.3%	2.8%	34.3%
	11.3%	3.8%	55.8%
	13.5%	6.0%	91.2%
	15.0%	7.5%	98.6%
10.0%	12.0%	2.0%	17.2%
	15.0%	5.0%	68.5%
	18.0%	8.0%	97.3%
	20.0%	10.0%	99.8%
12.0%	14.4%	2.4%	19.3%
	18.0%	6.0%	76.2%
	21.6%	9.6%	99.1%
	24.0%	12.0%	>99.9%

* Adjusted for interim analysis and 10% loss to follow-up
**Grade ≥ 3 INH/Placebo for INH related adverse events or drug discontinuation due to adverse effects from randomization to 48 weeks postpartum
***corresponds to 20%, 50%, 80% and 100% relative increase

A key secondary objective is to examine efficacy of providing immediate INH compared to deferred INH, where efficacy is assessed in terms of development of maternal TB, infant TB, all-cause maternal death, all-cause infant death, or any of these events. Depending on the efficacy endpoint being explored, the anticipated rate in the deferred arm ranges from about 2.5% to 12.5%. Table 2 provides power calculations for detecting a significant decrease in the endpoint rate by using immediate INH under varying true rates in the deferred and immediate arms. For example, if the true endpoint rate in the deferred arm is 5%, then there is about 68% power to detect a significant decrease in the event rate in the immediate arm if the true rate in the immediate arm is 2% (corresponding to an absolute decrease of 3% or a relative decrease of 60%). These are adjusted for one interim analysis and 10% loss to follow-up.

Table 2: Power* Calculations for the secondary Efficacy Endpoint Based on a Two-Sided Confidence Interval for the Difference in Proportions Between the Two Study Arms

True Efficacy Endpoint Rate In Deferred Arm	True Efficacy Endpoint Rate In Immediate Arm** (True Absolute Decrease)	Power for N=950
2.5%	0.5% (2.0%)	70.8%
	1.0% (1.5%)	40.0%
	1.5% (1.0%)	18.3%
	2.0% (0.5%)	8.1%
5.0%	1.0% (4.0%)	95.6%
	2.0% (3.0%)	67.6%
	3.0% (2.0%)	32.7%
	4.0% (1.0%)	10.9%
7.5%	1.5% (6.0%)	99.5%
	3.0% (4.5%)	84.7%
	4.5% (3.0%)	45.9%
	6.0% (1.5%)	14.4%
10.0%	2.0% (8.0%)	99.9%
	4.0% (6.0%)	94.7%
	6.0% (4.0%)	58.5%
	8.0% (2.0%)	17.7%
12.5%	2.5% (10.0%)	>99.9%
	5.0% (7.5%)	98.1%
	7.5% (5.0%)	68.8%
	10.0% (2.5%)	21.6%
* Adjusted for one interim analysis and 10% loss to follow-up **corresponds to 80%, 60%, 40% and 20% relative decrease		

Finally, for the immunology objective of assessing agreement among the different diagnostics tests for latent TB infection, a sample size of approximately 460 will be used. PBMC samples from 460 enrolled women (PBMC collection will be site-restricted) will be obtained for TB ELISPOT and will be compared with the corresponding TST and QGIT results in the same women. Studies report test agreement in the fair to moderate range ($0.40 \leq \text{Kappa} \leq 0.60$) among HIV-infected persons in low/middle income countries [111]. A sample size of 200 participants will be needed to be able to detect agreement higher than Kappa = 0.20 with at least 80% power using a 5% significance level, and assuming the true agreement is at least Kappa = 0.40 and each of the tests shows a positive result on 30% of the participants. The sample size is inflated to 460 to account for about 40% attrition rate due to lost or non-evaluable samples or participant loss to follow-up.

8.5 Monitoring

8.5.1 Routine Monitoring

Routine monitoring will be done by the P1078 Core team, which consists of the study chair, vice-chairs, medical officers, statisticians, data manager, and the clinical trials specialists (email group is impaact.corep1078@fstrf.org). All reports to team will be pooled across treatment arms.

The study statisticians and data manager will prepare administrative reports twice a year. These reports will include baseline information and will address protocol execution issues such as accrual, eligibility, co-enrollment, endpoint evaluability, and data completeness. Endpoint reviews will be performed at least every 3 months. An independent Endpoint Review Committee (assigned by the Tuberculosis Scientific Committee) will be assigned to review and adjudicate the primary safety endpoint, where data will be pooled across arms and no treatment assignment information will be provided; similarly for selected secondary endpoints. Review of the primary safety endpoint will be done monthly as needed and will include all new Grade 3 or 4 signs, symptoms, laboratory events and diagnoses, as well as deaths.

The study statisticians and data managers will not report any safety data (including primary endpoint and aggregate data) to the study team. However, since this study will be conducted under an FDA IND, the study NIH medical officer, or other NIH designee in charge of safety oversight and designated in the form FDA 1571, may review periodically aggregate safety data blinded to treatment assignment and to relationship attribution compiled by the endpoint review committee. Such review (as well as other safety reviews that may be required per sponsor procedures) will be performed independently of the study team and will insure compliance with sponsor obligations for safety oversight.

Accrual Rate Monitoring

For P1078, it is expected that 950 mother-infant pairs will be enrolled over a 96-week period. Accrual will be reported to the protocol team and reviewed on monthly calls with the expectation of approximately 38-42 enrollees per month, and a target of 238 enrollments every 6 months. Monitoring will begin 3 months after the first site has received its site activation notice. If the accrual is slower than expected or if two of the 6-month targets are missed, then a re-assessment of barriers to enrollment, site participation, sample size and eligibility criteria will be considered and suggestions of the Tuberculosis Scientific Committee and IMPAACT Network leadership will be solicited.

8.5.2 Interim Analyses

The study will be monitored by an NIAID-sponsored Data Safety Monitoring Board (DSMB). The DSMB reviews will address at least the following issues:

- Administrative issues such as accrual
- Safety of INH
- Potential need for sample size re-assessment or futility of the study

The DSMB will review the study at least annually after the first woman is enrolled. The number and timing of interim reviews will be conducted in consultation with the DSMB.

At each interim DSMB-scheduled analysis of the primary safety endpoint (including the early safety monitoring procedure described in Section 8.5.3), repeated confidence intervals (RCIs) (or hypothesis tests, if applicable) with a simultaneous coverage probability of 95% will be used. Nominal alpha values will be based on the Haybittle-Peto spending criteria. Based on the theory of repeated CIs, a 99.9% CI will be calculated for the difference in the primary safety outcome rates between the immediate arm and the deferred arm in each interim analysis. If the lower bound of the confidence interval is greater than 5% this will constitute evidence that immediate INH therapy is inferior and grounds for considering stopping the study early. If the upper bound of the computed interval is less than 5%, then this would suggest non-inferiority and stopping the trial may also be considered. The team recommends that consideration for stopping the trial based on the above guidelines may be done only during a full DSMB review, and based on the following computed estimates:

- Kaplan-Meier estimates at 48 weeks postpartum, where censoring occurs at the last clinic visit prior to loss to follow-up, death not associated with primary endpoint or permanent discontinuation of INH/Placebo for INH for TB preventive therapy for any reason other than adverse reaction to INH/Placebo for INH; estimate will be based on data from all enrolled women who would have reached 48 weeks postpartum at time of interim analysis; and
- Simple proportions, restricted to those reaching 48 weeks postpartum at time of interim analysis.

However, additional monitoring for safety, per Section 8.5.4, may be used.

If the trial continues, the final analysis will use a 95% CI that will result in 95% simultaneous coverage probability.

Predicted intervals (PIs) [112] will also be computed at the time of interim analysis and will be used to provide information regarding effect size estimates and precision. The results will be examined by the DSMB. Based on the prediction of the trial results upon trial continuation, the DSMB may provide timely recommendations such as sample size adjustments, discontinuation of a treatment arm due to futility, or continuation of the trial as planned.

Data on the secondary endpoints of maternal TB, maternal all-cause mortality, infant TB, infant all-cause mortality, or any of these endpoints may be presented to the DSMB as part of the interim analysis to help guide decisions on whether to continue the study or whether study modifications are needed.

Results of an interim analysis or results from another trial may trigger a recommendation from the DSMB to terminate or unblind the study arms. Please refer to the DAIDS SOP "Termination of a Trial or a Single Treatment Arm" for details.

8.5.3 Early Interim Analysis for Safety

In collaboration with the DSMB, the following procedure will be used to monitor early safety data in this study:

(a) The first analysis of primary endpoint data will take place when 25 women in the immediate arm have completed INH therapy or 15 endpoint events have occurred in the two arms combined, whichever happens earlier.
(b) The data will consist of primary endpoint data on both arms.
(c) Differences in the proportions of the cumulative number of events will be compared using Fisher's exact test, and the analysis will also include exact confidence intervals for the proportions of events in the individual treatment arms. Interpretation of the result should be done with caution, as the average time on INH between the two arms may (and will likely) not be identical at this point.
(d) A confidence interval for the relative risk comparing the two arms will also be computed. Interpretation of the result should be done with caution as the constant hazard rate assumption may (and will likely) not be true for this comparison.
(e) The analysis will be reviewed by a subgroup of the DSMB, including the Chair, at least one clinician, and at least one statistician. The DSMB subgroup will determine whether the analysis warrants a full DSMB review.
(f) After the initial analysis, the DSMB will recommend the timing of future monitoring.

Since unanticipated serious adverse reactions are not expected, enrollment will continue while the early safety review is taking place.

8.5.4 Additional Monitoring for Safety

In addition to the monitoring scheme specified in this protocol, additional monitoring of safety data (which may include additional or revised statistical guidelines) may be implemented based on DSMB recommendations during the conduct of the study. Details of such additions or changes will be included in the study monitoring plan.

8.6 Analyses

The primary analysis will be conducted on an intent-to-treat (ITT) basis; i.e., study participants will be analyzed according to their assigned study arm, regardless of whether or not they took their assigned prophylaxis regimen. However, given that this is a non-inferiority study, a per-protocol analysis, which will include and compare only participants who completed the regimen they actually received (24 to 28 weeks of INH preventive therapy), as well as an as-treated analysis, which will compare participants according to actual treatment received, will also be performed as part of the supplementary analyses.

Since standard of care is allowed to vary from site to site, supplementary analyses will consider site differences and their influence on the findings.

8.6.1 Primary Objective

To compare overall safety and toxicity of immediate versus deferred INH preventive therapy in HIV-infected pregnant women enrolled at ≥ 14 through ≤ 34 weeks gestation (34 weeks, 6 days)

Safety of INH will be assessed primarily by comparing rates of Grade ≥ 3 events possibly, probably or definitely associated with INH/Placebo for INH or permanent discontinuation of INH/Placebo for INH due to an adverse reaction between women in the immediate and deferred arms by 48 weeks postpartum. Events, which are defined as probably not related, will be analyzed in the not related category. For the primary analysis, a 95% confidence interval for the absolute difference in primary endpoint rates will be calculated from Kaplan-Meier curves stratified by gestational age. Post-stratified analysis by HAART use will also be performed, if feasible. Un-weighted (i.e., ignoring stratification by gestational age) estimates for the difference in rates will also be reported. Data will be censored at the latest clinic visit when the endpoint status was ascertained prior to or at the earliest of the following times: (1) date when lost to follow-up for any reason, (2) date of death due to reasons definitely not related to INH/Placebo for INH, (3) date of permanent discontinuation of INH/Placebo for INH as TB preventive therapy for any reason (other than an adverse reaction) including initiation of open label TB preventive therapy or treatment of presumed active TB disease.

Sensitivity analyses will be done to assess the impact of coding deaths of unknown cause and all deaths as events. Supplementary analyses will include estimation of the difference in primary endpoint rates between the two arms based on simple estimates of proportions stratified by gestational age, where strategies such as complete case analysis (only participants who completed study will be analyzed), worst case analysis (all cases lost to follow-up or who developed maternal TB coded as having reached endpoint), best case analysis (all cases lost to follow-up or who developed maternal TB coded as not reaching endpoint), will be considered. Un-weighted (i.e., ignoring stratification by gestational age) estimates for the difference in rates will also be reported. Multivariate analyses to adjust for maternal characteristics such as age, duration on HAART, CD4 count, gestational age at study entry, IGRA positivity at study entry in all women, and other potential confounders such as HBsAg serology status at entry will be performed using logistic regression modeling.

Finally, similar analyses will be performed on all Grade ≥ 3 AEs (regardless of INH/Placebo for INH attribution) as a way to check for bias in the primary endpoint analysis.

8.6.2 Secondary Objectives

8.6.2.1 To compare safety and toxicity of INH *in utero* exposure and on infants on study

Safety and toxicity of INH *in utero* exposure and on infants in the two treatment arms will be compared. Specifically the proportion of infants who are small for gestational age, have low birth weight, congenital anomalies, Grade 3 or higher events and laboratory abnormalities, HIV infection status, and stillbirths (fetal death) during study participation will be compared between study arms. Statistical analyses similar to that described in Section 8.6.1 will be performed for the comparison. Potential confounders relevant to these *in utero* exposure/infant outcomes will be considered in the multivariate modeling.

8.6.2.2 To compare TB incidence and all-cause mortality in HIV-infected women and their infants enrolled on study

Maternal TB, maternal death, infant TB, and infant death will be analyzed separately and as combined events (as listed in Section 8.2.2.2). Efficacy of INH will be assessed primarily by comparing event rates between women in the immediate and deferred arms by 48 weeks postpartum, using a 95% confidence interval for the absolute difference in event rates using Kaplan-Meier stratified by gestational age. Post-stratified analysis by HAART use will also be performed, if feasible. Un-weighted (i.e., ignoring stratification by gestational age) estimates for the difference in rates will also be reported. Strategies for censoring will vary depending on the efficacy outcome of interest. For analyses of maternal TB, any maternal death not caused by TB will be not be considered an event and any maternal death of unknown cause will be considered an event. Similarly, for analyses of infant TB, any infant death not caused by TB will not be considered an event and any infant death of unknown cause will be considered an event. Sensitivity analysis to assess the effect of this strategy includes coding death due to unknown cause as a non-event.

Supplementary analyses will include estimation of differences in these individual/combined endpoint rates between the two arms based on simple estimates for proportions, where strategies such as complete case analysis, worst-case analysis or best-case analysis will be considered. Other supplementary analysis may explore an expanded TB definition (e.g., adding “possible” TB as an endpoint and/or treating initiation of anti TB treatment as an endpoint). Multivariate analyses to adjust for potential confounders, such as age of mother, gestational age at enrollment, duration on HAART of mother, CD4 count of mother, IGRA positivity of mother at study entry, adherence to INH, infant HIV status and breastfeeding status, whenever applicable, will also be performed.

Additional similar analysis on these events will be performed, this time only for events up to 12 weeks postpartum.

8.6.2.3 To compare overall safety and hepatotoxicity, as well as evaluate risk factors for these outcomes, during pregnancy and immediate postpartum in women on immediate versus deferred INH therapy

A 95% confidence interval for the absolute difference in rates will be calculated from Kaplan-Meier curves stratified by gestational age. Post-stratified analysis by HAART use will also be performed, if feasible. Un-weighted (i.e., ignoring stratification by gestational age at study entry) estimates for the difference in rates will also be reported. Data will be censored at the latest clinic visit when the endpoint status was ascertained prior to or at the earliest of the following times: (1) date when lost to follow-up for any reason and (2) date of death.

Supplementary analyses will include estimation of the difference in rates between the two arms based on simple estimates of proportions stratified by gestational age, where strategies such as complete case analysis, worst-case analysis and best-case analysis will be considered. Un-weighted (i.e., ignoring stratification by gestational age) estimates for the difference in rates will also be reported. Multivariate analyses to adjust for maternal characteristics such as age, duration on HAART, CD4 count, INH levels in hair, gestational age at study entry, and other potential confounders such as HBsAg serology status at entry will be performed using logistic regression modeling.

Endpoint rates at each pregnancy stage (second trimester, third trimester) will also be estimated; rates for endpoints that occurred during the second trimester will be assessed only within women enrolled during their second trimester of pregnancy. Differences in rates of endpoints occurring during the third trimester by gestational age strata will also be assessed; similarly, for endpoints that occurred during the immediate postpartum period (delivery up to 12 weeks postpartum).

Safety endpoint rates between the two arms will also be compared during the 28-week period that the participant was on INH. These comparisons will be done using the same statistical methods described above.

8.6.2.4 To evaluate INH resistance among *M.tb.* isolates from HIV-infected women and infants who develop TB while on study

The proportion of women with culture confirmed *M.tb.* who have INH resistance will be compared between the two arms using Fisher's exact test. Similar comparisons will be performed among infants with culture confirmed *M.tb.*

8.6.2.5 To evaluate the intensive pharmacokinetics of INH and selected ARV drugs in a subset of HIV-infected pregnant and postpartum women receiving HAART

To evaluate whether INH affects the pharmacokinetics of selected ARV drugs in HIV-infected women during pregnancy and postpartum, comparison of antepartum and postpartum mean AUC for the ARV drugs between the selected subset of women in the immediate versus deferred arms will be performed using both parametric (two-sample t-test) and nonparametric (Wilcoxon rank sum test) methods. Similar unpaired comparisons with respect to the additional parameters C_{peak}, half-life ($t_{½}$), volume of distribution (V_d) and apparent clearance (CL/F) will also be performed.

To evaluate whether pharmacokinetic parameters of INH and selected ARV drugs differ between antepartum and postpartum, within-subject paired comparisons of antepartum and postpartum mean pharmacokinetic parameters for INH (only for women in Arm A) as well as the selected ARV drugs among the selected subset of women will be performed when feasible.

8.6.2.6 To evaluate and compare the performance characteristics of IGRA (TB ELISPOT and QGIT) with TST in HIV-infected women and their infants

Contingency tables showing results of TST with IGRA will be constructed. Degree of concordance of results between the IGRA (QGIT, TB ELISPOT) and TST tests for the women and their infants at week 44, and between IGRA and TST test results for the women at delivery, will be assessed using the Kappa measure of agreement. Test results will also be stratified by HIV infection status of the infant, if there are enough data in each stratum. Data from these tests will be compared by using the McNemar chi-square test.

Serial TB infection status (study Entry, Labor and Delivery/Birth visits, and Weeks 12, 44, and 48 postpartum) using QGIT and/or TB ELISPOT, as available in a subset of women and infants, will also be assessed using generalized linear modeling that will adjust for important covariates. Reversion and conversion rates will be estimated using observed proportions with corresponding 95% exact confidence intervals.

8.6.2.7 To compare adherence in women initiating immediate versus deferred INH preventative therapy via self-report and pill counts

Proportion of women adherent to INH (completers) will be compared between the two arms via the two adherence measures (self-report, pill counts) using Fisher's exact test. Logistic regression of adherence to IPT will be performed, with duration on HAART at study entry as one of the independent variables included in the model. Supplementary analyses will consider adherence as continuous or ordinal categorical variables. When used as a continuous outcome, the percentage of doses/pills taken will be compared between the two arms using either Student's two-sample t-test or Wilcoxon's rank sum test, as appropriate. Linear or quantile regression (as appropriate) of percentage of doses/pills taken will be performed with duration on HAART at study entry as one of the independent variables in the model.

8.6.3 Exploratory Objectives

8.6.3.1 To evaluate population pharmacokinetics and pharmacogenomics of INH and EFV in HIV-infected pregnant and postpartum women

Comparison of antepartum and postpartum mean AUC for EFV among women will be performed using methods for unpaired samples, considering both parametric (unpaired t-test) and nonparametric (Mann Whitney U test) methods. Similar unpaired comparisons with respect to the additional parameters C_{peak}, half-life ($t_{½}$), volume of distribution (V_d) and apparent clearance (CL/F) will also be performed.

DNA will be collected in all participants and banked until toxicity data are collected. Associations between presence of NAT2/2E1 variants, PK parameters, and INH hepatotoxicity will be evaluated using Fisher's exact test based on data from a nested case-control design. Conditional logistic regression of INH hepatotoxicity will also be performed, with presence of NAT2 variants and presence of 2E1 variants as variables in the model, and adjustments for potential confounders will be considered.

8.6.3.2 To assess the effects of INH preventive therapy on the functional characteristics of TB specific T-cell responses measured by TB ELISPOT in HIV-infected women and their infants on study

Change from baseline (study entry) to selected follow-up time points (for example, 12 weeks postpartum and/or 44 weeks postpartum) in different functional characteristics of TB T-cell responses will be compared between the two arms using two-sample tests for the mean.

Multiple regression analysis will also be performed to adjust for potential confounders.

8.6.3.3 To evaluate adherence and exposure to INH and EFV using drugs levels in hair and to analyze the association between these drug levels and adverse effects

INH levels will be measured in hair samples obtained throughout the study as indicated in the Schedule of Evaluations. The study will assess the association of adverse effects with a composite measure of hair INH levels over all of each woman's samples while on INH, as well as with a composite measure of hair EFV levels over all of each woman's samples while on EFV, while controlling for time on INH, time on EFV, concomitant drugs including HAART, pregnancy status, and adherence by self-report or pill count. The study will perform multiple logistic regression with Grade 3 or higher safety events as response variable and INH levels in hair as primary exposure variable, adjusting for potential confounders such as concomitant drugs/regimen including HAART, pregnancy status, and adherence by self-report or pill count.

8.6.3.4 To compare the two arms with respect to the overall (risk:benefit) clinical outcomes of the mother-infant pairs

To be specified in the statistical analysis plan (SAP)

8.6.3.5 To explore associations of maternal and infant specific TB responses and novel biomarkers with risk of maternal and infant TB infection and disease

Maternal and infant specific TB responses or biomarkers at baseline (study entry for mothers, at birth for infants) will be assessed as potential correlates of maternal/infant TB infection and disease. Generalized linear mixed modeling, Cox proportional hazards modeling, or Kaplan-Meier estimation (with antibody responses or biomarkers as covariates) will be performed, depending on the outcome or composite outcome of interest. A case-cohort design may be used to accommodate multiple outcomes of interest.

Trends of antibody responses and biomarker profiles over time will also be assessed in a subset of mothers and infants where plasma samples are collected longitudinally.

8.6.3.6 To explore the neurotoxicity of INH in combination with EFV in a subset of women

Incidence rates of neurotoxicity among women on EFV will be estimated in each arm using Kaplan-Meier estimates with 95% confidence intervals around these rates. The two arms will be compared by computing a 95% confidence interval of the difference in Kaplan-Meier estimates between these arms.

9.0 Clinical Pharmacology Plan

9.1 Pharmacology Objectives

9.1.1 To evaluate the pharmacokinetics (PK) of INH and HAART during pregnancy and in the early postpartum period

9.1.1.1 Intensive PK of INH/Placebo for INH during pregnancy
9.1.1.2 Intensive PK of HAART during pregnancy
9.1.1.3 Intensive PK of INH/Placebo for INH post-delivery (Week 16)
9.1.1.4 Intensive PK of HAART post-delivery (Week 16)
9.1.1.5 Population PK INH/Placebo for INH during pregnancy
9.1.1.6 Population PK INH/Placebo for INH post-delivery (Week 16)

9.1.2 To evaluate the pharmacogenomics and associated toxicities using NAT2, 2E1, and CYP2B6 genotypes, and relate genetic variants to the pharmacokinetics of INH (using sparse sampling in all women) in HIV-infected pregnant and postpartum women.

9.2 Study Design, Modeling, and Data Analysis

The overall goal of objective 9.1.1 is to determine the disposition of INH and HAART in the context of pregnancy and compare this to the pharmacokinetics (PK) of INH and HAART postpartum.

Intensive PK Assessment

A sufficient number of women will be enrolled to assure there are 18 evaluable women (total N=36) with antepartum and postpartum intensive PK assessments. Only women who are at ≥ 28 weeks age of gestation at entry into the study will be eligible to participate in the intensive PK. Each participant will be required to undergo serial pharmacokinetic sampling around administration of the dose of INH/Placebo for INH. Participants should have been on INH/Placebo for INH at a stable dose for at least 2 weeks to assure steady-state conditions. PK evaluations will occur during the third trimester of pregnancy (≥ 2 weeks after start of INH/Placebo for INH) during which time the greatest impact of pregnancy on drug disposition is likely to occur. PK evaluations must be repeated in the same women postpartum with these visits occurring at the Week 16 postpartum visit (± 4 weeks). Only women at selected sites and who are on stable HAART ante- and postpartum will be eligible for this set of intensive PKs.

On the day of each PK evaluation, each participant must hold her dose of INH/Placebo for INH and come to clinic (or clinical research site (CRS) if available). Timing of the dose should be scheduled so that it occurs close to 24 hours after the previous day's dose as possible and will not be given until after the baseline (0 time) blood sample is collected. HAART dosing should also be as close to ideal schedule as possible (e.g., every 12 or 24 hours). HAART administration on the day when intensive PK sampling is scheduled should ideally occur at the same time as INH administration. This assures PK sampling for both INH and HAART at appropriate times post-dosing. After arrival in clinic, a venous catheter will be placed in the participant's arm vein to permit collection of serial blood samples. Blood samples (4 mL each) will be collected in EDTA tubes prior to the dose (0 time) and then 1, 2, 4, 6, 8, and 12 hours post-dose. It is imperative that the precise time of dose administration (and the time of dose administration for the two preceding doses) and the time for each PK blood sample collection be noted and recorded on the P1078 PK CRFs.

Blood samples will be centrifuged at 800 G for 10 minutes and plasma will be harvested and aliquoted into 3 cryovials and immediately frozen at -70°C to await further processing.

Due to the marginal stability of INH at room temperature, each blood sample should be processed within 1 hour of collection and immediately stored in the freezer.

Samples will be analyzed for INH and selected ARV drugs via liquid chromatography tandem mass spectrometry methods within an IMPAACT-approved Pharmacology Laboratory using a CPQA approved analytical method. Selection of ARV drugs for analysis will depend on available plasma and prioritizing of drugs will be based on which drugs a) have limited information in pregnancy, b) have the potential to contribute to hepatotoxicity, c) are commonly used among women enrolled in the intensive PK cohort, and d) are of high interest to the

investigators. See the Laboratory Processing Chart (LPC) for P1078 and any related information, on the P1078 study site of the IMPAACT website: http://www.impaactnetwork.org/studies/P1078.asp.

Non-compartmental PK analysis (using WinNonlin®) will be used to estimate the area under the plasma concentration versus time curve (AUC) during pregnancy and postpartum and other PK parameters as specified in 8.6.2.5. Estimation of a 24-hour AUC (for INH and as appropriate for ART) will be estimated using the 0 hour concentration as also the 24-hour concentration since participants will be at steady-state. Enrollment of 36 women will permit paired comparison of the AUC for INH in women receiving active drug antepartum versus postpartum and permit detection of a 40% difference in AUC; a difference deemed clinically significant. AUC estimates calculated will be dose corrected since variable INH doses (based on mg/kg weight) are permitted by the study. Likewise, AUC estimates for ART (12 or 24 hours depending on the regimen) will also be dose corrected in the event variable ART doses are administered. The study is powered to determine a significant difference in INH antepartum versus postpartum as women may receive variable HAART regimens.

The overall goal of objective 9.1.2 is to assess the relationship between genetic variants to NAT2, 2E1, and INH induced hepatotoxicity.

NAT2 and 2E1 genotype DNA will be collected in all participants and banked until toxicity data are collected. After hepatotoxicity data has been collected for the P1078 participants, women with hepatotoxicity and a control group of women without hepatotoxicity will be evaluated for the presence of NAT2 and 2E1 variants. It is assumed that variant frequencies for NAT2 and 2E1 range from 15 to 34 % (see Section 1.2) and INH hepatotoxicity rates are at least 10% (e.g., 9% of participants had INH associated hepatotoxicity defined as ALT 3 X ULN with either bilirubin > 2 X ULN or symptoms suggestive of hepatitis or ALT or bilirubin > 5 X ULN). Genetic variants will also be related to INH PK exposure as determined through intensive PK assessments and random samples collected in all women (see Appendix I-A). INH sampling will only be done once for all women during pregnancy and then only once for all women postpartum.

Population PK Assessment

All women, except those participating in the intensive PK, will be asked to provide a single random blood sample collected between two and twelve hours post INH/Placebo for INH dosing for population PK analysis and, for those women also on EFV, between ten and fourteen hours post-EFV dose (if not possible to collect post-EFV dose within this timeframe, collect pre-dose). This will be done during the third trimester (28 to 40 weeks gestation) and repeated at the Week 16 postpartum visit. Sample analysis will only occur at the end of the study for the women undergoing pharmacogenetic testing. Population samples will be analyzed using standard nonlinear mixed-effect modeling techniques. Correlations between hair concentrations of INH at these time points and plasma levels of INH will be performed.

Table 4: Pharmacogenetic Subsample Proportions

Number of cases: controls	True proportion with NAT2 variants among controls	Minimum detectable proportion with NAT2 variants among cases
80:120	5%	18.8%
	15%	33.1%
	25%	45.1%
	35%	56.1%
60: 140	5%	19.6%
	15%	34.2%
	25%	46.5%
	35%	57.5%
40: 160	5%	21.9%
	15%	37.2%
	25%	49.7%
	35%	60.8%

Table 4 shows the minimum detectable proportions of women with, say, NAT2 variants among those with INH hepatotoxicity if comparisons were made using Fisher's exact test with 5% significance level and 80% power, under varying true proportions with NAT2 variants among women without INH hepatotoxicity and varying ratios of controls to cases. For example, if a ratio of 1.5 controls to one case (that is, 80 women with INH hepatotoxicity and 120 women without INH hepatotoxicity) is used and it is assumed to have 15% relative frequency with NAT2 variants among women without INH hepatotoxicity, then with 80% power, a difference in proportions between the case versus the control group can be detected if the true proportion with NAT2 variants among women with INH hepatotoxicity were no less than 33.1%.

Genetic testing will be carried out at a selected IMPAACT laboratory. Please refer to the LPC for sample processing and shipping information.

10.0 Human Subjects

10.1 Institutional Review Board and Informed Consent

This protocol, the sample informed consent documents (Appendices IV-B, IV-C, and IV-D), and any subsequent modifications must be reviewed and approved by the IRB and/or EC responsible for oversight of the study. Written informed consent must be obtained from the parents or legal guardians of participants who cannot consent for themselves, such as those below the legal age. The informed consent will describe the purpose of the study, the procedures to be followed, and the risks and benefits of participation. A copy of the consent form will be given to the participant (or parent or legal guardian).

Each site which receives US HHS funding and follows the United States Code of Federal Regulations Title 45-Public Welfare, Part 46-Protection of Human Subjects (also known as the Common Rule) should have on record at the site a plan that detects and addresses any change in guardianship occurring in pediatric participants and determines when a study participant must

have a consent process which involves a legally authorized representative (LAR) other than a family member with guardianship. The plan will include how the site determines when a LAR is initially or no longer needed and how frequently the LAR re-signs the consent. The plan should follow all national, local, and state guidelines. The plan should be documented and filed in the appropriate regulatory file at the site but not submitted to DAIDS PRO.

10.2 Participant Confidentiality

All laboratory specimens, evaluation forms, reports, and other records will be identified only by a coded number to maintain participant confidentiality. All records will be kept in a secured area. All computer entry and networking programs will be done with coded numbers only. Clinical information will not be released without written permission of the participant, or the participant's parent or legal guardian, except as necessary for monitoring by the US FDA, the host country regulatory authorities, the Office for Human Research Protections (OHRP), the NIAID, NICHD, and local IRB or EC.

10.3 Study Discontinuation

The study may be discontinued at any time by the US FDA, IMPAACT Network, NIAID, NICHD, the IRB or EC, OHRP, or other country-specific governmental agencies as part of their duties to ensure that research participants are protected.

11.0 Publication of Research Findings

Publication of the results of this trial will be governed by IMPAACT policies. Any presentation, abstract, or manuscript will be made available for review by the sponsors prior to submission.

12.0 Biohazard Containment

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

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) for specific instructions and to the AIDS Clinical Trials Network (ACTN) Guidelines for Shipment and Receipt of Category B Biological Substance Shipment and ACTN Instruction for Overnight Shipments documents at http://www.hanc.info/labs/labresources/procedures/Pages/actnShippingDemo.aspx.

Infection control for active TB cases and good laboratory practices for TB isolation and storage of *M.tb.* isolates will be according to WHO guidance and best practices locally to minimize TB transmission.

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Appendix I-A: Schedule of Evaluations for All Women

	ANTEPARTUM						POSTPARTUM						
	Screen [1]	Entry	4 weeks after entry (± 2 wks)	8 weeks after entry (± 2 wks)	Every 4 weeks (± 2 wks)	Labor & Delivery [2] (+ 5 days)	4 weeks (± 2 wks)	8 weeks (± 2 wks)	12 weeks (± 2 wks)	16 wks (± 2 wks)	Every 4 weeks (± 2 wks)	Suspected Active TB [3]	Early Discontinuation Or last study visit, Week 48 (± 2 wks) [4]
CLINICAL EVALUATIONS													
Informed consent	X												
Medical/Medication History [5]	X	X	X	X	X	X	X	X	X	X	X	X	X
Complete physical exam [6]	X	X	X	X	X	X	X	X	X	X	X	X	X
Peripheral neuropathy screening tool [7]	X	X	X	X	X	X	X	X	X	X	X	X	X
Obstetrical exam [8]	X	X	X	X	X							X	X
Adherence training		X											
Adherence assessments and pill count [9]			X	X	X	X	X	X	X	X	X	X	X
Pill dispensing [10]		X	X	X	X	X	X	X	X	X	X		
TST assessment [11]						X	X[11]				Wk 44		
Contraceptive counseling [12]							X	X	X	X	X		X
Study medicine counseling [12]	X	X	X	X	X	X	X	X	X	X	X	X	X
LABORATORY EVALUATIONS													
Confirmation/Documentation of HIV infection [1]	(6 mL)												
CD4/CD8 lymphocyte subsets [13]	3 mL					3 mL							3 mL
Hematology [14]	X					X							
Chemistries [15]	2 mL	2 mL	2 mL	2 mL	2 mL	2 mL	2 mL	2 mL	2 mL	2 mL	2 mL	2 mL	2 mL
HIV RNA RT-PCR [16]		6 mL										6 mL	
Pregnancy test							Urine (5 mL) or serum (1 mL blood in SST or NON tube) test is acceptable. Only collected/performed when pregnancy is suspected or considered clinically indicated by the study site clinician.						
Plasma (Heparin) [17]		15 mL							20 mL		4 or 20 mL (Wk 44)	20 mL	20 mL (Wk 48)

	ANTEPARTUM						POSTPARTUM						
	Screen [1]	Entry	4 weeks after entry (± 2 wks)	8 weeks after entry (± 2 wks)	Every 4 weeks (± 2 wks)	Labor & Delivery [2] (+ 5 days)	4 weeks (± 2 wks)	8 weeks (± 2 wks)	12 weeks (± 2 wks)	16 wks (± 2 wks)	Every 4 weeks (± 2 wks)	Suspected Active TB [3]	Early Discontinuation Or last study visit, Week 48 (± 2 wks) [4]
Viable PBMC [18]		from above							from above		from above	from above	from above
Serum (SST or NON) [19]		1 mL											
Hepatitis B Surface Antigen (HBsAg) testing [20]		2 mL											
Interferon Gamma Release Assay (IGRA) and supernatant storage [21]		3 mL				3 mL					3 mL (Wk 44)	3 mL	
Hair collection				At the visits that coincide with 8 and 28 wks post-entry and Wks 20 & 40 postpartum									
Total Blood Volume (mL) *excluding PK studies*	5 – 11 mL	29 mL	2 mL	2 mL	2 mL	8 mL	2 – 3 mL	2 – 3 mL	2 – 23 mL	2 – 3 mL	2 – 26 mL	31 – 32 mL	5 – 26 mL
Pharmacokinetics													
Population PK (all women except those participating in the Intensive PK) [22]			4 mL							4 mL (± 4 wks)			
Intensive PK (0, 1, 2, 4, 6, 8, and 12 hrs post-dose; 4 mL at each time point) [23]			28 mL							28 mL (± 4 wks)			
Blood for DNA and pharmacogenetic variants (all women) [24]				3 mL, at the visit that coincides with 8 wks post-entry									
Total Blood Volume (mL) *for PK substudies*			3 – 31 mL			3 mL	3 mL			4 or 28 mL			

For insufficient blood draws, priorities are as follows:

- At screening: HIV test (if required), hematology, liver enzymes and other chemistries, CD4
- At Entry and follow-up visits:
  1) Safety (liver enzymes, hematology)
  2) TB diagnostics
  3) TB immunology
  4) Pharmacokinetics
  5) Virology

The volume of blood drawn shall not exceed 10.5 mL/kg or 550 mL, whichever is smaller, over any eight-week period.

1. Evaluations should be completed within 30 days prior to study entry. The screening visit may take place on the same day as the entry visit, as long as all screening results are obtained prior to study randomization. If sufficient documentation of HIV status as specified in Section 4.1.1 is not available, HIV diagnostic testing is to be done according to the specified algorithm.
2. The target visit window for the Labor & Delivery visit is up to 5 days postpartum, with an allowable visit window of up to 2 weeks. Every effort should be made to conduct the visit within the target visit window.
3. Suspected Active TB Visits:
   Diagnosis of incident active TB will be made using definitions in Appendix 100. A complete TB evaluation documenting recent exposures/ill contacts, clinical history of illness (i.e., duration of signs/symptoms), and workup performed to make diagnosis will be completed and samples for AFB smear(s) x 2 (induced if necessary), and/or Xpert, and/or culture(s) as well as any other TB diagnostics will be performed on appropriate clinical samples for any enrolled women at this visit. Culture-confirmed *M.tb.* isolates will be stored for drug susceptibility testing. If the woman is seen for a Suspected Active TB visit, the infant should also have a Suspected Active TB visit for evaluation and recommendation for TB prophylaxis care or treatment per Appendix I-B. See P1078 MOP for the suggested work-up for women suspected of having active TB.
4. For women who permanently stop study treatment and refuse any further study follow-up, i.e., off treatment/off study, OR postpartum Week 48. Women who meet a toxicity/intolerance endpoint will be considered off treatment/on study and will follow the usual schedule of study visits but will not undergo study procedures that are specific for women on INH/Placebo for INH (i.e., adherence assessment, pill count, PK samples, hematologies, chemistries) but will come in to clinic for routine evaluation and blood draws as scheduled (CD4, QGIT, stored sample, incident TB, and last study visit). If a toxicity endpoint is reached, follow-up testing needs to be done until resolution of the toxicity (see Section 6.1 for details).
5. General medical history, TB history, medications, obstetrical history, allergies, counseling on signs and symptoms of hepatitis, and assessment of signs & symptoms for active TB disease. WHO clinical staging for HIV to be assessed at Screening only. Signs and symptoms of neurocognitive impairment (including depression, sleep, and memory) will also be assessed at entry, every 12 weeks during the antepartum period, and postpartum Weeks 4, 12, 24, 36, and 48.

6. Complete physical exam includes vital signs (temperature, pulse, blood pressure, and respiration), assessment of general appearance, lymph node exam, and liver and spleen size, when feasible. Height will be assessed at the entry visit only and weight will be measured at every study visit (so BMI and change in weight can be calculated). Mid-Upper Arm Circumference (MUAC) will be performed at the Entry visit only (see P1078 MOP).
7. Validated ACTG brief peripheral neuropathy screen will be utilized (see P1078 MOP for peripheral neuropathy screen information).
8. Obstetrical exam includes gestational age assessment at the Entry visit (as defined by local investigator), fundal height, and fetal heart tones at all antepartum visits.
9. Adherence assessments using the standardized ACTG adherence questionnaire and pill counts will be completed at each indicated study visit until Week 40 postpartum. INH/Placebo for INH and pyridoxine (vitamin B_6) will be assessed.
10. Pill dispensing will be done up to postpartum Week 36 visit only; participants will receive study treatment until Week 40 postpartum only.
11. Tuberculin skin testing (TST) will be performed using standardized methods (see P1078 MOP) and will be done in all women at the Labor & Delivery and postpartum Week 44 visits, after the blood draw for plasma and IGRA. If TST is not obtained at the Labor & Delivery visit, sites may obtain at the Week 4 visit. Ideally, TST should be read 2-3 days after placement. However, it can be read by a trained observer up to 7 days from administration. A TST is defined in women in P1078 as positive if $\geq$ 5 mm.
12. See P1078 MOP for contraception counseling guidelines and guidance on signs and symptoms of INH side effects.
13. CD4/CD8 lymphocyte subsets must be performed at DAIDS-IQA certified laboratories. Dual platform labs only must have a WBC and differential to complete lymphocyte subset testing.
14. Hematology assessments (complete blood count, cell differential, and platelet count) to be completed from blood collected for CD4/CD8 lymphocyte subsets at indicated visits and as clinically indicated.
15. Liver enzyme tests will be done per the table below:

Study Visit	Chemistry Assessment(s)	Targeted Women
Screen	AST, ALT, total bilirubin (or direct bilirubin, if on atazanavir), glucose, and creatinine	All women
Entry and all other specified study visits	ALT	All women
As needed per Section 6.1	AST, ALT, and total bilirubin (or direct bilirubin, if on atazanavir)	Women with Grade 1 or higher ALT result

16. Every effort should be made to avoid drawing viral load determinations within 14 days of vaccination, systemic infection, or genital HSV outbreak, because of the potential for a transient increase in viral load in response to vaccination or infection. Quantitative HIV-1 RNA PCR must be performed at DAIDS-VQA certified laboratories using a VQA/DCLOT approved method. *It is recommended that the same HIV RNA test be used through all protocol visits.* Note: All participants should have an Entry visit viral load. If HIV viral load is completed at the Screen visit to confirm HIV infection, then that result can be used for both confirmation and Entry assessments.

17. Plasma in Heparin should be stored at the specified visits for future HIV-related and TB-related testing (e.g., baseline vitamin D levels; baseline immune profiles [e.g., immune activation markers] or metabolomic biosignatures among TB cases and non-cases for biomarker discovery; future HIV and TB studies). Blood should ideally be drawn prior to placement of TST.

Study Visit	Volume	Targeted Population
Entry	15 mL	Plasma – All women PBMCs – Approximately 700 women. TB ELISPOT will only be performed in approximately 460 women and the remaining samples will be stored for future testing
Postpartum Week 12	20 mL	Plasma & PBMCs – Approximately 460 women (same women who contributed samples for TB ELISPOT at Entry, if feasible)
Postpartum Week 44	20 mL	Plasma & PBMCs – Approximately 460 women (same women who contributed samples for TB ELISPOT at Entry and Postpartum Week 12, if feasible)
	4 mL	Plasma – Remaining women
Postpartum Week 48	20 mL	Plasma & PBMCs – Approximately 260 women (same women who contributed samples for TB ELISPOT at Entry, Postpartum Week 12, and Postpartum Week 44, if feasible)
Suspected Active TB Visit	20 mL	Plasma & PBMCs – Women who are evaluated for suspected active TB

18. TB ELISPOT will be performed on cryopreserved viable PBMCs (as described in the table above) at the end of the study. Collection of PBMCs will be site restricted.
19. Collect and store as indicated above and in the LPC. This specimen will be stored for future use in TB biomarker, antibody, inflammation, nutrition, or other TB/HIV related studies.
20. Enrollment should not be delayed until the results are available since HBsAg is not part of the inclusion or exclusion criteria. Women with positive HBsAg and their infant(s) should receive best available local standard of care.
21. QGIT: See the P1078 MOP and LPC for information on performing QGIT. Testing should not be performed on participants with suspected or confirmed TB, if prior to the indicated visit. At all indicated visits, QGIT will be performed in a blinded fashion in all women and blood should be drawn prior to TST placement, if applicable. If results are not obtained or are indeterminate, the test should be repeated within 4 weeks. Repeat tests should be minimized as much as possible to avoid interference of the TST with the QGIT results. Refer to Section 3.2, the MOP, and LPC for details regarding QGIT testing.

Study Visit	Assessment(s)	Targeted Women
Entry	Blinded QGIT, Stored QGIT supernatants	All women
Labor & Delivery	Blinded QGIT	All women
	Stored QGIT Supernatants	Subset of 260 women, as in P1078 LPC
Week 44 Postpartum	Blinded QGIT	All women
	Stored QGIT Supernatants	Subset of 260 women, as in P1078 LPC
Suspected TB visit	Blinded QGIT	Women with whom this visit is conducted
	Stored QGIT Supernatants	Women with whom this visit is conducted

22. Collect during the third trimester of pregnancy and then at the Week 16 postpartum visit (± 4 weeks).
23. Collect for women randomized to this collection on HAART, during the third trimester of pregnancy, and ≥ 2 weeks after start of INH/Placebo for INH and at the Week 16 postpartum visit (± 4 weeks).
24. DNA and Pharmacogenetic variant samples will be batch shipped.

Appendix I-B: Schedule of Evaluations for Infant Follow-up

	Birth [1] (+ 5 days)	4 Weeks (± 2 weeks)	8 Weeks (± 2 weeks)	12 Weeks (± 2 weeks)	24 Weeks (± 4 weeks)	36 Weeks (± 4 weeks)	44 Weeks (± 2 weeks)	Suspected Active TB [2]	Early Discontinuation Or last study visit, 48 Week (± 2 weeks)
CLINICAL EVALUATIONS									
History [3]	X	X	X	X	X	X	X	X	X
Physical Exam [4]	X	X	X	X	X	X	X	X	X
LABORATORY EVALUATIONS									
Hematology [5]	1 mL	1 mL		1 mL	1 mL			1 mL	1 mL
ALT	1 mL	1 mL		1 mL	1 mL			1 mL	1 mL
HIV Nucleic Acid Test (NAT) [6]	3 mL							3 mL	3 mL
TST [7]							X	X	
IGRA [8]							3 mL		
Plasma [9]	3 mL			8 mL	3 mL		8 mL	8 mL	
Viable PBMC [9]				from above			from above	from above	
Hair Collection	X				X				
Total Infant Blood Volume	8 mL	2 mL	0 mL	10 mL	5 mL	0 mL	11 mL	13 mL	5 mL

For insufficient blood draws, priorities are as follows:
1) Safety (hematology, chemistries)
2) TB diagnostics
3) TB immunology
4) Virology

No more than 5 mL/kg may be drawn for research purposes in a single day. No more than 9.5 mL/kg may be drawn over any eight-week period.

1. The target visit window for the Birth visit through day 5 of life, with an allowable visit window of up to 2 weeks. Every effort should be made to conduct the visit within the target visit window.
2. Suspected Active TB Visits:
   If the infant is suspected to have active TB, if the mother is seen for a Suspected Active TB visit, or if the infant is exposed to a TB source case, the infant should have a Suspected Active TB visit. Diagnosis of incident active TB will be made using definitions in Appendix 100. A complete TB evaluation documenting recent exposures/ill contacts, clinical history of illness (i.e., duration of signs/symptoms), and TST in infants will be performed using standard algorithms and definitions. If gastric washing is done as part of TB diagnosis work-up, a separate specimen should be collected and stored for future TB testing. Culture-confirmed *M. tb.* isolates will be stored for drug susceptibility testing. See P1078 MOP for the suggested work-up for infants suspected of having TB or exposed to known TB case.
3. History: TB exposure, diagnoses, medications, signs and symptoms, method of infant feeding, immunization record.
4. Birth Physical Exam: Birth/newborn exam, birth weight and length, gestational age, congenital abnormalities, gender and race.
   Follow-up Physical Exam: Weight, length, vital signs (temperature, heart rate, blood pressure and respirations), and examination of neurological status, lymph nodes, lungs and abdomen. Collection of infant blood pressure is optional; follow local standard of care.
5. Hematology: CBC with differential and platelets.
6. Infant HIV infection status will be assessed by HIV nucleic acid test. HIV DNA PCR is preferred; if not available HIV RNA PCR can be used. Infants with one initial positive HIV NAT test must have a specimen drawn on a different day than the sample that originally tested positive to confirm the results and infection status. Must be performed in a laboratory that operates according to GCLP guidelines and participates in the appropriate external quality assurance (EQA) program. Store any remaining sample for repeat testing.
7. The TST will be performed after the QGIT/ELISPOT assay blood draw. Ideally, TST should be read at 2-3 days after placement. However, it can be read by a trained observer up to 7 days from administration. A TST is defined as positive as ≥ 10 mm in HIV-negative infants and as ≥ 5 mm in HIV-positive infants. See P1078 MOP for standardized TST method.
8. QGIT: blood will be drawn for QGIT prior to placement of TST (see P1078 MOP) at the Week 44 study visit. If results are not obtained or are indeterminate, the test should be repeated within 4 weeks. Repeat tests should be minimized as much as possible to avoid interference of the TST with the QGIT results. Refer to the Section 3.2, the MOP, and LPC for details regarding QGIT testing. TB ELISPOT will be performed on stored PBMCs as described in footnote 9 below.

9. Plasma and PBMCs will be collected and stored at the specified visits for future HIV-related and TB-related testing (e.g., TB biomarker, antibody, inflammation, or nutrition studies). Blood volumes will be according to age appropriate guidelines. Blood should be drawn prior to placement of TST at the Week 44 and Suspected TB visits. See P1078 MOP and LPC for collection, processing, and shipment instructions.

Study Visit	Targeted Population
Birth	Plasma – All infants
Week 12	Plasma and PBMCs – Infants of the approximately 460 women from whom plasma and PBMCs are collected at postpartum Week 12
Week 24	Plasma – All infants for future HIV diagnostic testing that is not done as part of local standard of care. If HIV DNA PCR or HIV RNA PCR is done as part of local standard of care, the plasma will be used for other HIV or TB related future testing
Week 44	Plasma – All infants PBMCs – Infants of the approximately 460 women from whom PBMCs is collected at postpartum Week 44
Suspected Active TB visit	Plasma and PBMCs – Infants who are evaluated for suspected active TB

Appendix II: Brief Peripheral Neuropathy Screening (BPNS)

A Brief Peripheral Neuropathy Screening will be done on all mothers at every visit while on study. The screening will evaluate:

1. Symptoms in the feet and legs
2. Vibration perception through the interphalangeal bone of the great toe
3. Deep tendon reflexes in the Achilles tendon

The table below will be used to determine the grade of Peripheral Neuropathy at each visit based on the final BPNS score.

Grading of BPNS

Grade	Final BPNS score	
0	11 or 00	Normal or Currently Absent
1	1 – 3	Mild PN
2	4 – 6	Moderate PN
3	7 – 10	Severe PN

Please refer to the P1078 MOP for detailed instructions on how to perform and grade the Brief Peripheral Neuropathy Screening.

Appendix III: Modified Grading Table for Hepatotoxicity

	Grade 1	Grade 2	Grade 3	Grade 4
ALT (SGPT)	>1.25 - ≤3 X ULN	>3 - ≤5 X ULN	>5 - ≤10 X ULN	>10 X ULN
AST (SGOT)	>1.25 - ≤3 X ULN	>3 - ≤5 X ULN	>5 - ≤10 X ULN	>10 X ULN
Total bilirubin†	>1.25 - ≤2 X ULN	>2 - ≤3 X ULN	>3 - ≤10 X ULN	>10 X ULN
Symptoms*	As per DAIDS grading criteria			
† In lieu of total bilirubin, a direct bilirubin measurement will be used to assess and grade toxicity in women using Atazanavir. Toxicity grading using direct bilirubin will follow the grading levels for total bilirubin.				
* Symptoms or signs suggestive of hepatotoxicity include *unexplained* anorexia, nausea or vomiting, liver tenderness or hepatomegaly, acholic stools, bilirubinuria, or jaundice. Malaise and new or worsening fatigue are often included but are common in pregnancy. All these symptoms in isolation are non-specific for hepatotoxicity but should be graded and monitored as per Section 6.1.4.				

Appendix IV-A: P1078 Informed Consent Glossary

Adherence assessment	A way to check how well you are taking your medication
Adherence training	To help you correctly take your medication
Blood Chemistries	Blood tests that check your blood sugar and how your kidneys are working
CBC (Hematology tests)	A complete blood count that shows how many red and white blood cells that you have
CD4 cell count	A measure of the T-cell, a type of white blood cell in the immune system that helps protect the body from infections. The test is a way of measuring how much damage has been done to your immune system.
CD4/CD8 cell count	A measure of the number of white blood cells (T-cells) in the immune system that fight infection. The test shows how strong your immune system is.
Contraceptive counseling	Discussion of ways to help you prevent getting pregnant
Gastric washing	A test used to find out if the TB bacteria are present in mucous that is swallowed and is taken from the stomach
Genetic testing	Blood test to check the genes that are related to the purpose of the study
HBV (Hepatitis B screening)	A blood test to determine if you have the liver disease hepatitis B
HIV Nucleic Acid Test	A number of HIV tests that are used to identify the genetic material of the HIV virus (the building blocks that make up the virus) in the body, such as in the different parts of the blood and in tissues.
HIV DNA PCR	A blood test to check if the HIV virus is present in your blood
HIV-1 RNA or HIV Viral Load	A blood test which measures the amount of HIV in your blood
IGRA (Interferon Gamma Release Assay)	Special blood tests for tuberculosis. The tests are used to check if you may have TB. They are also used to check if you have the TB bacteria even if you are not feeling sick (or the TB bacteria are asleep).
Liver enzymes	Blood tests that check how your liver is working
M. tb.	*Mycobacterium tuberculosis*, the bacteria that causes Tuberculosis or TB
M. tb. smear	A test for tuberculosis, that uses some of the mucous you can cough up, to determine if you have tuberculosis (TB)
PK (Pharmacokinetics) - Population PK - Intensive PK	Blood tests to measure medication levels - In a specific group of people taking the same medication - Over a certain time period
Suspected TB visit	A visit that will be done if you may have tuberculosis (TB)
TST (Tuberculin skin test)	A test placed on the skin of your arm using a small needle that can help determine if you have been exposed to tuberculosis (TB)

Note: This glossary should be given to each individual who is considering participating in the study along with the informed consent.

Appendix IV-B: Sample Informed Consent

DIVISION OF AIDS (DAIDS)
INTERNATIONAL MATERNAL PEDIATRIC ADOLESCENT AIDS CLINICAL TRIALS NETWORK (IMPAACT)

SAMPLE INFORMED CONSENT

P1078: A Phase IV Randomized Double-Blind Placebo-Controlled Trial to Evaluate the Safety of Immediate (Antepartum-Initiated) Versus Deferred (Postpartum-Initiated) Isoniazid Preventive Therapy Among HIV-infected Women in High TB Incidence Settings

SHORT Name: "TB APPRISE" Stands for TB Ante vs. Postpartum Prevention with INH in HIV Seropositive mothers and their Exposed infants

SHORT TITLE FOR THE STUDY: P1078: TB APPRISE

Version 2.0, dated 28 October 2015

INTRODUCTION

You and your baby are being asked to take part in this research study because you are infected with HIV (the virus that causes AIDS) and you are pregnant. You live in an area where an infection called tuberculosis (TB) is common, and are not taking anti-TB drugs. You do not have active TB. This study is sponsored by the National Institutes of Health (NIH) in the United States. The investigator in charge of this study at this site is: (insert name of Principal Investigator). Before you decide if you want to be a part of this study, we want you to know about the study.

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

There is a separate list of special words used in this consent form, and the list includes an explanation of the words. A copy of the list will be given to you by the study staff to help you understand the special words in this consent form.

WHY IS THIS STUDY BEING DONE?

The main reason for this study is to see if INH (Isoniazid, a medication commonly used to treat or prevent TB) is safe in HIV positive pregnant and postpartum (after delivery) women. We want to see if INH protects pregnant women and their babies from getting TB. This study will also try to find out if starting INH during pregnancy is as safe as waiting until after delivery for your newborn baby. There have been many studies of INH in HIV positive people but few in pregnant and postpartum women. This study will also try to find out other ways to diagnose TB

in both mothers and their babies; it will look at how INH can affect the way the immune system reacts to TB or the TB vaccine, Bacille Calmette-Guérin (BCG) and will check INH levels in mothers' blood.

The study medication used in this study is an anti-TB medication called isoniazid or INH. INH has been used for treatment and for preventing TB since the 1950s. It has been well studied in adults with and without HIV; however, there are limited data for the use of INH in pregnancy, particularly when used in combination with HAART. INH is associated with side effects such as damage to your liver, nerve problems in your hands and feet (called peripheral neuropathy), and in rare instances can cause death. Being pregnant or having recently delivered may increase some of these side effects. Close monitoring of participants on INH will reduce the risk of adverse side effects, which will be done in this study, but it is important to know that these side effects can occur. The vitamins used in this study are prenatal multivitamins and pyridoxine (called vitamin B_6). This study will provide the study medication, multivitamins, and pyridoxine (vitamin B_6) to you. During this study, you will continue your anti-HIV therapy, however the anti-HIV medications will not be provided by the study. You will need to continue to obtain them from your primary care doctor as you have been doing.

HIV positive people have a weakened immune system, they are less able to fight tuberculosis (TB) infection and are more likely to develop active TB. As a result, the current World Health Organization (WHO) guidelines are recommending that all children and adults living with HIV, including pregnant women, those receiving antiretroviral treatment (ART), and living in areas where there is a high rate of TB should take INH prevention therapy. The recommendation is that INH should be taken for 6 to 36 months or as a life-long treatment in settings where HIV and TB are very common. Additionally, HIV infected people who may have TB symptoms should be tested for active TB or other conditions so that they are able to access the appropriate treatments.

Based on the WHO recommendations, your primary care doctor no longer needs to do a Tuberculin Skin Test (TST) to check if you have been exposed to TB before starting you on an INH regimen. Since the current recommendation for INH treatment during pregnancy is based on information learned before the time of HIV and use of anti-HIV medications, the correct time to start INH in pregnant women is not included in these new WHO recommendations because this information is not known. There is also no information at this time on how safe INH is for pregnant women, especially pregnant women who are also taking anti-HIV medications. This study has been developed to try to answer the following important questions:

- How safe is INH in HIV infected pregnant and postpartum women?
- What are the bad and good effects of INH given at the same time as anti-HIV medications on HIV infected pregnant and postpartum women?
- What is the best time to start INH in HIV infected pregnant and postpartum women?
- Will INH protect HIV infected pregnant women and their babies from getting TB?
- How safe is INH in the unborn and newborn baby if INH is given to HIV infected pregnant women?

To make the answers to these questions easier to find in this study, participants will be assigned, by chance, to either a group receiving INH during pregnancy as per WHO recommendations, or a group receiving INH only after 12 weeks after the delivery of the baby. In other words, there is a 1 in 2 chance (or 50%) that the INH treatment you get will not follow the WHO recommendations. All women are expected to receive at least 6 to 7 months of INH by the end of their participation in the study. However, INH/Placebo for INH may need to be stopped earlier if you experience any severe side effects. Your doctor will discuss this with you.

It is important that you understand that even if you choose not to participate in this study, you can still be treated with INH if your primary care doctor says you need to, or if advised by your country/local public health office, or if after knowing of these new WHO recommendations you decide that is what you want to do. You will get INH the same way you get other medicines from your primary care doctor.

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

After you have read and signed this consent form, you will have a screening visit to see if you can be in the study.

Screening Visit:
[Sites: add local information regarding how long the screening visit will take.]

The purpose of screening is to see if you are eligible for the study, including screening to see if you have active TB. If you do not have active TB, you may be able to take part in the study.

If you do have active TB, you cannot be in the study, but you will be referred to your primary care doctor so that you can receive the care that you need.

You will have the following done at the screening visit:

- Your medical history: You will be asked to answer many questions. These questions will be about your medical history in general, your pregnancy, your medical history as related to TB, how you have been feeling for the past 30 days, medications you are taking now, medications you have taken in the past, and your lowest ever CD4 cell count (the number of a type of white blood cells that helps protect the body from infections). You will also be asked if you had close contact in the last few weeks with someone who is confirmed to have active TB. You may also be asked questions about your sexual history and any drug and alcohol use. Any information provided about drug usage will not be shared with law enforcement.
- Counseling about signs and symptoms of INH side effects
- A physical exam: This will include weight, tests for nerve problems in your hands and feet (peripheral neuropathy), and an exam for pregnant women (obstetrical exam). You will also be educated about the signs and symptoms of active TB and be asked to come in for a visit if any of the symptoms of active TB develop during the study.
- Blood tests: About 5 mL (1 teaspoon) of blood will be taken from a vein for routine safety tests (Complete Blood Count or CBC, blood chemistries and liver enzymes, and to measure the number of white blood cells that fight infection or CD4/CD8 cell count).

- A confirmation of your HIV infection: We may also take up to 6 mL of blood to test you to confirm your HIV status.

You will be told the results of these blood tests as soon as they are available.

If you do not enroll into the study:
If you do not take part in this study for any reason, we would still like to use some of your information. As part of the screening visit, some demographic (such as age, gender, race), clinical (such as disease condition, diagnosis), and laboratory (such as CD4 cell count) information will be collected so that IMPAACT researchers may help find out if there are patterns or common reasons why people do not join a study.

If you are eligible and decide to enroll in the study, you will have an entry visit within a month after screening.

Enrollment and Follow-up Visits:
You will be randomized (like the flip of a coin) to have an equal chance of starting INH immediately or waiting until 12 weeks after you deliver your baby to start INH. If you are not randomized to start INH immediately, you will start a placebo (a tablet that looks like INH but does not have any real medicine in it) and will be switched to INH 12 weeks after you deliver. If you are randomized to INH immediately, you will receive it for 28 weeks and then switch to Placebo for INH. You and the site staff will not know at which point you are receiving INH or Placebo for INH while you are in the study. This means you and the site staff are "blinded" to the treatment. All pregnant women entering the study will receive INH or Placebo for INH once a day until their baby is born. All women will receive INH or Placebo for INH up to 40 weeks after delivery, and then be followed in the study for 8 more weeks after finishing the study medication.

In addition to receiving INH or Placebo for INH, you will also be given vitamin B_6 and prenatal multivitamins to be taken by mouth once a day until 40 weeks after your baby is born.

You will come to the clinic about every 4 weeks while you are in the study. The study staff will let you know about how long the study visits and procedures will take. The study staff will also let you know if you need to come back to the clinic for additional visits to complete all of the study evaluations. This study has up to 21 visits for some women.

If you have any problems or have any new signs or symptoms, you should call the study investigator as soon as possible. The study staff will tell you about some of the specific risks from INH or Placebo for INH in the sections below. The study staff will also tell you what you should do if you develop any signs or symptoms from INH toxicity.

Table 1

	Entry	Every 4 Weeks Before Delivery	Labor & Delivery	Every 4 Weeks After Delivery	Sick Visit	Final Visit
History and review of medications	X	X	X	X	X	X
Physical Exam	X	X	X	X	X	X
Obstetrical Exam	X	X				
Peripheral Neuropathy Exam	X	X	X	X	X	X
Pill Dispensing	X	X	X	X		
Pill Count		X	X	X	X	X
Adherence Assessment		X	X	X	X	X
CBC			X			
CD4/CD8			X			X
Viral Load	X				X	
Liver Enzymes	X	X	X	X	X	X

At your entry visit you will have:

[*Sites: add local information regarding how long the entry visit will take*].

- The examinations and tests shown in Table 1 under the column "Entry."
- As part of your medical history, you will be asked to complete a questionnaire about any symptoms of depression or problems you may have with sleep, memory, or ability to focus. Your doctor will review your answers to this survey with you. If you have any signs or symptoms of depression or problems with sleep, memory, or ability to focus, or you would like to speak to someone about how you are feeling, your doctor will refer you to care according to local standards of care. You will also be asked to complete this questionnaire every 12 weeks before your delivery and at your week 4, 12, 24, 36, and 48 visits after you deliver your baby.
- A physical exam, including height (at entry visit only).
- Adherence training.
- Counseling about signs and symptoms of INH side effects.
- Blood tests – Up to about 29 mL (about 6 teaspoons) of blood will be taken from a vein:
  - About 10 mL (2 teaspoons) will be for the tests in Table 1 and Hepatitis B (HBV) screening. Note: The site investigator will receive the results of the Hepatitis tests and will discuss the results with you.
  - About 3 mL (a little more than ½ teaspoon) will be for a first type of Interferon Gamma Release Assay (IGRA) test (a special TB test). This test will be done in all women. If there are no results from the test, you will be asked to come back within 4 weeks to repeat the test.
  - About 15 mL (3 teaspoons) will be used for the following tests:
    - For all women, a portion of the blood will be stored for future tests.
    - For around 460 women from selected sites, another portion of the blood will be used for a second type of IGRA test.
    - For an additional group of around 240 women from selected sites, another portion of the blood will be stored for future tests.

    Note: There are 2 types of IGRA tests that will be used for this study, and both are special TB tests. All women will have the first type of IGRA test. The second type of IGRA test will only be done in some women throughout the study. The IGRA tests are for investigation only and have not been confirmed for pregnant women and adults with HIV. Because the tests are for investigation only, you or the site investigator will not be

told of the results.

The site investigator may ask you to come back to the clinic sooner than your next visit if any of your laboratory results are abnormal.

Every 4 weeks before delivery you will have:

[*Sites: add local information regarding how long the visits will take*].

- The examinations and tests shown in Table 1 under the column "Every 4 Weeks Before Delivery."
- Counseling about signs and symptoms of INH side effects.
- Blood tests – About 2 mL (less than ½ teaspoon) will be taken from a vein for the tests in Table 1.

  The site investigator may ask you to come back to the clinic sooner than your next visit if any of your laboratory results are abnormal.

At your labor and delivery visit you will have:

[*Sites: add local information regarding how long the visit will take*].

- The examinations and tests shown in Table 1 under the column "Labor & Delivery."
- Counseling about signs and symptoms of INH side effects.
- Blood tests – About 5 mL (1 teaspoon) of blood will be taken from a vein for the tests shown in Table 1.
- A Tuberculin Skin Test (TST) will also be done. A trained clinic staff member will try to read the test ideally within 2-3 days but up to 7 days afterwards. The staff will try to read the test while you are in the hospital after delivery. You may have to return to the clinic within 7 days after the TST was placed if your doctor says you can go home before the test is read. If you do not have a TST test done at your labor and delivery visit, you will have a TST test done at your Week 4 postpartum visit.
- About 3 mL (a little more than ½ teaspoon) of blood will be taken for an IGRA test (the same IGRA test that was done at entry). This will be done in all women.

The site investigator may ask you to come back to the clinic sooner than your next visit if any of your laboratory results are abnormal.

Study visits after you have your baby:

[*Sites: add local information regarding how long study visits will take*].

After you have your baby, you will come to the clinic every 4 weeks for 48 weeks (about 1 year). At each visit you will have:

- The examinations and tests shown in Table 1 under the column "Every 4 Weeks After Delivery."
- Blood tests – About 2 mL (less than ½ teaspoon) will be taken from a vein for the tests shown in Table 1.
- Contraceptive counseling and counseling about signs and symptoms of INH side effects.
- You may also be asked to give an additional 1 mL of blood or a urine sample to test for pregnancy if you, the site investigator, or nurse think(s) you may be pregnant.
- At 12 weeks after delivery, around 460 women (the same 460 women who had the second type of IGRA test at entry) will have 20 mL (4 teaspoon) of blood taken for another IGRA test and a portion stored for future tests.
- In addition, at 44 weeks after you have your baby you will have:

- A TST will be done. You will need to return to the clinic ideally within 2-3 days, but up to 7 days, afterwards so the TST can be read by a trained clinic staff.
- About 3 mL (a little more than ½ teaspoon) of blood will be taken for the first type of IGRA test. If there are no results from the test, you will be asked to come back within 4 weeks to repeat the test.
- In addition, about 4 – 20 mL (a little less than 1 teaspoon – 4 teaspoons) of blood will be taken for the following tests:
  - For around 460 women (the same 460 women who had the second type of IGRA test at entry and 12 weeks after having their baby), 20 mL (4 teaspoons) of blood will be taken. A portion of the blood will be stored for future tests and another portion will be used for the second type of IGRA test.
  - If you are not part of the group of 460 women, 4 mL of blood (a little less than 1 teaspoon) will be taken and will be stored for future tests.

The site investigator may ask you to come back to the clinic sooner than your next visit if any of your laboratory results are abnormal.

Sick Visit (Suspected Active TB Visit):
If you or the site investigator thinks you may have TB at any time during the study, you will have the examinations and tests listed under sick visit in Table 1 under the column "Sick Visit."

In addition, you will have:
- A physical and, if you are pregnant, obstetrical exam.
- Counseling about signs and symptoms of INH side effects.
- You may also be asked to give an additional 1 mL of blood or a urine sample to test for pregnancy if you, the site investigator, or nurse think(s) you may be pregnant.
- Blood tests – About 31 mL (about 7 teaspoons) of blood will be taken from a vein:
  - About 8 mL (about 2 teaspoons) will be for the tests shown in Table 1.
  - About 3 mL (a little more than ½ teaspoon) of blood will be taken for the first type of IGRA test.
  - About 20 mL (4 teaspoons) will be used for the following tests:
    - A portion of the blood will be stored for future tests.
    - Another portion of the blood will be used for the second type of IGRA test.
- Samples will also be taken for an *M. tb.* (*Mycobacterium tuberculosis*, the bacteria that causes Tuberculosis or TB) smear to check if you have TB and a test to check what medications will work for your TB.
- Other tests may be done if the site investigator feels they are needed to diagnose TB.

At your early discontinuation or last study visit you will have:
The examinations and tests shown in Table 1 under the column "Final Visit."
- Contraceptive counseling and counseling about signs and symptoms of INH side effects.
- Blood tests – About 5 mL (1 teaspoon) of blood will be taken from a vein for the tests shown in Table 1.
- At the last study visit or 48 weeks after delivery, around 260 women (the same women who had the second type of IGRA test at entry, 12 weeks after having their baby and 44 weeks after having their baby) will have 20 mL (4 teaspoon) of blood taken for another IGRA test and a portion stored for future tests.

- You may also be asked to give an additional 1 mL of blood or a urine sample to test for pregnancy if you, the site investigator, or nurse think(s) you may be pregnant.

Intensive Pharmacokinetics (PK) (about 36 women are needed for this special study):
There is a special PK study (and a separate consent for it) that requires about 28 mL (a little less than 6 teaspoons) of blood and 12 hours of your time. This special PK study will be done two times, one while you are pregnant and the other after you have your baby. The tests will measure the amount of INH and the amount of some anti-HIV medications in your blood over a specific time period. You must be at least 28 weeks pregnant when you enter this study to be able to participate in the special PK study. Please ask the site investigator, if you are interested in this.

- The first blood sample will be taken at a scheduled visit when you are in your third trimester of pregnancy.
- The second blood sample will be taken at a scheduled visit about 16 weeks after your baby is born.

Population Pharmacokinetics (PK) (done for all women except those that will be in the Intensive PK):
You will have two blood samples taken and stored to be used later for a population PK test, one while you are pregnant and the other after you have your baby. The sample will be taken at a time point at least 2 hours but not more than 12 hours after you receive INH or Placebo for INH. If you are taking the medicine efavirenz (EFV), the sample will be taken at a time point at least 10 hours but no more than 14 hours after you have taken EFV. The site staff will let you know when this sample will be taken. You may be asked to remain in the clinic or return later in the day to have this blood sample taken. The amount of blood that will be taken for both PK samples is about 4 mL (a little less than 1 teaspoon). These tests will measure the amount of INH in your blood.

- The first blood sample will be taken at a scheduled visit when you are in your third trimester of pregnancy.
- The second blood sample will be taken at a scheduled visit about 16 weeks after your baby is born.

Not all the blood will be tested. The test will only be done on the samples from women who have some liver damage while in the study and on about the same amount of samples from a group of women who do not get liver damage while in the study (or the same women who will have the genetic testing that is described next). The samples that will be tested will be chosen after the study is completed. You or the site investigator will not be told the results because the test is for investigation only and will be done after the study is completed.

Blood for genetic testing (done for all women):
You will have about 3 mL (a little more than ½ teaspoon) of blood taken about 8 weeks after you enter the study for a test to check the genes that are related to what we are looking at in this study. The blood will be stored, and the test will be done at the end of the study. Not all the blood will be tested. The test will be done on the samples from women who get some liver damage while in the study. The test will also be done on about the same amount of samples from

women who do not get liver damage while in the study. The samples that will be tested will be chosen after the study is completed. You or the site investigator will not be told of the results because the test is for investigation only and will be done after the study is completed.

Study visits for baby(ies) born to mom in the study:

Table 2

	Birth	4 weeks	8 weeks	12 weeks	24 weeks	36 weeks	44 weeks	Sick Visit	Final Visit
History	X	X	X	X	X	X	X	X	X
Physical Exam	X	X	X	X	X	X	X	X	X
CBC	X	X		X	X			X	X
Liver Enzymes	X	X		X	X			X	X
HIV Nucleic Acid Test	X							X	X

Your baby will be seen for the visits shown in Table 2 until you (mother) complete the 48 weeks on study after you have your baby. These visits will be at the same time as yours and will be scheduled at the same time as your well-baby visits as much as possible. At each scheduled visit:

- Your baby will have the examinations and tests shown in Table 2 under the column for each specific visit.
- You will be asked questions about your baby's TB exposure, signs and symptoms that may mean your baby has active TB, medications, other current illnesses you have and how you feed your baby. You will also be asked questions about how your baby is doing.
- Your baby will have blood tests – About 2 mL - 11 mL (less than ½ teaspoon to a little more than 2 teaspoons) of blood will be taken for:
  - About 2 mL - 5 mL (less than ½ teaspoon to 1 teaspoon) will be for the tests at Birth, 4 weeks, 12 weeks, and 24 weeks that are shown in Table 2. If the result of the HIV Nucleic Acid Test (NAT) test at birth shows that the HIV virus is present in your baby's blood, the test will be repeated on a different day to confirm the result.
  - At birth and 24 weeks, about 3 mL (a little more than ½ teaspoon) will be for future HIV and TB testing if it is needed. If future HIV testing is not needed, the blood will be used for other future HIV or TB related tests.
  - At 44 weeks, about 3 mL (a little more than ½ teaspoon) will be for the first type of IGRA test.
- In addition, at 44 weeks your baby will have a TST. Your baby will need to return to the clinic ideally within 2-3 days but up to 7 days afterwards so the TST can be read by a trained clinic staff.
- At 12 weeks, the babies of around 460 women (the 460 women who have the second type of IGRA test at entry and 12 weeks after having their baby) will have 8 mL (a little more than 1 ½ teaspoon) of blood taken for the second type of IGRA and a portion will be stored for future tests.
- At 44 weeks, an additional 8 mL (a little more than 1 ½ teaspoon) of blood will be taken and used for the following tests:
  - For all babies, a portion of the blood will be stored for future HIV and TB tests.

- For the babies of around 460 women (the 460 women who have the second type of IGRA test at entry, 12 weeks after having their baby and 44 weeks after having their baby), another portion of the blood will be used for the second type of IGRA test.

NOTE: The IGRA tests used in this study are for investigation only and have not been confirmed for children and babies. Because the tests are for investigation only, you or the site investigator will not be told of the results.

No more than 13 mL (about 3 teaspoons) of blood will be taken from your baby for any of the visits in the study.

Sick Visit (Suspected Active TB Visit) for the baby:

If you or the site investigator thinks your baby may have TB at any time during the study, your baby will have the examinations and tests listed under "Sick Visit" in Table 2. The following will also be done during the sick visit:

- You will be asked questions about your baby's TB exposure, signs and symptoms that may mean your baby has active TB, and other current illnesses that your baby may have.
- Blood tests – About 13 mL (about 3 teaspoons) of blood will be taken from a vein:
  - About 5 mL (1 teaspoon) will be for the tests shown in Table 2.
  - About 8 mL (a little less than 2 teaspoons) will be used for the second type of IGRA test and will be stored for future tests.
- A TST will be done. Your baby will need to return to the clinic ideally within 2-3 days but up to 7 days afterwards so the TST can be read by a trained clinic staff.
- Additional tests as needed to confirm that your baby has TB. If a mucous sample is not available from your baby, a test called gastric washing may have to be done. The test will check if there are any *M. tb.* bacteria in a sample of liquid taken from your baby's stomach. The site investigator can explain how the test is done.
- If the *M. tb.* bacteria are found in a sample or samples taken from your baby, it will be used for a test to check what medications work with your baby's TB.
- Other tests may be done if the site investigator feels it is needed to diagnose TB.

If you (mother) have a sick visit because you may have TB, your baby will also have a sick visit to check if your baby may have TB. If you (mother) have been started on anti-TB medications because you may have TB or your baby had confirmed contact with someone who may have TB, your baby will also have a sick visit to check if your baby may have TB.

Hair collection:

With your permission, a small sample of hair (about 100 strands) will be cut from your and your baby's heads so that so that we can measure levels of INH and some anti-HIV medications in this small hair sample. Your hair will be cut at 8 and 28 weeks after you enter the study and at 20 and 40 weeks after your delivery. Your baby's hair will be cut at birth and 24 weeks after birth. Drug levels in hair may give us a better idea of long-term exposure to a drug. Please note, humans lose about 100 hairs from their head every day naturally, so this amount of hair removal should not be noticeable. You or the site investigator will not be told the results of this test because the test is for investigation only and will be done after the study is completed.

You will be asked if you agree to have your and your baby's hair collected when you sign this consent form. If you do not agree to have you and your baby's hair collected, or you change your mind later, you can still participate in this study.

Specimen storage and future use for mother and baby:
With your permission, some of your and your baby's blood will be stored as described in previous sections of this consent form. In addition, any leftover or unused samples that are taken for the tests in this study may also be stored after the tests are done instead of being destroyed. All the samples that will be stored may be used for future IMPAACT-approved HIV-related and TB-related research studies. There will be no information that directly identifies you or your baby on the blood samples that will be stored. The samples may be sent to the US or any of our approved IMPAACT partners for storage and testing. You will not be told the results of these tests because they will be done in the future.

Your and your baby's samples may be stored at a special laboratory facility in the US called a repository. Only approved researchers will have access to them. People who work at the facility will also have access to your and your baby's samples to keep track of them. These people will not have information that directly identifies you or your baby. Your and your baby's samples will not be sold or directly used to produce commercial products. All proposed research studies using your and your baby's samples will be reviewed by the National Institutes of Health (NIH). There is no time limit on how long your or your baby's samples will be stored.

The researchers will not contact you or your baby's primary care doctor with the results of studies done using your or your baby's stored samples. This is because research studies are often done with experimental procedures or may be done several years after the study has ended. The results of such studies should not be used to make decisions about you or your baby's medical care. If the researchers decide that the result of a certain study provides important information for your or your baby's medical care, the site investigator will be notified. If you would like to be contacted with this sort of information, you must notify the study staff of any changes in your address or phone number.

You will be asked if you agree to have your and your baby's samples stored when you sign this consent form. You may decide that you do not want your or your baby's samples stored for future research studies. You and your baby can still participate in this study even if you make this decision. You may withdraw your consent for the storage and use of your or your baby's samples at any time. If you withdraw your consent, these stored samples will be destroyed.

OTHER INFORMATION

Information provided throughout this study about sexual history and any drug and alcohol use will not be shared with parents or caretakers of adolescent participants.
[Sites should modify the preceding language about confidentiality of sexual activity and any drug and alcohol use to conform to their local practice, regulations and IRB/EC requirements.]

HOW MANY PEOPLE WILL TAKE PART IN THIS STUDY?

About 950 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 48 weeks after you have your baby.

Your baby will be in this study for about 48 weeks.

WHY WOULD THE SITE INVESTIGATOR TAKE ME/MY BABY OFF THIS STUDY EARLY?

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

- The study is cancelled by the US Food and Drug Administration (FDA), IMPAACT Network, National Institute of Allergy and Infectious Diseases (NIAID), National Institute of Child Health and Human Development (NICHD), 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 or your baby are not able to attend the study visits as required by the study.

The site investigator may also need to take you off the study medication without your permission if:

- You are diagnosed with TB disease or TB infection.
- Continuing the study medication may be harmful to you or your baby.
- You start taking the anti-TB medication INH that is provided outside of the study.
- You or your baby need(s) a treatment that you or your baby may not take while on the study medication.
- You are not able to take the study medication as required by the study.
- You become pregnant.
- You experience some severe side effects from the study medication.

During the study:
If you must permanently stop taking study-provided anti-TB medication (INH), prenatal multivitamins, and vitamin B_6 before your study participation is over, the study staff will discuss other options that may be of benefit to you or your baby. The site investigator may ask you and your baby to continue to be part of the study and return for some study visits and procedures.

After the study:
If continuing to take these or similar medications or vitamins would be of benefit to you, the study staff will discuss how you may be able to obtain them.

WHAT ARE THE RISKS OF THE STUDY?

Side effects of INH

There may be an increase in some liver function tests indicating that there may be some damage to the liver. The risk may also be increased during pregnancy and within three months after you give birth. The risk may also be more serious or more common if you are receiving antiretroviral medications for HIV, if you already have some liver damage, if you drink alcohol regularly, if you are older, or if you are using injection drugs.

Signs of liver problems may include: loss of appetite, weight loss, nausea (feeling sick to the stomach) and vomiting; pain in upper abdomen; stools lighter in color; increased weakness and fatigue; and/or yellowing of eyes or skin. Other signs of liver problems may include: changes in the color of urine; loose or watery stools; skin rash; or fever.

These side effects are usually temporary. However, in rare cases, liver damage from INH can be very serious or even cause death.

PLEASE NOTE: If you experience any of these symptoms, immediately stop taking INH or Placebo for INH, seek immediate medical attention, and contact the site investigator as soon as possible.

INH can sometimes cause nerve damage. Signs of nerve damage may include tingling and numbness in the hands and feet. This is the most common side effect.

Other side effects may include: memory loss, confusion, trouble sleeping, changes in behavior or mood, changes in vision, clumsiness, unsteadiness or dizziness, seizures, low blood counts, high blood sugar, joint pain, and lower vitamin B_6 levels. (Vitamin B_6 is a vitamin that helps with many functions in your body.)

Some medications used to treat TB may also cause diarrhea (loose or watery bowels), including bloody diarrhea, which may be serious.

Side Effects of Placebo for INH

Placebo for INH side effects may include mild nausea and the feeling of being sick to your stomach.

Tuberculosis

If you develop or your baby develops TB, you and your baby will be followed as part of clinical care. 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.

There is a risk of resistance to INH and that this anti-TB medication may not work as well, if you do develop TB.

Risks of Blood Draws

In this study, there are risks from drawing blood. You or your baby may feel some discomfort when blood is drawn for this study. Other risks may include bleeding, bruising, and swelling or a small blood clot may form where the needle enters the body. There is a small risk of a minor infection where the needle for blood drawing enters the body. In rare cases lightheadedness or fainting can occur.

Other risks

There may be other risks to taking part in this study that are not known at this time. For your and your baby's safety, you must tell the site investigator or nurse about all medications you and your baby are taking/getting 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 site investigator or nurse before you or your baby enrolls in any other clinical trials while on this study.

If you join this study, some hospital staff and all study staff will know that you have HIV. These workers are very serious about your privacy (see CONFIDENTIALITY). Study staff will make every possible effort to be sure that others do not learn your HIV status. However, sometimes if you receive special treatment or attend a special clinic, it may make others wonder if you have HIV.

ARE THERE RISKS RELATED TO PREGNANCY?

It is not known if the anti-TB medication (INH) may harm unborn babies. After you have your baby, you must agree not to become pregnant again, while taking INH or Placebo for INH. You and your partner must use reliable birth control that you discuss with the site investigator and/or the study staff.

You must continue to use the birth control until 1 month after stopping the anti-TB medication.

Breastfeeding

If you are breastfeeding your baby, he or she can get some of the anti-TB and multivitamin medicines that you are taking from the breast milk. It is unknown whether the anti-TB medication may cause harm to your baby.

WHAT ABOUT CONFIDENTIALITY?

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

Your records and your baby's records may be reviewed by the US 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, and host country regulatory authorities.

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

ARE THERE BENEFITS TO TAKING PART IN THIS STUDY?

If you and your baby take(s) part in this study, there may be a direct benefit to you and your baby, but no guarantee can be made. Taking an anti-TB medication like INH may be of benefit to you and your baby. Taking a prenatal multivitamin and 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 you and your baby may receive no benefit from being in this study. Information learned from this study may help others who have HIV.

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

Instead of being in this study you have the choice of:
- Continuing standard of care for you and your baby.
- Treatment with other anti-TB medications available to you or your baby, if necessary. INH is an option in addition to other anti-TB medications.
- Treatment with experimental drugs, if you or your baby qualify.

Please talk to the site investigator about these and other choices available to you and your baby. The site investigator will explain the risks and benefits of these choices.

[Note: For sites where INH is routinely provided to HIV-infected pregnant women, please complete the SIC addendum in Appendix IV-D.]

WHAT ARE THE COSTS TO ME?

Taking part in this study may lead to added costs to you and your insurance company. In some cases, it is possible that your insurance company will not pay for these costs because you and your baby are taking part in a research study.
[Sites: modify or delete language regarding insurance as appropriate for your site and insert appropriate language for local costs]

WILL I RECEIVE ANY PAYMENT?

You and your baby may receive reimbursement for some expenses for this study. You and/or your baby may receive payment for transportation or meals. *[Site-specific-TBD]*

WHAT HAPPENS IF I AM/MY BABY IS INJURED?

If you and/or your baby are 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 take part/not to allow your baby to take part in this study or leave this study/take your baby out of the study at any time.

Your decision will not have any impact on your or your baby's participation in other studies and will not affect your access to medical care. We will tell you about new information from this or other studies that may affect your or your baby's health, welfare, or willingness to stay in this study. If you want the results of the study, let the study staff know.

WHAT DO I DO IF I HAVE QUESTIONS OR PROBLEMS?

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

For questions about your or 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 read and explained to you), all of your questions have been answered, and you agree for you and your baby to take part in this study, please indicate your choices and sign your name below.

A parent or legal guardian that agrees for a minor pregnant woman to take part in the study and signs below also agrees and signs for the newborn infant to participate in the study.

Stored specimens, including blood, plasma, and serum:

____ Yes ____ No You agree to the storage and use of your stored specimens and your baby's stored specimens for future tests as discussed in this consent form, including genetic testing.

_____ Yes ____ No You agree to the storage and use of your stored specimens and your baby's stored specimens for future tests as discussed in this consent form, EXCEPT for genetic testing.

Hair:

____ Yes ____ No You agree to the storage and use of your and your baby's hair as discussed in this consent form.

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

Appendix IV-C: Pharmacokinetic Analysis of Isoniazid (INH) Intensive Pharmacokinetic Subset Consent

PHARMACOKINETIC ANALYSIS OF ISONIAZID (INH)

INTENSIVE PHARMACOKINETIC SUBSET CONSENT

P1078: A Phase IV Randomized Double-Blind Placebo-Controlled Trial to Evaluate the Safety of Immediate (Antepartum-Initiated) Versus Deferred (Postpartum-Initiated) Isoniazid Preventive Therapy Among HIV-infected Women in High TB Incidence Settings

SHORT Name: "TB APPRISE" Stands for TB Ante vs. Postpartum Prevention with INH in HIV Seropositive mothers and their Exposed infants

SHORT TITLE FOR THE STUDY: P1078: TB APPRISE

Version 2.0, dated 28 October 2015

WHY IS THIS STUDY BEING DONE?

You have agreed to be in a study to see if the anti-TB medication Isoniazid (INH) may prevent you and your (unborn) baby from becoming ill or infected with tuberculosis (TB). To help us determine whether or not the INH dose that you are taking makes a difference in the amount of illness you or your baby has, you will have repeat blood samples taken while you are pregnant and after you have your baby, to measure the amount of INH in your blood. This is called a pharmacokinetics or PK study.

WHAT DO I HAVE TO DO TO TAKE PART IN THIS INTENSIVE PHARMACOKINETICS (PK) STUDY?

If you are at least 28 weeks pregnant when you enter the main part of the study, you may be selected to take part in an intensive PK study if you are on highly active antiretroviral medication (HAART) and INH or Placebo for INH. You will have to stay at the clinic or hospital for over 12 hours and have blood drawn at 7 time-points for the PK study. A total of 36 women are needed for the intensive PK study.

Intensive PK study (while you are pregnant AND after you have your baby)

- The first blood sample will be taken while you are in the third trimester of your pregnancy at least 2 weeks after you start INH or Placebo for INH.
- The second blood sample will be taken at a scheduled visit about 16 weeks after your baby is born.

At each of the two visits, you will have a little less than 1 teaspoon of blood (4 mL) taken before you take your medications (time 0). While in the clinic, you will be given your dose of INH or Placebo for INH, prenatal multivitamin and vitamin B_6 without food (either fasting 1 hour before a meal or 2 hours after a meal). You will also be given your HAART medication at the same

time that you are given your dose of INH or Placebo for INH. At 1, 2, 4, 6, 8, and 12 hours after you have taken your anti-TB and HAART medications, a little less than 1 tsp of blood (4 mL) will be taken at each time point to measure the amount of INH in your blood during the day. Sometimes a heparin-lock is used when more than one blood sample is taken over a period of time. A heparin-lock is a small tube left in the vein until all of the blood samples have been taken. Then it is removed. This allows blood to be taken from a vein many times without sticking you again. A little less than 6 teaspoons (about 28 mL) of blood will be taken in all, for the PK tests.

HOW LONG WILL I BE IN THIS PK STUDY?

You will be in the intensive PK study as part of a scheduled visit, for the main study. The intensive PK study will take more than 12 hours, on that visit day. The 12 hour study will be done once during your third trimester of pregnancy at least 2 weeks after you start INH or Placebo for INH, and again about 16 weeks after your baby is born.

HOW MANY WOMEN WILL TAKE PART IN THIS PK STUDY?

About 36 women are needed for this intensive PK study.

WHAT ARE THE RISKS OF THIS PK STUDY?

Blood drawing may cause some pain, discomfort, bleeding, or bruising where the needle enters the skin. Blood drawing may also cause a lightheaded feeling, and in rare cases, fainting. A small blood clot may form at the site where the needle enters the skin or swelling of the surrounding skin may occur. There is also a small risk of a minor infection at the blood draw site.

WHAT ABOUT CONFIDENTIALITY?

Efforts will be made to keep your personal information confidential. We cannot guarantee absolute confidentiality. Your personal information may be disclosed if required by law. Any publication of this study will not use your name or identify you personally.

Your records may be reviewed by the US 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, and host country regulatory authorities.

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

ARE THERE ANY BENEFITS TO TAKING PART IN THIS STUDY?

You will receive no benefit from taking part in this study but the results may let us learn if INH works differently in the same women, when they are pregnant and after their baby is born.

WILL I RECEIVE ANY PAYMENT?

You will be reimbursed for expenses such as childcare and travel to take part in the intensive PK study. *[Site-specific-TBD]*

WHAT DO I DO IF I HAVE QUESTIONS OR PROBLEMS?

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

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

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

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

SIGNATURE PAGE

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

All other information that is contained in the main study consent you signed also applies to this addendum consent.

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

Appendix IV-D: Supplement to Appendix IV-B, Sample Informed Consent: For sites where INH is routinely provided to HIV-infected pregnant women

P1078: A Phase IV Randomized Double-Blind Placebo-Controlled Trial to Evaluate the Safety of Immediate (Antepartum-Initiated) Versus Deferred (Postpartum-Initiated) Isoniazid Preventive Therapy Among HIV-infected Women in High TB Incidence Settings

SHORT Name: "TB APPRISE" Stands for TB Ante vs. Postpartum Prevention with INH in HIV Seropositive mothers and their Exposed infants

SHORT TITLE FOR THE STUDY: P1078: TB APPRISE

Version 2.0, dated 28 October 2015

Isoniazid (INH) may be immediately available to individuals infected with HIV, including pregnant women, through the study site or through the local government clinic that cares for people who have or could get TB. This is one option available to you to receive INH without participating in this study. Please see the study doctor or your own doctor if you would like to learn more about this.

If you decide to participate in the study and complete the study, you may also be able to receive up to 36 months of INH through the local government clinic or the study site.

If you understand that you have other ways of receiving INH without being in the study and you are still interested in participating in the study, please sign the consent below.

Participant's Name (print)	Participant's Signature and Date
Participant's Legal Guardian (print)	Legal Guardian's Signature and Date
Study Staff Conducting Consent Discussion (print)	Study Staff's Signature and Date
Witness' Name (print) (As appropriate)	Witness' Signature and Date
Father's Name (If father's signature is required)	Father's Signature and Date (If father's signature is required)