IMPAACT P1106
(DAIDS Document ID 11882)
Pharmacokinetic Characteristics of Antiretrovirals and Tuberculosis Medicines in Low Birth Weight Infants

A Multi-center International Trial of the International Maternal Pediatric Adolescent AIDS Clinical Trials Group (IMPAACT)

This file contains the current IMPAACT P1106 protocol, which is comprised of the following documents, presented in reverse chronological order:

- Letter of Amendment #3, dated 30 January 2018
- Letter of Amendment #2, dated 13 February 2017
- Clarification Memorandum #2, dated 16 January 2017
- Letter of Amendment #1, dated 3 June 2016
- Clarification Memorandum #1, dated 4 March 2016
- Protocol Version 1.0, dated 23 April 2013
Letter of Amendment #3 for:

IMPAACT P1106
Pharmacokinetic Characteristics of Antiretrovirals and Tuberculosis Medicines in Low Birth Weight Infants
Version 1.0, dated 23 April 2013

(DAIDS Document ID 11882)

Letter of Amendment Date: 30 January 2018

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Letter of Amendment #3
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Information/Instructions to Study Sites from the Division of AIDS

The information contained in this Letter of Amendment (LoA) impacts the IMPAACT P1106 study, including the sample informed consent forms (ICF) for Arms 1-6 and must be submitted to site Institutional Review Boards (IRBs) and/or Ethics Committees (ECs) as soon as possible for their review and approval. Approval must also be obtained from site regulatory entities if applicable per the policies and procedures of the regulatory entities. All IRB/EC and regulatory entity requirements must be followed.

Before this LoA can be implemented at each site:

- All IRB/EC approvals and any other applicable regulatory entity approvals must be obtained, AND
- An “Implementation Notice” from the IMPAACT Operations Center must have been issued for the LoA, confirming that all operational requirements for implementing the LoA at the network level have been completed.

Before the above two requirements are met, study implementation will continue under the previously-approved version of the protocol (including any prior LoAs). Once the above two requirements are met, the site will immediately proceed to implement the LoA. Re-consenting with the updated ICFs is required for all participants presently on study, for all newly enrolled participants, and for all normal birth weight infants; site IRBs/ECs may also require re-consenting for participants who have completed their study participation.

Sites are required to submit a LoA registration packet to the DAIDS Protocol Registration Office (DAIDS PRO) at the Regulatory Support Center (RSC). Sites will receive a registration notification for the LoA after the DAIDS PRO verifies that all required registration documents have been received and are complete. Sites must await the Implementation Notice from the IMPAACT Operations Center before implementing this LoA; however, they should not await the Registration Notice from the DAIDS PRO.

This LoA and all associated IRB/EC and regulatory entity correspondence, the notifications from the IMPAACT Operations Center and the DAIDS PRO, and all correspondence with the DAIDS PRO must be maintained in the site’s essential documents files for P1106. If the P1106 protocol is amended in the future, the contents of this LoA will be incorporated into the next version of the protocol.
I will conduct this study in accordance with the provisions of this protocol and all applicable protocol-related documents. I agree to conduct this study in compliance with United States (US) Health and Human Service regulations (45 CFR 46); applicable US Food and Drug Administration regulations; standards of the International Conference on Harmonization Guideline for Good Clinical Practice (E6); Institutional Review Board/Ethics Committee determinations; all applicable in-country, state, and local laws and regulations; and other applicable requirements (e.g., US National Institutes of Health, Division of AIDS) and institutional policies.

______________________________  ______________________________
Signature of Investigator of Record  Date

______________________________
Name of Investigator of Record (printed)
Summary of Modifications and Rationale

1. Clarifies the definition for low birth weight (LBW), for consistency with WHO definitions, to infants less than 2500 grams (<2500gm or 2499 grams or less). The protocol was previously inconsistent in defining LBW as less than or equal to 2500 grams (≤2500 grams) compared to less than 2500 grams (<2500 grams). This serves to clarify the definition of LBW throughout the protocol to less than 2500 grams (<2500 grams). Of note, no participants have enrolled with a birth weight equal to 2500 grams.

2. Updates study objectives to include assessment of normal birth weight (NBW) infants consistent with modifications implemented in LoA#2.

3. Revises sample size targets for Arms 2-4 to provide sufficient power for the population PK analyses, as described in protocol Section 9.1. These modifications also allow for robust population PK sub-analyses of the relationship between weight and INH PK parameters. Modifications and additional rationale for each change as follows:
   - For Arm 2 (NVP + INH) and Arm 3 (NVP + INH + RIF): Since protocol finalization, regimens prescribed as standard of care in site settings for infants with TB exposure or infection have changed. Infants exposed to tuberculosis are now typically given INH alone, without RIF. In response to this shift and during review of accrual progress, the Study Monitoring Committee recommended elimination of Arm 3, as the combination of medications originally specified to be studied was no longer clinically relevant. This was implemented by the protocol team in November 2016. Since the use of INH with RIF is no longer clinically relevant, 18 of the 28 enrollment slots originally allocated to Arm 3 (NVP + INH + RIF), have been shifted to Arm 2 (NVP + INH). This change will provide twice as many Arm 2 participants as originally allocated while not changing overall total protocol enrollment.
   - For Arm 4 (INH or INH+RIF): Arm 4 previously allowed for a minimum of 18 enrollments for INH-RIF and an overall accrual of 18-36 participants. The minimum requirement for infants on INH-RIF has been removed due to the lack of clinical relevance for the use of INH+RIF. Thus, Arm 4 will have a sample size of 18-36 participants on INH (note that use of RIF will not be exclusionary).

   For consistency with the original objectives to study LBW infants, enrollment of NBW infants will be limited to eight participants in Arm 2 and four participants in Arm 4.

4. Updates requirements for HIV testing for all HIV exposed infants: Infant HIV status is a key secondary outcome measure of the study, as noted in Section 8.22. It is also a key safety and participant management issue. To provide additional safety assessments and standardized testing results, requirements for study-specific HIV nucleic acid testing (NAT) are added for all HIV exposed infants (Arms 1-3, 5-6) at the first study visit (Screening or Entry). The maximum blood volume for this testing has also been increased, as required by available testing platforms.

5. Clarifies the study duration, follow-up, and Schedules of Evaluations (SoEs) for consistency with changes implemented in LoA#2, related to participants who enroll between 15 and 84 days of life in Arms 2 and 4.

6. Clarifies requirements for grading adverse events for infants enrolled with a birth weight ≥2500-≤4000gm: The protocol originally used a diagnosis based approach to toxicity monitoring as many diagnoses, clinical events, and abnormal laboratory values related to prematurity are expected in the population of LBW infants originally under study. However, with the expansion in LoA#2 to allow enrollment of participants who are NBW (≥2500-≤4000gm), it is not anticipated that these infants would have the same type of expected adverse events, as listed in protocol Appendix IV, Table for Grading Expected Adverse Events. Therefore, the DAIDS Table for Grading the Severity of Adult and Pediatric Adverse Events, Version 1.0, dated December 2004 (Clarification dated August 2009), will be used to grade all adverse events observed in infants enrolled with a birth weight ≥2500-≤4000gm. Updates are made throughout the protocol as described below; in particular, an additional weight sub-stratification was added for the largest weight band to assist in tracking grading and management for NBW and LBW infants.
7. Updates requirements and procedures for safety monitoring: For consistency with current monitoring procedures, the information and study data included in routine safety monitoring reports, as reviewed by the protocol team, have been updated. Requirements for site consultation and notification for participant deaths, new hospitalizations, and certain laboratory toxicity events have been added to facilitate quick review and consultation with the protocol team. Requirements for follow-up and monitoring of participants in Arms 5 and 6 with abnormal ECG results have been added to ensure appropriate management for participants who may have multiple co-morbidities related to increased risk and/or may be on multiple medications with QTc prolongation risk.

8. Clarifies Inclusion Criteria 4.11, 4.23, and 4.3 related to requirements for documentation of infant HIV and TB exposure and of maternal NVP exposure.

9. Updates to regulatory entities who may review study data per ICH E6 (R2) 4.8.10(n).

10. Modifications to the Schedules of Evaluation in Appendices I-A through I-B are grouped for ease of reference.

11. Modifications to the Sample Informed Consents in Appendices V-A through V-C are grouped for ease of reference.

12. Updates to the protocol team roster have been incorporated.

13. For ease of reference and implementation, the full Schedule of Evaluations for Arms 1-4, incorporating changes from all prior protocol updates, is included at the end of this document as Implementation Item #13.

Implementation

The modifications included in this LoA are listed by modification and will be incorporated into the next protocol amendment as specified below. Additions to the text are indicated in bold; deletions are indicated by strikethrough. For clarity, changes from LoA#1 and LoA#2 have been incorporated into this LoA where relevant.

1. Clarify the definition of low birth weight to infants less than 2500 grams (<2500gm)

   Throughout the protocol, the revision shown below is implemented and, in particular, Schema (Regimens, Arms 1, 2, 3) and Sections 4.13 and 8.1. When this modification appears in additional portions modified in the LoA, this change is incorporated.

   ≤2500gms <2500gm

2. Update study objectives to include assessment of normal birth weight infants

   The study objectives have been modified to include LBW infants and infants with birth weights ≥2500-≤4000gm. The revision shown in bold below has been made in the Schema (Study Objectives), Sections 2.0, 3.0, 8.1, 8.2, 9.11, 9.121-9.123, 9.31 (titles of Tables 2 and 3 for pharmacokinetic sampling), and 9.5:
   in LBW infants and normal birth weight (NBW) infants ≥2500-≤4000gm

3. Revise sample size targets for Arms 2, 3, and 4

   a) The revised by weight targets for Arms 2 and 3 are shown below and updated in the Schema (Sample Size, Stratify by Birth Weight, and Study Design Schematic), Sections 8.4 and 9.31, and Table 2:
Arm 2: n=36 48
<1400gm: n=10 6
1400-1800gm: n=10 6
1800-≤4000gm: n=16 6
(maximum of 8 NBW participants)

Arm 3 (closed): n=10 28
<1400gm: n=4 8
1400-1800gm: n=4 8
1800-≤4000gm: n=2 42

b) The minimum requirements for participants in Arm 4 to be on INH or INH+RIF have been removed as shown below. This update is made to the Schema (Stratify by Birth Weight) and Section 8.4:
Arm 4: n=18-36 stratified by birth weight as:
<1400gm: n=6 to 12; with a minimum of 6 each for INH and RIF PK analyses
1400-1800gm: n=6 to 12; with a minimum of 6 each for INH and RIF PK analyses
1800-≤4000gm: n=6 to 12 (maximum of 4 NBW participants); with a minimum of 6 each for INH and RIF PK analyses

4. HIV nucleic acid testing (NAT) is added for all HIV-exposed infants
Relevant modifications to the Schedules of Evaluation and Sample Informed Consent Forms are grouped at the end of the document.

Section 3.0, second-to-last and last paragraph:
Trial-related blood loss will not exceed 3% of the total blood volume during a period of four weeks. Assuming a total blood volume estimated at 80 to 90 mL/kg body weight, 3% is 2.4 ml blood per kg body weight for an infant weighing 1 kg. The only blood drawing required by the protocol will be collection of PK samples, and chemistry tests (if not done as part of clinical care), HIV NAT, and hematology tests. All other blood test results will come from tests done as part of routine clinical care. The size of PK blood samples will be minimized so that blood collection from even the smallest infants will meet the limit of 2.4 mL/kg per four weeks.

See Appendix I-A for infants in Arms 1, 2, 3 and 4 and Appendix I-B for infants in Arms 5 and 6 for a complete description of the procedures to be performed. Infants who were enrolled in Arms 1, 2 or 3 later determined to be HIV infected are eligible to register to Arms 5 or 6, as appropriate, and follow the schedule of evaluations in Appendix I-B. Infants who are HIV exposed will have study-specific HIV NAT as outlined in the relevant appendices. In the event that the infant HIV NAT performed is positive, the infant should be recalled to the clinic as soon as possible for confirmatory testing.

5. Clarify the study duration and follow-up among participants
Relevant modifications to the Schedules of Evaluation (SoEs) are grouped at the end of the document.

a) Schema, Study Duration:
Arms 1-4: approximately 24 weeks of age

b) Section 6.1, Toxicity Management, fourth paragraph, second sentence:
Study mandated clinical laboratory tests will be limited to those chemistry studies listed in Appendix I-A at Entry the day 7 to 14 and week 6 visits for subjects in Arms 1, 2, 3, and 4, and in Appendix I-B at the weeks 2, 6 and 16 visits after initiation of LPV/r for subjects in Arms 5 and 6 and hematology evaluations listed in Appendices I-A and I-B at Weeks 10 and 24.

c) Section 8.1, General Design Issues, third paragraph:
Infants in Arms 1-4 will be on study until 24 weeks after birth of postpartum (if enrolled between 0-14 days) and infants in Arms 1-4 will be on study until 24 weeks after study entry.
(if enrolled between 15-84 days), while Infants in Arms 5 and 6 will be on study until 24 weeks after initiation of LPV/r.

d) **Section 9.31, General Design, Table 2:**

<table>
<thead>
<tr>
<th>Arm</th>
<th>Subjects (N)</th>
<th>Age Wk2</th>
<th>Age Wk4</th>
<th>Age Wk6</th>
<th>Age Wk10</th>
<th>Age Wk16</th>
<th>Age Wk24</th>
<th>Samples (N/subject)</th>
</tr>
</thead>
</table>

Note: For infants enrolled within 7-14 days of life, study visits weeks are based on time elapsed from birth. For infants enrolled within 15-84 days of life, study visits are based on time elapsed from Entry.

6. Clarify requirements for grading adverse events for participants who enroll(ed) with birth weights ≥2500 gm-≤4000gm

a) **Schema (Stratify by Birth Weight and Study Design Schematic), Sections 8.3 and 8.4:**

Participants enrolled in the largest birth weight groups (1800-≤4000gm) in Arm 2 and Arm 4 will be further stratified between 1800-<2500gm and ≥2500-≤4000gm to track the enrollment cap of NBW infants. Enrollment of NBW infants will be limited to a maximum of eight infants in Arm 2 and four infants in Arm 4.

b) **Section 6.1, Toxicity Management, sixth paragraph, fourth sentence:**

See Appendix IV, Table for Grading Expected Adverse Events, for grading these events and diagnoses among LBW infants; the DAIDS Table for Grading the Severity of Adult and Pediatric Adverse Events, as referenced in Section 7.1, should be used to grade any events and diagnoses among infants with birth weights ≥2500gm.

c) **Section 7.1, Adverse Event Reporting to DAIDS, second paragraph:**

Toxicities for LBW infants outside of the established list of diagnoses and clinical events listed in Section 6.0 will be classified by the Division of AIDS Table for Grading the Severity of Adult and Pediatric Adverse Events, Version 1.0, dated December 2004, (Clarification dated August 2009), which is available on the RSC web site. Where toxicity grading is not available, local standard laboratory values for low birth weight infants will be used. For toxicity grading not available, the team will have a standing SMC define toxicity grading in an independent fashion. A site investigator may determine that a LBW infant’s adverse event, even if included in the list of diagnoses/clinical events in Appendix IV, does not meet the relationship to LBW under the Expected Adverse Event category. If that is the case, these adverse events will be assessed as unexpected adverse events and graded using the Division of AIDS Table for Grading the Severity of Adult and Pediatric Adverse Events, Version 1.0, dated December 2004, (Clarification dated August 2009) (e.g., sepsis or a laboratory assessment may or may not fit into the low birth weight-related Expected Adverse Events). Investigators should use clinical judgment in determining which category is appropriate for LBW infants (Appendix IV, Table for Grading Expected Adverse Events, or DAIDS Table for Grading). The study team should be consulted if questions arise.

7. Update safety monitoring requirements and procedures

a) **Section 6.1, Toxicity Management, added as last paragraph:**

Site investigators should notify the protocol team of the following events as soon as possible and within three business days of site awareness:

- All deaths
• Any hospitalizations subsequent to enrollment (not including hospitalization at the time of enrollment)
• Grade 4 laboratory toxicities, which should be followed weekly until Grade 2 or less. Sites should consult the protocol team with any questions related to the toxicity or resolution.

b) Section 8.5, Monitoring, second paragraph:
The safety of the ARVs and TB drugs of interest on infants will be monitored by means of adverse events reports and toxicity reports presenting laboratory and clinical events. It is the responsibility of the protocol team to interpret the toxicity data. Any decisions needed to protect subjects from undue risk will be made by the subject’s clinician in consultation with the protocol team. The IMPAACT Network will appoint a Study Monitoring Committee (SMC) which would meet every 6 months and as needed to review the summary report of the safety data, following policies described in the IMPAACT Manual of Procedures and DAIDS policies. In accordance with IMPAACT and DAIDS procedures, this committee will be composed of one clinician from the IMPAACT Protocol Development and Monitoring Committee; two clinicians appointed by the IMPAACT HIV Treatment Scientific Committee associated with the network but not directly involved in the conduct of study; and an independent statistician appointed by the IMPAACT Statistical and Data Management Center (SDMC). The SMC will all be independent of the P1106 protocol team. Per IMPAACT/DAIDS procedures, members of the P1106 SMC will have:
   1) no financial interest in the study;
   2) no planned authorship in publication of study results; and
   3) no involvement in the conduct of the study.

c) Appendix III, Electrocardiogram/echocardiogram (ECG/ECHO) studies, Bullet 3:
If either the ECG and/or ECHO is/are deemed abnormal, the subject’s medication may be stopped, and appropriate workup will be done (e.g. cardiac enzymes, viral studies) at the discretion of the attending pediatrician/cardiologist. In addition, investigators should seek specialist advice from a cardiologist to determine the infant’s clinical status for all participants with the following events:
• QTc >450 msec (based on the Harriet Lane Handbook; grade 3)
• Changes of QTc >60 msec from baseline (calculated using Bazett’s formula; grade 3)
• Any clinically significant abnormal ECG results
• Symptomatic arrhythmia

8. Clarifications to requirements for Inclusion Criteria 4.11, 4.23, and 4.3

a) Clarifications for maternal NVP exposure requirements for infants are added in Section 3.0, Study Design, second paragraph, and following Section 4.11:
   Note that infants of women who received one intrapartum NVP dose will be allowed to enroll.

b) Note added to Inclusion Criteria 4.11 and 4.3, to clarify requirements for documentation of infant HIV exposure:
   Note that infant HIV exposure must be source documented, based on medical records, to fulfill requirements for eligibility confirmation.
c) Note added to Inclusion Criterion 4.23, to clarify requirements for documentation of infant TB exposure:
Note that infant TB exposure to mother with active TB disease must be source documented, based on medical records, to fulfill requirements for eligibility confirmation.

9. Update regulatory entities who may review clinical study information
Relevant modifications to the Sample Informed Consent Forms are grouped at the end of the document.

Section 10.2, Subject Confidentiality, last sentence:
Clinical information will not be released without written permission of the subject, except as necessary for monitoring by the Office of Human Research Protections (OHRP), the NIAID, the local IRB or Ethics Committee, other local, US, and international regulatory agencies, IMPAACT, study staff, and study monitors.

10. Modifications to the Schedules of Evaluations

a) Appendix I-A, Schedule of Evaluations for Arms 1, 2, 3, and 4, HIV nucleic acid testing (NAT) is added for all HIV-exposed infants at the Screening visit; visit weeks are clarified for infants screened and enrolled within 15-84 days of life; total blood volumes for Entry and Week 6 are corrected:

<table>
<thead>
<tr>
<th>EVALUATION</th>
<th>Screening within 0-14 days of life</th>
<th>Entry within 7–14 days of life</th>
<th>Week 4 of life</th>
<th>Week 6 of life</th>
<th>Week 10 of life</th>
<th>Week 16 of life</th>
<th>Week 24 of life</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Screening within 15-84 days of life</td>
<td>Entry within 15-84 days of life</td>
<td>Week 4 after Entry</td>
<td>Week 6 after Entry</td>
<td>Week 10 after Entry</td>
<td>Week 16 after Entry</td>
<td>Week 24 after Entry</td>
</tr>
<tr>
<td>VIROLOGY</td>
<td>HIV NAT (e.g., RNA PCR or DNA PCR)</td>
<td>0.5-1.0 mL</td>
<td>0.4 0.8 - 1.3mL</td>
<td>0.2 0.6 - 1.3mL</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>TOTAL BLOOD VOLUME</td>
<td>0.5-1.0 mL</td>
<td>0.4 0.8 - 1.3mL</td>
<td>0.2 0.6 - 1.3mL</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

For infants enrolled within 7-14 days of life, STUDY VISITS WEEKS ARE BASED ON TIME ELAPSED FROM BIRTH. For infants enrolled within 15-84 days of life, study visits are based on time elapsed from Entry.

For ease of reference and implementation, the full Schedule of Evaluations for Arms 1-4, incorporating changes from all prior protocol updates, is included at the end of this document as Item #13.
APPENDIX I-A FOOT NOTES:

9. See the Laboratory Processing Chart (LPC) on the P1106 Protocol Specific Webpage on the IMPAACT Website (http://impaactnetwork.org/studies/p1106.asp http://www.impaactgroup.org) for collection, processing and shipping instructions.

11. For HIV-exposed infants: HIV NAT (e.g., RNA PCR or DNA PCR) must be whole blood, serum, or plasma using methods approved by the IMPAACT Laboratory Center and must be tested in a VQA-certified laboratory. Any infant with an initial positive HIV NAT result should be recalled to the clinic as soon as possible for confirmatory testing.

b) Appendix I-B, Schedule of Evaluations for Arms 5 and 6, the total allowable blood volume for HIV NAT is updated and footnote 3 is updated to include HIV NAT for all HIV-exposed infants at the Entry visit:

<table>
<thead>
<tr>
<th>EVALUATION</th>
<th>Entry within 7 days prior to LPV/r initiation</th>
</tr>
</thead>
<tbody>
<tr>
<td>VIROLOGY</td>
<td></td>
</tr>
<tr>
<td>HIV NAT (e.g., RNA PCR or DNA PCR)</td>
<td>0.5-1.0 mL</td>
</tr>
<tr>
<td>TOTAL BLOOD VOLUME</td>
<td>0.5-1.0 mL</td>
</tr>
</tbody>
</table>

APPENDIX I-B FOOT NOTES:

3. HIV NAT (e.g., RNA PCR or DNA PCR) must be whole blood, serum, or plasma using methods approved by the IMPAACT Laboratory Center and must be tested in a VQA-certified laboratory. Confirmation of HIV-1 infection is defined as positive results from two samples collected at different time points. For HIV-exposed infants: Any infant with an initial positive HIV NAT result should be recalled to the clinic as soon as possible for confirmatory testing. For HIV-infected infants: Confirmatory HIV NAT (e.g., RNA PCR or DNA PCR) may be drawn prior to entry or at the entry visit.

11. Modifications to the Sample Informed Consent Forms

a) Appendix V-A, Infants in Arms 1 (NVP) and 2 (NVP plus INH)

WHY IS THIS STUDY BEING DONE?:

Your baby was low birth weight (less than 2.5 kg) or was normal birth weight (2.5 kg to 4 kg) and is receiving the anti-HIV medicine called nevirapine to prevent infection with HIV. The study was first looking at babies who were low birth weight. Now the study is also looking at babies who were normal birth weight. There is little information to tell us what the best dose of nevirapine is for smaller than average babies who were low birth weight or those that were normal birth weight. The purpose of this study is to collect some information about how much nevirapine is in the blood of small babies who were low birth weight or those who were normal birth weight, so that we can figure out the best nevirapine dose. If your baby is taking other anti-HIV medicines or a medicine called cotrimoxazole, the study will also collect some information about how much anti-HIV medicine or cotrimoxazole medicine is in the blood of babies so that we can figure out the best dose of these medicines.

Your baby may also be receiving isoniazid and/or rifampicin to prevent or treat infection with tuberculosis. There is also little information to tell us what the best doses of these medicines are in smaller than average babies who were low birth weight or who were normal birth weight. Another purpose of this study is to collect some information about how much tuberculosis
medicine(s) is in the blood of small babies so that we can figure out the best doses of these medicines.

**WHAT DOES MY BABY HAVE TO DO IF SHE/HE IS IN THIS STUDY?, Screening Visit To See If Your Baby Can Be In The Study, added as Fourth Bullet:**

- **We will draw blood to check if your baby has HIV. The total amount of blood needed for this test is 0.5-1.0 mL (less than a quarter of a teaspoon).**

**On-Study Visits, First, Third and Fourth Bullets:**

- **You will be asked to bring your baby to the clinic 3-5 additional times. These visits will be when your baby has been in the study for is 4, 6, 10, 16, and 24 weeks old.**
- **When your baby has been in the study for is 6 weeks old, we will draw blood to check how well your baby’s liver and kidneys are functioning if your baby’s doctor has not already done this as part of your baby’s routine care. The total amount of blood to be drawn for this test if it needs to be done will be 0.5mL (less than a quarter of a teaspoon). [Note to sites: add locally relevant description of blood volume].**
- **At 2 of these visits, when your baby has been in the study for is 10 weeks and 24 weeks old, we will draw blood to check the percentage of red blood cells in your baby’s blood. The amount of blood needed for this test is 0.5mL (less than a quarter of a teaspoon).**

**WHAT DOES MY BABY HAVE TO DO IF SHE/HE IS IN THIS STUDY?, On-Study Visits, second and third paragraphs:**

If your baby is receiving anti-tuberculosis medicine to prevent infection with tuberculosis but is later found to have tuberculosis, you will be asked to allow your baby to continue in the study and complete each scheduled study visit until your baby has been in the study for is 24 weeks of age.

If your baby has to stop taking his/her anti-HIV medicine and/or tuberculosis medicine(s) before the study ends, you will be asked to allow your baby to continue in the study until your baby has been in the study for is 24 weeks of age, to make sure your baby is continuing to do well. At each of the scheduled study visits, we will take a medical history and perform a physical exam, but no blood will be drawn.

**HOW LONG WILL MY BABY BE IN THE STUDY?**

Your baby will be in this study for 24 weeks until your baby is 24 weeks of age.

**WHAT ABOUT CONFIDENTIALITY?, second paragraph:**

Your baby’s records may be reviewed by the Ministry of Public Health in your country, the Office of Human Research Protections (OHRP), the NIH, (insert name of site) IRB, Ethics Committee (EC), other local, US, and international regulatory entities, study staff, and study monitors.

b) **Appendix V-B, Infants in Arm 4 (INH alone or INH plus RIF)**

**WHY IS THIS STUDY BEING DONE?:**

Your baby was low birth weight (less than 2.5 kg) weights less than the average baby or was normal birth weight (2.5 kg to 4 kg) and is receiving isoniazid alone or isoniazid with rifampicin to prevent or treat infection with tuberculosis. **The study was first looking at babies who were low birth weight. Now the study is also looking at babies who were normal birth weight. There is little information to tell us what the best dose of these medicines are for smaller than average babies who were low birth weight or those who were normal birth weight.** The
The purpose of this study is to collect some information about how much tuberculosis medicine(s) are in the blood of small these babies so that we can figure out the best doses of these medicines.

**WHAT DOES MY BABY HAVE TO DO IF SHE/HE IS IN THIS STUDY?, Screening Visit To See If Your Baby Can Be In The Study**, added as Fourth Bullet:

- We will draw blood to check if your baby has HIV. The total amount of blood needed for this test is 0.5-1.0 mL (less than a quarter of a teaspoon).

**WHAT DOES MY BABY HAVE TO DO IF SHE/HE IS IN THIS STUDY?, On-Study Visits, Third and fourth bullets:**

- When your baby has been in the study for is 6 weeks old, we will draw blood to check how well your baby’s liver and kidneys are functioning if your baby’s doctor has not already done this as part of your baby’s routine care. The total amount of blood to be drawn for this test if it needs to be done will be 0.5mL (less than a quarter of a teaspoon). [Note to sites: add locally relevant description of blood volume].
- At 2 of these visits, when your baby has been in the study for is 10 weeks and 24 weeks old, we will draw blood to check the percentage of red blood cells in your baby’s blood. The amount of blood needed for this test is 0.5mL (less than a quarter of a teaspoon).

**WHAT DOES MY BABY HAVE TO DO IF SHE/HE IS IN THIS STUDY?, On-Study Visits, second and third paragraphs:**

If your baby is receiving anti-tuberculosis medicine to prevent infection with tuberculosis but is later found to have tuberculosis, you will be asked to allow your baby to continue in the study and complete each scheduled study visit until your baby has been in the study for is 24 weeks of age.

If your baby has to stop taking his/her tuberculosis medicine(s) before the study ends, you will be asked to allow your baby to continue in the study until your baby has been in the study for is 24 weeks of age, to make sure your baby is continuing to do well. At each of the scheduled study visits, we will take a medical history and perform a physical exam, but no blood will be drawn.

**HOW LONG WILL MY BABY BE IN THE STUDY?**

Your baby will be in this study for 24 weeks until your baby is 24 weeks of age.

**WHAT ABOUT CONFIDENTIALITY?, second paragraph:**

Your baby’s records may be reviewed by the Ministry of Public Health in your country, the Office of Human Research Protections (OHRP), the NIH, (insert name of site) IRB, Ethics Committee (EC), other local, US, and international regulatory entities, study staff, and study monitors.

c) **Appendix V-C, Infants in Arms 5 (LPV/r and no RIF but may be receiving INH) and 6 (LPV/r plus RIF and may be receiving INH)**

**WHY IS THIS STUDY BEING DONE?:**

Your baby was low birth weight (less than 2.5 kg) smaller than average or was normal birth weight (2.5 kg to 4 kg) at birth and your doctor plans to start your baby on the anti-HIV medicine called lopinavir/ritonavir with or without tuberculosis medicines. The study was first looking at babies who were low birth weight. Now the study is also looking at babies who are normal birth weight. There is little information to tell us what the best dose of lopinavir/ritonavir is for smaller than average babies who were low birth weight or those who were normal birth weight. The purpose of this study is to collect some information about how much lopinavir/ritonavir is in the blood of small these babies so that we can figure out the best doses of
these medicines. **If your baby is taking other anti-HIV medicines, the study will also collect some information about how much anti-HIV medicines are in the blood of babies so that we can figure out the best dose of these medicines.**

**WHAT DOES MY BABY HAVE TO DO IF HE/SHE IS IN THIS STUDY?, Entry Visit, fifth and sixth bullets:**
- Blood will be drawn to check to check **if your baby has HIV or** the amount of HIV in your baby’s blood.
- The total amount of blood drawn at this visit will be 0.5-1.0mL (less than a quarter of a teaspoon). *[Note to sites: add locally relevant description of blood volume]*.

**WHAT ABOUT CONFIDENTIALITY?, second paragraph:**
Your baby’s records may be reviewed by the Ministry of Public Health in your country, the Office of Human Research Protections (OHRP), the NIH, *(insert name of site)* IRB, Ethics Committee (EC), **other local, US, and international regulatory entities**, study staff, and study monitors.

12. **Updates to protocol team roster**

*To reflect current protocol team membership, Mary Elizabeth Smith, JL Ariansen, and Chris Hensel are removed from the protocol team roster; Renee Browning, Emily Brown, Anna Leviere, Oswald Dadson, and Mark Lojacono are added:*

- **NIAID Medical Officer**
  - Renee Browning RN, MSN
- **Maternal Adolescent and Pediatric Research Branch, Prevention Sciences Program/ DAIDS/NIAID/NIH**
  - 5601 Fishers Lane, 8B29
  - Rockville, MD 20852
  - Phone: 240-292-4781
  - Email: browningr@niaid.nih.gov

- **Clinical Trials Specialists**
  - Emily Brown, MA
  - IMPAACT Operations Center, FHI 360
  - 359 Blackwell Street, Suite 200
  - Durham, NC 27701, USA
  - Phone: 919-544-7040 x 11123
  - Email: embrown@fhi360.org

- **Anna Leviere, MPH**
  - IMPAACT Operations Center, FHI 360
  - 359 Blackwell Street, Suite 200
  - Durham, NC 27701, USA
  - Phone: 919-544-7040 x11585
  - Email: aleviere@fhi360.org

- **Laboratory Data Managers**
  - Oswald Dadson, MS
  - Frontier Science and Technology Research Foundation
  - 4033 Maple Road
  - Amherst, NY 14226
  - Phone: 716-834-0900 ext. 7238
  - Email: dadson@fstrf.org

- **Mark Lojacono, MA, MSc**
  - Frontier Science and Technology Research Foundation
  - 4033 Maple Road
  - Amherst, NY 14226
  - Phone: 716-834-0900 ext. 7346
  - Email: lojacono@fstrf.org
13. Appendix I-A, Schedule of Evaluations for Arms 1, 2, 3, and 4

APPENDIX I-A

SCHEDULE OF EVALUATIONS FOR ARMS 1, 2, 3 and 4*

*INFANTS WHO WERE ENROLLED IN ARMS 1, 2, OR 3 AND LATER PRESCRIBED LPV/r SHOULD REGISTER TO ARM 5 OR 6, AS APPROPRIATE, AND FOLLOW THE SCHEDULE OF EVALUATIONS IN APPENDIX I-B.

<table>
<thead>
<tr>
<th>EVALUATION</th>
<th>Screening within 0-14 days of life</th>
<th>Entry within 7-14 days of life</th>
<th>Week 4 of life</th>
<th>Week 6 of life</th>
<th>Week 10 of life</th>
<th>Week 16 of life</th>
<th>Week 24 of life</th>
<th>On study/off drug</th>
</tr>
</thead>
<tbody>
<tr>
<td>ARM 1 (NVP), ARM 2 (NVP PLUS INH), ARM 3 (NVP PLUS INH PLUS RIF), ARM 4 (INH ALONE OR INH PLUS RIF)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Visit Windows</td>
<td>-</td>
<td>-</td>
<td>±4days</td>
<td>±7days</td>
<td>±7days</td>
<td>±14days</td>
<td>±14days</td>
<td>±7days</td>
</tr>
<tr>
<td>CLINICAL</td>
<td></td>
<td></td>
<td></td>
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<td></td>
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<td></td>
</tr>
<tr>
<td>Informed Consent</td>
<td>X</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>History</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td></td>
</tr>
<tr>
<td>Physical Exam&lt;sup&gt;1&lt;/sup&gt;</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td></td>
</tr>
<tr>
<td>LABORATORY</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hematology (Hgb)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>0.5mL</td>
</tr>
<tr>
<td>Chemistry (ALT, Cr, GGT)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>0.9mL&lt;sup&gt;2&lt;/sup&gt;</td>
</tr>
<tr>
<td>VIROLOGY</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>HIV NAT (e.g., RNA PCR or DNA PCR)&lt;sup&gt;11&lt;/sup&gt;</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>0.5-1.0 mL</td>
</tr>
<tr>
<td>PHARMACOLOGY&lt;sup&gt;9&lt;/sup&gt;</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>PK sampling for Arm 1 (NVP)&lt;sup&gt;8&lt;/sup&gt;</td>
<td>0.4mL&lt;sup&gt;3&lt;/sup&gt;</td>
<td>0.2mL&lt;sup&gt;4&lt;/sup&gt;</td>
<td>0.2mL&lt;sup&gt;4&lt;/sup&gt;</td>
<td>0.2mL&lt;sup&gt;4&lt;/sup&gt;</td>
<td>0.2mL&lt;sup&gt;4&lt;/sup&gt;</td>
<td>0.2mL&lt;sup&gt;4&lt;/sup&gt;</td>
<td></td>
<td></td>
</tr>
<tr>
<td>PK sampling for Arm 2 (NVP plus INH)&lt;sup&gt;8&lt;/sup&gt;</td>
<td>0.4mL&lt;sup&gt;5&lt;/sup&gt;</td>
<td>0.6mL&lt;sup&gt;6&lt;/sup&gt;</td>
<td>0.4mL&lt;sup&gt;5&lt;/sup&gt;</td>
<td>0.4mL&lt;sup&gt;5&lt;/sup&gt;</td>
<td>0.4mL&lt;sup&gt;5&lt;/sup&gt;</td>
<td>0.4mL&lt;sup&gt;5&lt;/sup&gt;</td>
<td></td>
<td></td>
</tr>
<tr>
<td>PK sampling for Arm 3 (NVP plus INH plus RIF)&lt;sup&gt;8&lt;/sup&gt;</td>
<td>0.4mL&lt;sup&gt;5&lt;/sup&gt;</td>
<td>0.4mL&lt;sup&gt;5&lt;/sup&gt;</td>
<td>0.4mL&lt;sup&gt;5&lt;/sup&gt;</td>
<td>0.4mL&lt;sup&gt;5&lt;/sup&gt;</td>
<td>0.4mL&lt;sup&gt;5&lt;/sup&gt;</td>
<td>0.4mL&lt;sup&gt;5,7&lt;/sup&gt;</td>
<td></td>
<td></td>
</tr>
<tr>
<td>PK sampling for Arm 4 (INH alone or INH plus RIF)&lt;sup&gt;8&lt;/sup&gt;</td>
<td>0.4mL&lt;sup&gt;5&lt;/sup&gt;</td>
<td>0.4mL&lt;sup&gt;5&lt;/sup&gt;</td>
<td>0.4mL&lt;sup&gt;5&lt;/sup&gt;</td>
<td>0.4mL&lt;sup&gt;5&lt;/sup&gt;</td>
<td>0.4mL&lt;sup&gt;5,7&lt;/sup&gt;</td>
<td>0.4mL&lt;sup&gt;5,7&lt;/sup&gt;</td>
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<td></td>
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<tr>
<td>PHARMACOGENETICS&lt;sup&gt;9&lt;/sup&gt;</td>
<td></td>
<td></td>
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<td></td>
<td></td>
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<tr>
<td>Genotyping</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>X&lt;sup&gt;10&lt;/sup&gt;</td>
</tr>
<tr>
<td>TOTAL BLOOD VOLUME</td>
<td>0.5-1.0 mL</td>
<td>0.4-1.3 mL</td>
<td>0.2-0.6 mL</td>
<td>0.2-1.3 mL</td>
<td>0.7-0.9 mL</td>
<td>0.2-0.4 mL</td>
<td>0.7-0.9 mL</td>
<td></td>
</tr>
</tbody>
</table>

For infants enrolled within 7-14 days of life, STUDY VISIT WEEKS ARE BASED ON TIME ELAPSED FROM BIRTH.

For infants enrolled within 15-84 days of life, study visits are based on time elapsed from Entry.

Letter of Amendment #3
IMPAACT P1106 Protocol Version 1.0
Page 14 of 15
30 January 2018
APPENDIX I-A FOOT NOTES:

1. Physical exam includes length, weight, head circumference, temperature, heart rate, respiratory rate
2. If not done as part of clinical care
3. Collect 0.2mL at pre-dose and 2 hours (1.5 to 2.5 hours) post-dose
4. Collect 0.2mL at pre-dose
5. Collect 0.2mL at 1.5 hours (1 to 2 hours) and 4 hours (4 to 6 hours) post-dose
6. Collect 0.2mL at pre-dose, 1.5 hours (1-2 hours) and 4 hours (4 to 6 hours) post-dose
7. No PK sampling is required for Arm 4 (subjects receiving INH plus RIF)
8. Infants meeting any of the following criteria on the day of a scheduled PK assessment should not have pharmacokinetic sampling performed on that day:
   1) Hypotension and/or poor perfusion requiring treatment with volume expansion and/or vasopressors
   2) Exchange transfusion within 24 hours preceding a PK evaluation
   3) Urine output less than 0.5 mL/kg/hr within 24 hours preceding a PK evaluation
   4) Missed doses of study drugs within preceding 72 hours
      PK sampling not performed due to the above criteria should be rescheduled after consultation with the protocol team. In addition, the protocol team should be contacted regarding any interruption in study drug administration greater than 24 hours. Infants whose study drug(s) are discontinued will not have further PK sampling but will continue to be followed for safety and toxicity monitoring. Infants who have been discontinued from one or more study drug(s) but remain on at least one study drug (e.g., Arm 2 infant discontinuing NVP but continuing INH) should continue to have PK sampling and be followed for safety and toxicity monitoring.
   
   Infants who were enrolled in Arms 1, 2 or 3 and later prescribed LPV/r should be re-evaluated for enrollment in Arms 5 or 6, as appropriate, and if eligible, should follow the Schedule of Evaluations in Appendix IB.
9. See the Laboratory Processing Chart (LPC) on the P1106 Protocol Specific Webpage on the IMPAACT Website (http://impaactnetwork.org/studies/p1106.asp) for collection, processing and shipping instructions.
10. Genotyping will be performed on all subjects and will include assessment of polymorphisms in NAT2 if subject receiving INH and CYP 2B6 if subject receiving NVP.
11. For HIV-exposed infants: HIV NAT (e.g., RNA PCR or DNA PCR) must be whole blood, serum, or plasma using methods approved by the IMPAACT Laboratory Center and must be tested in a VQA-certified laboratory. Any infant with an initial positive HIV NAT result should be recalled to the clinic as soon as possible for confirmatory testing.

Priority of blood draw should be as follows:
1) Chemistries
2) Hematology
3) Pharmacokinetics
Letter of Amendment #2 for:

IMPAACT P1106
Pharmacokinetic Characteristics of Antiretrovirals and Tuberculosis Medicines in Low Birth Weight Infants
Version 1.0, dated 23 April 2013

(DAIDS Document ID 11882)

Letter of Amendment Date: 13 February 2017

Information/Instructions to Study Sites

The information contained in this Letter of Amendment (LoA) impacts the IMPAACT P1106 study, including the informed consent forms (ICF) for Arms 1, 2, and 3; Arm 4; and Arms 5 and 6, and must be submitted to site Institutional Review Boards and/or Ethics Committees (IRBs/ECs) as soon as possible for their review and approval. Approval must also be obtained from 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, each site should immediately begin implementing this LoA and using the updated ICFs. Unless directed by site IRBs/ECs, re-consenting is not required for current study participants.

Sites are required to submit a LoA registration packet to the DAIDS Protocol Registration Office (DAIDS PRO) at the Regulatory Support Center (RSC). Sites will receive a registration notification for the LoA after the DAIDS PRO verifies that all required registration documents have been received and are complete. Sites should not await this notification before implementing this LoA.

Please file this LoA, all associated IRB/EC and regulatory entity correspondence, and all correspondence with the DAIDS PRO in your essential documents files for P1106. If the P1106 protocol is amended in the future, the contents of this LoA will be incorporated into the next version of the protocol.

Summary of Modifications and Rationale

Unique developmental and physiological changes influencing drug disposition early in life\textsuperscript{1,2} make it essential to characterize the pharmacokinetic (PK) profile and safety of antituberculosis and antiretroviral drugs in premature and term newborns. Limited PK and safety data are available for newborns initiated on isoniazid (INH) and lopinavir/ritonavir (LPV/r). Therefore, the following modifications are included in this LoA:

- **Expand the upper limit for birth weight for participants for all arms open to accrual (i.e., Arm 2 and 4-6) from 2500 grams to 4000 grams:** The team will continue to encourage enrollment of LBW infants $\leq$2500 grams at birth and will actively track distribution of weight in the highest weight band and, if there is an inequality in the weight distribution amongst new participants, the team will consider restricting enrollment weight to $\leq$2500 grams; however, allowing enrollment of infant participants up to 4000 grams ($\leq$4000 grams) is expected to improve overall enrollment into Arms 2 and 4-6.

- **Allow LPV/r for treatment or prophylaxis in Arms 5 and 6 and remove requirement of LPV/r with 2 NRTIs:** Lopinavir/ritonavir (LPV/r) is widely used to treat HIV-infected children, including infants,\textsuperscript{3-5} and has been used to prevent HIV postnatal transmission in breastfeeding infants (aged 7 days up to 50 weeks).\textsuperscript{6} However, a paucity of LPV/r pharmacokinetic (PK) data exists to inform dosing guidelines for prevention and treatment in newborns.

- **Expand the allowable window for entry to up to 84 days of age (from up to 14 days) for infants in Arms 2-4 as some drugs (including for TB) are started multiple weeks after delivery:** Despite routine
administration of isoniazid (INH) to TB-exposed newborns for prophylaxis and treatment. Limited PK data are available in newborns to inform dosing. This change will further increase enrollment and capture those newborns initiated on INH because of maternal postpartum TB diagnosis.

- **Increase the total allowable blood volume for chemistry assessments by a minimal volume of 0.4mL:** The protocol team anticipated that some of the protocol-specific chemistry tests would be performed per standard of care practices; however, sites have found that standard of care assessments do not always align with protocol requirements. Therefore, additional blood volume is added for the existing chemistry assessments.

### Implementation

The modifications included in this Letter of Amendment are listed in order of appearance in the protocol and will be incorporated into the next protocol amendment as specified below. Additions to the text are indicated in **bold**; deletions are indicated by *strikethrough*. For clarity, changes from LoA#1 have been incorporated into this LoA where relevant.

1. **Schema: Population, Regimens, Sample Size, Stratify by Birth Weight, and Study Design Schematic**

   **POPULATION:** Lower birth weight (LBW) and normal birth weight infants ≤4000 2500 grams at birth who are receiving or will be receiving as part of clinical care nevirapine (NVP) prophylaxis, tuberculosis (TB) prophylaxis or treatment and/or combination antiretroviral (ARV) treatment containing lopinavir/ritonavir (LPV/r) prophylaxis or treatment.

   **REGIMENS:** For Arms 1, 2, 3:
   
   Breastfeeding infants 7 to 14 days of age with birth weight ≤2500 grams in Arms 1 and 3; and 7 days to ≤84 days with birth weight ≤4000 grams in Arm 2 born to HIV-infected mothers not receiving maintenance ARV therapy that includes NVP OR formula feeding infants 7 to 14 days of age with birth weight ≤2500 grams in Arm 1 and 7 days to ≤84 days with birth weight ≤4000 grams in Arm 2 born to HIV-infected mothers

   For Arm 4:
   
   Arm 4: Breast or formula feeding infants 7 days to ≤84 days 14 days of age with low birth weight ≤4000 2500 grams born to HIV-uninfected mothers with active TB disease; infant receiving INH alone or INH plus RIF for TB prophylaxis/treatment

   For Arms 5 and 6:
   
   Breast or formula feeding infants newly diagnosed with HIV infection weighing ≤4000 2500 grams at birth and are ≤12 weeks 84 days of age. Infants who were enrolled in Arms 1, 2 or 3 and later determined to be HIV infected are then eligible to enroll in Arms 5 or 6 if started on an LPV/r regimen.

   Arm 5: Infants initiating treatment/prophylaxis with LPV/r plus 2 NRTIs, and not receiving RIF (but may be receiving INH)

   Arm 6: Infants initiating treatment/prophylaxis with LPV/r plus 2 NRTIs, and receiving RIF (and may be receiving INH)

**STRATIFY BY BIRTH WEIGHT:**

<table>
<thead>
<tr>
<th>Arm 2</th>
<th>Arm 4</th>
</tr>
</thead>
<tbody>
<tr>
<td>1800 – 4000 2500gm: n=6</td>
<td>1800 – 4000 2500gm: n=6 to 12; with a minimum of 6 each for INH and RIF PK analyses</td>
</tr>
</tbody>
</table>
STUDY DESIGN SCHEMATIC:

<table>
<thead>
<tr>
<th>Arm</th>
<th>Infant Study Treatment</th>
<th>Infant Feeding</th>
<th>Infant Age at Entry</th>
<th>Sample Size (evaluable subjects, total and per weight band)</th>
<th>Infant Birth Weight Bands</th>
<th>Maternal HIV status</th>
<th>Infant TB Status</th>
<th>Maternal ART</th>
</tr>
</thead>
<tbody>
<tr>
<td>2</td>
<td>NVP + INH</td>
<td>Breastfeeding or formula feeding</td>
<td>7 - ≤84 days ≤14 days</td>
<td>N=18&lt;br&gt;N=6&lt;br&gt;N=6&lt;br&gt;N=6</td>
<td>Total&lt;br&gt;1400gm&lt;br&gt;1400 - &lt;1800gm&lt;br&gt;1800 - ≤4000gm&lt;br&gt;≤2500gm</td>
<td>HIV-infected</td>
<td>TB exposed or treated</td>
<td>If breastfeeding: No NVP&lt;br&gt;If formula feeding: NA</td>
</tr>
<tr>
<td>4</td>
<td>INH or INH + RIF</td>
<td>Breastfeeding or formula feeding</td>
<td>7 - ≤84 days ≤14 days</td>
<td>N=18-36&lt;br&gt;N=6-12&lt;br&gt;N=6-12&lt;br&gt;N=6-12</td>
<td>Total&lt;br&gt;1400gm&lt;br&gt;1400 - &lt;1800gm&lt;br&gt;1800 - ≤4000gm&lt;br&gt;≤2500gm</td>
<td>HIV-uninfected</td>
<td>TB exposed</td>
<td>No</td>
</tr>
<tr>
<td>5</td>
<td>LPV/r + 2 NRTIs ± INH</td>
<td>Breastfeeding or formula feeding</td>
<td>≤84 days ≤12 weeks</td>
<td>N=24</td>
<td>≤4000gm ≤2500gm</td>
<td>HIV-infected</td>
<td>± TB exposed</td>
<td>±</td>
</tr>
<tr>
<td>6</td>
<td>LPV/r + 2 NRTIs + RIF ± INH</td>
<td>Breastfeeding or formula feeding</td>
<td>≤84 days ≤12 weeks</td>
<td>N=12</td>
<td>≤4000gm ≤2500gm</td>
<td>HIV-infected</td>
<td>TB exposed or treated</td>
<td>±</td>
</tr>
</tbody>
</table>

2. Section 1.1, Background, Ninth Paragraph, Last Sentence:
P1106 will use an opportunistic approach, so that infants enrolling in the LPV/r arms will have documented HIV infection and will have been started on LPV/r solution as part of clinical care.

3. Section 3.0, Study Design:
Second Paragraph: Arms 1, 2 and 3: Breastfeeding or formula feeding LBW infants born to HIV-infected mothers who are receiving either no ARV therapy or ARV therapy that does not include NVP:

Third Paragraph, First Sentence: HIV-exposed infants (Arms 1, 2 and 3) will enroll between 7 and 14 days of life and HIV-exposed infants in Arm 2 will enroll between 7 days and ≤84 days of life and will have their first PK samples collected prior to the standard increase in NVP dose from 2 mg/kg to 4 mg/kg at age 2 weeks.

Eighth Paragraph: Arms 5 and 6: HIV-infected or exposed infant ≤84 days 12 weeks of age whose birth weight was ≤4000 grams:
Arm 5: Infants initiating treatment/prophylaxis with LPV/r plus 2 NRTIs, and not receiving RIF (but may be receiving INH)
Arm 6: Infants initiating treatment/prophylaxis with LPV/r plus 2 NRTIs, and receiving RIF (and may be receiving INH)

Ninth Paragraph, First Sentence: While nearly all infants enrolling in Arms 5 and 6 will be new to the protocol, infants in Arms 1, 2 or 3 who become HIV infected and who are prescribed the ARVs of interest can terminate enrollment in the initial arm and re-enroll in Arms 5 or 6, and will then follow the schedule of evaluations for Arms 5 and 6.

Ninth Paragraph, Last Sentence: HIV-infected or exposed infants (Arms 5 and 6) will enroll prior to the start of LPV/r treatment/prophylaxis so that pretreatment cardiology studies can be obtained.

Last Paragraph, Second Sentence: Infants who were enrolled in Arms 1, 2, or 3 later prescribed LPV/r determined to be HIV-infected are eligible to register to Arms 5 or 6, as appropriate, and follow the schedule of evaluations in Appendix I-B.

4. Section 4.0, Selection and Enrollment of Subjects:
4.1 Inclusion Criteria for Arms 1, 2, and 3 (HIV-exposed infants)
4.12 Age 7 to 14 days (Arms 1 and 3) and 7 days to ≤84 days (Arm 2)
4.13 Birth weight ≤ 2500 grams for Arms 1 and 3; Birth weight ≤ 4000 grams for Arm 2
4.2 Inclusion Criteria for Arm 4 (HIV-unexposed but TB exposed infants)
   4.21 Age 7 days to ≤ 84 days
   4.22 Birth weight ≤ 4000 grams

4.3 Inclusion Criteria for Arms 5 and 6 (HIV-infected or exposed infants)
   4.31 Documentation of HIV-1 infection defined as positive HIV nucleic acid test (NAT, e.g., RNA PCR or DNA PCR) done as part of clinical care. An HIV NAT (e.g., RNA PCR or DNA PCR) confirmatory test must be done at study entry but results may be pending at time of enrollment.
   4.32 Birth weight ≤ 4000 grams
   4.34 Intention by clinical care provider to prescribe LPV/r plus 2 NRTIs and no RIF (Arm 5) or LPV/r plus 2 NRTIs plus RIF (Arm 6)

5. Section 4.5, Enrollment Procedures, Sixth Paragraph: Infants enrolled in Arms 1, 2, or 3 who are subsequently prescribed LPV/r diagnosed as HIV infected are eligible to register to Arm 5 or 6, as appropriate, by using the DMC Subject Enrollment System (SES) and follow the schedule of evaluations listed in Appendix I-B.

6. Section 5.0, Study Treatment, Third paragraph: Those infants receiving treatment/prophylaxis for HIV infection with LPV/r plus 2 NRTIs will be dosed according to standard of care and receiving locally available drug formulations.

7. Section 6.1, Toxicity Management, Fourth Paragraph, Fourth Sentence: As cardiac conditions may impact the use of LPV/r, results of these tests will be reviewed by the clinical care provider and local site cardiologist before initiating and during LPV/r treatment/prophylaxis.

8. Section 8.1, General Design Issues, First Paragraph: This is a Phase IV prospective pharmacokinetic study to evaluate the PK and safety of currently prescribed HIV and TB drugs in lower birth weight infants (<2500 grams in Arms 1 and 3; and ≤4000 grams in Arms 2, 4-6 at birth). There are 6 arms representing the regimens of study interest based on what the infant is or will be receiving as part of his/her clinical care. No study-supplied treatment will be given to the infants during this study. Arms 1, 2 and 3 are for breastfeeding or formula feeding, LBW infants 7-14 days of age born to HIV-infected mothers; mothers of breastfeeding infants should not be receiving NVP containing ARV regimen. Arm 4 is for breast or formula feeding LBW infants 7-14 days of age born to HIV-uninfected but TB-infected mothers. Arms 5 and 6 are for breastfeeding or formula feeding HIV-infected LBW infants ≤12 weeks of age. The infant will be assigned to one of the following study arms based on the HIV/TB drug regimen that the infant is receiving or will be receiving as part of his/her clinical care at study entry:

   - Arm 1: Receiving HIV prophylaxis with NVP (no TB prophylaxis/treatment)
   - Arm 2: Receiving HIV prophylaxis with NVP and TB prophylaxis with INH (no RIF)
   - Arm 3: Receiving HIV prophylaxis with NVP and TB prophylaxis/treatment with INH plus RIF
   - Arm 4: Not receiving any HIV drugs but receiving TB prophylaxis/treatment with INH alone or INH plus RIF
   - Arm 5: Infants initiating treatment/prophylaxis with LPV/r plus 2 NRTIs, and not receiving RIF (but may be receiving INH)
   - Arm 6: Infants initiating treatment/prophylaxis with LPV/r plus 2 NRTIs, and receiving RIF (and may be receiving INH)

   Infants in Arms 1, 2, or 3 who are later diagnosed as HIV-infected and prescribed LPV/r the ARVs of interest may re-enroll to Arms 5 and 6.
9. Section 8.3, Randomization and Stratification, Second Paragraph, First Sentence: Subjects will be stratified into 3 weight bands (Arm 1 and 3: <1400 vs. 1400 – <1800 vs 1800 – 2500 grams; Arms 2 and 4: <1400 vs. 1400 – <1800 vs. 1800 – 4000 grams) to ensure adequate representation over the full weight range of LBW infants. Stratum accrual limits for each arm are described in Section 8.4. Weight band stratification will be used for Arms 1, 2, 3, and 4, but not for 5 and 6, since the team anticipates that the number of HIV-infected LBW infants in Arms 5 and 6 (Arms 5 and 6) will be too low to accomplish this form of stratification.

10. Section 8.4, Sample Size and Accrual, Arms 2 and 4, 1800 – 2500gm weight bands
   Arm 2: 1800 – 4000 gm: n=6
   Arm 4: 1800 – 4000 gm: n=6 to 12; with a minimum of 6 each for INH and RIF PK analyses

11. Appendix I-A

    SCHEDULE OF EVALUATIONS FOR ARMS 1, 2, 3, AND 4*

    *INFANTS WHO WERE ENROLLED IN ARMS 1, 2, OR 3 AND LATER PRESCRIBED LPV/r
determined to be HIV-infected should register to ARM 5 OR 6, AS APPROPRIATE,
    AND FOLLOW THE SCHEDULE OF EVALUATIONS IN APPENDIX I-B.

<table>
<thead>
<tr>
<th>EVALUATION</th>
<th>Screening within 0-84 days of life</th>
<th>Entry within 7-14 days of life</th>
<th>Week 6 of life</th>
</tr>
</thead>
<tbody>
<tr>
<td>Chemistries (ALT, Cr, GGT)</td>
<td>0.9 ± 0.5 mL²</td>
<td>0.8-1.3 mL</td>
<td>0.9 ± 0.5 mL²</td>
</tr>
<tr>
<td>TOTAL BLOOD VOLUME</td>
<td></td>
<td>0.4-0.9 mL</td>
<td>0.6-1.3 mL</td>
</tr>
</tbody>
</table>

Appendix I-A, Footnote 8, Last Sentence: Infants who were enrolled in Arms 1, 2, or 3 and later prescribed LPV/r determined to be HIV-infected should be re-evaluated for enrollment in Arms 5 or 6, as appropriate, and if eligible, should follow the Schedule of Evaluations in Appendix I-B.

12. Appendix I-B, Schedule of Evaluations for Arms 5 and 6

<table>
<thead>
<tr>
<th>ARMS</th>
<th></th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>ARM 5 (LPV/r plus 2 NRTIs AND NO RIF BUT MAY BE RECEIVING INH)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>ARM 6 (LPV/r plus 2 NRTIs PLUS RIF AND MAY BE RECEIVING INH)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>EVALUATION</td>
<td>Week 2 after LPV/r initiation</td>
<td>Week 6 after LPV/r initiation</td>
<td>Week 16 after LPV/r initiation</td>
</tr>
<tr>
<td>Chemistries (ALT, Cr, potassium, calcium, osmolality)</td>
<td>0.9 ± 0.5 mL²</td>
<td>0.9 ± 0.5 mL²</td>
<td>0.9 ± 0.5 mL²</td>
</tr>
<tr>
<td>PK Sampling</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Arm 5 (LPV/r plus 2 NRTIs, no RIF)²</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Arm 6 (LPV/r plus 2 NRTIs plus RIF)²</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>TOTAL BLOOD VOLUME</td>
<td>1.0-1.5 mL</td>
<td>0.6-1.1 mL</td>
<td>0.6-1.1 mL</td>
</tr>
<tr>
<td></td>
<td>0.6-1.1 mL</td>
<td>0.2-0.7 mL</td>
<td>0.2-0.7 mL</td>
</tr>
</tbody>
</table>

Appendix I-B, Footnote 3: For HIV-infected infants: Confirmatory HIV RNA PCR may be drawn prior to entry or at the entry visit. The results may be pending at entry visit, but results must be available prior to LPV/r initiation. Results of confirmatory HIV RNA PCR must indicate HIV infection.

13. APPENDIX V-A

WHAT DOES MY BABY HAVE TO DO IF SHE/HE IS IN THIS STUDY?, Screening Visit To See If Your Baby Can Be In The Study, First Bullet:
- The screening visit will happen when your baby is less than 84 days 14 days old.

WHAT DOES MY BABY HAVE TO DO IF SHE/HE IS IN THIS STUDY?, Entry Visit, Third and Fifth Bullet:
- We will draw blood to check how well your baby’s liver and kidneys are functioning if your baby’s doctor has not already done this as part of your baby’s routine care. The total amount of blood to be drawn for this test if it needs to be done will be approximately 0.5mL (less than a quarter of a teaspoon).
  [Note to sites: add locally relevant description of blood volume].
• The total amount of blood drawn at this visit will vary from **approximately** 0.4mL to 0.9mL (less than a quarter of a teaspoon) depending on the type of test. [Note to sites: add locally relevant description of blood volume].

**WHAT DOES MY BABY HAVE TO DO IF SHE/HE IS IN THIS STUDY?, On-Study Visits, First, Third and Eighth Bullets:**

• You will be asked to bring your baby to the clinic 3-5 additional times. These visits will be when your baby is 4, 6, 10, 16, and 24 weeks old.

• **If your baby is in the study** when your baby is 6 weeks old, we will draw blood to check how well your baby’s liver and kidneys are functioning if your baby’s doctor has not already done this as part of your baby’s routine care. The total amount of blood to be drawn for this test if it needs to be done will be **approximately** 0.5mL (less than a quarter of a teaspoon). [Note to sites: add locally relevant description of blood volume].

• The total amount of blood drawn at these different study visits will be between **approximately** 0.2mL to 0.9mL (less than a quarter of a teaspoon) depending on the type of test. [Note to sites: add locally relevant description of blood volume].

14. **APPENDIX V-B**

**WHAT DOES MY BABY HAVE TO DO IF SHE/HE IS IN THIS STUDY?, Screening Visit To See If Your Baby Can Be In The Study, First Bullet:**

• The screening visit will happen when your baby is less than 84 days old.

**WHAT DOES MY BABY HAVE TO DO IF SHE/HE IS IN THIS STUDY?, Entry Visit, Third and Fifth bullet:**

• We will draw blood to check how well your baby’s liver and kidneys are functioning if your baby’s doctor has not already done this as part of your baby’s routine care. The total amount of blood to be drawn for this test if it needs to be done will be **approximately** 0.5mL (less than a quarter of a teaspoon). [Note to sites: add locally relevant description of blood volume].

• The total amount of blood drawn at this visit will vary from **approximately** 0.4mL to 0.9mL (less than a quarter of a teaspoon) depending on the type of test. [Note to sites: add locally relevant description of blood volume].

**WHAT DOES MY BABY HAVE TO DO IF SHE/HE IS IN THIS STUDY?, On-Study Visits, First, Third, and Ninth bullets:**

• You will be asked to bring your baby to the clinic 5 additional times. These visits will be when your baby is 4, 6, 10, 16, and 24 weeks old.

• The total amount of blood to be drawn for this test if it needs to be done will be **approximately** 0.5mL (less than a quarter of a teaspoon). [Note to sites: add locally relevant description of blood volume].

• The total amount of blood drawn at the different study visits will be between **approximately** 0.4mL to 0.9mL (less than a quarter of a teaspoon) depending on the type of test. [Note to sites: add locally relevant description of blood volume].

15. **APPENDIX V-C**

**TITLE:** (For use with Appendix I-B) DIVISION OF AIDS INTERNATIONAL MATERNAL PEDIATRIC ADOLESCENT AIDS CLINICAL TRIALS GROUP (IMPAACT) SAMPLE INFORMED CONSENT FOR INFANTS IN ARMS 5 (LPV/r PLUS 2NRTIs AND NO RIF BUT MAY BE RECEIVING INH AND ARM 6 (LPV/r PLUS 2NRTIs PLUS RIF AND MAY BE RECEIVING INH)

**INTRODUCTION, First Sentence:** You are being asked to allow your baby to take part in this research study because you are infected with HIV and your doctor plans to start your baby on anti-HIV medicine. your baby is infected with the Human Immunodeficiency Virus (HIV).
WHY IS THIS STUDY BEING DONE?, First sentence: Your baby was smaller than average at birth and your baby has HIV infection. Your baby’s doctor plans to start your baby on the anti-HIV medicine called lopinavir/ritonavir in addition to other anti-HIV medicines and with or without tuberculosis medicines.

WHAT DOES MY BABY HAVE TO DO IF SHE/HE IS IN THIS STUDY?, On-Study Visits, Third and Eleventh bullets:

- At 3-4 of these visits, we will draw blood to check how well your baby’s liver and kidneys are functioning if your baby’s doctor has not already done this as part of your baby’s routine care. The total amount of blood to be drawn for this test if it needs to be done will be approximately 0.5mL (less than a quarter of a teaspoon). [Note to sites: add locally relevant description of blood volume].
- The total amount of blood drawn at the different study visits will vary from approximately 0.2mL to 1.1mL (less than a quarter of a teaspoon) depending on the type of test. [Note to sites: add locally relevant description of blood volume].

References
Clarification Memorandum #2 for:

IMPAACT P1106

Pharmacokinetic Characteristics of Antiretrovirals and Tuberculosis Medicines in Low Birth Weight Infants
Version 1.0, dated 23 April 2013

(DAIDS Document ID 11882)

Clarification Memorandum Date: 16 January 2017

Information/Instructions to Study Sites

This Clarification Memorandum (CM) has been approved by the DAIDS Medical Officer. Institutional Review Board/Ethics Committee (IRB/EC) approval of this Clarification Memorandum is not required by the sponsor prior to implementation; however, sites may submit it to the responsible IRBs/ECs for their information or, if required by the IRBs/ECs, for their approval prior to implementation.

This Clarification Memorandum should be maintained in each site’s essential documents file for IMPAACT P1106. It is the responsibility of the Investigator of Record to ensure that all study staff are made aware of and follow this Clarification Memorandum.

Summary of Clarifications and Rationale

This CM clarifies that the intent of the protocol is to allow the electrocardiogram and/or echocardiogram to be rescheduled at any visit and LPV/r given, as indicated in Appendix III. This CM also contains a minor correction to Appendix I-B.

Implementation

The modifications included in this CM will be incorporated into the next protocol amendment. Modifications are shown below as they appear in the protocol, using strikethrough for deletions and bold type for additions.

1. Correction to Appendix I-B, Schedule of Evaluations for Arms 5 and 6.

<table>
<thead>
<tr>
<th>EVALUATION</th>
</tr>
</thead>
<tbody>
<tr>
<td>Electrocardiogram (See Appendix III)</td>
</tr>
<tr>
<td>Echocardiogram (See Appendix III)</td>
</tr>
</tbody>
</table>

2. Appendix III, Electrocardiogram/echocardiogram (ECG/ECHO) studies, Bullet 4:
The ECG and /or ECHO should be rescheduled if the healthcare provider (neonatologist) determines that the infant is unable to tolerate the investigation at a scheduled time point. (LPV/r will be given if attending doctors [neonatal /infectious disease] think it is appropriate). This would apply to all visits where ECG and ECHO are indicated in Appendix I-B.
Letter of Amendment #1 for:

IMPAACT P1106

Pharmacokinetic Characteristics of Antiretrovirals and Tuberculosis Medicines in Low Birth Weight Infants
Version 1.0, dated 23 April 2013

(DAIDS Document ID 11882)

Letter of Amendment Date: 3 June 2016

Information/Instructions to Study Sites

The information contained in this Letter of Amendment (LoA) impacts the P1106 study and must be submitted to site Institutional Review Boards and/or Ethics Committees (IRBs/ECs) as soon as possible for their review and approval. Approval must also be obtained from 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, each site should immediately begin implementing this LoA. Unless directed by site IRBs/ECs, re-consenting is not required for current study participants.

Sites are required to submit a LoA registration packet to the DAIDS Protocol Registration Office (DAIDS PRO) at the Regulatory Support Center (RSC). Sites will receive a registration notification for the LoA after the DAIDS PRO verifies that all required registration documents have been received and are complete. Sites should not await this notification before implementing this LoA.

Please file this LoA, all associated IRB/EC and regulatory entity correspondence, and all correspondence with the DAIDS PRO in your essential documents files for P1106. If the P1106 protocol is amended in the future, the contents of this LoA will be incorporated into the next version of the protocol.

Summary of Modifications and Rationale

The purpose of this LoA is (a) to expand testing options for documentation of HIV infection, (b) allow for breast or formula feeding participant enrollment into Arms 1, 2 and 3 and (c) to clarify that sites should assess hemoglobin under the term “hematology”.

(a) As currently specified in protocol Section 4.31, participants who are HIV-infected a positive HIV DNA PCR and a confirmatory HIV RNA PCR to enroll in the study. To align with updated standards of care and expand the allowable testing options, HIV-1 testing options will include HIV RNA testing for the initial test done as part of clinical care and for the confirmatory test done at study entry.

(b) Originally, to enroll in Arms 1, 2 and 3, participant’s mothers must have intended to breastfeed. Infants who are formula fed were initially excluded, as they would receive NVP for a shorter period of time than for breastfeeding infants. The team has concluded that allowing enrollment of formula feeding infants in Arms 1, 2 and 3 will improve overall enrollment and will provide important NVP pharmacokinetic data (Arms 1-3) as well as isoniazid and rifampicin pharmacokinetic data (Arms 2-3).

(c) Hematocrit (Hct) is changed to hemoglobin (Hgb), where the term “hematology” is used, consistent with clinical practice.
Implementation

The modifications included in this Letter of Amendment are listed below by update and in order of appearance in the protocol and will be incorporated into the next protocol amendment as specified below. Additions to the text are indicated in **bold**; deletions are indicated by *strikethrough*.

(a) Update to HIV-1 Confirmatory Testing

Section 4.31  
Documentation of HIV-1 infection defined as positive HIV **nucleic acid test** (NAT, e.g., **RNA PCR** or **DNA PCR**) done as part of clinical care. An HIV **NAT** (e.g., **RNA PCR** or **DNA PCR**) confirmatory test must be done at study entry but results may be pending at time of enrollment.

**Appendix I-B**

<table>
<thead>
<tr>
<th>EVALUATION</th>
<th>Entry within 7 days prior to LPV/r initiation</th>
</tr>
</thead>
<tbody>
<tr>
<td>VIROLOGY</td>
<td></td>
</tr>
<tr>
<td>HIV NAT (e.g., RNA PCR or DNA PCR)</td>
<td>0.5mL³</td>
</tr>
</tbody>
</table>

**Appendix I-B, Footnote 3**
Confirmatory HIV **NAT** (e.g., RNA PCR or DNA PCR) may be drawn prior to entry or at the entry visit. The results may be pending at entry visit, but results must be available prior to LPV/r initiation. Results of confirmatory HIV **NAT** (e.g., RNA PCR or DNA PCR) must indicate HIV infection.

(b) Removing infant feeding requirement to enroll in Arms 1-3

**SCHEMA REGIMENS:**
For Arms 1, 2, 3:
Breastfeeding feeding infants 7 to 14 days of age with birth weight ≤2500 grams born to HIV-infected mothers not receiving maintenance ARV therapy that includes including NVP OR formula feeding infants 7 to 14 days of age with birth weight ≤2500 grams born to HIV-infected mothers

**STUDY DESIGN SCHEMATIC:**

<table>
<thead>
<tr>
<th>Arm</th>
<th>Infant Study Treatment</th>
<th>Infant Feeding</th>
<th>Infant Age at Entry</th>
<th>Sample Size (evaluable subjects, total and per weight band)</th>
<th>Infant Entry Weight Bands</th>
<th>Maternal HIV status</th>
<th>Infant TB Status</th>
<th>Maternal ART</th>
</tr>
</thead>
</table>
| 1   | NVP                   | Breastfeeding or formula feeding | 7-14 days | N=40  
N=12  
N=16 | Total  
<1400gm  
1400 - <1800gm  
1800 - <2500gm | HIV-infected | TB not exposed | If breastfeeding: No NVP  
If formula feeding: NA |
| 2   | NVP + INH             | Breastfeeding or formula feeding | 7-14 days | N=18  
N=6  
N=6 | Total  
<1400gm  
1400 - <1800gm  
1800 - <2500gm | HIV-infected | TB exposed or treated | If breastfeeding: No NVP  
If formula feeding: NA |
| 3   | NVP + INH + RIF       | Breastfeeding or formula feeding | 7-14 days | N=28  
N=8  
N=8  
N=12 | Total  
<1400gm  
1400 - <1800gm  
1800 - <2500gm | HIV-infected | TB exposed or treated | If breastfeeding: No NVP  
If formula feeding: NA |
Section 3.0, Study Design, Second Paragraph, First Sentence:
Arms 1, 2 and 3: Breastfeeding LBW infants born to HIV-infected mothers who are receiving either no ARV therapy or ARV therapy that does not include NVP OR formula feeding LBW infants born to HIV-infected mothers:

Section 3.0, Study Design, Third Paragraph, Fourth Sentence:
Enrollment in Arms 1, 2 and 3 will be limited to breastfeeding HIV-exposed infants whose mothers are receiving either no ARV therapy or ARV therapy that excludes NVP and formula feeding HIV-exposed infants.

Section 3.0, Study Design, Fourth Paragraph:
Formula fed infants are included in excluded from Arms 1, 2 and 3; however, enrollment of formula fed infants may be more challenging for study interpretation because they generally only receive NVP prophylaxis for a shorter period of time than for breastfeeding infants. The goal of the protocol is to characterize the developmental changes in NVP pharmacokinetics over the first 6 months of life. There is no known interaction between mode of infant feeding and NVP PK, so NVP PK data obtained from breast fed infants can be extrapolated to formula fed infants and vice versa.

Section 4.1, Selection and Enrollment of Subjects
4.11 Breastfeeding infants born to HIV-infected mothers who are receiving either no ARV therapy or ARV therapy that does not include NVP OR formula feeding infants born to HIV-infected mothers

Section 8.1, General Design Issues, First Paragraph, Fourth Sentence:
Arms 1, 2 and 3 are for breastfeeding or formula feeding, LBW infants 7-14 days of age born to HIV-infected mothers; mothers of breastfeeding infants should not be receiving NVP-containing ARV regimen.

Section 9.31, First Paragraph, Sixth Sentence:
Subjects missing more than one PK sample through week 6 but with five six or more PK samples across all their visits will also be considered PK evaluable.

Appendix I-A, Schedule of Evaluations for Arms 1, 2, 3 and 4, Footnote 8, point 4:
4) Missed doses of study drugs within preceding 72 hours
PK sampling not performed due to the above criteria should be rescheduled after consultation with the protocol team. In addition, the protocol team should be contacted regarding any interruption in study drug administration greater than 24 hours. Infants whose study drug(s) are discontinued will not have further PK sampling but will continue to be followed for safety and toxicity monitoring. Infants who have been discontinued from one or more study drug(s) but remain on at least one study drug (e.g., Arm 2 infant discontinuing NVP but continuing INH) should continue to have PK sampling and be followed for safety and toxicity monitoring.

Appendix V-A, Introduction, First Sentence:
You are being asked to allow your baby to take part in this research study because you are infected with the Human Immunodeficiency Virus (HIV) and are formula feeding your baby OR are not taking any anti-HIV medicine or are taking anti-HIV medicine that does not include nevirapine (NVP) and are breastfeeding your baby.

Appendix V-A, On Study Visits, Following the First Paragraph:
If your baby has to stop taking some of his/her anti-HIV medicine and/or tuberculosis medicine(s), but continues to take at least one of the anti-HIV medicine and/or tuberculosis medicine(s) before the study ends, you will be asked to allow your baby to continue in the study until your baby is 24 weeks of age.
If your baby has to stop taking **all** his/her anti-HIV medicine and/or tuberculosis medicine(s) before the study ends, you will be asked to allow your baby to continue in the study until your baby is 24 weeks of age, to make sure your baby is continuing to do well. At each of the scheduled study visits, we will take a medical history and perform a physical exam, but no blood will be drawn.

(c) Assess hemoglobin (Hgb), rather than hematocrit (Hct), as part of the hematology assessment.

<table>
<thead>
<tr>
<th>Appendices I-A and I-B</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>EVALUATION</strong></td>
</tr>
<tr>
<td><strong>LABORATORY</strong></td>
</tr>
<tr>
<td>Hematology (Hgb Hct)</td>
</tr>
</tbody>
</table>
Clarity Memorandum #1 for:

IMPAACT P1106
Pharmacokinetic Characteristics of Antiretrovirals and Tuberculosis Medicines in Low Birth Weight Infants
Version 1.0, dated 23 April 2013

(DAIDS Document ID 11882)

Clarification Memorandum Date: 4 March 2016

Information/Instructions to Study Sites

This Clarification Memorandum (CM) has been approved by the DAIDS Medical Officer. Institutional Review Board/Ethics Committee (IRB/EC) approval of this Clarification Memorandum is not required by the sponsor prior to implementation; however, sites may submit it to the responsible IRBs/ECs for their information or, if required by the IRBs/ECs, for their approval prior to implementation.

This Clarification Memorandum should be maintained in each site’s essential documents file for IMPAACT P1106. It is the responsibility of the Investigator of Record to ensure that all study staff are made aware of and follow this Clarification Memorandum.

Summary of Clarifications and Rationale

This CM clarifies that the intent of the protocol team is to study the PK of selected TB drugs in low birth weight infants receiving these drugs as part of clinical care, whether for prophylaxis against infection or for treatment of presumed or proven infection. This CM also contains updated protocol team roster and contact information.

Implementation

The modifications included in this CM will be incorporated into the next protocol amendment. Modifications are shown below, using strikethrough for deletions and bold type for additions.

1. Specifications of use of TB regimens for prophylaxis or treatment have been clarified throughout the protocol.

   Schema, Regimens
   Arm 4: Breast or formula feeding infants 7 to 14 days of age with birth weight ≤ 2500 grams born to HIV-uninfected mothers with active TB disease; infant receiving INH alone or INH plus RIF for TB prophylaxis/treatment

   Section 3.0, Study Design, Third and Eight Paragraphs:
   Arm 4: Infant receiving INH alone or INH plus RIF for TB prophylaxis/treatment
Sections 4.14 and 4.23, Section and Enrollment of Subjects

4.14 Receiving or will be receiving prophylaxis/treatment as prescribed by clinical care provider as follows: NVP (Arm 1), NVP plus INH (Arm 2), NVP plus INH plus RIF (Arm 3)

4.23 Receiving prophylaxis/treatment with INH alone or INH plus RIF as prescribed by clinical care provider

2. To reflect current protocol team membership, Lynne Mofenson, Elizabeth Hawkins, Ashraf Coovadia, Gad Bihabwa, Tony Bloom, Gary Reubenson, and Delania Lawrence are removed from the protocol team roster; Jack Moye, Katie McCarthy, JL Ariansen, Adrie Bekker, Amy James Loftis, Stephanie Popson, Nasreen Abraham, Chris Hensel, and Reenu Thomas are added to the protocol team roster, with contact information as follows:

**Protocol Vice-Chair**
Adrie Bekker, MBChB, MMed (Paeds)
Faculty of Medicine and Health Sciences
Department of Paediatrics and Child health
Stellenbosch University
PO Box 241
Cape Town, South Africa 8000
Phone: 021 938 9198
E-mail: adrie@sun.ac.za

**Protocol Data Manager**
Stephanie Popson, PhD
FSTRF
4033 Maple Road
Amherst, NY 14226-1056, USA
Phone: 716-834-0900 x7356
Email: popson@fstrf.org

**Laboratory Technologist**
Amy James Loftis
Retrovirology Core Lab
University of North Carolina at Chapel Hill
School of Medicine
709 Mary Ellen Jones Building
116 Manning Drive
Chapel Hill, NC 27599 USA
Phone: 919-966-6963
Email: amy_james@med.unc.edu

**Clinical Trials Specialists**
Katie McCarthy, MPH
IMPAACT Operations Center, FHI 360
359 Blackwell Street, Suite 200
Durham, NC 27701, USA
Phone: 919-544-7040 x11439
Email: kmccarthy@fhi360.org

JL Ariansen, MS
IMPAACT Operations Center, FHI 360
359 Blackwell Street, Suite 200
Durham, NC 27701, USA
Phone: 919-544-7040 x11185
Email: jariansen@fhi360.org

**Laboratory Data Manager**
Chris Hensel
FSTRF
4033 Maple Road
Amherst, NY 14226-1056, USA
Phone: 716-834-0900 x7478
Email: chensel@fstrf.org
Neonatologist
Reenu Thomas, MBChB, FCPaed
Consultant at Division of Neonatology
Department of Pediatrics
Chris Hani Baragwanath Academic Hospital
Metabolic Unit
P.O. Bertsham, 2013
Phone: 0829296310
Email: Reenu.thomas@wits.ac.za
IMPAACT P1106

PHARMACOKINETIC CHARACTERISTICS OF ANTIRETROVIRALS AND TUBERCULOSIS MEDICINES IN LOW BIRTH WEIGHT INFANTS

A Limited Center, International Trial of the International Maternal Pediatric Adolescent AIDS Clinical Trials Group (IMPAACT)

Sponsored by:

The National Institute of Allergy and Infectious Diseases (NIAID)

and

The Eunice Kennedy Shriver National Institute of Child Health and Human Development (NICHD)

DAIDS ES #: 11882

The HIV Treatment Scientific Committee Chair: Elaine Abrams, M.D.

Protocol Co-Chairs: Mark Cotton, M.Med (Paed), FCPaed (SA), DCH (SA), DTM&H, PhD
Mark Mirochnick, M.D.

NIAID Medical Officer: Elizabeth Smith, M.D.

NICHD Medical Officer: Lynne Mofenson, M.D., F.A.A.P.

Clinical Trials Specialist: Elizabeth Hawkins, M.A.

Version 1.0
FINAL
April 23, 2013
All questions concerning this protocol should be sent via e-mail to impaact.teamp1106@fstrf.org. Remember to include the subject’s PID when applicable. The appropriate team member will respond to questions via e-mail with a "cc" to impaact.teamp1106@fstrf.org. A response should generally be received within 24 hours (Monday - Friday). For protocol registration questions, e-mail 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. For EAE questions, e-mail DAIDSRSCSafetyOffice@tech-res.com or call 1-800-537-9979 or 1-301-897-1709 or fax 1-800-275-7619 or 301-897-1710. To order study agent, call the Clinical Research Products Management Center at (301) 294-0741. For randomization or enrollment questions, contact the Data Management Center at 716-834-0900 or by email at sdac.random.desk@fstrf.org.

Protocol Co-Chair
Mark Cotton, M.Med, FCPaed (SA), DCH (SA), DTM&H, PhD
Department Paediatrics & Child Health
Faculty of Health Science
KIDCRU, Stellenbosch University
P.O. Box 19063
Tygerberg, 7505
South Africa
Phone: 27 21 938 4219
E-mail: mcot@sun.ac.za

Protocol Co-Chair and Pharmacologist
Mark H. Mirochnick, M.D.
Chief, Division of Neonatology
Boston Medical Center
771 Albany Street, Room 4111
Boston, MA 02118
Phone: 617-414-3754
E-mail: markm@bu.edu

NIAID Medical Officer
Mary Elizabeth Smith, M.D.
IMAPB/DAIDS/NIAID/NIH/DHHS
6700B Rockledge Drive
Room 5157
Bethesda, MD 20892
Phone: 301-402-3226
E-mail: betsysmith@niaid.nih.gov

NICHID Medical Officer
Lynne Mofenson, M.D., F.A.A.P.
Branch Chief
Maternal and Pediatric Infectious Disease Branch
Eunice Kennedy Shriver National Institute of Child Health & Development
6100 Executive Blvd., Room 4B11
Bethesda, MD 20892
Phone: 301-435-6870
E-mail: lm65d@nih.gov

Protocol Statisticians
Mae P. Cababasay, M.S., M.A.
Center for Biostatistics in AIDS Research
Harvard School of Public Health
651 Huntington Avenue
Boston, MA 02115
Phone: 617-432-4516
E-mail: maec@sdac.harvard.edu

Protocol Vice Chair
Ashraf Coovadia, MB,ChB, D.C.H.
Head of Paediatric HIV Services
Department of Paediatrics and Child Health
Rahima Moosa Mother and Child Hospital
University of The Witwatersrand
Johannesburg, 0001, South Africa
Phone: 27 11 470 9290
E-mail: Ashraf.Coovadia@wits.ac.za
IMPAACT P1106 PROTOCOL TEAM ROSTER

Jiajia Wang, M.S.
Center for Biostatistics in AIDS Research
Harvard School of Public Health
651 Huntington Avenue
Boston, MA 02115
Phone: 617-432-1464
Email: jwang@sdac.harvard.edu

Protocol Pharmacologist
Edmund Capparelli, Pharm.D.
Pediatric Pharmacology Research Unit
University of California San Diego
7910 Frost Street #360
San Diego, CA 92123
Phone: 858-246-0001
E-mail: ecapparelli@popmail.ucsd.edu

Clinical Trials Specialist
Elizabeth Hawkins, M.A.
IMPAACT Operations Center
Social & Scientific Systems, Inc.
8757 Georgia Avenue
Silver Spring, MD 20910
Phone: 301-628-3335
E-mail: ehawkins@s-3.com

Protocol Data Manager
Bobbie Graham, B.A.
Frontier Science and Technology Research Foundation
4033 Maple Road
Amherst, NY 14226
Phone: 716-834-0900
E-mail: graham@fstrf.org

Laboratory Technologist
Gad Bihabwa, HDMLT
Makerere University-Johns Hopkins Research
Upper Mulago Hill Road
MUJHU Research House
Kampala, Uganda
Phone: 25 63 133 07286
E-mail: gbihabwa@idi.co.ug

Field Representative
Joan Coetzee
Ward J8-KID CRU
Tygerberg Hospital
Francie van Zijl Drive
Cape Town, South Africa, 7700
Phone: 27 21 938-4157
Email: joan@sun.ac.za

Central Laboratory Specialist
Carolyn Yanavich
Children's Hospital of Los Angeles
4546 Sunset Boulevard
Smith Research Tower Room 902
Los Angeles CA 90027
Phone: 443-249-3851
E-mail: cyanavich@chla.usc.edu

Laboratory Data Manager
Tony Bloom, B.A.
Frontier Science and Technology Research Foundation
4033 Maple Road
Amherst, NY 14226
Phone: 716-834-0900
E-mail: bloom@fstrf.org
IMPAACT P1106 PROTOCOL TEAM ROSTER

Investigators
Diana Clarke, Pharm.D.
Section of Pediatric Infectious Diseases
Boston Medical Center
670 Albany Street, 6th Floor
Boston, MA 02118
Phone: 617-414-7580
E-mail: diana.clarke@bmc.org

Helen McIlleron, M.D.
Division of Pharmacology
University of Cape Town
K45 Old Main Building
Groote Schuur Hospital, Observatory 7925
Cape Town, South Africa
Phone: 27 21 406 6292
E-mail: Helen.mcilleron@uct.ac.za

James McIntyre, M.D., Ch.B., FRCOG
Executive Director
Anova Health Institute
12 Sherborne Road, Parktown
Johannesburg 2193, South Africa
Phone: 27 11 715 5802
E-mail: mcintyre@pixie.co.za

Peter Smith, PhD.
Division of Pharmacology
University of Cape Town
K45 Old Main Building
Groote Schuur Hospital, Observatory, 7925
Cape Town, South Africa
Phone: 27 21 406 6289
E-mail: peter.smith@uct.ac.za

Elaine J. Abrams, M.D.
Columbia University
Mailman School of Public Health
722 W 168th Street
New York, NY 10032
Phone: 212-342-0543
E-mail: eja1@mail.cumc.columbia

Gary Reubenson, MBBCh, FCPaeds, DCH
DTM&H
Department of Paediatrics and Child Health
Rahima Moosa Mother & Child Hospital
University of the Witwatersrand
Private Bag X01, Newclare
Johannesburg, 0001, South Africa
Phone: 27 11 470 9397
E-mail: Gary.Reubenson@wits.ac.za

Helena Rabie, M.Med, M.D.
Department of Paediatrics and Child Health
Faculty of Health Sciences
Tygerberg Hospital
Francie van Zijl Drive
Tygerberg, 7505
Cape Town, South Africa
Phone: 27 21 938 4298
E-mail: hrabie@sun.ac.za
NEONATOLOGISTS:

Chris Hani Baragwanath Hospital
Martha Mayer, FCPaed (SA)
Division of Neonatology, Department of Paediatrics
Metabolic Unit
Chris Hani Baragwanath Academic Hospital
Chris Hani Road
Soweto, South Africa
Phone: 27 11 933 9516 (office); 27 72 225 3273 (mobile)
Email: mayernte@gmail.com

Firdose Nakwa, FCPaed (SA)
Division of Neonatology, Department of Paediatrics
Metabolic Unit
Chris Hani Baragwanath Academic Hospital
Chris Hani Road, Diepkloof, Soweto
Johannesburg, South Africa
Phone: 27 11 933 9321 (office); 27 72 414 0622 (mobile)
Email: firdose.nakwa@wits.ac.za

Sithembiso Velaphi, FCPaed (SA)
Division of Neonatology, Department of Paediatrics
Metabolic Unit
Chris Hani Baragwanath Academic Hospital
Chris Hani Road, Diepkloof, Soweto
Johannesburg, South Africa
Phone: 27 11 933 8400 (office); 27 84 557 7999 (mobile)
Email: sithembiso.velaphi@wits.ac.za

Rahima Moosa Mother & Child Hospital
Delania Lawrence, FCPaed (SA)
Rahima Moosa Mother and Child Hospital
Phone: 0846240486
E-mail: delania@discoverymail.co.za

Tygerberg Hospital
Sandi Holgate, FCPaed (SA)
Department of Neonatology
Stellenbosch University
Tygerberg Hospital
Francie van Zijl Drive, Tygerberg, 7505
Phone: 27 21 938 9673
E-mail: sandi@sun.ac.za

Adrie Bekker, FCPaed (SA)
Department of Neonatology
Stellenbosch University
Tygerberg Hospital
Francie van Zijl Drive, Tygerberg, 7505
Phone: 27 21 938 9673
E-mail: adrie@sun.ac.za

King Edward VII
Radhika Singh FCPaed (SA)
Department of Paediatrics and Child Health
Nelson R. Mandela School of Medicine
University of KwaZulu-Natal
Private Bag 7, Congella
Phone: 312604355
E-mail: singhr2@ukzn.ac.za
IMPAACT P1106 PROTOCOL TEAM ROSTER

CARDIOLOGISTS:

Chris Hani Baragwanath Hospital
Professor Antoinette Cilliers
Division of Paediatric Cardiology
Department of Paediatrics
Chris Hani Baragwanath Hospital
P.O. Bertsham, 2013
Johannesburg, South Africa
Phone: 08 33 435 8030
E-mail: antoinette.cilliers@wits.ac.za

Tygerberg Hospital
John Lawrenson
Department of Paediatrics and Child Health
Stellenbosch University
Tygerberg Children’s Hospital
Phone: 27 82 685 1658
Email: john.lawrenson@pgwc.gov.za

King Edward VII
Ebrahim M Hoosen
Inkosi Albert Luthuli Central Hospital
Durban, South Africa
Phone: 27 03 124 0100
E-mail: ebrahimhoo@ialch.co.za

CARDIOLOGY CONSULTANTS:

Dr. Gcina Dumani
E-mail: dumgci@gmail.com

Dr. Barend Fourie
E-mail: drbarendfourie@gmail.com
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# GLOSSARY

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<th>Abbreviation</th>
<th>Definition</th>
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<tr>
<td>3TC</td>
<td>Lamivudine</td>
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<tr>
<td>d4T</td>
<td>Stavudine</td>
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<tr>
<td>ABC</td>
<td>Abacavir</td>
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<tr>
<td>AE</td>
<td>Adverse Event</td>
</tr>
<tr>
<td>AIDS</td>
<td>Acquired Immune Deficiency Syndrome</td>
</tr>
<tr>
<td>ALT</td>
<td>Alanine transaminase</td>
</tr>
<tr>
<td>ARV</td>
<td>Antiretroviral</td>
</tr>
<tr>
<td>AGA</td>
<td>Appropriate for Gestational Age</td>
</tr>
<tr>
<td>AUC</td>
<td>Area Under the Curve</td>
</tr>
<tr>
<td>ATV</td>
<td>Atazanavir</td>
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<tr>
<td>BMI</td>
<td>Body Mass Index</td>
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<tr>
<td>CL/F</td>
<td>Clearance (Apparent)</td>
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<tr>
<td>CLIA</td>
<td>Clinical Laboratory Improvement Amendment</td>
</tr>
<tr>
<td>Cr</td>
<td>Creatinine</td>
</tr>
<tr>
<td>CRF</td>
<td>Case Report Form</td>
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<tr>
<td>CYP</td>
<td>Cytochrome P450</td>
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<tr>
<td>DAERS</td>
<td>DAIDS Adverse Experience Reporting System</td>
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<td>DAIDS</td>
<td>Division of AIDS</td>
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<tr>
<td>DMC</td>
<td>Data Management Center</td>
</tr>
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<td>DSMB</td>
<td>Data and Safety Monitoring Board</td>
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<tr>
<td>EAE</td>
<td>Expedited Adverse Event</td>
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<tr>
<td>EC</td>
<td>Ethics Committee</td>
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<td>ECG</td>
<td>Electrocardiogram</td>
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<td>ECHO</td>
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<td>FTC</td>
<td>Emtricitabine</td>
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<td>GGT</td>
<td>Gamma-glutamyl transpeptidase</td>
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<tr>
<td>HIV</td>
<td>Human Immunodeficiency Virus</td>
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<tr>
<td>IMPAACT</td>
<td>International Maternal Pediatric Adolescent AIDS Clinical Trials Group</td>
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<tr>
<td>INH</td>
<td>Isoniazid</td>
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## GLOSSARY

<table>
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<th>Acronym</th>
<th>Definition</th>
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<tr>
<td>IRB</td>
<td>Institutional Review Board</td>
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<tr>
<td>LBW</td>
<td>Low Birth Weight</td>
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<td>LPV/r</td>
<td>Lopinavir/ritonavir</td>
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<tr>
<td>NAT2</td>
<td>N-acetyl-transferase -2</td>
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<tr>
<td>NIAID</td>
<td>National Institute of Allergy and Infectious Diseases</td>
</tr>
<tr>
<td>NICHD</td>
<td>The Eunice Kennedy Shrive National Institute of Child Health and Human Development</td>
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<tr>
<td>NICU</td>
<td>Neonatal Intensive Care Unit</td>
</tr>
<tr>
<td>NNRTI</td>
<td>Non-nucleoside Reverse Transcriptase Inhibitor</td>
</tr>
<tr>
<td>NRTI</td>
<td>Nucleoside Reverse Transcriptase Inhibitor</td>
</tr>
<tr>
<td>NVP</td>
<td>Nevirapine</td>
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<tr>
<td>OHRP</td>
<td>Office for Human Research Protections</td>
</tr>
<tr>
<td>PCP</td>
<td><em>Pneumocystis jiroveci pneumonia</em></td>
</tr>
<tr>
<td>PID</td>
<td>Patient Identification Number</td>
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<tr>
<td>PK</td>
<td>Pharmacokinetic</td>
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<tr>
<td>PRO</td>
<td>Protocol Registration Office</td>
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<tr>
<td>PZA</td>
<td>Pyrazinamide</td>
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<tr>
<td>RE</td>
<td>Regulatory Entity</td>
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<tr>
<td>RIF</td>
<td>Rifampicin</td>
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<td>RSC</td>
<td>Regulatory Support Center</td>
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<td>RTV</td>
<td>Ritonavir</td>
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<tr>
<td>SAE</td>
<td>Serious Adverse Event/Serious Adverse Experience</td>
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<tr>
<td>SGA</td>
<td>Small for Gestational Age</td>
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<tr>
<td>SMC</td>
<td>Study Monitoring Committee</td>
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<tr>
<td>SMX</td>
<td>Sulfamethoxazole</td>
</tr>
<tr>
<td>SIP</td>
<td>Site Implementation Plan</td>
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<tr>
<td>TB</td>
<td>Tuberculosis</td>
</tr>
<tr>
<td>TDM</td>
<td>Therapeutic Dose Monitoring</td>
</tr>
<tr>
<td>TMP-SMX</td>
<td>Trimethoprim-Sulfamethoxazole</td>
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<tr>
<td>V/F</td>
<td>Volume of Distribution (Apparent)</td>
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<td>VQA</td>
<td>Virology Quality Assurance</td>
</tr>
<tr>
<td>WHO</td>
<td>World Health Organization</td>
</tr>
<tr>
<td>ZDV</td>
<td>Zidovudine</td>
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SCHEMA

PHARMACOKINETIC CHARACTERISTICS OF ANTIRETROVIRALS AND TUBERCULOSIS MEDICINES IN LOW BIRTH WEIGHT INFANTS

DESIGN: Phase IV prospective pharmacokinetic (PK) study

POPULATION: Low birth weight (LBW) infants ≤2500 grams at birth who are receiving or will be receiving as part of clinical care nevirapine (NVP) prophylaxis, tuberculosis (TB) prophylaxis or treatment and/or combination antiretroviral (ARV) treatment containing lopinavir/ritonavir (LPV/r).

REGIMENS: For Arms 1, 2, 3:
Breastfeeding infants 7 to 14 days of age with birth weight ≤2500 grams born to HIV-infected mothers not receiving maintenance ARV therapy including NVP.

Arm 1: Mother HIV-infected and TB negative; infant receiving NVP prophylaxis but not TB prophylaxis or treatment

Arm 2: Mother HIV-infected with active TB disease; infant receiving NVP prophylaxis plus isoniazid (INH) but not rifampicin (RIF) for TB prophylaxis

Arm 3: Mother HIV-infected with active TB disease; infant receiving NVP prophylaxis plus INH plus RIF for TB prophylaxis or treatment

For Arm 4:
Arm 4: Breast or formula feeding infants 7 to 14 days of age with birth weight ≤2500 grams born to HIV-uninfected mothers with active TB disease; infant receiving INH alone or INH plus RIF for TB prophylaxis

For Arms 5 and 6:
Breast or formula feeding infants newly diagnosed with HIV infection weighing ≤2500 grams at birth and are ≤12 weeks of age. Infants who were enrolled in Arms 1, 2 or 3 and later determined to
be HIV infected are then eligible to enroll in Arms 5 or 6 if started on an LPV/r regimen.

Arm 5: Infants initiating treatment with LPV/r plus 2 NRTIs, and not receiving RIF (but may be receiving INH)

Arm 6: Infants initiating treatment with LPV/r plus 2 NRTIs, and receiving RIF (and may be receiving INH)

**SAMPLE SIZE:**

Maximum of 158 PK evaluable infants

Arm 1: n=40
Arm 2: n=18
Arm 3: n=28
Arm 4: n=18 minimum; 36 maximum
Arm 5: n=24
Arm 6: n=maximum of 12

**STRATIFY BY BIRTH WEIGHT:**

Arm 1:
<1400gm: n=12
1400 - <1800gm: n=12
1800 – 2500gm: n=16

Arm 2:
<1400gm: n=6
1400 – <1800gm: n=6
1800 – 2500gm: n=6

Arm 3:
<1400gm: n=8
1400 - <1800gm: n=8
1800 – 2500gm: n=12

Arm 4:
<1400gm: n=6 to 12; with a minimum of 6 each for INH and RIF PK analyses
1400 – <1800gm: n=6 to 12; with a minimum of 6 each for INH and RIF PK analyses
1800 – 2500gm: n=6 to 12; with a minimum of 6 each for INH and RIF PK analyses

Arms 5 and 6: No stratification
STUDY DESIGN SCHEMATIC:

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<th>Infant Feeding</th>
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<th>Sample Size (evaluable subjects, total and per weight band)</th>
<th>Infant Entry Weight Bands</th>
<th>Maternal HIV Status</th>
<th>Infant TB Status</th>
<th>Maternal ART</th>
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<td>Breastfeeding</td>
<td>7-14 days</td>
<td>N=40</td>
<td>Total</td>
<td>HIV-infected</td>
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<td>≥2500gm</td>
<td>HIV-infected</td>
<td>TB exposed or treated</td>
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STUDY DURATION:
Arms 1-4: 24 weeks of age
Arms 5-6: 24 weeks after initiation of LPV/r

Infants whose study drugs are discontinued will continue to be followed for safety and toxicity monitoring.

STUDY OBJECTIVES:

Primary:
1. To describe the pharmacokinetics (PK) and safety of NVP, INH, RIF, and LPV/r in LBW infants receiving the drug(s) as part of clinical care.

Secondary:
1. To describe the PK and safety of TMP-SMX, ZDV, d4T, ABC and 3TC in LBW infants receiving the drug(s) as part of clinical care.
2. To develop population PK models of ARVs, TB drugs and TMP-SMX in LBW infants.
3. To describe the impact of CYP 2B6 genetic variants on NVP metabolism and NAT2 genetic variants on INH metabolism in LBW infants.
4. To describe the association of PK parameters and drug exposures with birth weight, gestational age, postnatal age, HIV/TB infection status and other clinical variables.
5. To use population PK models to perform Monte Carlo simulations of current and alternative dosing regimens for ARVs, TB drugs and TMP-SMX.
1.0 INTRODUCTION

1.1 Background

Current trends in the use of antiretrovirals and antituberculosis medications demonstrate a continued increase in their use in newborns. World Health Organization (WHO) and South African guidelines now recommend that all HIV-exposed neonates regardless of birth weight whose mothers are not receiving triple antiretroviral (ARV) prophylaxis receive daily nevirapine (NVP) for 4 to 6 weeks after birth and that NVP treatment should continue in breastfeeding infants until 1 week after cessation of breastfeeding. Infants born to mothers receiving triple ARV prophylaxis should receive either zidovudine (ZDV) or NVP daily for 4 to 6 weeks (1),(2). These guidelines further recommend that all infants diagnosed with HIV infection should begin therapy as soon as their diagnosis is known (3). In South Africa combination regimens used in HIV-infected infants include the protease inhibitor (PI) lopinavir/ritonavir (LPV/r) together with 2 nucleoside reverse transcriptase inhibitors (NRTIs). For the latter, ZDV and lamivudine (3TC) are preferred for low birth weight infants. For older infants, the combination of abacavir (ABC) and 3TC is preferred. Stavudine (d4T) usually replaces ZDV if anemia is present, especially if thought to be due to ZDV. The WHO and South African guidelines also recommend that HIV-infected or indeterminate infants and those receiving breast milk from HIV-infected mothers should be started on trimethoprim/sulfamethoxazole (TMP-SMX) for Pneumocystis jiroveci pneumonia (PCP) prophylaxis starting at 4 to 6 weeks of age.

These guidelines for the use of ARVs and TMP-SMX apply to LBW as well as normal birth weight full term infants. In mid and lower income settings, prematurity and/or LBW occurs in 20% of pregnancies (4). HIV is associated with both conditions (5). The physiologic immaturity of premature and LBW infants has a major impact on pharmacokinetics, which must be studied directly in such infants in order for them to be treated safely and effectively. Available pharmacokinetic (PK) data for ARVs in LBW infants are very limited. The only ARV that has been well studied in LBW infants is ZDV. These data demonstrated reduction in ZDV elimination associated with prematurity/LBW and resulted in developing a specific ZDV dosing regimen for premature/LBW infants (6). There are no TMP-SMX PK data from LBW infants.

The only NVP PK data in LBW infants is from a study of NVP decay kinetics following exposure to peripartum single dose NVP. This study demonstrated that NVP concentrations in LBW neonates were adequate
for prevention of HIV transmission for the first 7 days of life after single 2 mg/kg NVP doses both with and without single dose of NVP given to the mother (7). Nevirapine clearance was slower in small for gestational age (SGA) than appropriate for gestational age (AGA) infants, suggesting that placental insufficiency might delay the maturation of liver enzymes necessary for the elimination of NVP. Median birth weight was 2100g and median gestational age 35 weeks in this study, so that smaller and more premature infants were under-represented. There are no data describing NVP PK in LBW infants receiving chronic therapy with NVP.

An audit of routine NVP therapeutic dose monitoring (TDM) in 107 LBW infants receiving NVP (2 mg/kg/day for the first 2 weeks, then 4 mg/kg/day) for prevention of HIV intrapartum and breast milk transmission in several South African hospitals has recently been completed. All NVP plasma concentrations were above 100 ng/mL in all infants and were above 10,000 ng/mL in 3 infants. While these data suggest that NVP exposure is adequate with this dosing regimen, they were collected outside of a formal research structure and have numerous deficiencies. The majority of the infants were sampled at only one time point and most of the samples were obtained early in the treatment course. Much of the associated study data, including dose times, dose sizes, sample timing and patient clinical characteristics are incomplete or unreliable. A rigorously conducted study of NVP concentrations in LBW infants is still necessary for the following reasons:

1. To confirm that from birth through age 6 months NVP exposures are appropriate for prophylaxis with this dosing regimen
2. To allow PK modeling that can be used to:
   a) Distinguish the effects of prematurity and in utero growth on NVP clearance
   b) Characterize maturation of NVP clearance with postnatal age
   c) Evaluate alternative prophylactic dosing regimens, such as the WHO weight band NVP regimens, for LBW infants
   d) Develop an NVP dosing regimen for HIV-infected LBW infants designed to maintain treatment NVP exposures (trough concentrations above 3000 ng/mL)
   e) Determine the age or size when transition to WHO standard dosing is appropriate
   f) Assess NVP concentration in LBW subpopulations, such as those with respiratory distress, feeding intolerance or other comorbidities.

Studies of NVP PK in infants, children and adults have shown that CYP 2B6 genetic variants have a significant effect on NVP pharmacokinetics and clinical response (8-10). As there are no data describing the effect of CYP2B6 genetic variants on PK in LBW infants, we will determine
CYP2B6 genetic variants in study infants and will investigate their relationship to NVP PK and exposure.

Treatment of HIV infected LBW infants presents serious challenges. As access to HIV testing and ARV’s have expanded, it has become common for HIV infected LBW infants to be diagnosed in the first days or weeks of life. These infants generally have extremely high HIV RNA viral loads, often exceeding one million copies/mL. While there are no data addressing the optimal time to start ARV treatment in such infants, there is a general consensus that deferring treatment for a long period is not optimal. Selection of ARV’s for these infants is difficult. Formulations suitable for administration to LBW infants are often lacking. Further complicating the choice of ARV’s for use in LBW infants infected with HIV is the limited availability of ARV’s in many of the locales where these infants are born. In South Africa, combination regimens used in HIV infected infants are generally limited to ZDV, 3TC, d4T, ABC and LPV/r.

While ZDV can be safely used in these infants, choice of another NRTI for a combination ART backbone is difficult. Lamivudine is the most common choice, but it is eliminated predominantly via the kidney as unmetabolized drug and PK studies in full term infants show that the normal reduction in renal function in the term newborn requires a 50% dosing reduction during the first month of life (11). Premature infants have a further reduction in renal function, and a further dose reduction is likely to be necessary. Emtricitabine (FTC) is also eliminated predominantly by the kidney as unmetabolized drug and while a 50% dosing reduction is recommended for term infants in the first 3 months of life, there are no PK data in LBW infants (12). Stavudine is often used in place of ZDV in South African premature infants, especially for anemia. A reduced d4T dose is recommended for term infants during the first 2 weeks of life, but again there are no PK data in LBW infants. There are no PK data for other NRTI’s in the first weeks of life, including ABC, didanosine (ddI) and tenofovir (TFV).

Choosing the NNRTI or PI component of an ARV regimen for a LBW infant is also challenging. These infants have generally been exposed to NVP for prophylaxis of intrapartum and/or breast milk transmission, making them likely to harbor NVP resistant virus, thereby eliminating NVP or EFV as treatment options. If they have not had NNRTI exposure, NVP is an option, although the minimal LBW PK data available describes NVP PK following dosing to achieve trough concentrations above 100 ng/mL, the target for prophylactic regimens, rather than above 3000 ng/mL, the trough concentration target used for treatment regimens. EFV is not an option, as it is not approved for use in infants less than 3 years of
age. The choice of protease inhibitors is limited as well. There are no atazanavir (ATV) PK data in children in the first years of life and ATV is not recommended for neonates due to its impairment of bilirubin glucuronidation and the resulting risk of kernicterus. Nelfinavir is available in a powder formulation that can be used in neonates, but PK data in term newborns show erratic exposures, most likely due to variable absorption, and no reliable dose in the term newborn has been established (13).

LPV/r is commonly used in clinical practice in HIV infected South African LBW neonates, despite a lack of PK data and recent safety concerns reported by the US Food and Drug Administration (FDA). There are limited LPV PK data in term or LBW infants during the first weeks of life. In a study of HIV infected term infants less than 6 weeks of age receiving LPV doses of 300 mg/m$^2$, LPV concentrations were lower than in older populations (14). A population PK study of LPV/r in infants less than 2 years of age with weights ranging from 1.16 to 10.4 kg showed that CL/F and V/F were dependent on body weight on an allometric basis and post-menstrual age. These data were used to recommend an idiosyncratic and unvalidated dosing regimen of 40 mg in infants 1-2 kg, 80 mg in infants 2-6 kg and 120 mg in infants 6-10 kg (15). Recent data on 8 LBW premature infants, median birth weight 1.295g and gestational age 31 weeks given LPV/r, with dosage adjusted through therapeutic drug monitoring of trough LPV levels showed a need for frequent dose adjustment up to 500mg/m$^2$ per dose (16). The United States Food and Drug Administration has recently reported 10 cases of life-threatening events associated with the use of LPV/r in premature infants, raising concerns over the safety of these drugs in this population (17-19). The infants in these reports ranged in gestational age at birth from 28 to 34 weeks and 8 of 10 were started on treatment within a day of birth. The infants experienced heart block, cardiomyopathy, metabolic acidosis, renal failure, hyperkalemia, anemia, respiratory failure, central nervous system depression, abdominal distension and/or gastrointestinal dysfunction. LPV/r solution is 42% ethanol and 15% propylene glycol. LPV is metabolized primarily by CYP3A. Ethanol is primarily metabolized by alcohol dehydrogenase. Alcohol dehydrogenase metabolism is also responsible for 55-75% of propylene glycol elimination, with unchanged renal excretion accounting for 25-45%. CYP3A and alcohol dehydrogenase activity are low in premature infants, as is renal function. It is unclear if the serious events reported with LPV/r use in premature infants are the result of excessive exposure to LPV/r, ethanol and/or propylene glycol. These reports resulted in a change to US labeling for LPV/r that advises against its use in infants under postnatal age 2 weeks and postmenstrual age 42 weeks. However, the label also says that if the benefit of using LPV/r oral solution to treat HIV infection in infants
immediately after birth outweighs the potential risks, infants should be monitored closely for toxicities and total amounts of alcohol and propylene glycol given from all medications should be monitored to avoid excess exposure to these excipients. Recent review with South African neonatologists of their current clinical practice revealed that they continue to treat HIV infected LBW infants with LPV/r. In their judgment, prematurely born HIV-infected newborns urgently require treatment to reduce viral load and prevent seeding of viral reservoirs, especially in the central nervous system (CNS). Since these infants have been exposed to perinatal NVP PMTCT prophylaxis, they are likely to have NVP resistance; therefore NVP is not recommended for use. There is no alternative protease inhibitor with PK and safety data in this population and a formulation that can be administered to neonates. For clinicians providing care for HIV-infected LBW infants, there are no safer alternatives and the benefits of LPV/r are believed to outweigh the potential risks. P1106 will use an opportunistic approach, so that infants enrolling in the LPV/r arms will have documented HIV infection and will have been started on LPV/r solution as part of clinical care.

Another potential toxicity associated with LPV/r use in neonates has recently been described. In a report comparing 50 HIV-exposed newborns treated with LPV/r after birth to 108 HIV-exposed neonates treated with ZDV alone, elevated concentrations of 17-hydroxyprogesterone and dehydroepiandrosterone-sulfate, consistent with impairment of 21α-hydroxylase activity, were seen only in the LPV exposed infants. All term infants were asymptomatic but 3 of 8 preterm infants had life-threatening symptoms including hyponatremia, hyperkalemia and cardiogenic shock, consistent with adrenal insufficiency. All 3 symptomatic infants had also been exposed in utero to LPV/r (20). These observations have not been confirmed in other populations and clinicians providing care for HIV-infected LBW infants treated with LPV/r in South Africa have not observed this constellation of symptoms in their clinical practice. However, this report of another serious potential toxicity associated with LPV/r use in premature infants highlights the need for an organized study of LBW infants receiving these drugs. In South Africa NVP is the drug of choice for pregnant women, combined with 2 NRTIs. LPV/r is reserved for women who have failed first line therapy or in whom NVP cannot be used, such as after a hypersensitivity reaction.

Antiretroviral dosing in LBW infants is further complicated when concomitant prophylaxis or treatment of TB is needed. The peak incidence of TB in women in sub-Saharan Africa is in those of child-bearing age (21). Tuberculosis occurs commonly in HIV-infected mothers in South Africa and has adverse effects on mother and infant. In KwaZulu-Natal, co-infection with HIV and TB during pregnancy is
associated with increased maternal mortality of 85/1000, high rates of premature delivery (46%), intrauterine growth retardation (46%) and LBW (66%), and vertical transmission rates for TB of 16% and HIV of 25-40% (22,23). Neonatal TB, from either congenital or perinatal infection, is being increasingly recognized (24). South African neonates born to mothers co-infected with HIV and TB are treated with post-exposure prophylaxis with isoniazid (INH) for 6 months or INH and rifampicin (RIF) for 3 months. Infants diagnosed with congenital or neonatal tuberculosis are treated with INH, RIF and pyrazinamide (PZA), and at some South African sites ethambutol (EMB) or ethionamide is added (25). There are no data describing the PK of these TB drugs in LBW infants. Isoniazid undergoes metabolism by acetylation with N-acetyltransferase 2 (NAT2) (26). NAT2 activity is polymorphically expressed and studies in adults have shown that slow acetylators have a longer half-life 2-5 hours compared to approximately 1 hour in rapid acetylators (27,28). Recent data from IMPAACT P1041 suggest immature NAT2 activity, particularly in rapid acetylators with acquisition of activity to adult values occurring over the first 2 years of life. However, it is unknown how prematurity impacts maturation of NAT2 especially during the first few months of life (29). Preliminary data from a pilot study of INH concentrations in South African LBW infants at Tygerberg Hospital in Cape Town indicate good absorption of INH from an extemporaneous preparation (Personal communication, Adrie Bekker).

In addition, RIF induces CYP 3A4 and P-glycoprotein expression, increasing LPV and NVP metabolism. In older children, LPV clearance increased by 30% when administered with RIF. Increasing RTV dosing to a 1:1 ratio with LPV was shown to partially offset the rifampicin effect (30). Patients on NVP-based ART commonly have sub-therapeutic NVP concentrations during RIF-based TB treatment (31-33). The impact of TB treatment on NVP concentrations in LBW infants receiving NVP for HIV prophylaxis must be investigated to determine if increased NVP doses are required in this population as well.

The decision of whether to treat HIV infected LBW infants and if so, when and with what, are difficult due to the lack of PK and safety data for these drugs in this population. Clinicians in South Africa and other countries caring for HIV infected LBW infants struggle regularly with the paucity of ARV PK data relevant to this population. Clinicians caring for LBW infants exposed to or infected with TB in addition to HIV have even more difficult choices. The majority will “superboost” LPV by adding additional ritonavir (RTV) to achieve mg for mg parity with lopinavir when using rifampicin (30). There is an urgent need for data describing the safety and PK of both the HIV and the TB drugs in LBW infants.
LBW infants may be born small because of prematurity, intrauterine growth restriction, or a combination of the two. While both prematurity and intrauterine growth restriction have an impact on PK parameters in LBW infants, assessments of gestational age are likely to be inaccurate in the projected study population. Mothers delivering LBW infants at the proposed study sites often have uncertain last menstrual periods and lack early prenatal care, including early ultrasounds. Gestational age assessments made late in pregnancy by history or ultrasound or after birth by infant examination are imprecise, varying by as much as 1-2 weeks in either direction. For this reason, birth weight will be used to determine eligibility for enrollment in the protocol and the HIV exposed infants receiving prophylactic NVP/TMP-SMX will be stratified into birth weight cohorts. A best clinical assessment of gestational age using obstetrical history and infant examination will be made for each subject. These assessments will be incorporated into the analysis plan in an effort to delineate the effects of prematurity and of adequacy of fetal growth on PK parameters.

The protocol will use an opportunistic design, studying LBW infants receiving the drugs of interest as part of their clinical care. The clinical caregivers will prescribe all drugs and will be responsible for monitoring and managing toxicities. The one exception will be for LPV/r. Due to the recently reported toxicities in premature infants as described above, all infants participating in this protocol and receiving LPV/r will have monitoring for cardiac toxicity with serial electrocardiograms and echocardiograms and for renal/endocrinologic toxicity with creatinine, electrolyte and osmolality determinations.

1.2 Rationale

As access to ARVs and associated therapy expands, increasing numbers of LBW infants are being exposed to these drugs in routine clinical care for prophylaxis and treatment of HIV and its associated morbidities. LBW infants born to HIV-infected mothers receive NVP after birth for prevention of intrapartum and/or breast milk HIV transmission and may receive TMP-SMX starting at 4-6 weeks of life for prevention of PCP. Those LBW infants who become infected with HIV should receive combination ARV therapy (cART) as soon as possible after diagnosis and should continue to receive TMP-SMX until at least age 1 year. Tuberculosis occurs commonly in HIV-infected women. Their infants, in whom both prematurity and LBW are common, may require prophylaxis or treatment with TB drugs for congenital or perinatal TB. While drug disposition and exposure may be markedly different in LBW infants compared to full term and older infants, PK data for these drugs in LBW infants are limited. The goal of this protocol is to describe the PK and
safety of ARVs, TMP-SMX and TB drugs in LBW infants receiving these drugs as part of clinical care.

**Study Sites:** The protocol will be performed at 4 hospitals in South Africa: 1) Chris Hani Baragwanath Hospital, Johannesburg; 2) Rahima Moosa Mother and Child Hospital, Johannesburg; 3) KIDCRU, Tygerberg Children’s Hospital, Tygerberg; 4) King Edward VII Hospital, Durban, and their affiliated IMPAACT research units. All of these sites have extremely busy inpatient delivery and neonatology services. Combined they care for approximately 3500 HIV-exposed LBW neonates per year. The vast majority of these infants breastfeed and receive NVP prophylaxis until cessation of breastfeeding. The current HIV infection rate for these infants is 1-2%. These sites also care for approximately 75 LBW neonates per year who receive TB prophylaxis because their mothers have active TB infection and these sites treat 5-10 LBW infants per year for TB infection. Additional IMPAACT sites with appropriate patient populations and clinical infrastructure may also participate in the protocol.

### 2.0 STUDY OBJECTIVES

#### 2.1 Primary Objective

2.11 To describe the pharmacokinetics (PK) and safety of NVP, INH, RIF, and LPV/r in LBW infants receiving the drug(s) as part of clinical care.

#### 2.2 Secondary Objectives

2.21 To describe the PK and safety of TMP-SMX, ZDV, d4T, ABC and 3TC in LBW infants receiving the drug(s) as part of clinical care.

2.22 To develop population PK models of ARVs, TB drugs and TMP-SMX in LBW infants.

2.23 To describe the impact of CYP 2B6 genetic variants on NVP metabolism and NAT2 genetic variants on INH metabolism in LBW infants.

2.24 To describe the association of PK parameters and drug exposures with birth weight, gestational age, postnatal age, HIV/TB infection status and other variables.
To use population PK models to perform Monte Carlo simulations of current and alternative dosing regimens for ARVs, TB drugs and TMP-SMX.

3.0 STUDY DESIGN

This is a Phase IV prospective pharmacokinetic study to describe the PK and safety of selected ARV and TB drugs used for prophylaxis and/or treatment in LBW infants. The main drugs of interest are NVP, INH, RIF and LPV/r. Drugs of secondary interest are TMP-SMX, ZDV, d4T, ABC and 3TC. The study will enroll a maximum of 158 PK evaluable low birth weight infants as described below:

Arms 1, 2 and 3: Breastfeeding LBW infants born to HIV-infected mothers who are receiving either no ARV therapy or ARV therapy that does not include NVP:

Arm 1: Infant receiving NVP prophylaxis but not TB prophylaxis or treatment
Arm 2: Infant receiving NVP prophylaxis plus INH but not RIF for TB prophylaxis
Arm 3: Infant receiving NVP prophylaxis plus INH plus RIF for TB prophylaxis or treatment

HIV-exposed infants (Arms 1, 2 and 3) will enroll between 7 and 14 days of life and will have their first PK samples collected prior to the standard increase in NVP dose from 2 mg/kg to 4 mg/kg at age 2 weeks. Subsequent PK assessments will be performed as described in Section 9.3, Table 2. Enrollment in Arms 1, 2 and 3 will be stratified by birth weight. Enrollment in Arms 1, 2 and 3 will be limited to breastfeeding HIV-exposed infants whose mothers are receiving either no ARV therapy or ARV therapy that excludes NVP. Currently, the vast majority of South African HIV-infected mothers do not receive postpartum maintenance ARV therapy. Those mothers who do receive postpartum combination ARV therapy generally receive d4T/3TC/NVP and will pass significant amounts of NVP to their infants via breast milk (34,35). Quantifying the dose of NVP received via breast milk, although critical in characterizing NVP pharmacokinetics in such infants, is difficult. The difficulty in estimating infant dose via breast milk is complicated by our lack of knowledge of the impact of heat sterilization of breast milk, widely practiced in South Africa, on degradation of breast milk NVP. In order to keep this initial study in this very challenging patient population as simple as possible, we will exclude breastfeeding infants whose mothers are receiving NVP from Arms 1, 2 and 3. The number of mothers on combination ARV therapy will undoubtedly increase over the next few years. We envision including infants born to such mothers in a subsequent and more
complex version of this protocol that will include study of breast milk ARV transfer.

Formula fed infants are excluded from Arms 1, 2 and 3 because they only receive NVP prophylaxis for 6 weeks and the goal of the protocol is to characterize the developmental changes in NVP pharmacokinetics over the first 6 months of life. There is no known interaction between mode of infant feeding and NVP PK, so NVP PK data obtained from breast fed infants can be extrapolated to formula fed infants.

Infants in Arms 2 and 3 who as part of clinical care convert from TB prophylaxis (1 or 2 drugs) to TB treatment (3 or more drugs) will remain on study. The laboratory will be notified of the use of the additional drugs and will assay study samples for those drugs if sufficient sample remains after other study drug assays are completed. While we anticipate very few infants shifting from TB prophylaxis to treatment, we will collect drug concentration data for the additional TB drugs as a pilot study for use in planning future investigations.

Arm 4: Breast or formula feeding LBW infants born to HIV-uninfected mothers with active TB:

Arm 4: Infant receiving INH alone or INH plus RIF for TB prophylaxis. The data on INH PK and safety will be based on infants on INH alone and those on INH plus RIF while the RIF PK and safety data will be based on infants on INH plus RIF.

There is no restriction in enrollment in Arm 4 based on mode of infant feeding. Infants in Arm 4 will be studied according to the same schedule of evaluations as infants in Arms 1, 2 and 3 but their PK samples will be assayed only for the TB drugs they are receiving. Infants in Arm 4 who as part of clinical care convert from TB prophylaxis (2 drugs) to TB treatment (3 or more drugs) will remain on study. The laboratory will be notified of the use of the additional drugs and will assay study samples for those drugs if sufficient sample remains after other study drug assays are completed. While we anticipate very few infants shifting from TB prophylaxis to treatment, we will collect drug concentration data for the additional TB drugs as a pilot investigation for use in planning future investigations.

Arms 5 and 6: HIV-infected infant ≤12 weeks of age whose birth weight was ≤2500 grams:

Arm 5: Infants initiating treatment with LPV/r plus 2 NRTIs, and not receiving RIF (but may be receiving INH)
Arm 6: Infants initiating treatment with LPV/r plus 2 NRTIs, and receiving RIF (and may be receiving INH)

While nearly all infants enrolling in Arms 5 and 6 will be new to the protocol, infants in Arms 1, 2 or 3 who become HIV infected and are prescribed the ARVs of interest can terminate enrollment in the initial arm and re-enroll in Arm 5 or 6, and will then follow the schedule of evaluations for Arms 5 and 6. There is no restriction in enrollment in Arms 5 and 6 based on mode of infant feeding or maternal HIV treatment. Both breast and formula fed infants are eligible for enrollment in Arms 5 and 6, since both groups of infants will receive chronic ARV therapy of indefinite duration. The main drug of interest in Arms 5 and 6 is LPV/r and breastfeeding infants whose mothers are receiving combination ARV treatment are not likely to be receiving LPV/r as part of their ARV regimen. If a breastfeeding mother of an infected infant is receiving LPV/r, it is unlikely that significant amounts of LPV/r will be transferred to the infant via breast milk due to the relatively low maternal plasma concentrations and extensive protein binding of LPV/r. HIV-infected infants (Arms 5 and 6) will enroll prior to the start of LPV/r treatment so that pretreatment cardiology studies can be obtained.

Initial PK sampling in Arms 5 and 6 will be performed 2 weeks after enrollment and subsequent PK sampling will be performed as described in Section 9.3, Table 3. Infants in Arms 5 and 6 who as part of clinical care convert from TB prophylaxis (1 or 2 drugs) to TB treatment (3 or more drugs) will remain on study. The laboratory will be notified of the use of the additional drugs and will assay study samples for those drugs if sufficient sample remains after other study drug assays are completed. While we anticipate very few infants shifting from TB prophylaxis to treatment, we will collect drug concentration data for the additional TB drugs as a pilot study for use in planning future investigations.

**Real Time Assays:** The following drug concentration assays will be performed in real time: NVP assay results for subjects in Arms 1, 2 and 3, LPV/r assay results for subjects in Arms 5 and 6. Pharmacokinetic analyses will be performed as described in the pharmacology section of the protocol.

Infants meeting any of the following criteria on the day of a scheduled PK assessment should not have pharmacokinetic sampling performed on that day:

1) Hypotension and/or poor perfusion requiring treatment with volume expansion and/or vasopressors
2) Exchange transfusion within 24 hours preceding a PK evaluation
3) Urine output less than 0.5 mL/kg/hr within 24 hours preceding a PK evaluation
4) Missed doses of study drugs within preceding 72 hours
PK sampling not performed due to the above criteria should be rescheduled after consultation with the protocol team. In addition, the protocol team should be contacted regarding any interruption in study drug administration greater than 24 hours. Infants whose study drug(s) are discontinued will not have further PK sampling but will continue to be followed for safety and toxicity monitoring.

Trial-related blood loss will not exceed 3% of the total blood volume during a period of four weeks. Assuming a total blood volume estimated at 80 to 90 mL/kg body weight, 3% is 2.4 ml blood per kg body weight for an infant weighing 1 kg. The only blood drawing required by the protocol will be collection of PK samples and chemistry tests (if not done as part of clinical care). All other blood test results will come from tests done as part of routine clinical care. The size of PK blood samples will be minimized so that blood collection from even the smallest infants will meet the limit of 2.4 mL/kg per four weeks.

See Appendix I-A for infants in Arms 1, 2, 3 and 4 and Appendix I-B for infants in Arms 5 and 6 for a complete description of the procedures to be performed. Infants who were enrolled in Arms 1, 2 or 3 later determined to be HIV infected are eligible to register to Arms 5 or 6, as appropriate, and follow the schedule of evaluations in Appendix I-B.

4.0 SELECTION AND ENROLLMENT OF SUBJECTS

4.1 Inclusion Criteria for Arms 1, 2 and 3 (HIV-exposed infants)

4.11 Breastfeeding infants born to HIV-infected mothers who are receiving either no ARV therapy or ARV therapy that does not include NVP

4.12 Age 7 to 14 days

4.13 Birth weight ≤ 2500 grams

4.14 Receiving or will be receiving prophylaxis as prescribed by clinical care provider as follows: NVP (Arm 1), NVP plus INH (Arm 2), NVP plus INH plus RIF (Arm 3)

4.15 Parent or legal guardian able and willing to provide written informed consent. [Note to sites: modify per locally relevant language].

4.2 Inclusion Criteria for Arm 4 (HIV-unexposed but TB exposed infants)
4.21 Age 7 to 14 days

4.22 Birth weight ≤ 2500 grams

4.23 Receiving prophylaxis with INH alone or INH plus RIF as prescribed by clinical care provider

4.24 Not receiving any therapy for HIV prophylaxis or treatment

4.25 Parent or legal guardian able and willing to provide written informed consent. [Note to sites: modify per locally relevant language].

4.3 Inclusion Criteria for Arms 5 and 6 (HIV-infected infants)

4.31 Documentation of HIV-1 infection defined as positive HIV DNA PCR done as part of clinical care. An HIV RNA confirmatory test must be done at study entry but results may be pending at time of enrollment.

4.32 Birth weight ≤ 2500 grams

4.33 Age ≤ 12 weeks (defined as 84 days)

4.34 Intention by clinical care provider to prescribe LPV/r plus 2 NRTIs and no RIF (Arm 5) or LPV/r plus 2 NRTIs plus RIF (Arm 6)

4.35 Parent or legally acceptable representative able and willing to provide written informed consent. [Note to sites: modify per locally relevant language].

4.4 Exclusion Criteria for All Arms

Any severe congenital malformation or other medical condition incompatible with life or that would interfere with study participation or interpretation, as judged by the examining clinician.

4.5 Enrollment Procedures

Prior to implementation of this protocol, and any subsequent full version amendments, each site must have the protocol document 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.

A Site Implementation Plan (SIP) is required from each site participating in the study. Each site SIP will describe the prescribed drug dosing regimens administered by local care providers and the site’s standard protocol for monitoring hematology and chemistry tests in premature infants. The plan must be submitted to the Protocol Team for review and approval before protocol registration can occur.

Infants enrolled in Arms 1, 2, or 3 who are subsequently diagnosed as HIV infected are eligible to register to Arm 5 or 6, as appropriate, by using the DMC Subject Enrollment System (SES) and follow the schedule of evaluations listed in Appendix I-B. Infants who do not re-enroll to Arms 5 or 6 will be followed for safety following the schedule of the current arm.

4.6 **Co-enrollment Procedures**

Co-enrollment is permitted except for protocols that would violate the exclusion criteria and where permitted by local/country regulations. All co-enrollments in protocols require the assent of the protocol chairs of the main protocol and the co-enrollment protocols.
5.0 STUDY TREATMENT

No treatment or intervention will be provided as part of this study. All drugs, including those being studied at non-standard doses, must be prescribed by subjects’ clinical care providers. Subjects may receive either innovator or generic formulations for all drugs being studied within this protocol. For innovator or generic formulations, the name of the manufacturer must be recorded at the time of the pharmacokinetic sampling. For extemporaneously prepared formulations (i.e., those prepared by the pharmacist), the name of the manufacturer of the active drug, the manufactured type, generic code and drug formulation will be recorded.

Those infants receiving NVP for HIV prophylaxis and INH alone or INH plus RIF for TB prophylaxis will be dosed according to standard of care and receiving locally available/prepared drug formulations.

Those infants receiving treatment for HIV infection with LPV/r plus 2NRTIs will be dosed according to standard of care and receiving locally available drug formulations.

6.0 SUBJECT MANAGEMENT

6.1 Toxicity Management

This study will enroll LBW infants in the first weeks of life who often have complex clinical courses with multiple major morbidities. This protocol includes no drug dosing or administration outside of clinical care. All drugs being studied are prescribed and administered by local care providers according to local and/or WHO guidelines.

NVP concentration assay results for Arms 1, 2 and 3 subjects and LPV/r concentration assay results for Arms 5 and 6 will be performed and reported back to the clinical site in real time. Clinical care providers may adjust dosing based on these results. A study pharmacologist will be available for consultation to aid in interpretation of real time assay results.

Management of adverse experiences will be the responsibility of the site clinical care provider in collaboration with site research staff, and not the protocol team. The clinical care provider of a study subject will decide whether adverse experiences are associated with study drug(s) and whether the balance of risk and benefit supports the continuation or discontinuation of study drug(s). The SMC will review all subjects who discontinue study drug(s) due to adverse experiences to monitor the incidence and severity of adverse events thought to be related to study.
drugs. Subjects whose study drug(s) are discontinued will not have further PK sampling but will continue to be followed for safety and toxicity monitoring.

Each neonatal unit has a standard protocol for monitoring hematology and chemistry tests in premature infants which will be described in the site’s SIP. Study mandated clinical laboratory tests will be limited to those chemistry studies listed in Appendix I-A at the day 7 to 14 and week 6 visits for subjects in Arms 1, 2, 3, and 4, and in Appendix I-B at the weeks 2, 6 and 16 visits after initiation of LPV/r for subjects in Arms 5 and 6. Monitoring of electrocardiogram (ECG) and echocardiogram (ECHO) will be done for subjects in Arms 5 and 6 (see Appendix III, Cardiology Evaluations). As cardiac conditions may impact the use of LPV/r, results of these tests will be reviewed by the clinical care provider and local site cardiologist before initiating and during LPV/r treatment. Intermittent batched central review of ECG/ECHO studies for final study interpretations will be done by independent South African pediatric cardiologists not otherwise associated with the study.

Many diagnoses, clinical events and abnormal laboratory values related to prematurity and/or LBW are expected in this critically ill group of infants. These diagnoses, events and laboratory values will be common and will not require the generation of an SAE or DAERS report. Data describing these diagnoses and events will be collected on study CRFs and will be reviewed regularly by the team and, if necessary by an SMC (see Section 8.5), which will independently review the events with comparisons between arms and to relevant non-study populations to determine any unusual patterns requiring further investigation or additional collecting of data. The content and recommendations of the team reviews will be available for review by DAIDS and regulatory authorities on a regular basis, at least every 6 months, and also on an expedited basis should an unusual or concerning pattern be detected. Reviews and recommendations by the SMC will be forwarded to DAIDS and the IMPAACT Network Executive Committee and then to the protocol team and the IMPAACT HIV Prevention Scientific Committee.

A diagnosis based approach to toxicity monitoring will be used. Toxicity monitoring will be performed by recording continuing and new diagnoses and their significant associated clinical factors that have occurred since the previous study visit or since birth for the first visit. This approach was successfully used in PACTG P331, *The Safety, Tolerance and Pharmacokinetics of Zidovudine in Premature Infants Exposed to HIV* (6). See Appendix IV, Table for Grading Expected Adverse Events, for grading these events and diagnoses. Additional diagnoses, clinical events and/or laboratory abnormalities may be recorded if the site clinical care provider
thinks they represent significant morbidities not captured by the established list of diagnoses.

6.2 Criteria for Discontinuation

Subjects must be discontinued from the study if:

- The parent/guardian refuses further participation.
- The subject’s family or clinical care provider wishes to remove the subject from study.
- The investigator determines further participation would be detrimental to the subject’s health or well-being.
- The study is cancelled at the discretion of IMPAACT, NIAID, the Office for Human Research Protections (OHRP), the local or national IRB or EC, or other national regulatory agencies.

7.0 EXPEDITED ADVERSE EVENT REPORTING

7.1 Adverse Event Reporting to DAIDS

Due to the nature of the study population and the lack of study mandated dosing, SAE reporting will be required only for deaths and for those events that the clinical care provider determines to be unrelated to the underlying diagnoses of LBW and/or prematurity or the diagnosis of HIV, AIDS or TB.

Toxicities outside of the established list of diagnoses and clinical events listed in Section 6.0 will be classified by the Division of AIDS Table for Grading the Severity of Adult and Pediatric Adverse Events, Version 1.0, dated December 2004, (Clarification dated August 2009), which is available on the RSC web site. Where toxicity grading is not available, local standard laboratory values for low birth weight infants will be used. For toxicity grading not available, the team will have a standing SMC define toxicity grading in an independent fashion.

Adverse events and discontinuations of study drug(s) will be reviewed by the protocol team on monthly conference calls and reported to DAIDS.

Requirements, definitions and methods for expedited reporting of Serious Unexpected Suspected Adverse Events (6.1s) are outlined in Version 2.0 of the DAIDS EAE Manual, which is available on the RSC website at http://rsc.tech-res.com/safetyandpharmacovigilance/.
The DAIDS Adverse Experience Reporting System (DAERS) internet-based reporting system must be used for expedited SUSARs reporting to DAIDS. In the event of system outages or technical difficulties, expedited SUSARs 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 SUSARs by documenting the information on the current DAIDS EAE Form. This form is available on the RSC website: http://rsc.techres.com/safetyandpharmacovigilance/. For questions about EAE reporting, please contact the RSC (DAIDSRSCSafetyOffice@techres.com).

7.2 Reporting Requirements for This Study

The study agents for which relationship assessments are required are nevirapine, lopinavir/ritonavir, isoniazid and rifampicin.

7.3 Expedited AE Reporting Period

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

8.0 STATISTICAL CONSIDERATIONS

8.1 General Design Issues

This is a Phase IV prospective pharmacokinetic study to evaluate the PK and safety of currently prescribed HIV and TB drugs in low birth weight infants (≤2500 grams at birth). There are 6 arms representing the regimens of study interest based on what the infant is or will be receiving as part of his/her clinical care. No study-supplied treatment will be given to the infants during this study. Arms 1, 2 and 3 are for breastfeeding, LBW infants 7-14 days of age born to HIV-infected mothers not receiving NVP-containing ARV regimen. Arm 4 is for breast or formula feeding LBW infants 7-14 days of age born to HIV-uninfected but TB-infected mothers. Arms 5 and 6 are for breastfeeding or formula feeding HIV-infected LBW infants ≤12 weeks of age. The infant will be assigned to one of the following study arms based on the HIV/TB drug regimen that
the infant is receiving or will be receiving as part of his/her clinical care at study entry:

- **Arm 1:** Receiving HIV prophylaxis with NVP (no TB prophylaxis/treatment)
- **Arm 2:** Receiving HIV prophylaxis with NVP and TB prophylaxis with INH (no RIF)
- **Arm 3:** Receiving HIV prophylaxis with NVP and TB prophylaxis/treatment with INH plus RIF
- **Arm 4:** Not receiving any HIV drugs but receiving TB prophylaxis/treatment with INH alone or INH plus RIF
- **Arm 5:** Infants initiating treatment with LPV/r plus 2 NRTIs, and not receiving RIF (but may be receiving INH)
- **Arm 6:** Infants initiating treatment with LPV/R plus 2 NRTIs, and receiving RIF (and may be receiving INH)

Infants in Arms 1, 2 or 3 who are later diagnosed as HIV infected and prescribed the ARVs of interest may re-enroll to Arms 5 and 6. These infants who re-enroll to Arm 5 or 6 will follow the schedule of evaluations for the new arm and PK and safety data collected under the new arm will be analyzed as part of the new arm. Infants who do not re-enroll to Arms 5 or 6 will be followed for safety following the schedule of the current arm.

Infants in Arms 1-4 will be on study until 24 weeks of postpartum while infants in Arms 5 and 6 will be on study until 24 weeks after initiation of LPV/r. Infants whose study drug(s) are discontinued will have no further PK sampling but will continue to be followed for safety and toxicity monitoring. For PK evaluable subjects, PK data and analyses are described in detail in Section 9.0. Safety data from enrollment onwards will be used to describe the safety for the drugs of interest. The safety data will include signs/symptoms, diagnoses, study-mandated and hematology/chemistry tests, and hematology/chemistry tests done as part of regular clinical care of the infants. Infants in Arms 5 and 6 will also have electrocardiogram and echocardiogram monitoring while the infants are on the study drugs of interest.

The study will accrue subjects until the target number of PK evaluable subjects has been enrolled. The sample size has been determined by the protocol pharmacologist to provide enough information needed to describe the PK of the drugs of interest in LBW infants.
The primary objective is to study the PK and safety of NVP, INH, RIF, and LPV/r in HIV-exposed or infected LBW infants receiving the drug(s) as part of clinical care.

8.2 Outcome Measures

8.21 Primary Outcome Measures:
- PK parameters (described in Section 9) for NVP, INH, RIF and LPV/r
- Primary Safety Endpoints:
  - Adverse events of Grade 3 or 4 severity
  - Death
  - Serious adverse clinical events occurring in LBW infants, as listed in Section 6.1

8.22 Secondary Outcome Measures:
- PK parameters (described in Section 9.0) for TMP-SMX, ZDV, d4T, ABC and 3TC
- CYP 2B6 genetic variants
- NAT2 genetic variants
- Birth weight
- Gestational age (A best assessment of gestational age will be made using obstetrical history and new Ballard score (36). Infant growth will be classified as small, appropriate or large for gestational age using the Fenton Chart (37).)
- postnatal age
- HIV status
- TB status

8.3 Randomization and Stratification

There will be no randomization. There are 6 arms representing the regimens of study interest based on what the subject is receiving as part of his/her clinical care.

Subjects will be stratified into 3 weight bands (<1400 vs. 1400 – <1800 vs 1800 – 2500 grams) to ensure adequate representation over the full weight range of LBW infants. Stratum accrual limits for each arm are described in Section 8.4. Weight band stratification will be used for Arms 1, 2, 3 and 4 but not for 5 and 6, since the team anticipates that the number of HIV-infected LBW infants (Arms 5 and 6) will be too low to accomplish this form of stratification.
8.4 Sample Size and Accrual

The study will enroll subjects until the following number of PK evaluable infants are accrued:

Arm 1: \( n = 40 \) stratified by birth weight as:
- \( \leq 1400 \text{gm} \): \( n = 12 \)
- 1400 - <1800gm: \( n = 12 \)
- 1800 – 2500gm: \( n = 16 \)

Arm 2: \( n = 18 \) stratified by birth weight as:
- <1400gm: \( n = 6 \)
- 1400 – <1800gm: \( n = 6 \)
- 1800 – 2500gm: \( n = 6 \)

Arm 3: \( n = 28 \) stratified by birth weight as:
- <1400gm: \( n = 8 \)
- 1400 - <1800gm: \( n = 8 \)
- 1800 – 2500gm: \( n = 12 \)

Arm 4: \( n = 18 \)–36 stratified by birth weight as:
- <1400gm: \( n = 6 \) to 12; with a minimum of 6 each for INH and RIF PK analyses
- 1400 - <1800gm: \( n = 6 \) to 12; with a minimum of 6 each for INH and RIF PK analyses
- 1800 – 2500gm: \( n = 6 \) to 12; with a minimum of 6 each for INH and RIF PK analyses

Arm 5  \( n = 24 \)

Arm 6: \( n = \) maximum of 12 (while at least one of the other study arms is open for accrual)

These sample sizes reflect the number of PK evaluable subjects needed for the PK analyses specified in Section 9.0. The team estimates that at maximum, 20% of the subjects will not be evaluable. Accrual would be increased to account for PK non-evaluable subjects.

All infants enrolled to the study, including those not evaluable for the PK analysis, will be included in the safety analyses. The study is not powered for hypothesis testing with respect to safety analysis. However, descriptive statistics will be calculated and will consist of estimating the proportions of subjects meeting the safety endpoints and presenting the corresponding 90% Exact Clopper-Pearson confidence intervals around
them. Given the relatively small study sample, the precision of the estimates will be relatively low and the confidence interval estimates will be relatively wide. Table 1 shows the width of the confidence intervals (CI) around potential point estimates and potential sample sizes representing the subgroups of interest sizes in case estimation is done per arm-stratum combination or per arm (i.e. pooled across strata). There is a possible confounding between the arm and birth weight so that the initial analyses would be per arm-stratum combination. The per arm analyses will only be done if initial per arm-stratum estimates show no such confounding.

Table 1: Confidence Limits and Width of the 90% Exact Clopper-Pearson Confidence Interval for Proportion of Infants Meeting the Safety Endpoint

<table>
<thead>
<tr>
<th>Number of subjects</th>
<th>Proportion of subjects meeting toxicity endpoint</th>
<th>Clopper-Pearson 90% CI</th>
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<tr>
<td>6</td>
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<td>Proportion of subjects meeting toxicity endpoint</td>
<td>Clopper-Pearson 90% CI</td>
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### 8.5 Monitoring

Reports on accrual and toxicity, compiled by the Data Management Center (DMC), will be reviewed and discussed by the Protocol Team on conference calls held monthly. The toxicity reports will present events as reported on diagnoses, signs and symptoms, chemistry and hematology case report forms. The toxicity reports for infants in Arms 5 and 6 will also include the electrocardiogram and echocardiogram results. Conference calls will also be scheduled as needed in response to any adverse event that requires the immediate attention of the Protocol Team. Notification of team members will be by e-mail or phone depending on time differences.

The safety of the ARVs and TB drugs of interest on infants will be monitored by means of adverse events reports and toxicity reports presenting laboratory and clinical events. It is the responsibility of the protocol team to interpret the toxicity data. Any decisions needed to protect subjects from undue risk will be made by the subject’s clinician in
consultation with the protocol team. The IMPAACT Network will appoint a Study Monitoring Committee (SMC) which would meet every 6 months and as needed to review the summary report of the safety data. In accordance with IMPAACT and DAIDS procedures, this committee will be composed of one clinician from the IMPAACT Protocol Development and Monitoring Committee; two clinicians appointed by the IMPAACT HIV Treatment Scientific Committee associated with the network but not directly involved in the conduct of study; and an independent statistician appointed by the IMPAACT Statistical and Data Management Center (SDAC). The SMC will all be independent of the P1106 protocol team. Per IMPAACT/DAIDS procedures, members of the P1106 SMC will have:

1) no financial interest in the study;
2) no planned authorship in publication of study results; and
3) no involvement in the conduct of the study.

Accrual to this study will be monitored by the IMPAACT leadership in accordance with standard operating procedures. The team will monitor feasibility quarterly, first based on site registration and then on accrual. Initially, the team will monitor site registration quarterly to ensure that an adequate number of sites have registered to complete the protocol. If less than one-third of eligible sites have registered after the protocol has been approved for 6 months, the team will re-assess the feasibility of the protocol and the reasons why sites have not registered, and will amend the protocol accordingly. Once a third of eligible sites have registered, the team will assess accrual on a quarterly basis. If the protocol has not accrued half its subjects within a year of opening, the team will identify problems in accrual and possibly amend the protocol accordingly.

A full monitoring plan that describes study monitoring will be developed before the study opens to accrual. A separate PK monitoring plan will be developed and will contain the details for monitoring the specimens and data needed for the pharmacokinetic analyses.

8.6 Analyses

PK analyses are described in Section 9.0.

The primary safety analyses will consist of estimating the proportions of subjects meeting the safety endpoints and presenting the corresponding 90% Exact Clopper-Pearson confidence intervals around them. These will be initially calculated by weight band for each of the study arms. Data will be pooled across weight band strata within a study arm only if there are neither statistically or clinically significant differences across strata.
One of the secondary objectives is to describe the association of PK parameters and drug exposures with birth weight, gestational age, postnatal age, HIV/TB infection status and other clinical variables. Due to the small sample size within each arm, only bivariate analyses will be done. Spearman correlation coefficient will be calculated to describe and test the association between PK parameters and drug exposures with birth weight, gestational age and postnatal age. Wilcoxon sum-rank test will be done to compare PK parameters and drug exposures of HIV/TB infected VS uninfected infants. It is expected that the precision of the calculated descriptive statistics will be low and the test statistics will have low power due to the small sample sizes.

9.0 CLINICAL PHARMACOLOGY PLAN

9.1 Pharmacology Objectives

9.11 Primary

To describe the pharmacokinetics (PK) and safety of NVP, INH, RIF, and LPV/r in LBW infants receiving the drug(s) as part of clinical care.

9.12 Secondary

9.121 To describe the PK and safety of TMP-SMX, ZDV, d4T, ABC and 3TC in HIV-exposed or infected LBW infants receiving the drug(s) as part of clinical care.

9.122 To develop population PK models of ARVs, TB drugs and TMP-SMX in LBW infants.

9.123 To describe the impact of CYP 2B6 genetic variants on NVP metabolism and NAT2 genetic variants on INH metabolism in LBW infants.

9.124 To describe the association of PK parameters and drug exposures with birth weight, gestational age, postnatal age, HIV/TB infection status and other clinical variables.

9.2 Primary and Secondary Data
The PK analysis will be performed on drug concentration data collected and summarized for each study arm. There will also be population PK analyses performed on all concentrations for each drug across study arms. Arm 1 samples will have NVP concentrations determined, Arm 2 samples will have INH and NVP concentrations determined. Arm 3 samples will have INH, RIF and NVP concentrations determined. The first 40 Arm 2 and 3 subjects that also receive TMP-SMX prophylaxis will also have their samples assayed for TMP and SMX concentrations. Arm 4 will have INH and RIF concentrations determined. Arm 5 samples will have LPV/r, RTV and other ARV concentrations determined. Arm 6 samples will have the same drugs measured as Arm 5 with the additional measurement of RIF concentrations. It is expected that the overwhelming majority of Arm 2 and 3 infants will be receiving TMP-SMX prophylaxis and will be able to provide the 40 subjects needed for the TMP-SMP population PK analysis. However, if less than 40 infants from Arms 2 and 3 can provide TMP-SMX PK data, then samples from subjects in Arm 1 that are receiving TMP-SMX prophylaxis will be included to augment the PK analysis to ensure TMP-SMX PK data from 40 subjects are available.

The majority of pharmacokinetic assays will be performed in batch mode at convenient intervals during and at the end of the study. However, LPV/r concentrations (Arms 5 and 6) and NVP concentrations in subjects receiving NVP (Arms 1, 2 and 3) that are shipped to the pharmacology laboratory within 3 weeks of collection will be processed in real-time. These PK results will be provided to subjects’ clinical caregivers. Real-time pharmacokinetic results will sent to the clinical care givers and P1106 team using the DMC web utility within 2 weeks of PK sample receipt by the pharmacology laboratory.

All pharmacokinetic samples will be registered in the Lab Data Management System (LDMS) database. Pharmacokinetic samples will be sent to the Pharmacology laboratory of the University of Cape Town for analysis. For samples with real-time PK assessments (Arms 1, 2, 3, 5 and 6), data collected on PK CRFs will be provided to the pharmacologists in real-time. These data will include the study arm, current weight, current height, dose, date and time of the current and most recent doses, date and times of sample collections and all relevant comments on the pharmacokinetic CRF. Post-natal age, gestational age at birth,
birth weight and gender will be provided by the DMC for pharmacokinetic analysis.

Nevirapine and LPV/r assay results will be made available to the treating clinicians within 2 weeks of receipt of the specimen by the pharmacology laboratory. Assays for other drugs will be run in batches. Plasma samples from Arms 5 and 6 will also be assayed for propylene glycol at the end of the study.

Pharmacologic data summaries will be created by study arm and by individual drug, and will be evaluated by weight band strata. These will include clinical information on ALT. The CYP 2B6 genotype for subjects receiving NVP and the NAT2 genotype for subjects receiving INH will also be included.

9.3 Pharmacology Study Model and Data Analysis

9.3.1 General Design

Study enrollment targets will be 40 evaluable subjects for Arm 1, 18 evaluable subjects in Arm 2, 28 evaluable subjects in Arm 3, 18-36 evaluable subjects in Arm 4, 24 evaluable subjects in Arm 5 and a maximum of 12 evaluable subjects in Arm 6. Combined these arms will contribute 86 subjects receiving NVP prophylaxis, 76 to 94 subjects receiving INH, 58 receiving RIF and 24-36 subjects receiving LPV/r. Additionally 40 subjects receiving TMP-SMX (from across Arms 2 and 3) will also have their samples assayed for PK evaluation. Overall the design will result in 878 NVP PK samples, 946 to 1162 INH PK samples, 712 RIF PK samples and 396 LPV/r PK samples. For purposes of being considered PK evaluable, subjects will need to complete PK sample collection through at least week 6 and missing no more than 1 PK sample during week 2, 4 and 6 visits. Subjects missing more than one PK sample through week 6 but with six or more PK samples across all their visits will also be considered PK evaluable. Subjects who fail to meet the PK evaluable criteria will not be considered in determining the study subject numbers. However, any usable PK data collected in these subjects will be included in population PK analyses.

Pharmacokinetic sample collections will be determined by study arm and designed to provide informative samples based on the expected pharmacokinetics profile. Study Arms 1, 2 and 3 subjects will have 7 to 13 PK samples collected at 6 visits over 24 weeks. Study Arm 4 subjects will have 8-12 samples collected at 4 to 6
visits over 12 to 24 weeks. Study Arms 5 and 6 subjects will have 11 PK samples collected at 5 visits over 24 weeks. Samples will be collected to provide near peak and trough measurements. This will ensure that the study data are informative regarding apparent CL and V in this population. The repeated samples (predominant trough) will help characterize maturational changes. This is a similar design that was used in preterm infants to successfully characterize ZDV pharmacokinetics in PACTG 331.

Table 2: Pharmacokinetic Sampling Times for Study Arms 1, 2, 3 and 4 in Low Birth Weight HIV-exposed and Unexposed Infants

<table>
<thead>
<tr>
<th>Arm</th>
<th>Subjects (N)</th>
<th>Age Wk2</th>
<th>Age Wk4</th>
<th>Age Wk6</th>
<th>Age Wk10</th>
<th>Age Wk16</th>
<th>Age Wk24</th>
<th>Samples (N/subject)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>40</td>
<td>Pre, 2h</td>
<td>Pre</td>
<td>Pre</td>
<td>Pre</td>
<td>Pre</td>
<td>Pre</td>
<td>7</td>
</tr>
<tr>
<td>2</td>
<td>18</td>
<td>1.5, 4h</td>
<td>1.5, 4h</td>
<td>1.5, 4h</td>
<td>1.5, 4h</td>
<td>1.5, 4h</td>
<td>1.5, 4h</td>
<td>13</td>
</tr>
<tr>
<td>3</td>
<td>28</td>
<td>1.5, 4h</td>
<td>1.5, 4h</td>
<td>1.5, 4h</td>
<td>1.5, 4h</td>
<td>1.5, 4h</td>
<td>1.5, 4h</td>
<td>13</td>
</tr>
<tr>
<td>4</td>
<td>18-36</td>
<td>1.5, 4h</td>
<td>1.5, 4h</td>
<td>1.5, 4h</td>
<td>1.5, 4h</td>
<td>1.5, 4h*</td>
<td>1.5, 4h*</td>
<td>8-12</td>
</tr>
</tbody>
</table>

*Only for Arm 4 on INH alone (INH plus RIF will only receive 12 weeks of therapy)

Pharmacokinetic sample time collection windows are:

1.5 hours = 1 to 2 hours
2 hours = 1.5 to 2.5 hours
4 hours = 4 to 6 hours

Table 3: Pharmacokinetic Sampling Times for Study Arms 5 and 6 in Low Birth Weight HIV-infected Infants

<table>
<thead>
<tr>
<th>Arm</th>
<th>Subjects (N)</th>
<th>Study Wk2</th>
<th>Study Wk6</th>
<th>Study Wk10</th>
<th>Study Wk16</th>
<th>Study Wk24</th>
<th>Samples (N/subject)</th>
</tr>
</thead>
<tbody>
<tr>
<td>5</td>
<td>24</td>
<td>Pre, 1.5, 4h</td>
<td>Pre</td>
<td>Pre, 1.5, 4h</td>
<td>Pre</td>
<td>Pre, 1.5, 4h</td>
<td>11</td>
</tr>
<tr>
<td>6</td>
<td>12</td>
<td>Pre, 1.5, 4h</td>
<td>Pre</td>
<td>Pre, 1.5, 4h</td>
<td>Pre</td>
<td>Pre, 1.5, 4h</td>
<td>11</td>
</tr>
</tbody>
</table>

Pharmacokinetic sample time collection windows are:

1.5 hours = 1 to 2 hours
4 hours = 4 to 6 hours
9.32 Pharmacokinetic Studies

Summary descriptive pharmacokinetic results will be compiled based on study arms. In addition, population PK analyses will be performed for each drug across study arms. The initial goal in the population PK analysis is to estimate the typical PK parameters (CL/F and V/F) with parameter estimates +/- 15% (normalized SEM) of the true population value. Furthermore, we are interested in exploring the relationship between population PK parameters and the following patient attributes: gestational age at birth, post natal age, weight, gender, concomitant RIF, RTV concentrations, HIV-status. NAT-2 and CYP 2B6 genotype will be determined to see the impact of poor metabolizer genotype on INH and NVP CL/F. The NONMEM analysis planned uses a mixed-effects analysis that will incorporate fixed effects based on subject characteristics. While this model based approach does not lend itself to standard power calculations, if the covariates are adequately described and the remaining unexplained inter-subject variability is 50% or less, our samples size between 24-40 should result in parameter estimates that fall within between 80-120% of the true population value. The prior population PK evaluation of ZDV in 40 preterm pharmacokinetics from PACTG 331 suggested that half or more of inter-subject pharmacokinetic parameters variability in the base model (55-65%) could be explained by fixed effects (GA, PNA and serum creatinine) and the full covariate model resulted in unexplained inter-subject variability of 33% or less for CL, V and F while also reducing standard error of each parameter estimate. Other population PK literature suggests a minimum of 24 to 40 subjects (with estimated PK parameter CVs of 35-50%) with repeat PK evaluations will be needed to characterize the typical clearance for each drug and its developmental changes. Based on the current design we expect to have sufficient data to characterize the age related changes for each drug by study arm. Larger sample sizes are needed to assess additional PK parameter covariates. The overall larger sample size for NVP (86 subjects) will allow characterize maturation effects and also the assessment of the RIF drug-interaction and impact CYP 2B6 genotype in this population. Based on an expected CYP 2B6 poor metabolized frequency of 20%, approximately 19 CYP 2B6 poor metabolizers will be enrolled.

Pharmacokinetic assessments will also be performed on the other ARVs (NRTIs) received by subjects in Arms 5 and 6. Descriptive statistics will be complied for each NRTI and stratified by based on study week. Since the individual NRTIs are not specified by the study, the number of study subjects receiving any particular NRTI combination cannot be known in advance. However, any NRTI with pharmacokinetic data available from at least 24 individuals will have population pharmacokinetics models...
developed. Based on current use patterns we expect to have sufficient NRTI data to develop population PK models for ZDV and 3TC.

9.33 CYP 2B6 and N-acetyl transferase type 2 (NAT-2) genotype

Cell pellets from PK sampling at week 2 will be combined and stored for a DNA extraction, amplification, and gel electrophoresis (see the Laboratory Processing Chart for details). The genotype analysis will be completed one time per study participants. All subjects receiving INH will be genotyped for NAT2. All subjects receiving NVP will be genotyped for CYP 2B6. These genotypes will be used as covariates in the population PK analyses of NVP and INH to determine their impact on CL/F.

9.4 Procedures for Pharmacologic Studies

9.41 Procedures for Population Pharmacokinetics

The actual individual concentration data, collection times and dosing histories will be used to calculate population NVP, INH, RIF, TMP, SMX and LPV/r parameters using the computer program NONMEM (Ver. 6 or later). Additional population PK models will be developed for ARVs commonly used in Arms 5 and 6. The data will be modeled using two stages in a nonlinear hierarchical model development. The first stage introduces the structural model (e.g. one compartment open model), the population parameters, individual effects and the within-subject variation. The second portion of the model development involves characterizing the variation between subjects in the pharmacokinetic parameters and attempting to determine clinical characteristics (covariates) that may identify sources of pharmacokinetic variability. Initially a one-compartment model with first order absorption and elimination will be utilized. Alternative models will be explored if indicated by the data. Nested models will be compared graphically and with a likelihood ratio test.

Typical population pharmacokinetic parameter estimates, their inter-subject variability and the residual error will be determined. The correlation between plasma concentrations and/or pharmacokinetic parameters with demographic factors (gestational age at birth, post-natal age, SGA, weight, sex, race, NAT-2, CYP 2B6 and...
concomitant therapy) will be investigated. Empiric Bayesian post-hoc individual subject pharmacokinetic parameter estimates will be determined from the final model. Monte Carlo simulations of the final PK models will be generated to optimize dosing strategies for the NVP, ARV, anti-TB, TMP-SMX and other ARVs. Individual subject estimates for $T_{1/2}$ (the terminal half-life), CL/F (apparent clearance) V/F (apparent volume of distribution) and AUC (area under the curve) will be generated and summarized (n, mean, standard deviation (SD), coefficient of variation, minimum, median, and maximum). For presentation purposes, scheduled sampling times will be used in tables, listings and graphs. The exact time and date of sample collection and the dosing history information will be recorded on the Pharmacokinetics CRF and used in the population analyses.

9.42 Real-time Pharmacokinetic Assessments and Dose Modifications

This study is opportunistic in design and will not dictate drug dosages. However, NVP and LPV/r PK results will be provided to the clinical caregivers of subjects enrolled in Arms 1, 2, 3, 5 and 6 to assist with their clinical management. NVP results will be reported in real time for subjects in Arms 1, 2 and 3 and LPV/r results will be reported in real time for subjects in Arms 5 and 6. While the results will be reported to the clinical caregivers, there will be no dosage modifications mandated by the study. However, the protocol pharmacologist will be available to clinical caregivers for consultation on interpretation of the PK results.

9.43 Monte Carlo Simulations

The population PK models for NVP, INH, RIF, TMP, SMX and LPV/r will be used as input for Monte Carlo simulations. One thousand virtual subjects will be generated for each weight strata (3000 virtual subjects for each drug) across the age continuum of study subjects using the most common dosing. Ninety-five percent confidence intervals for the concentrations vs. time profiles will be generated for each drug. The projected frequency of NVP trough concentrations <0.1 mcg/mL, <1.0 mcg/mL, <3.0 mcg/mL and >10 mcg/mL (approximately double the
adult typical value) will be calculated. The projected frequency of LPV/r trough concentrations <1.0 mcg/mL, <3.0 mcg/mL and >15.0 mcg/mL (approximately the adult typical value) will be calculated. The projected distributions of AUC for each drug will also be generated from these Monte Carlo simulations.

9.5 Anticipated Outcomes

The pharmacokinetic analyses will generate population models that describe the maturational changes in metabolism and elimination for the study drugs. The Monte Carlo simulations for each drug will allow a critical evaluation of current and alternative dosing strategies. The ARV, anti-TB and TMP-SMX the systemic exposures will be compared to existing adult and pediatric mean values to assist in improving drug dosing in LBW infants.

10.0 HUMAN SUBJECTS

10.1 Institutional Review Board and Informed Consent

This protocol, the informed consent documents (Appendix V-A, V-B, Appendix V-C), and any subsequent modifications must be reviewed and approved by the IRB or EC responsible for oversight of the study. Written informed consent must be obtained from the subject’s parent or legal guardian. 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 subject’s 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 subjects and determines when a study subject 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 IRB/EC, local, state, national and/or host country guidelines. Confirmation of such a plan at a site should be submitted with protocol registration materials.

10.2 Subject Confidentiality
All laboratory specimens, evaluation forms, reports, and other records will be identified only by a coded number to maintain subject 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 subject, except as necessary for monitoring by the Office for Human Research Protections (OHRP), the NIAID, the local IRB or Ethics Committee, local or national regulatory agencies, IMPAACT, study staff, and study monitors.

10.3 Study Discontinuation

The study may be discontinued at any time by the NIAID, IMPAACT, OHRP, the IRB or EC, other governmental agencies, or local or national regulatory agencies as part of their duties to ensure that research subjects are protected.

11.0 PUBLICATION OF RESEARCH FINDINGS

Publication of the results of this trial will be governed by IMPAACT policies.

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.

All infectious specimens will be sent using the ISS-1 SAF-T-PAK mandated by the International Air Transport Association Dangerous Goods Regulations-Packing Instruction 602. Refer to individual carrier guidelines (e.g., Federal Express or Airborne) for specific instructions.
13.0 REFERENCES


### APPENDIX I-A

**SCHEDULE OF EVALUATIONS FOR ARMS 1, 2, 3 and 4**

*INFANTS WHO WERE ENROLLED IN ARMS 1, 2, OR 3 AND LATER DETERMINED TO BE HIV INFECTED SHOULD REGISTER TO ARM 5 OR 6, AS APPROPRIATE, AND FOLLOW THE SCHEDULE OF EVALUATIONS IN APPENDIX I-B.*

<table>
<thead>
<tr>
<th>EVALUATION</th>
<th>Screening within 0-14 days of life</th>
<th>Entry within 7-14 days of life</th>
<th>Week 4 of life</th>
<th>Week 6 of life</th>
<th>Week 10 of life</th>
<th>Week 16 of life</th>
<th>Week 24 of life</th>
<th>On study/off drug</th>
</tr>
</thead>
</table>
| **STUDY VISIT WEEKS ARE BASED ON TIME ELAPSED FROM BIRTH**

ARM 1 (NVP), ARM 2 (NVP PLUS INH), ARM 3 (NVP PLUS INH PLUS RIF), ARM 4 (INH ALONE OR INH PLUS RIF)

<table>
<thead>
<tr>
<th>Visit Windows</th>
<th>-</th>
<th>-</th>
<th>±4days</th>
<th>±7days</th>
<th>±7days</th>
<th>±14days</th>
<th>±14days</th>
<th>±7days</th>
</tr>
</thead>
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<td><strong>CLINICAL</strong></td>
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<tr>
<td>Informed Consent</td>
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<td></td>
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<tr>
<td>History</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
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</tr>
<tr>
<td>Physical Exam</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
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<td><strong>LABORATORY</strong></td>
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<tr>
<td>Hematology (Hct)</td>
<td></td>
<td></td>
<td>0.5mL</td>
<td>0.5mL</td>
<td>0.5mL</td>
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<tr>
<td>Chemistries (ALT, Cr, GGT)</td>
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<td></td>
<td>0.5mL</td>
<td>0.5mL</td>
<td>0.5mL</td>
<td>0.5mL</td>
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<tr>
<td><strong>PHARMACOLOGY</strong></td>
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<tr>
<td>PK sampling for Arm 1 (NVP)</td>
<td></td>
<td></td>
<td>0.4mL</td>
<td>0.2mL</td>
<td>0.2mL</td>
<td>0.2mL</td>
<td>0.2mL</td>
<td>0.2mL</td>
</tr>
<tr>
<td>PK sampling for Arm 2 (NVP plus INH)</td>
<td></td>
<td></td>
<td>0.4mL</td>
<td>0.6mL</td>
<td>0.4mL</td>
<td>0.4mL</td>
<td>0.4mL</td>
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<tr>
<td>PK sampling for Arm 3 (NVP plus INH plus RIF)</td>
<td></td>
<td></td>
<td>0.4mL</td>
<td>0.4mL</td>
<td>0.4mL</td>
<td>0.4mL</td>
<td>0.4mL</td>
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<tr>
<td>PK sampling for Arm 4 (INH alone or INH plus RIF)</td>
<td></td>
<td></td>
<td>0.4mL</td>
<td>0.4mL</td>
<td>0.4mL</td>
<td>0.4mL</td>
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<tr>
<td><strong>PHARMACOGENETICS</strong></td>
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<tr>
<td><strong>TOTAL BLOOD VOLUME</strong></td>
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<tr>
<td></td>
<td>0.4-0.9mL</td>
<td>0.2-0.6mL</td>
<td>0.2-0.9mL</td>
<td>0.7-0.9mL</td>
<td>0.2-0.4mL</td>
<td>0.7-0.9mL</td>
<td>0.7-0.9mL</td>
<td>0.7-0.9mL</td>
</tr>
</tbody>
</table>
APPENDIX I-A FOOT NOTES:

1. Physical exam includes length, weight, head circumference, temperature, heart rate, respiratory rate
2. If not done as part of clinical care
3. Collect 0.2mL at pre-dose and 2 hours (1.5 to 2.5 hours) post-dose
4. Collect 0.2mL at pre-dose
5. Collect 0.2mL at 1.5 hours (1 to 2 hours) and 4 hours (4 to 6 hours) post-dose
6. Collect 0.2mL at pre-dose, 1.5 hours (1-2 hours) and 4 hours (4 to 6 hours) post-dose
7. No PK sampling is required for Arm 4 (subjects receiving INH plus RIF)
8. Infants meeting any of the following criteria on the day of a scheduled PK assessment should not have pharmacokinetic sampling performed on that day:
   1) Hypotension and/or poor perfusion requiring treatment with volume expansion and/or vasopressors
   2) Exchange transfusion within 24 hours preceding a PK evaluation
   3) Urine output less than 0.5 mL/kg/hr within 24 hours preceding a PK evaluation
   4) Missed doses of study drugs within preceding 72 hours
   PK sampling not performed due to the above criteria should be rescheduled after consultation with the protocol team.
   In addition, the protocol team should be contacted regarding any interruption in study drug administration greater than 24 hours. Infants whose study drug(s) are discontinued will not have further PK sampling but will continue to be followed for safety and toxicity monitoring.
Infants who were enrolled in Arms 1, 2 or 3 and later determined to be HIV infected should be re-evaluated for enrollment in Arms 5 or 6, as appropriate, and if eligible, should follow the Schedule of Evaluations in Appendix IB.
9. See the Laboratory Processing Chart (LPC) on the P1106 Protocol Specific Webpage on the IMPAACT Website (http://www.impaactgroup.org) for collection, processing and shipping instructions.
10. Genotyping will be performed on all subjects and will include assessment of polymorphisms in NAT2 if subject receiving INH and CYP 2B6 if subject receiving NVP.

Priority of blood draw should be as follows:
1) Chemistries
2) Hematology
3) Pharmacokinetics
## APPENDIX I-B
### SCHEDULE OF EVALUATIONS FOR ARMS 5 AND 6

<table>
<thead>
<tr>
<th>EVALUATION</th>
<th>Entry within 7 days prior to LPV/r initiation</th>
<th>3-5 days after LPV/r initiation</th>
<th>7-9 Days after LPV/r initiation</th>
<th>Week 2 after LPV/r initiation</th>
<th>Week 6 after LPV/r initiation</th>
<th>Week 10 after LPV/r initiation</th>
<th>Week 16 after LPV/r initiation</th>
<th>Week 24 after LPV/r initiation</th>
<th>On study/off drug</th>
</tr>
</thead>
<tbody>
<tr>
<td>VISIT WINDOWS</td>
<td>-</td>
<td>-</td>
<td>±4 days</td>
<td>±7 days</td>
<td>±7 days</td>
<td>±14 days</td>
<td>±14 days</td>
<td>±7 days</td>
<td>-</td>
</tr>
<tr>
<td><strong>CLINICAL</strong></td>
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<td>Physical Exam(^1)</td>
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<td>X</td>
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<td>X</td>
<td>X</td>
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<td>Electrocardiogram (See Appendix II)</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
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<tr>
<td>Echocardiogram (See Appendix II)</td>
<td>X</td>
<td>X</td>
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<td>X</td>
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<tr>
<td><strong>LABORATORY</strong></td>
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<td></td>
<td></td>
<td>0.5mL</td>
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<td>0.5mL</td>
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<tr>
<td>Hematology (Hct)</td>
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<tr>
<td>Chemistries (ALT, Cr, potassium, calcium, osmolality)</td>
<td></td>
<td></td>
<td></td>
<td>0.5mL(^2)</td>
<td>0.5mL(^2)</td>
<td>0.5mL(^2)</td>
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<tr>
<td><strong>VIROLOGY</strong></td>
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<td>0.5mL(^3)</td>
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<tr>
<td>HIV RNA PCR</td>
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<tr>
<td><strong>PHARMACOLOGY(^7)</strong></td>
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<tr>
<td>PK sampling Arm 5 (LPV/r plus 2 NRTIs, no RIF)(^6)</td>
<td></td>
<td></td>
<td></td>
<td>0.6mL(^4)</td>
<td>0.2mL(^5)</td>
<td>0.6mL(^4)</td>
<td>0.2mL(^5)</td>
<td>0.6mL(^4)</td>
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<tr>
<td>Arm 6 (LPV/r plus 2 NRTIs plus RIF)(^6)</td>
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<td></td>
<td>0.6mL(^4)</td>
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<td>0.6mL(^4)</td>
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<tr>
<td><strong>PHARMACOGENETICS(^7)</strong></td>
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<td>Genotyping</td>
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<td>X(^8)</td>
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<tr>
<td><strong>TOTAL BLOOD VOLUME</strong></td>
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<td>1.1mL</td>
</tr>
</tbody>
</table>

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\(^1\) Physical Exam includes renal ultrasonic and ABG

\(^2\) Chemistries collected in duplicate

\(^3\) HIV RNA PCR collected in duplicate

\(^4\) PK sampling: Arm 5 (LPV/r plus 2 NRTIs, no RIF) collects 0.6mL on study and 0.6mL on drug

\(^5\) PK sampling: Arm 6 (LPV/r plus 2 NRTIs plus RIF) collects 0.2mL on study and 0.2mL on drug

\(^6\) Arm 5 and Arm 6 are on therapy for 24 weeks

\(^7\) PK sampling: Arm 5 (LPV/r plus 2 NRTIs, no RIF) collects 0.6mL on study and 0.6mL on drug

\(^8\) Genotyping: X on study only
APPENDIX I-B FOOT NOTES:

1. Physical exam includes length, weight, head circumference, temperature, heart rate, respiratory rate
2. If not done as part of clinical care
3. Confirmatory HIV RNA PCR may be drawn prior to entry or at the entry visit. The results may be pending at entry visit, but results must be available prior to LPV/r initiation. Results of confirmatory HIV RNA PCR must indicate HIV infection.
4. Collect 0.2mL at pre-dose, 1.5 hours (1-2 hours) and 4 hours (4 to 6 hours) post-dose
5. Collect 0.2mL at pre-dose
6. Infants meeting any of the following criteria on the day of a scheduled PK assessment should not have pharmacokinetic sampling performed on that day:
   1) Hypotension and/or poor perfusion requiring treatment with volume expansion and/or vasopressors
   2) Exchange transfusion within 24 hours preceding a PK evaluation
   3) Urine output less than 0.5 mL/kg/hr within 24 hours preceding a PK evaluation
   4) Missed doses of study drugs within preceding 72 hours
   PK sampling not performed due to the above criteria should be rescheduled after consultation with the protocol team.
   In addition, the protocol team should be contacted regarding any interruption in study drug administration greater than 24 hours. Infants whose study drug(s) are discontinued will not have further PK sampling but will continue to be followed for safety and toxicity monitoring.
7. See the Laboratory Processing Chart (LPC) on the P1106 Protocol Specific Webpage on the IMPAACT Website (http://www.impaactgroup.org) for collection, processing and shipping instructions.
8. Genotyping only performed if subject receiving INH (for NAT2 polymorphisms).

Priority of blood draw should be as follows:
1) Chemistries
2) Hematology
3) Pharmacokinetics
APPENDIX II
P1106 TESTING LABORATORIES

Pharmacology
Peter Smith, Lab Director
Jennifer Norman, QA and Projects Manager
Division of Pharmacology Laboratory
University of Cape Town
K50 Old Main Building
Groote Schuur Hospital
Observatory 7925
Cape Town, South Africa
Phone: 27 21 406 6289 or 6295
Email: peter.smith@uct.ac.za
   jennifer.norman@uct.ac.za

Genotyping
Professor Paul V. Helden
Director, MRC Centre for Molecular and Cellular Biology
Head, Dept. Medical Biochemistry
ATTN: Cedric Werely
Room F412A (Secretary)
Faculty of Health Sciences
Stellenbosch University
Francie van Zijl Drive
Tygerberg, South Africa
Phone: 27 21 938 9401 or 9124
E-mail: pvh@sun.ac.za
APPENDIX III
CARDIOLOGY EVALUATIONS

Cardiac conditions may impact the use of lopinavir/ritonavir (LPV/r) and require caution. Discussion is required between the cardiologists, neonatologists and infectious disease specialists caring for the infant prior to the initiation of LPV/r. Local cardiologists will provide immediate interpretation of ECG/ECHO studies to site caregivers for clinical purposes. Independent South African pediatric cardiologists not otherwise associated with the study will perform intermittent batched reviews of ECG/ECHO studies for final study interpretations.

These conditions include:

- Underlying cardiac dysrhythmia (brady- or tachy-arrhythmia)
- Non-reversible prolonged PR (e.g. subjects with endocardial cushion defects) or QT interval on 1st (baseline) electrocardiogram (ECG)
- Myocardial dysfunction
- Non-correctable hypokalaemia or hypocalcaemia

Electrocardiogram/echocardiogram (ECG/ECHO) studies:

- All echocardiograms (ECHO) are to be digitally captured and retained as a permanent record of the study, and for possible independent third party examination.
- All clearly labeled hard copies of the ECGs are to be retained as a record of the examination, and for possible third party examination.
- If either the ECG and/or ECHO is/are deemed abnormal, the subject’s medication may be stopped, and appropriate workup will be done (e.g. cardiac enzymes, viral studies) at the discretion of the attending pediatrician/cardiologist.
- The ECG and/or ECHO should be rescheduled if the healthcare provider (neonatologist) determines that the infant is unable to tolerate the investigation at a scheduled time point. (LPV/r will be given if attending doctors [neonatal/infectious disease] think it is appropriate)

How to do a pediatric ECG in a neonate:

PRECORDIAL LEADS
- V1 4th intercostal space – right sternal border
- V2 4th intercostal space – left sternal border
- V3 4th intercostal space – midway between V2 and V4
- V4 4th intercostal space – left midclavicular line
- V5 4th intercostal space – left anterior axillary line
- V6 4th intercostal space – left midaxillary line

LIMB LEADS
- Right arm: red
- Left arm: yellow
- Left leg: green
- Right leg: black (earthing)

1. Enrolment (HIV PCR Confirmation of infection)
   - **Baseline ECG and ECHOCARDIOGRAM** prior to starting medication

2. 2nd ECG at 72-96 hours (3-5 days)

3. 3rd ECG and second ECHOCARDIOGRAM examination
   - Done at approximately 1 week (7-9 days)

4. 4th ECG at 2 weeks of age

5. 5th ECG and third ECHOCARDIOGRAM examination at 6 weeks age
## APPENDIX IV
### TABLE FOR GRADING EXPECTED ADVERSE EVENTS

<table>
<thead>
<tr>
<th>PARAMETER</th>
<th>GRADE 1 MILD</th>
<th>GRADE 2 MODERATE</th>
<th>GRADE 3 SEVERE</th>
<th>GRADE 4 POTENTIALLY LIFE-THREATENING</th>
</tr>
</thead>
<tbody>
<tr>
<td>Apnea</td>
<td>&lt;6 spells* per day</td>
<td>6-&lt;12 spells* per day or nasal cannula for apnea</td>
<td>12 or more spells* per day or nasal continuous positive airway pressure (NCPAP) for apnea</td>
<td>Requires intubation for apnea</td>
</tr>
<tr>
<td>Anemia</td>
<td>Hgb 8-10 g/dL</td>
<td>Hgb ≤ 8 g/dL</td>
<td>Requires packed red cell transfusion, no clinical signs</td>
<td>Requires packed red cell transfusion, clinical signs of shock</td>
</tr>
<tr>
<td>Congenital Anomalies</td>
<td>Minor (no impairment of function)</td>
<td>Minor (no impairment of function), future treatment may be needed</td>
<td>Major (impairment of function), no immediate treatment needed</td>
<td>Major (impairment of function), immediate treatment needed</td>
</tr>
<tr>
<td>Congenital Heart Disease</td>
<td>Minor (no impairment of function), no treatment needed</td>
<td>Minor (no impairment of function), future treatment may be needed</td>
<td>Major (impairment of function), no immediate treatment needed</td>
<td>Major (impairment of function), immediate treatment needed</td>
</tr>
<tr>
<td>Electrolyte/Metabolic Disorders</td>
<td>---------------</td>
<td>Electrolyte/metabolic disorder, no systemic signs</td>
<td>---------------</td>
<td>Electrolyte/metabolic disorder with systemic signs</td>
</tr>
<tr>
<td>GI dysfunction</td>
<td>Not ill, abnormal abdominal exam, no treatment needed (e.g., abdominal distension but not NPO)</td>
<td>Mild illness, NPO &lt;3 days (e.g., R/O necrotizing enterocolitis (NEC) evaluation, Stage I NEC)</td>
<td>Moderate illness, NPO 3-7 days, or medical treatment (e.g., Stage II NEC)</td>
<td>Severe illness, NPO &gt; 7 days, or surgical treatment needed (e.g., Stage III NEC)</td>
</tr>
<tr>
<td>Hypertension</td>
<td>Systolic BP &gt; 80-100, no treatment</td>
<td>Systemic BP &gt; 100, no treatment</td>
<td>Treatment with one agent</td>
<td>Treatment with multiple agents</td>
</tr>
<tr>
<td>Hypotension</td>
<td>Mild clinical signs, no treatment needed</td>
<td>Symptomatic, treated with IV fluids</td>
<td>Symptomatic, treated with single medication</td>
<td>Clinical signs of shock or requiring use of multiple medications</td>
</tr>
<tr>
<td>Intraventricular</td>
<td>Germinal matrix</td>
<td>Blood in ventricle,</td>
<td>Blood in ventricle,</td>
<td>Parenchymal</td>
</tr>
<tr>
<td>Condition</td>
<td>Description</td>
<td>Treatment</td>
<td></td>
<td></td>
</tr>
<tr>
<td>------------------------------------------------</td>
<td>-----------------------------------------------------------------------------</td>
<td>---------------------------------------------------------------------------</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hemorrhage</td>
<td>hemorrhage</td>
<td>no enlargement with ventricular enlargement hemorrhage and/or need for ventricular drainage</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Jaundice</td>
<td>Mild jaundice, no treatment</td>
<td>Phototherapy and/or IVIG</td>
<td>Exchange transfusion</td>
<td>Acute bilirubin encephalopathy</td>
</tr>
<tr>
<td>Neonatal Abstinence Syndrome (NAS)</td>
<td>NAS signs, no medical treatment</td>
<td>NAS controlled with single drug</td>
<td>NAS controlled with two drugs</td>
<td>NAS with seizures</td>
</tr>
<tr>
<td>Neurologic compromise</td>
<td>Mildly abnormal neurologic exam, no clinical or EEG seizure activity</td>
<td>Stage I hypoxic-ischemic encephalopathy (HIE) or possible clinical or EEG seizure activity but no treatment</td>
<td>Stage II HIE or single drug seizure therapy</td>
<td>Stage III HIE or induced hypothermia or multiple drug seizure therapy</td>
</tr>
<tr>
<td>Neutropenia</td>
<td>ANC &lt;1000/mm$^3$</td>
<td>ANC &lt;500/mm$^3$</td>
<td>Treated with GCSF</td>
<td>WBC transfusion</td>
</tr>
<tr>
<td>Patent Ductus Arteriosus</td>
<td>Clinical signs, no treatment</td>
<td>Treatment with fluid restriction or diuretics</td>
<td>Treatment with indomethacin or ibuprofen</td>
<td>Surgical ligation</td>
</tr>
<tr>
<td>Persistent Pulmonary Hypertension</td>
<td>Supplemental O2 but no mechanical ventilation</td>
<td>Conventional ventilator &lt;5 days and/or alkalinization</td>
<td>Conventional ventilation 5-10 days, alternative ventilation (e.g., high frequency oscillatory ventilation (HFOV), sildenafil and/or nitric oxide)</td>
<td>Mechanical ventilation &gt;10 days</td>
</tr>
<tr>
<td>Renal Dysfunction</td>
<td>Urine output 1-&lt;1.5 mL/kg/hr</td>
<td>Urine output 0.5-&lt;1.0 mL/kg/hr</td>
<td>Urine output 0-&lt;0.5 mL/kg/hr</td>
<td>Prolonged anuria</td>
</tr>
<tr>
<td>Respiratory Insufficiency</td>
<td>Nasal cannula oxygen with FiO2 &lt; 0.5</td>
<td>Continuous positive airway pressure (CPAP) or nasal cannula with FiO2 &gt; 0.5</td>
<td>Conventional ventilation</td>
<td>Alternative ventilation (e.g., HFOV)</td>
</tr>
<tr>
<td>Retinopathy of Prematurity (ROP)</td>
<td>Incomplete vascularization</td>
<td>Pre-threshold ROP</td>
<td>Threshold ROP or ROP treatment</td>
<td>Retinal detachment</td>
</tr>
<tr>
<td>Sepsis</td>
<td>Septic evaluation, no treatment</td>
<td>R/O sepsis, antibiotics for &lt; 72 hours</td>
<td>Clinical sepsis, &gt;72 hours antibiotics, no</td>
<td>Clinical sepsis, &gt; 72 hours antibiotics with</td>
</tr>
<tr>
<td></td>
<td>septic shock or meningitis</td>
<td>septic shock or meningitis</td>
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<tr>
<td>Thrombocytopenia</td>
<td>75,000-100,000</td>
<td>50,000-&lt;75,000</td>
<td>25,000-&lt;50,000</td>
<td>&lt;25,000 or platelet transfusion</td>
</tr>
</tbody>
</table>

*Apnea spell defined as apnea event >20s or associated with bradycardia, hypoxia or cyanosis*
INTRODUCTION

You are being asked to allow your baby to take part in this research study because you are infected with the Human Immunodeficiency Virus (HIV), are not taking any anti-HIV medicine or are taking anti-HIV medicine that does not include nevirapine (NVP) and are breastfeeding your baby.

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 allow your baby to take part in this study, you will be asked to sign this consent form. You will get a copy to keep.

WHY IS THIS STUDY BEING DONE?

Your baby weighs less than the average baby and is receiving the anti-HIV medicine called nevirapine to prevent infection with HIV. There is little information to tell us what the best dose of nevirapine is for smaller than average babies. The purpose of this study is to collect some information about how much nevirapine is in the blood of small babies so that we can figure out the best nevirapine dose.

Your baby may also be receiving isoniazid and/or rifampicin to prevent infection with tuberculosis. There is also little information to tell us what the best doses of these medicines are in smaller than average babies. Another purpose of this study is to collect some information about how much tuberculosis medicine(s) is in the blood of small babies so that we can figure out the best doses of these medicines.

WHAT DOES MY BABY HAVE TO DO IF HE/SHE IS IN THIS STUDY?

Your baby will continue take his/her anti-HIV medicine and/or tuberculosis medicine(s) as prescribed by your baby’s doctor. None of these medicines are supplied by this study.

Screening Visit To See If Your Baby Can Be In The Study:
The screening visit may be done as a separate visit or as part of your baby’s first study visit when your baby enters the study. If you decide you want your baby to be in this study, we will do some tests to see if your baby is able to enter the study.

- The screening visit will happen when your baby is less than 14 days old.
- We will ask questions about your baby’s medical history including questions about your baby’s health and what symptoms, medications, and illnesses your baby has had.
- We will do a physical exam including length, weight, head measurement, and vital signs (temperature, heart rate and respiratory rate).

Entry Visit:
If your baby is found to be able to be in this study, you will be asked to bring your baby to the clinic for an entry visit. The following tests will be done:

- We will ask questions about your baby’s medical history including questions about your baby’s health and what symptoms, medications, and illnesses your baby has had.
- We will do a physical exam including length, weight, head measurement, and vital signs (temperature, heart rate and respiratory rate).
- We will draw blood to check how well your baby’s liver and kidneys are functioning if your baby’s doctor has not already done this as part of your baby’s routine care. The total amount of blood to be drawn for this test if it needs to be done will be 0.5mL (less than a quarter of a teaspoon). [Note to sites: add locally relevant description of blood volume].
- Blood will be drawn 2 times over 2 hours, or 2 times over 4 hours (depending on which medicines your baby is taking) to measure the amount of anti-HIV medicine and/or tuberculosis medicine(s) in your baby’s blood. Your baby’s doctor will decide how blood will be taken, depending on what he/she thinks will be best for your baby. Either a small needle will be put into the vein each time or a small plastic catheter (a tube) will be placed and kept in a vein so that blood can be drawn multiple times, without having to stick your baby with a needle each time. The tube will then stay in place during the visit until all of the blood samples are drawn. The amount of blood needed for each time blood is drawn is 0.2mL or 0.4mL total (less than a quarter of a teaspoon). [Note to sites: add locally relevant description of blood volume].
- The total amount of blood drawn at this visit will vary from 0.4mL to 0.9mL (less than a quarter of a teaspoon) depending on the type of test. [Note to sites: add locally relevant description of blood volume].
- This visit will take about ___ to complete. [Note to sites: add locally relevant length of study visit].

On Study Visits:
- You will be asked to bring your baby to the clinic 5 additional times. The visits will be when your baby is 4, 6, 10, 16 and 24 weeks old.
- At each visit, we will take a medical history and perform a physical exam.
- When your baby is 6 weeks old, we will draw blood to check how well your baby’s liver and kidneys are functioning if your baby’s doctor has not already done this as part of your baby’s routine care. The total amount of blood to be drawn for this test if it needs to be done will be 0.5mL (less than a quarter of a teaspoon). [Note to sites: add locally relevant description of blood volume].
- At 2 of these visits, when your baby is 10 weeks and 24 weeks old, we will draw blood to check the percentage of red blood cells in your baby’s blood. The amount of blood needed for this test is 0.5mL (less than a quarter of a teaspoon).
- At each of these visits, blood will be drawn 1, 2 or 3 times over 2 or 4 hours (depending on which medicines your baby is taking) to measure the amount of anti-HIV medicine and/or tuberculosis medicine(s) in baby’s blood. The amount of blood needed for each time blood is drawn is 0.2mL 0.4mL, or 0.6mL total (less than a quarter of a teaspoon). [Note to sites: add locally relevant description of blood volume].
- Your baby will have one drop of blood taken once during the study to check your baby’s DNA (genes) to see how they break down the medicines your baby is taking. Some people break down medicines differently based on their DNA and this can change the levels of the medicines in their bodies.
You may decide that you do not want your baby’s DNA to be tested. Your baby can still participate in this study even if you make this decision. Please read the following statement carefully and then mark your initials in the appropriate space provided:
I agree to allow my baby’s DNA to be tested.
Yes_______ No_________ Initials ________ Date __________

The total amount of blood drawn at these different study visits will be between 0.2mL to 0.9mL (less than a quarter of a teaspoon) depending on the type of test. [Note to sites: add locally relevant description of blood volume].

The amount of blood needed to be drawn from your baby is within the approved guidelines for low birth weight babies and will not affect your baby’s health.

Most of these visits will take about ___ hours to complete. [Note to sites: add locally relevant length of study visit].

If your baby is receiving anti-tuberculosis medicine to prevent infection with tuberculosis but is later found to have tuberculosis, you will be asked to allow your baby to continue in the study and complete each scheduled study visit until your baby is 24 weeks of age.

If your baby has to stop taking his/her anti-HIV medicine and/or tuberculosis medicine(s) before the study ends, you will be asked to allow your baby to continue in the study until your baby is 24 weeks of age, to make sure your baby is continuing to do well. At each of the scheduled study visits, we will take a medical history and perform a physical exam, but no blood will be drawn.

HOW MANY BABIES WILL TAKE PART IN THIS STUDY?

The study will enroll a maximum of 158 infants.

HOW LONG WILL MY BABY BE IN THIS STUDY?

Your baby will be in this study until your baby is 24 weeks of age.

WHY WOULD THE DOCTOR TAKE MY BABY OFF THIS STUDY EARLY?

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

- The study is cancelled by the IMPAACT network, National Institutes of Health (NIH), the Office for Human Research Protections (OHRP), other national regulatory agencies, or the site’s Institutional Review Board (IRB) or Ethics Committee. An IRB is a committee that watches over the safety and rights of research subjects.
- Your baby is not able to attend the study visits as required by the study.
- Your baby needs a treatment that your baby may not take while on study.
- Your baby is not able to take the medicine required by the study.
- Your baby is found to be HIV infected. If this happens, your baby may be able to enroll in another part of the study that studies babies receiving other HIV medicines. You will be given more detailed information about the other part of the study and be asked to sign another consent form to allow your baby to participate.
WHAT ARE THE RISKS OF THE STUDY?

Risks of Anti-HIV and Tuberculosis Medicines

The medicines that your doctor has prescribed for your baby may have side effects. Your doctor will explain the possible side effects of the medicines your baby is taking.

Risks of Drawing Blood

Drawing blood from a vein or heel stick can cause pain, bruising or bleeding at the place where the needle goes into the skin. There is a small risk of a minor infection at the blood draw site. Because your baby is small, these risks from drawing blood may be greater than in children who are older.

ARE THERE BENEFITS TO TAKING PART IN THIS STUDY?

If you allow your baby to take part in this study, there may be a direct benefit to your baby, but no guarantee can be made. Your baby may benefit by having some additional tests that are not done as part of your baby’s routine care. Information learned from this study may help others who are taking these medicines.

WHAT ABOUT CONFIDENTIALITY?

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

Your baby’s records may be reviewed by the Ministry of Public Health in your country, the Office of Human Research Protections (OHRP), the NIH, (insert name of site) IRB, Ethics Committee (EC), study staff, and study monitors.

WHAT ARE THE COSTS TO ME?

There is no cost to you for your baby’s study visits, examinations, or blood tests. Taking part in this study may lead to added costs to you and your insurance company. In some cases it is possible that your insurance company will not pay for these costs because your baby is taking part in a research study. You will not receive payment for your baby’s participation in this study. [Note to sites: Modify or delete language regarding insurance as appropriate for your site, and insert appropriate language for added local costs or for reimbursement of time and transportation, if relevant].

WHAT HAPPENS IF MY BABY IS INJURED?

If your baby is injured as a result of being in this study, your baby will be given immediate treatment for your baby’s injuries. The cost for this treatment will be charged to you or your insurance company. [Note to sites: Language related to insurance can be deleted if it is not relevant to your site.] 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.
WHAT ARE MY BABY’S RIGHTS AS A RESEARCH SUBJECT?

Taking part in this study is completely voluntary. You may choose not to allow your baby to take part in this study or leave this study at any time. Your decision will not have any impact on your baby’s participation in other studies conducted by NIH and will not result in any penalty or loss of benefits to which your baby is otherwise entitled.

We will tell you about new information from this or other studies that may affect 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 baby’s rights as a research subject, 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 allow your baby to take part in this study, please sign your name below.

____________________________
Name of Participant

____________________________                ____________________________________
Participant’s Legal Guardian (print)                Legal Guardian’s Signature and Date
(As appropriate)  

________________________                        ____________________________________
Study Staff Conducting                        Study Staff Signature and Date

________________________                        ____________________________________
Witness’ Name (print)                        Witness’s Signature and Date
APPENDIX V-B: (For use with Appendix I-A) DIVISION OF AIDS INTERNATIONAL MATERNAL
PEDIATRIC ADOLESCENT AIDS CLINICAL TRIALS GROUP (IMPAACT) SAMPLE INFORMED
CONSENT FOR INFANTS IN ARM 4 (INH ALONE OR INH PLUS RIF)

IMPAACT P1106: Pharmacokinetic Characteristics of Antiretrovirals and Tuberculosis Medicines in Low Birth Weight Infants, Version 1.0, dated April 23, 2013

INTRODUCTION

You are being asked to allow your baby to take part in this research study because you have tuberculosis (TB) and your baby is receiving anti-tuberculosis medicines.

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 allow your baby to take part in this study, you will be asked to sign this consent form. You will get a copy to keep.

WHY IS THIS STUDY BEING DONE?

Your baby weighs less than the average baby and is receiving isoniazid alone or isoniazid with rifampicin to prevent infection with tuberculosis. There is little information to tell us what the best doses of these medicines are in smaller than average babies. The purpose of this study is to collect some information about how much tuberculosis medicine(s) is in the blood of small babies so that we can figure out the best doses of these medicines.

WHAT DOES MY BABY HAVE TO DO IF HE/SHE IS IN THIS STUDY?

Your baby will continue take his/her tuberculosis medicine(s) as prescribed by your baby’s doctor. None of these medicines are supplied by this study.

Screening Visit To See If Your Baby Can Be In The Study:
The screening visit may be done as a separate visit or as part of your baby’s first study visit when your baby enters the study. If you decide you want your baby to be in this study, we will do some tests to see if your baby is able to enter the study.

- The screening visit will happen when your baby is less than 14 days old.
- We will ask questions about your baby’s medical history including questions about your baby’s health and what symptoms, medications, and illnesses your baby has had.
- We will do a physical exam including length, weight, head measurement, and vital signs (temperature, heart rate and respiratory rate).

Entry Visit:
If your baby is found to be able to be in this study, you will be asked to bring your baby to the clinic for an entry visit. The following tests will be done:

- We will ask questions about your baby’s medical history including questions about your baby’s health and what symptoms, medications, and illnesses your baby has had.
We will do a physical exam including length, weight, head measurement, and vital signs (temperature, heart rate and respiratory rate).

We will draw blood to check how well your baby’s liver and kidneys are functioning if your baby’s doctor has not already done this as part of your baby’s routine care. The total amount of blood to be drawn for this test if it needs to be done will be 0.5mL (less than a quarter of a teaspoon). [Note to sites: add locally relevant description of blood volume].

Blood will be drawn 2 times over 4 hours to measure the amount of tuberculosis medicines in your baby’s blood. Your baby’s doctor will decide how blood will be taken, depending on what he/she thinks will be best for your baby. Either a small needle will be put into the vein each time or a small plastic catheter (a tube) will be placed and kept in a vein so that blood can be drawn multiple times, without having to stick your baby with a needle each time. The tube will then stay in place during the visit until all of the blood samples are drawn. The amount of blood needed for each time blood is drawn is 0.2mL or 0.4mL total (less than a quarter of a teaspoon). [Note to sites: add locally relevant description of blood volume].

The total amount of blood drawn at this visit will vary from 0.4mL to 0.9mL (less than a quarter of a teaspoon) depending on the type of test. [Note to sites: add locally relevant description of blood volume].

This visit will take about ___ to complete. [Note to sites: add locally relevant length of study visit]

On Study Visits:

- You will be asked to bring your baby to the clinic 5 additional times. The visits will be when your baby is 4, 6, 10, 16 and 24 weeks old.
- At each visit, we will take a medical history and perform a physical exam.
- When your baby is 6 weeks old, we will draw blood to check how well your baby’s liver and kidneys are functioning if your baby’s doctor has not already done this as part of your baby’s routine care. The total amount of blood to be drawn for this test if it needs to be done will be 0.5mL (less than a quarter of a teaspoon). [Note to sites: add locally relevant description of blood volume].
- At 2 of these visits, when your baby is 10 weeks and 24 weeks old, we will draw blood to check the percentage of red blood cells in your baby’s blood. The amount of blood needed for this test is 0.5mL (less than a quarter of a teaspoon).
- If your baby is taking isoniazid alone, at 5 of these visits blood will be drawn 2 times over 4 hours to measure the amount of tuberculosis medicine in your baby’s blood. Your baby’s doctor will decide how blood will be taken, depending on what he/she thinks will be best for your baby. Either a small needle will be put into the vein each time or a small plastic catheter (a tube) will be placed and kept in a vein so that blood can be drawn multiple times, without having to stick your baby with a needle each time. The tube will then stay in place during the visit until all of the blood samples are drawn. The amount of blood needed for each time blood is drawn is 0.2mL or 0.4mL total (less than a quarter of a teaspoon). [Note to sites: add locally relevant description of blood volume].
- If your baby is taking isoniazid and rifampicin, at 3 of these visits blood will be drawn 2 times over 4 hours to measure the amount of tuberculosis medicines in your baby’s blood. Your baby’s doctor will decide how blood will be taken, depending on what he/she thinks will be best for your baby. Either a small needle will be put into the vein each time or a small plastic catheter (a tube) will be placed and kept in a vein so that blood can be drawn multiple times, without having to stick your baby with a needle each time. The tube will then stay in place during the visit until all of the blood samples are drawn. The
amount of blood needed for each time blood is drawn is 0.2mL or 0.4mL total (less than a quarter of a teaspoon). [Note to sites: add locally relevant description of blood volume].

- Your baby will have one drop of blood taken once during the study to check your baby’s DNA (genes) to see how they break down the medicines your baby is taking. Some people break down medicines differently based on their DNA and this can change the levels of the medicines in their bodies.
- You may decide that you do not want your baby’s DNA to be tested. Your baby can still participate in this study even if you make this decision. Please read the following statement carefully and then mark your initials in the appropriate space provided:

  I agree to allow my baby’s DNA to be tested.

  Yes_______ No_________ Initials ________ Date ________

- The total amount of blood drawn at the different study visits will be between 0.4mL to 0.9mL (less than a quarter of a teaspoon) depending on the type of test. [Note to sites: add locally relevant description of blood volume].
- The amount of blood needed to be drawn from your baby is within the approved guidelines for low birth weight babies and will not affect your baby’s health.
- Most of these visits will take about ___ hours to complete. [Note to sites: add locally relevant length of study visit].

If your baby is receiving anti-tuberculosis medicine to prevent infection with tuberculosis but is later found to have tuberculosis, you will be asked to allow your baby to continue in the study and complete each scheduled study visit until your baby is 24 weeks of age.

If your baby has to stop taking his/her tuberculosis medicine(s) before the study ends, you will be asked to allow your baby to continue in the study until your baby is 24 weeks of age, to make sure your baby is continuing to do well. At each of the scheduled study visits, we will take a medical history and perform a physical exam, but no blood will be drawn.

**HOW MANY BABIES WILL TAKE PART IN THIS STUDY?**

The study will enroll a maximum of 158 babies.

**HOW LONG WILL MY BABY BE IN THIS STUDY?**

Your baby will be in this study until your baby is 24 weeks of age.

**WHY WOULD THE DOCTOR TAKE MY BABY OFF THIS STUDY EARLY?**

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

- The study is cancelled by the IMPAACT network, National Institutes of Health (NIH), the Office for Human Research Protections (OHRP), other national regulatory agencies, or the site’s Institutional Review Board (IRB) or Ethics Committee. An IRB is a committee that watches over the safety and rights of research subjects.
- Your baby is not able to attend the study visits as required by the study.
- Your baby needs a treatment that your baby may not take while on study.
• Your baby is not able to take the medicine required by the study.

WHAT ARE THE RISKS OF THE STUDY?

Risks of Tuberculosis Medicines

The medicines that your doctor has prescribed for your baby may have side effects. Your doctor will explain the possible side effects of the TB medicines your baby is taking.

Risks of Drawing Blood

Drawing blood from a vein or heel stick can cause pain, bruising or bleeding at the place where the needle goes into the skin. There is a small risk of a minor infection at the blood draw site. Because your baby is small, these risks from drawing blood may be greater than in children who are older.

ARE THERE BENEFITS TO TAKING PART IN THIS STUDY?

If you allow your baby to take part in this study, there may be a direct benefit to your baby, but no guarantee can be made. Your baby may benefit by having some additional tests that are not done as part of your baby’s routine care. Information learned from this study may help others who are taking these medicines.

WHAT ABOUT CONFIDENTIALITY?

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

Your baby’s records may be reviewed by the Ministry of Public Health in your country, the Office of Human Research Protections (OHRP), the NIH, (insert name of site) IRB, Ethics Committee (EC), study staff, and study monitors.

WHAT ARE THE COSTS TO ME?

There is no cost to you for your baby’s study visits, examinations, or blood tests. Taking part in this study may lead to added costs to you and your insurance company. In some cases it is possible that your insurance company will not pay for these costs because your baby is taking part in a research study. You will not receive payment for your baby’s participation in this study. [Note to sites: Modify or delete language regarding insurance as appropriate for your site, and insert appropriate language for added local costs or for reimbursement of time and transportation, if relevant].

WHAT HAPPENS IF MY BABY IS INJURED?

If your baby is injured as a result of being in this study, your baby will be given immediate treatment for your baby’s injuries. The cost for this treatment will be charged to you or your insurance company. [Note to sites: Language related to insurance can be deleted if it is not relevant to your site.] 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.

WHAT ARE MY BABY’S RIGHTS AS A RESEARCH SUBJECT?

Taking part in this study is completely voluntary. You may choose not to allow your baby to take part in this study or leave this study at any time. Your decision will not have any impact on your baby’s participation in other studies conducted by NIH and will not result in any penalty or loss of benefits to which your baby is otherwise entitled.

We will tell you about new information from this or other studies that may affect 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 baby’s rights as a research subject, 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 allow our baby to take part in this study, please sign your name below.

__________________________________________
Name of Participant

__________________________________________
Participant’s Legal Guardian (print) (As appropriate) Legal Guardian’s Signature and Date

__________________________________________
Study Staff Conducting Study Staff Signature and Date

__________________________________________
Witness’ Name (print) Witness’s Signature and Date
APPENDIX V-C: (For use with Appendix I-B) DIVISION OF AIDS INTERNATIONAL MATERNAL PEDIATRIC ADOLESCENT AIDS CLINICAL TRIALS GROUP (IMPAACT) SAMPLE INFORMED CONSENT FOR INFANTS IN ARMS 5 (LPV/r PLUS 2NRTIs AND NO RIF BUT MAY BE RECEIVING INH AND ARM 6 (LPV/r PLUS 2NRTIs PLUS RIF AND MAY BE RECEIVING INH)

IMPAACT P1106: Pharmacokinetic Characteristics of Antiretrovirals and Tuberculosis Medicines in Low Birth Weight Infants, Version 1.0, dated April 23, 2013

INTRODUCTION

You are being asked to allow your baby to take part in this research study because your baby is infected with the Human Immunodeficiency Virus (HIV).

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 allow your baby to take part in this study, you will be asked to sign this consent form. You will get a copy to keep.

WHY IS THIS STUDY BEING DONE?

Your baby was smaller than average at birth and has HIV infection. Your doctor plans to start your baby on the anti-HIV medicine called lopinavir/ritonavir in addition to other anti-HIV medicines and with or without tuberculosis medicines. There is little information to tell us what the best dose of lopinavir/ritonavir is for smaller than average babies. The purpose of this study is to collect some information about how much lopinavir/ritonavir is in the blood of small babies so that we can work out the best dose to give to small babies.

WHAT DOES MY BABY HAVE TO DO IF HE/SHE IS IN THIS STUDY?

Your baby will continue take his/her anti-HIV medicines and tuberculosis medicines as prescribed by your baby’s doctor. None of these medicines are supplied by this study.

Entry Visit:
If you agree to allow your baby to be in this study, you will be asked to bring your baby to the clinic within 7 days before your doctor plans to start your baby on the anti-HIV medicine called lopinavir/ritonavir, for an entry visit. The following tests will be done:

- We will ask questions about your baby’s medical history including questions about your baby’s health and what symptoms, medications, and illnesses your baby has had.
- We will do a physical exam including length, weight, head measurement, and vital signs (temperature, heart rate and respiratory rate).
- An echocardiogram (also called an ECHO) will be taken of your baby’s heart. An echocardiogram is a test that uses sound waves to create a moving picture of the heart. The picture is much more detailed than a plain x-ray and involves no radiation exposure.
- An electrocardiogram (also called an ECG or EKG) will be taken of your baby’s heart. An ECG is a painless test that is used to get information about the electrical activity of the heart, such as the rate and regularity of the heartbeat. The size and position of the heart chambers as well as any damage to the
heart can also be obtained through an ECG.

- Blood will be drawn to check the amount of HIV in your baby’s blood.
- The total amount of blood drawn at this visit will be 0.5mL (less than a quarter of a teaspoon). [Note to sites: add locally relevant description of blood volume].
- This visit will take about ____to complete. [Note to sites: add locally relevant length of study visit].

On Study Visits:

- You will be asked to bring your baby to the clinic 7 additional times. The visits will be 3-5 days, 7-9 days and 2, 6, 10, 16 and 24 weeks after your baby starts taking lopinavir/ritonavir.
- At 6 of these visits, we will take a medical history and perform a physical exam.
- At 4 of these visits, we will draw blood to check how well your baby’s liver and kidneys are functioning if your baby’s doctor has not already done this as part of your baby’s routine care. The total amount of blood to be drawn for this test if it needs to be done will be 0.5mL (less than a quarter of a teaspoon). [Note to sites: add locally relevant description of blood volume].
- At 2 of these visits, when your baby is 10 weeks and 24 weeks old, we will draw blood to check the percentage of red blood cells in your baby’s blood. The amount of blood needed for this test is 0.5mL (less than a quarter of a teaspoon).
- At 2 of these visits, we will take another echocardiogram of your baby’s heart.
- At 4 of these visits, we will take another electrocardiogram of your baby’s heart.
- At 2 of these visits, blood will be drawn right before your baby takes his/her first dose of medicine to measure the amount of medicine in your baby’s blood. The amount of blood needed for each time blood is drawn is 0.2mL (less than a quarter of a teaspoon). [Note to sites: add locally relevant description of blood volume].
- At 3 of these visits, blood will be drawn 3 times over 4 hours to measure the amount of medicine in baby’s blood. The doctor looking after the infant will decide how blood will be taken, depending on what he/she thinks will be best for the baby. Either a small needle will be put into the vein each time or a small plastic catheter (a tube) will be placed and kept in a vein so that blood can be drawn multiple times, without having to stick your baby with a needle each time. The tube will then stay in place during the visit until all of the blood samples are drawn. The amount of blood needed for each time blood is drawn is 0.2mL, or 0.6mL total (less than a quarter of a teaspoon). [Note to sites: add locally relevant description of blood volume].
- Your baby will have one drop of blood taken once during the study to check your baby’s DNA (genes) to see how they break down the medicines your baby is taking. Some people break down medicines differently based on their DNA and this can change the levels of the medicines in their bodies.
- You may decide that you do not want your baby’s DNA to be tested. Your baby can still participate in this study even if you make this decision. Please read the following statement carefully and then mark your initials in the appropriate space provided:
  I agree to allow my baby’s DNA to be tested.
  Yes_____ No_________ Initials __________ Date __________
- The total amount of blood drawn at the different study visits will vary from 0.2mL to 1.1mL (less than a quarter of a teaspoon) depending on the type of test. [Note to sites: add locally relevant description of blood volume].
- The amount of blood needed to be drawn from your baby is within the approved guidelines for low birth weight babies and will not affect your baby’s health.
Most of these visits will take about ___ hours to complete.  [Note to sites: add locally relevant length of study visit].

If your baby is receiving anti-tuberculosis medicine to prevent infection with tuberculosis but is later found to have tuberculosis, you will be asked to allow your baby to continue in the study and complete each scheduled study visit until your baby is 24 weeks of age.

If your baby has to stop taking his/her anti-HIV medicine before the study ends, you will be asked to allow your baby to continue in the study until your baby is 24 weeks of age, to make sure your baby is continuing to do well.  At each of the scheduled study visits, we will take a medical history and perform a physical exam, but no blood will be drawn.

HOW MANY BABIES WILL TAKE PART IN THIS STUDY?

The study will enroll a maximum of 158 babies.

HOW LONG WILL MY BABY BE IN THIS STUDY?

Your baby will be in this study until 24 weeks after your baby starts taking lopinavir/ritonavir prescribed by your baby’s doctor.

WHY WOULD THE DOCTOR TAKE MY BABY OFF THIS STUDY EARLY?

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

- The study is cancelled by the IMPAACT network, National Institutes of Health (NIH), the Office for Human Research Protections (OHRP), other national regulatory agencies, or the site’s Institutional Review Board (IRB) or Ethics Committee.  An IRB is a committee that watches over the safety and rights of research subjects.
- Your baby is not able to attend the study visits as required by the study.
- Your baby needs a treatment that your baby may not take while on study.
- Your baby is not able to take the medicine required by the study.

WHAT ARE THE RISKS OF THE STUDY?

Risks of the anti-HIV and TB medicines

The medicines that your doctor has prescribed for your baby may have side effects. Your doctor will explain the possible side effects of the medicines your baby is taking.

Risks of Drawing Blood

Blood drawing may cause some discomfort, bleeding or bruising where the needle enters the body. A small blood clot may form at the site where the blood was drawn or there may be swelling in the area. There is a small risk of a minor infection at the blood draw site.
Risks of Echocardiogram and Electrocardiogram

There are no known side effects associated with echocardiograms or electrocardiograms. They are painless, fast, and safe and do not require your baby's active participation or involve any radiation exposure.

ARE THERE BENEFITS TO TAKING PART IN THIS STUDY?

If you allow your baby to take part in this study, there may be a direct benefit to your baby, but no guarantee can be made. Your baby may benefit by having some additional tests that are not done as part of your baby’s routine care. Information learned from this study may help others who are taking these medicines.

WHAT ABOUT CONFIDENTIALITY?

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

Your baby’s records may be reviewed by the Ministry of Public Health in your country, the Office of Human Research Protections (OHRP), the NIH, (insert name of site) IRB, Ethics Committee (EC), study staff, and study monitors.

WHAT ARE THE COSTS TO ME?

There is no cost to you for your baby’s study visits, examinations, or blood tests. Taking part in this study may lead to added costs to you and your insurance company. In some cases it is possible that your insurance company will not pay for these costs because your baby is taking part in a research study. You will not receive payment for your baby’s participation in this study. [Note to sites: Modify or delete language regarding insurance as appropriate for your site, and insert appropriate language for added local costs or for reimbursement of time and transportation, if relevant].

WHAT HAPPENS IF MY BABY IS INJURED?

If your baby is injured as a result of being in this study, your baby will be given immediate treatment for your baby’s injuries. The cost for this treatment will be charged to you or your insurance company. [Note to sites: Language related to insurance can be deleted if it is not relevant to your site.] 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.

WHAT ARE MY BABY’S RIGHTS AS A RESEARCH SUBJECT?

Taking part in this study is completely voluntary. You may choose not to allow your baby to take part in this study or leave this study at any time. Your decision will not have any impact on your baby’s participation in other studies conducted by NIH and will not result in any penalty or loss of benefits to which your baby is otherwise entitled.
We will tell you about new information from this or other studies that may affect 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 baby’s rights as a research subject, 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 allow our baby to take part in this study, please sign your name below.

____________________________
Name of Participant

____________________________                ____________________________________
Participant’s Legal Guardian (print)                Legal Guardian’s Signature and Date
(As appropriate)

____________________________
Study Staff Conducting                Study Staff Signature and Date

________________________                        ____________________________________
Witness’ Name (print)                Witness’s Signature and Date