

Summary of Changes Included in the Full Protocol Amendment of:

**IMPAACT P1078
(DAIDS Document ID 10732)**

A Phase IV Randomized Double-Blind Placebo-Controlled Trial to Evaluate the Safety of Immediate (Antepartum-Initiated) versus Deferred (Postpartum-Initiated) Isoniazid Preventative 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

The Amended Protocol is Identified as:

Version 2.0, Dated 28 October 2015

Information/Instructions to Study Sites from the Division of AIDS

The information contained in this protocol amendment impacts the IMPAACT P1078 study, including the study informed consents forms (ICFs), and must be submitted to site Institutional Review Boards and/or Ethics Committees (IRBs/ECs) as soon as possible for review and approval. Approval must also be obtained from other site regulatory entities if applicable per the policies and procedures of the regulatory entities. All IRB/EC and regulatory entity requirements must be followed and all required approvals of this amendment must be obtained before initiating this study.

Upon receiving IRB/EC approval and any other applicable regulatory entity approvals, all sites should immediately begin implementing this amendment and using the updated ICFs. After all required approvals are obtained, the updated ICFs should be used for all new participants. In addition, unless otherwise directed by site IRBs/ECs, all previously enrolled participants must re-consent to ongoing study participation using the updated ICF for screening and enrollment.

Re-consenting should take place at each enrolled participant’s next study visit after all required approvals are obtained. Unless otherwise directed by site IRBs/ECs, re-consenting is not required for specimen storage and future use.

All study sites must submit an amendment registration packet to the DAIDS Protocol Registration Office (PRO). Approval from the DAIDS PRO is not required prior to implementing the amendment.

This Summary of Changes, Version 2.0 of the protocol, corresponding site-specific ICFs, and all associated IRB/EC and regulatory entity correspondence should be retained in each site’s essential document files for IMPAACT P1078.

Summary of Revisions and Rationale

This protocol amendment clarifies the study eligibility criteria related to confirmation of HIV infection; responds to results from other TB-related studies and recent updates of World Health Organization (WHO) guidelines; decreases the frequency of some study evaluations; incorporates prior protocol Clarification Memoranda (CMs) and Letters of Amendment (LoAs); and includes other updates, corrections, and clarifications, as follows:

1. Throughout the protocol, the version number was updated to Version 2.0 and the version date was updated to 28 October 2015.
2. The protocol team and site investigator rosters were updated to reflect current team membership and contact details.
3. Study-specific communication procedures described in the Study Management section were updated to reflect current procedures; the glossaries at the beginning of the protocol and in Appendix IV-C were also updated and the IMPAACT network website link was updated throughout the protocol.
4. References to “subject” has been replaced with “participant” throughout the protocol.
5. The background, rationale, and attendant references were updated to reflect the current WHO guidelines, including the 2011 guidelines and 2015 update; additional relevant published data; and evolving standards of care in the settings where the study is being conducted (Section 1.0 and throughout the protocol, where relevant).
6. The planned stratification of participants by maternal HAART use at entry was removed, as it is now expected that most pregnant women entering the study will be on a triple ARV regimen due to developing changes in WHO perinatal HIV transmission guidelines since approval of protocol Version 1.0; additional rationale was included in Section 8.1 and the expected percentage of women on HAART at entry was modified in Section 8.4 from 40-50% to 90-100%. This estimate reflects data from the first 485 pregnant women enrolled in the study as well as the known standard of care in study countries. References to HAART use stratification were removed or modified in the Schema: Stratification and Primary Objective, Sections 1.1, 1.2, 2.1, 8.1, 8.3, 8.4, 8.6.1, 8.6.2.2, and 8.6.2.3.
7. An investigation of the use of hair as a biomarker of maternal adherence and infant exposure to INH and selected ARV drugs has been added. With the known limitations of self-reported drug adherence data, objective biomarkers are critical for monitoring drug use, particularly when used as prophylaxis. However, collection, processing and testing of specimens typically used to measure drug levels is expensive and burdensome in many settings. Adherence and exposure to INH for mothers and their infants will be assessed by measuring hair drug concentrations in a longitudinal fashion on selected samples, in addition to testing for selected ARV drugs. At the end of the study, the relationship between hair drug concentration levels and TB infection and/or disease will also be assessed. Participation in this investigation is optional for individual participants and requires collection of small hair

samples from mothers and their infants. No additional study visits associated with this investigation are required. The description of this substudy was added to Sections 1.1 and 1.2. The Schema: Pharmacokinetic Studies was revised; Exploratory Objective 3 was added in the Schema and Sections 2.3; Sections 8.2.3.3, 8.6.2.3, 8.6.3.3, and 9.2 were modified or added to include hair sample collection, additional pharmacology objectives and additional information about the hair substudy. The maternal and infant Schedules of Evaluation (Appendices I-A and I-B) and the Sample Informed Consent Form (Appendix IV-B) have been modified to allow for collection of hair samples.

8. An investigation of efavirenz (EFV) pharmacokinetics (PK) and pharmacogenomics was added as part of Exploratory Objective 1, due to known INH/EFV interactions and the expected increased use of EFV in the study population. Recent PK data from HIV-infected pregnant women in South Africa found that INH for prophylaxis or treatment reduced EFV clearance, especially those with slow NAT-2 acetylator status. It is known that INH influences EFV concentrations via inhibition of CYP2B6. This investigation will further explore this interaction in a large, multi-country population of HIV-infected pregnant women. The Schema: Exploratory Objectives and Sections 1.2, 2.3, 8.2.3.1, 8.6.3.1, 9.1.2, and 9.2 were modified to include this analysis. This change is also reflected in the sample informed consent form (Appendix IV-B).
9. Related to Exploratory Objective 1, Exploratory Objective 6 was added to explore neurotoxicity of INH and EFV using several instruments. 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 EFV metabolism. A three-item neurocognitive impairment tool as well as several questions from the Pittsburgh Sleep Quality Index will also be assessed. No additional study visits associated with this investigation are required. The Schema: Exploratory Objectives and Sections 1.2, 2.3, 8.2.3.6, 8.6.3.6, and Appendix I-A were modified to include this analysis. This change is also reflected in the sample informed consent form (Appendix IV-B).
10. An additional infant plasma collection was added at birth to 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 (Schema: Immunology Studies, Section 1.2, Appendix I-B). This change is also reflected in the sample informed consent forms (Appendix IV-B).
11. Secondary Objective 1 was modified to clarify the study will examine the safety and toxicity of INH *in utero* exposure (Schema and Sections 2.2, 8.2.2.1, 8.6.2.1). Section 8.2.2.1 was also revised to clarify that all grade 3 or higher AEs and those considered related to INH/Placebo for INH would be an outcome as well as adding infant hospitalization as an outcome and provided a definition for low birth weight in infants.

12. An exploratory objective related to assessing overall clinical outcomes in the mother-infant pair was added to the study as Exploratory Objective 4 (Schema, Sections 2.3, 8.2.3.4, and 8.6.3.4). This analysis will assign a score to the mother-infant pair based on the severity of total clinical outcomes, including maternal and/or infant death, TB, and safety events.
13. Exploratory Objective 5 was added to the study to allow for biomarker discovery and measurement of maternal TB-specific antibodies and subsequent maternal and infant TB antibodies, infection and disease (Schema and Sections 2.3, 8.2.3.5, 8.6.3.5).
14. A note was added to inclusion criterion 4.1.7 to allow site flexibility to use direct bilirubin results (rather than total bilirubin) for participants on atazanavir. Similarly, a note was added in the Schedule of Evaluations (Appendix I-A).
15. Additional detail on the purpose and planned analyses for IGRA tests, included in Secondary Objective 6, formerly Secondary Objective 5, was added and clarified in Sections 1.2, 8.1, and 8.6.2.6. Similarly, additional clarification was added to Secondary Objective 3, formerly Secondary Objective 7 (Schema, Sections 2.2, 8.2.2.3, and 8.6.2.3) to describe statistical analyses for safety and hepatotoxicity. The protocol team plans to analyze safety outcomes focusing on pregnancy through delivery and through 12 weeks postpartum as well as analyzing hepatotoxicity events using the DAIDS grading system and the protocol-specific system.
16. The approximate sample size for collection of viable peripheral blood mononuclear cells (PBMCs) was increased to compensate for less than expected collection among early samples as follows: at study entry, increased from approximately 500 to 700 women (with a subset increase from 260 to 460 women); and at postpartum Weeks 12 and 44, increase from 260 to 460 mother-infant pairs. Sections 1.2, 3.2, and 8.4 were revised as well as the maternal and infant Schedules of Evaluations (Appendices I-A and I-B). This change is also reflected in the sample informed consent forms (Appendix IV-B).
17. To address operational challenges with scheduling pharmacokinetic assessments to align with scheduled visits, the window for the antepartum collection was expanded from 32 ± 4 weeks gestation to during the third trimester of pregnancy (28 weeks to 40 weeks gestation); similarly, the postpartum collection window was expanded from 12 – 16 weeks postpartum, to 16 ± 4 weeks postpartum. The language related to timing of collection was also revised from ‘morning’ to ‘day,’ to facilitate scheduling. Sections 3.1 and 9.2 were revised as well as the maternal Schedule of Evaluation (Appendix I-A) and Sample Informed Consent (Appendix IV-B).
18. Serum collection was added for mothers at study entry to be used for future TB biomarker and inflammation investigations (Appendix I-A). LTBI infection may induce changes in metabolism and inflammatory state in HIV-infected hosts, and there is current discovery work underway to assess the detection of products in serum both for LTBI diagnosis and for monitoring treatment responses. Therefore, serum storage was added to assist in the study of potentially novel LTBI biosignatures.

19. To ease the operational challenges associated with the intensity of study visits and procedures at labor and delivery, the target window for completion of the maternal labor/delivery and infant birth evaluations has been widened to ‘within 5 days, with an allowable visit window of up to 2 weeks’ (from within 72 hours) (Sections 3.2 and 3.5, Appendices I-A and I-B). In addition, the timeframe for administration of the TST has been expanded to allow administration at the Week 4 postpartum visit, if not administered at Labor and Delivery (Appendix I-A). These changes do not affect participant safety and will enhance site capacity to complete visits in a timely manner. Similarly, the timeframe for reading TST tests has been widened to ‘ideally within 2-3 days after placement but up to 7 days afterward’ (from within 72 hours). This modification is included in Sections 1.2, 3.2, and 3.5; and Appendices I-A and I-B. These changes are also reflected in the sample informed consent forms (Appendix IV-B).
20. Co-enrollment procedures have been modified to allow more flexibility (Section 4.6); in addition, reference to co-enrollment in the IMPAACT 1077 (PROMISE) studies has been removed, as the PROMISE studies are no longer enrolling (Section 1.2).
21. Related to the eligibility criteria for entry into the study, the requirements for confirmation of HIV infection prior to study entry are updated to reflect current IMPAACT network policies and site capabilities (Section 4.1.1). The update also modifies the definition of a positive result for quantitative HIV RNA PCR. This change is also reflected in the sample informed consent forms (Appendix IV-B).
22. Additional screening test options available to sites to assess active tuberculosis, including Xpert (Gene Xpert MTB RIF assay) or any other rapid TB screening test, were added to Section 1.2, Exclusion Criterion 4.2.2 and described further in Section 3.3. Similarly, options to assess active tuberculosis were added to the possible assessments for mothers and infants at suspected active TB visits (Appendices I-A and I-B).
23. The procedures and requirements for screening and enrollment were updated in Section 4.5.2 to align with current procedures.
24. A note was added in Sections 5.1 and 5.1.2 to indicate that site investigators may increase dosing of pyridoxine (vitamin B₆) up to 100 mg for management of peripheral neuropathy at the discretion of the site investigator, consistent with the revised guidance in the toxicity management for peripheral neuropathy in Section 6.1.3.
25. Directions related to antacid and ddI use with INH/Placebo for INH were removed from Section 5.1.2, as this information is no longer included in the INH package insert.
26. Requirements for storage of study products were updated in Section 5.2 to match the manufacturer’s instructions.
27. Reference to procedures for unused study products at US sites was removed from Section 5.3.3, as no sites in the United States are participating.

28. Throughout the protocol and in Section 6.0, guidance on toxicity management for mothers has been updated for clarity and consistency and to expand investigator discretion to manage participant care (Sections 6.1 and 6.1.1-6.1.4). Throughout the toxicity management section, management instructions are provided for INH/Placebo for INH, allowing for site investigator discretion and standard of care procedures to determine management of prenatal multivitamins and pyridoxine (vitamin B₆). Additional instruction for sites to provide counseling and messaging to participants related to holding INH/Placebo for INH was added to the toxicity management sections (Sections 6.1.1 and 6.1.4); similarly, language was added and updated in the sample informed consent templates (Appendices I-A and IV-B).
29. Reporting requirements for the study were updated to include expedited reporting for any fetal deaths of any gestational age (Section 7.2).
30. Definitions for a positive TST in the study populations (Section 8.2.2.6, Appendices I-A and I-B) were clarified.
31. In consultation with the study's Data Safety and Monitoring Board (DSMB), additional note of monitoring for safety per the DSMB's reviews and recommendations has been added as Section 8.5.4. The template informed consent (Appendix IV-B) was also modified to include specific note of hepatotoxicity and risks of INH and clearly describe the potential side effects, grouped by categories.
32. Section 8.6.2.6 has been modified to include analysis for assessment of TB infection status for women and infants participating in the IGRA subset at entry and postpartum Weeks 12 and 48 visits.
33. Modifications to the Schedules of Evaluations are noted below. In addition to these modifications, minor clarifications regarding assessments have been incorporated where relevant and in the sample informed consent forms (Appendix IV).

Maternal Schedule of Evaluations

- Added row and revised counseling footnote to emphasize counseling on study medication side effects and risks
- Allowed TST to be administered at Week 4 postpartum, if not administered at Labor & Delivery
- Removed hematologies from all visits except those with CD4/CD8 assessments (entry; antepartum Week 4; postpartum Weeks 4, 12, 16, 24, and 48; and suspected active TB visits)
- Removed glucose and creatinine testing at entry, Labor & Delivery, suspected active TB, and early discontinuation or last study visits
- Allowed pregnancy testing through serum or urine and revised collection from 'every 12 weeks postpartum' to 'only when pregnancy is suspected or considered clinically indicated'
- Removed HCV testing at entry as known low prevalence in study countries
- Changed maternal viral load assessment to allow screening value to be used at entry

- Removed urine storage at suspected active TB and early discontinuation or last study visits
- Added serum storage at entry for future use in TB biomarker, antibody, inflammation, nutrition, or other TB/HIV related studies
- Added hair collection at antepartum Week 8, at the visit that coincides with 28 weeks post-entry, and postpartum Weeks 20 and 40
- Revised and combined footnotes related to suspected active TB visits for clarity and operational ease
- Clarified that QGIT should not be collected if participant already determined to have suspected or confirmed active TB prior to the indicated QGIT collection; also clarified that if QGIT result not obtained or indeterminate from any assessment, should be repeated within 4 weeks
- Throughout the SOE removed reference to specific shipping directions or locations, as this may vary by site and may change over the course of the study. Details will be provided in the LPC

Infant Schedule of Evaluations

- Increased infant blood volume to allow sites flexibility with testing
- Removed urine collection at Week 24, suspected active TB, and early discontinuation or last study visits
- Revised and combined footnotes related to suspected active TB visits for clarity and operational ease
- Added plasma collection at birth

34. Additional language has been added to the sample informed consent (Appendix IV-B) to include the following:
- Discussion of risk and side effects associated with INH use during pregnancy and postpartum and highlighting the limited data currently available as well as additional reminders for participants to contact study investigators if there are any problems or new signs or symptoms
 - Updated potential side effects of INH, based on the DAIDS-approved drug risk list and in consultation with the DSMB
 - Description related to the procedures required for ClinicalTrials.gov; this information was also added to Appendix IV-C
 - All changes noted in part 33 above concerning study procedures
35. Additional language has been added to the supplement to Appendix IV-B (Appendix IV-D) to inform participants that they may be able to receive up to 36 months of INH through local programs.
36. Clarifications and modifications included in all prior protocol CMs and LoAs are incorporated.
37. Other minor corrections and clarifications are incorporated.