SUMMARY OF CHANGES

INCLUDED IN THE FULL PROTOCOL AMENDMENT OF:

IMPAACT P1026s
Pharmacokinetic Properties of Antiretroviral and Related Drugs During Pregnancy and Postpartum

(DAIDS Document ID 10040)

IND # 64,535 held by NIAID

THE AMENDED PROTOCOL IS IDENTIFIED AS:

Version 10.0, Dated 2 February 2016

Information/Instructions to Study Sites from the Division of AIDS

The information contained in this protocol amendment impacts the IMPAACT P1026s study and must be submitted to site Institutional Review Boards and/or Ethics Committees (IRBs/ECs) as soon as possible for review and approval. This amendment impacts the study informed consent forms (ICFs); all study sites must prepare updated ICFs and obtain IRB/EC approval of the updated forms. 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.

Upon obtaining 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, updated ICFs should be used for all new participants. In addition, previously enrolled participants, at the next study visit, must be re-consented using the updated ICFs unless otherwise directed by the IRB/EC.

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

This Summary of Changes, Version 10.0 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 P1026s.

Summary of Revisions and Rationale

This protocol amendment adds additional study arms for newly approved or soon to be approved antiretroviral drugs likely to move into use during pregnancy; adds additional arms to look at the interaction of ARVs with hormonal contraceptives; adds an additional arm to look at second line TB drugs used during pregnancy in both HIV-infected and uninfected pregnant women; closes fully enrolled arms; closes an arm that has not had any enrollments; incorporates the prior protocol Clarification Memorandum; updates the DAIDS Table for Grading the Severity of Adult and Pediatric Adverse Events to Version 2.0, and includes other minor updates, corrections, and clarifications.
The changes and rationale are summarized briefly below, generally in order of first appearance in the protocol. Throughout the protocol, the version number was updated to Version 10.0 and the version date was updated to 2 February 2016.

The protocol team and site investigator rosters were updated to reflect current membership and contact details; the glossary was also updated.

The background and rationale section has been updated to indicate that the IMPAACT network and its stakeholders would support the use of P1026s data for any possible label modification for use of a drug during pregnancy or in the context of contraceptive usage, should that become a feasible possibility. Section 1.1 2nd paragraph.

The 24 week follow-up visit for mothers enrolled during pregnancy has been removed and the 24 week follow-up visit for infants has been modified to 16 – 24 weeks. The Schema; Appendix IA, IB, IC, and II; and the Sample informed Consent forms have been updated. The last follow-up visits for women enrolled during pregnancy and infants are as follows:
- HIV-infected pregnant women without tuberculosis (TB) will be followed for 6 – 12 weeks after delivery with the exception of women on DRV/r who will be followed for 2 – 3 weeks after delivery.
- HIV-infected and non-infected women receiving TB treatment (first or second line) will be followed for 2 – 8 weeks after delivery.
- Infants will be followed for 16 – 24 weeks of life.

The background, rationale and attendant references were updated to add study drug information for arms that were added and to remove information for arms that were closed. Sections 1.31, 1.32, 1.33, 1.35, 1.41, 1.42, 1.5, and 1.6 were added/updated.

The History of Versions 1.0 – 9.0 (Section 1.8) was updated and moved to Protocol Appendix VII.

Reference for the DAIDS Table for Grading the Severity of Adult and Pediatric Adverse Events has been updated to the new version: Version 2.0, dated November 2014. Section 6.3 was updated.

The following modifications have been made to the study arms:
- Five antepartum arms for HIV-infected pregnant women NOT on tuberculosis treatment – tenofovir alafenamide fumarate TAF 25 mg unboosted (modified from 10 mg q.d.), tenofovir alafenamide fumarate 10 mg q.d. with cobicistat, tenofovir alafenamide fumarate 10 mg q.d. with ritonavir, darunavir/cobicistat and atazanavir/cobicistat – have been added.
- The antepartum arms for ARVs with first line tuberculosis treatment have been modified to not require rifampicin containing TB treatment and the nevirapine arm was closed due to futility.
- One new antepartum arm for second line tuberculosis treatment for drug resistant tuberculosis with or without ARVs (HIV-infected/uninfected pregnant women) has been added.
- Two new postpartum arms – darunavir or atazanavir/cobicistat plus oral contraceptives and darunavir or atazanavir/cobicistat plus implanted contraceptives – were added.
- Two antepartum arms for HIV-infected women not on tuberculosis treatment – etravirine and increased dose lopinavir/ritonavir (African sites only) – were closed to further enrollments.
- Two postpartum arms that were fully enrolled – atazanavir/ritonavir/tenofovir with implanted contraceptives and efavirenz with implanted contraceptives – were closed.
- Primary objective (2.13) was added to the Schema, and Sections 2.1, 8.1, 8.212, 8.6, and 9.1 to describe the pharmacokinetics of second line TB drugs.

- A secondary objective was added to the Schema and Sections 2.27, 8.227 and 9.1 to describe the pharmacokinetics of ARV drug combinations in women receiving second line TB treatment.

- Tuberculosis drug concentrations in addition to ARV drug concentrations was added to the secondary objectives in the Schema and Sections 2.21, 2.24 and 2.26.

- The schema, entry criterion (Section 4.112) for ARVs with first line tuberculosis treatment, and Section 8.6 are modified to indicate that rifampicin containing TB treatment (first-line) is not required for enrollment.

- The schema and entry criterion (Section 4.112) for ARVs with first line tuberculosis treatment, are modified to remove the NVP arm.

- The Schema and entry criteria in Sections 4.111 and 4.115 (renumbered from 4.114) were updated to remove closed/fully enrolled arms and add new arms.

- The study design Section 3.0 was updated to address the sample size for the newly added second line tuberculosis treatment arm.

- Hormonal Contraceptive PK Sampling Section 3.22 is updated to reflect the closure of atazanavir/ritonavir/tenofovir etonogesterol implant and efavirenz etonogesterol implant postpartum contraceptive arms and addition of darunavir/cobicistat and atazanavir/cobicistat postpartum contraceptive arms.

- Section 5.1, Toxicity Monitoring has been updated to remove closed arms and add new arms.

- Section 6.2, in addition to all SAEs as defined in Section 6.2 only the following events are to be reported expeditiously fetal demise and Grade 4 hepatotoxicities whether or not symptomatic or related to study drug. [Requirements to report < Grade 3 malignancies, hepatotoxicities ≤ Grade 3 and all other related Grade 3 or 4 related toxicities have been eliminated.]

- The list of disallowed medicines in Section 7.0 was updated to reflect the current study drug regimens. Section 7.5 was removed and subsequent sections re-numbered.

- Sections 8.1, and 8.41 are updated to address the sample size required for the new TB second line drug arm.

- Section 8.42 is updated to reflect the current accrual and enrollment projections.

- Table A, Guidelines for Using Schedule of Evaluations (Appendices I-A through I-D) was updated to reflect the addition of the Second Line TB Treatment Arm.

- Appendices IB, IC and II have been updated to include an audiology assessment during follow-up for mothers and infants of mothers treated with any injectable TB medication. This assessment can be completed at any-time during follow-up or abstracted from the chart.
- Appendices IB and IC have been updated to include TSH/tT4 testing at the 2<sup>nd</sup> trimester, 3<sup>rd</sup> trimester at 2-8 week postpartum for participants treated with ethionamide and/or para-aminosalicylic acid.

- APPENDIX III: Maternal Intensive PK Sampling Schedule for Antiretroviral Medicines, Tuberculosis Treatment and Hormonal Contraceptives has been updated with the regimens for the closed arms removed and the regimens for the new arms added.

- APPENDIX IV has been updated to include dietary recommendations for the new arms.

- Appendices VI-A, VI-B, VI-C and VI-D (Sample Informed Consent Forms) were updated to remove closed/fully enrolled arms and add new arms (see below).

  - Eligibility criterion 4.14 was clarified with the following information for the postpartum arms added; HIV-infected postpartum women on hormonal contraceptives must be planning to continue on ARV and contraceptive regimens until final PK sampling is completed. The intent remains unchanged.

  - To reflect the latest version of the IMPAACT definition of HIV infection and HIV non-infection for eligibility in IMPAACT Clinical Trials. Sections 4.15 and 4.16.

  - Reference to co-enrollment in 1077HS have been removed due to 1077HS no longer enrolling subjects. Section 4.6, Appendix I-A.

  - The Pharmacology Laboratory of the University of Cape Town was added to Section 9.31 under methods to be used for consistency throughout the protocol; this is not a change.

  - The requirement for infant washout PK sample collected at delivery has been modified to indicate that collection can be omitted, with team approval, if there are circumstances that prohibit collection (i.e. delivery at a non-study facility). Appendix II.

  - Clarifications have been made throughout Section 10.0, Data Collection Requirements.

  - Schema, Sections 3.0, and 8.42 were updated to project the number of anticipated maternal and infant enrollments under Version 10.0.

  - Clarifications and modifications included in the prior Clarification Memorandum were incorporated.

  - Throughout the protocol ‘subject’ was replaced with ‘participant’.

  - Vaginal secretion sample collection has been removed for HIV-infected pregnant women on TB drugs, Section 3.21, Appendix I-B, and Appendix VI-B (Sample Consent Form For Women on ARV Medicines).

  - The requirement for cord blood and maternal delivery sample collection for HIV-infected women on TB treatment (first line or second line) has been modified to indicate that collection can be omitted if there are circumstances that prohibit collection (i.e. delivery at a non-study facility or delivery during non-business hours). Appendix IB.

  - Section 3.2 was updated to reflect that the Adherence Questionnaire is only administered to HIV-infected women. This was a protocol inconsistency.
- APPENDIX V: Maternal PK Parameter Targets has been updated to remove closed arms and add new arms.

- Removed the indication that TAF requires special PK collection procedures, Appendices IA and II.

- Other minor corrections and clarifications were incorporated throughout the protocol.

**Modifications to the Sample Informed Consent Forms; Appendix VI-A, VI-B, VI-C and VI-D:**

- The Sample Consent Forms are updated throughout for clarity and consistency.

- The Sample Consent Forms are updated to remove closed/fully enrolled arms and add new arms.

- The blood volumes have been updated.

Additional modifications follow:

**Appendix VI-A:**

- Modified the last study visit to 2 – 3 weeks postpartum for women on DRV/r and 6-12 weeks postpartum for all other arms from 24 weeks and modified the last study visit for infants to 16 – 24 weeks of life from 24 weeks.

- Updated the procedures for vaginal secretion sampling to allow more flexibility with sampling techniques.

- Updated HIV medication eligibility criteria in the introduction with removing and adding the appropriate HIV medications and updating these medications in section “After Delivery.”

- Updated “During Pregnancy,” “Additional study tests if you are taking darunavir/ritonavir twice daily,” and “After Delivery” sections with removing paragraph regarding lopinavir/ritonavir usage.

- Updated section “Checking the Amount of HIV Medicine in Your Blood.”

- Updated section “Checking the Amount of HIV Medicine in Your Vagina.”

- Updated age at which baby will be examined in section “Study Visits for Your Baby.”

- Updated the Sections “During Pregnancy and “After Delivery: to include an adherence assessment.

**Appendix VI-B:**

- Modified the last study visit to 2 – 8 weeks postpartum from 24 weeks for women and modified the last study visit for infants to 16 – 24 weeks of life from 24 weeks.

- Collection of vaginal secretion samples has been removed.

- Updated HIV and TB medication eligibility criteria with tables in the introduction with adding and removing appropriate HIV and TB medications.

- Removed statement on how well medications get into vaginal sections in section “Why is this study is being done?”

- Removed the collection of vaginal samples in sections “Checking the Amount of HIV Medicine in Your Vagina” and “Risks of Collecting Vaginal Fluid and Vaginal Swabs.”
• Removed blood samples from baby and updated age at which baby will be examined in section “Study Visits for Your Baby.”
• Added an audiology assessment for mothers and their infants if the mother received injectable TB drug
• Updated the Sections “During Pregnancy and “After you Delivery Your Baby’ to include an adherence assessment.
Appendix VI-C:

- Modified the last study visit to 2 – 8 weeks postpartum from 24 weeks for women and modified the last study visit for infants to 16 – 24 weeks of life from 24 weeks.
- Updated HIV and TB medication eligibility criteria with tables in the introduction with adding and removing appropriate HIV and TB medications.
- Updated section “Checking the Amount of Tuberculosis Medicine in Your Blood.”
- Updated age at which baby will be examined in section “Study Visits for Your Baby.”
- Updated section “Genetic Testing” for clarity.
- Updated section “ARE THERE BENEFITS TO TAKING PART IN THIS STUDY?”
- Sections “Study Visits for your Baby” and “Genetic Testing” have been corrected to remove reference to the 5 – 9 day visit.
- Added an audiology assessment for mothers and their infants if the mother received injectable TB drugs.

Appendix VI-D:

- Updated HIV medications in section “WHY IS THIS STUDY BEING DONE?”
- Updated blood testing procedure in section “2-12 weeks after you deliver your baby.”
- Updated genetic testing procedure in section “Genetic Testing.”
- Updated section “ARE THERE BENEFITS TO TAKING PART IN THIS STUDY?”
- Updated Section “2-12 weeks after you deliver your baby” and “6 to 7 weeks after you delivery your baby” to include the adherence assessment.