Summary of Changes Included in the Full Protocol Amendment of:

IMPAACT P1092
Phase IV Evaluation of the Steady State Pharmacokinetics of Zidovudine, Lamivudine, and Lopinavir/Ritonavir in Severely Malnourished HIV-1-Infected Children

The Amended Protocol is Identified as:

Version 2.0, dated 11 February 2015

DAIDS ES # 11689

Information/Instructions to Study Sites from the Division of AIDS

The information contained in this protocol amendment impacts the IMPAACT P1092 study, including the study informed consent forms (ICFs), 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 and all required approvals of this amendment must be obtained before initiating this study. Likewise, all participants must provide written informed consent for this study using site-specific informed consent forms that correspond to this amendment.

Upon receiving IRB/EC approval, and approval of any other applicable regulatory entities, study sites must submit an amendment registration packet to the DAIDS Protocol Registration Office (DAIDS PRO) at the Regulatory Support Center (RSC). Sites will receive a registration notification for the amendment after the DAIDS PRO verifies that all required registration documents have been received and are complete. This notification must be received prior to initiation of this study. Because this study was not initiated under protocol Version 1.0, all required approvals for protocol Version 2.0, including registration notification, will be confirmed as part of the study activation process for this study. No site may begin this study until after receipt of a site-specific study activation notice for protocol Version 2.0.

Please file this Summary of Changes, Version 2.0 of the protocol, corresponding site-specific ICFs, all associated IRB/EC and regulatory entity correspondence, and all correspondence with the DAIDS PRO in your essential documents files for IMPAACT P1092.
Summary and Rationale

The main purpose of this amendment is to update protocol specifications for consistency with current (2013) World Health Organization (WHO) guidelines for treatment of HIV-infected children and children with severe acute malnutrition (SAM). These updates are included in Sections A and B of this Summary of Changes document. This amendment also:

- Updates the description of the study population, eligibility criteria, and screening and enrollment process. Given that current guidelines for treatment of HIV-infected children specify initiation of antiretroviral therapy (ART) upon identification of infection, the eligibility criteria are modified to allow for initiation of ART prior to study entry. The protocol title is updated to reflect this change and the study objectives and outcomes are updated to specify timeframes from the date of study entry rather than from the date of initiation of ART. Descriptions of the study entry process are similarly updated. The eligibility criteria are also updated to reflect current IMPAACT policies for documentation of HIV infection and to further clarify the following: minimum age for inclusion; interpretation of normalized electrolytes and stable temperature for inclusion; expectations that severely malnourished children will be in an inpatient rehabilitation unit at the time of enrollment; and descriptions of exclusionary conditions (see Section C).

- Updates specimen collection volumes to reflect elimination of urinalysis as a required study evaluation, to reflect additional safety monitoring evaluations at study Weeks 4 and 8, and to accommodate different volumes required for different HIV-1 RNA PCR assays used across sites (see Section D).

- Updates certain aspects of protocol specifications for toxicity grading, toxicity management, expedited adverse event (EAE) reporting, and monitoring (see Section E).

- Updates certain aspects of protocol specifications for pharmacokinetic evaluations (see Section F).

- Updates the protocol team roster to reflect current membership and references to pharmaceutical support partners; adds information on case report form (CRF) requirements; and incorporates other updates and corrections to enhance the clarity and precision of protocol specifications (Section G).

Implementation

Modifications of protocol text are shown in Sections A-G below, using strikethrough for deletions and bold type for additions. Within each section, modifications are generally shown in order of appearance in the protocol.
A. Updates for consistency with 2013 WHO guidelines for treatment of HIV-infected children


1. In Sections 1, 5, 6 (text and figures), and 9, all original references to stavudine (d4T) are replaced with references to abacavir (ABC).

2. In Section 1.251 (re-numbered as Section 1.261 in amended protocol), Zidovudine (ZDV, Retrovir®), second paragraph, third and fourth sentences:

   The WHO currently recommends **lopinavir/ritonavir plus an NRTI backbone of** either zidovudine or abacavir (ABC) paired with lamivudine as a **the** first line NRTI backbone regimen **for children less than three years of age** paired with a PI for therapy initiation in infants exposed to NVP at birth. Non-NVP exposed infants and older children can pair the NRTI backbone with an NNRTI.

3. In Section 4.1, Inclusion Criterion 4.16 (re-numbered as 4.14 in amended protocol):

   Eligible for HAART: as defined by WHO 2013 pediatric guidelines, described below for infants and children: **ART should be initiated in all children infected with HIV below five years of age, regardless of WHO clinical stage or CD4 cell count.**

   **Initiate ART for all HIV-infected children below 24 months of age irrespective of CD4 count or WHO clinical stage.**

   **Initiate ART for all HIV-infected children between 24 and 59 months of age with CD4 count ≤ 750 cells/mm³ or % CD4 ≤ 25%, whichever is lower, irrespective of WHO clinical stage.**

   **Initiate ART for all HIV-infected children with WHO HIV clinical stages 3 and 4, irrespective of CD4 count.**

4. In Section 5.1, Drug Regimens, Administration and Duration, second paragraph:

   There will only be one regimen **All children will receive the same starting regimen**: a LPV/r-based regimen, with ZDV/3TC as the backbone. The doses will be based on WHO weight band dosing for HAART. **See the At each visit, dosing will be adjusted to the current WHO weight band dose** (see Dosing Table below). The study treatment duration is 48 weeks.

5. In Section 5.1, study-supplied ARV dosing table (re-formatted and updated):

<table>
<thead>
<tr>
<th>Drug</th>
<th>Strength</th>
<th>3.0-5.9 kg</th>
<th>6.0-9.9 kg</th>
<th>10.0-13.9 kg</th>
<th>14.0-19.9 kg</th>
<th>20.0-24.9 kg</th>
</tr>
</thead>
<tbody>
<tr>
<td>ZDV</td>
<td>10 mg/mL</td>
<td>6 mL</td>
<td>9 mL</td>
<td>12 mL</td>
<td>15 mL</td>
<td>18 mL</td>
</tr>
<tr>
<td>3TC</td>
<td>10 mg/mL</td>
<td>3 mL</td>
<td>4 mL</td>
<td>6 mL</td>
<td>8 mL</td>
<td>10 mL</td>
</tr>
<tr>
<td>LPV/r</td>
<td>80/20 mg/mL</td>
<td>1 mL</td>
<td>1.5 mL</td>
<td>2 mL</td>
<td>2.5 mL</td>
<td>3 mL</td>
</tr>
</tbody>
</table>
If a subject vomits within 30 minutes of dosing, he or she should be re-dosed one time to replace the vomited dose. If the vomiting occurs on a day of PK sampling, the sampling may proceed if the subject vomited within 30 minutes of the first dose and can be re-dosed with a full dose that is not subsequently vomited. Otherwise, the PK sampling should occur on the following day.

6. In Section 5.3, Drug Supply, Distribution and Pharmacy:

Zidovudine 10 mg/mL syrup and lamivudine 10 mg/mL oral solution will be supplied by GlaxoSmithKline Viiv Healthcare Ltd. Lopinavir 80 mg/ritonavir 20 mg per milliliter oral solution will be supplied by Abbott Laboratories. Stavudine (d4T) will not be supplied by the study and must be obtained from the subject’s clinical care provider.

Each drug is manufactured by the company that is supplying the drug. Study products will be available through the NIAID Clinical Research Products Management Center (CRPMC). The site pharmacist can obtain the study products for this protocol by following the instructions in the manual Pharmacy Guidelines and Instructions for DAIDS Clinical Trials Networks in the Section Study Product Management Responsibilities.

Abacavir (ABC) will not be supplied by the study and must be obtained from the subject’s clinical care provider; WHO weight band dosing is provided in the tables below. Serious and sometimes fatal hypersensitivity reactions have been associated with ABC containing products. Please refer to the ABC package insert for complete prescribing information.

<table>
<thead>
<tr>
<th>Drug</th>
<th>Strength</th>
<th>Dose Volume by Weight Band for LIQUID Formulation (twice daily)</th>
</tr>
</thead>
<tbody>
<tr>
<td>ABC</td>
<td>20 mg/mL</td>
<td>3 mL</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Drug</th>
<th>Strength</th>
<th>Number of Tablets by Weight Band for DISPERSIBLE TABLET Formulation (twice daily)</th>
</tr>
</thead>
<tbody>
<tr>
<td>ABC</td>
<td>60 mg</td>
<td>1</td>
</tr>
</tbody>
</table>

7. In Section 6.22 (re-numbered as Section 6.32 in amended protocol), Virologic Endpoints:

The following constitutes a virologic endpoint: confirmed plasma HIV-1 RNA level >400 copies/mL at 24 weeks. Virologic criteria must be confirmed before the subject will be considered to have met a virologic endpoint.

Virologic criteria must be confirmed before the subject will be considered to have met a virologic endpoint. Confirmation of the virologic end point will be done within 4 weeks of the previous results. At each scheduled viral load testing time point during follow-up, if an HIV-1 RNA level >400 copies/mL is identified, the subject will be recalled to the clinic within 4 weeks for confirmatory testing.

Subjects who achieve virologic endpoint will be allowed to continue therapy if the subject is clinically stable. If viral load is >5,000 >1000 copies/ml, the site investigator will begin to intensify work intensively with the subject’s family to ensure adherence and if need be effect a change in ARV therapy.
8. In Appendix V, Sample Informed Consent Form for Enrollment, WHAT ARE THE COSTS TO ME?, first paragraph:

There is no cost to you for the study visits, examinations, blood tests or the anti-HIV study drugs, zidovudine, lamivudine or lopinavir/ritonavir your child is required to take. If your doctor needs to switch your child to another anti-HIV medication, such as stavudine abacavir, there may be a cost to you as this drug is not provided by the study. [Note to sites: This statement can be modified as needed for your site.]

**B. Updates for consistency with 2013 WHO guidelines for treatment of SAM**

http://www.who.int/nutrition/publications/guidelines/updates_management_SAM_infantandchildren/en/

1. In Section 1.11, Severe Acute Malnutrition (SAM), first paragraph, fourth sentence:

Severe acute malnutrition (SAM) **in children age 6-59 months** is defined anthropometrically by the World Health Organization (WHO) (2013) as a weight for height ≤ -3 SD below the mean or ≤ 70% below the median less than -3 Z score using the WHO growth charts standards, or a mid-upper arm circumference (MUAC) ≤ 11 cm in children age 6–60 months less than 115 mm (11.5 cm), or any degree of bilateral edema.

2. In Section 3.1, Stage 1: Pre-Entry/Screening, Cohort 1: Severely malnourished children, first paragraph:

Severe acute malnutrition (SAM) **in children age 6-59 months** is defined by WHO (2013) as a weight-for-height ≤ -3 SD below the mean or ≤ 70% below the median less than -3 Z score using the WHO growth charts standards, or a mid-upper arm circumference (MUAC) ≤ 11 cm in children age 6–60 months less than 115 mm (11.5 cm), or any degree of bilateral edema in children age 1–5 years.

Sites will identify severely malnourished children admitted to the nutrition rehabilitation unit; however, children with edematous malnutrition will not be included in this study. All sites will manage these children will be managed according to WHO (2013) guidelines on managing children with severe malnutrition.

3. In Section 3.1, Nutritional Rehabilitation:

**Third paragraph**

Children with SAM should also receive may also require vitamin A, zinc, and antibiotics; all study sites will follow WHO guidelines related to provision of these therapies. Also consistent with WHO guidelines, SAM children with diarrhea should be managed with a low osmolarity oral rehydration solution (ReSoMal), fluid management will depend on the extent of dehydration, whether the child is in shock, and whether the child has cholera or profuse watery diarrhea.

**Fifth paragraph, first sentence**

If children survive the immediate rehabilitation stabilization phase, the focus of care and management is to initiate and sustain catch up growth.
Sixth paragraph
Increase in appetite is one of the most important signs indicating that the child is entering the rehabilitation phase. In HIV uninfected children this usually takes about one week following admission and appropriate management of sepsis and electrolyte disturbances. Once HIV uninfected children are stabilized and have appetite and edema has resolved (in children with kwashiorkor) and starting to gain weight, children, they are ready to move into the rehabilitation phase, and should be are transitioned from F75 to and are given another milk formulation called F100 or an equivalent but non-milk therapeutic food called Ready-to-Use Therapeutic Feed (RUTF). The transition should occur over 2-3 days as tolerated and the recommended energy intake during this period is 100-135 kcal/kg/day.

Fourth bullet point following sixth paragraph
Expected daily weight gain of HIV uninfected children in recovery rehabilitation phase of Severe Acute Malnutrition:

Seventh paragraph
HIV-infected children with SAM should be managed with the same therapeutic feeding approaches as children who are HIV-uninfected. Children with HIV infection will be managed in a similar way namely to treat intercurrent infections, correct electrolyte abnormalities, prevent complications and start feeds. Children will be started on F75 as for HIV uninfected children and also transition to either F100 or RUTF. However, while resolution of clinical signs such as edema and anorexia are similarly expected, early weight recovery may not be as significant as for HIV uninfected children.

Eighth paragraph
Discharge criteria:
For children without HIV, Readiness for discharge from hospital is usually indicated by reaching a weight for height > 85% should be based on the anthropometric indicator that was used to identify SAM when the child was admitted:

- If SAM was identified based on weight-for-height, discharge should be considered when the Z score is ≥-2 and the child has had no edema for at least two weeks
- If SAM was identified based on mid-upper arm circumference, discharge should be considered when mid-upper arm circumference is ≥125 mm (12.5 cm) and the child has had no edema for at least two weeks

4. In Section 3.1, Stage 1: Pre-Entry/Screening, Cohort 2: Normal nutrition-mild malnutrition children, first paragraph:

HIV-infected children with normal nutrition–mild malnutrition as defined by:

Normal nutrition = WHZ score > -1 SD
Mild malnutrition = WHZ score > -2 SD ≤ -1 SD
5. In Section 4.1, Inclusion Criterion 4.13:

Meets WHO classification for severe malnutrition (non-edematous), and normal nutrition status, or and mild malnutrition as described below:

- Severe non-edematous malnutrition defined as weight for height z (WHZ) score ≤ -3 SD < -3 or MUAC < 115 mm
- Normal nutrition status defined as weight for height z (WHZ) score > -1 SD
- Mild malnutrition defined as weight for height z (WHZ) score > -2 SD ≤ -1 SD

6. In Appendix II, World Health Organization Approach to the Management of Severe Acute Malnutrition, modifications are incorporated consistent with items B.1 through B.4 above.

C. Updates of study population description, eligibility criteria, and screening and enrollment process

1. In the protocol title:

Phase IV Evaluation of the Steady State Pharmacokinetics of Zidovudine, Lamivudine, and Lopinavir/Ritonavir in Severely Malnourished HIV-1-Infected Antiretroviral Naïve Children Who Are Initiating HAART

2. In the Schema; Section 2, Study Objectives; Section 8.2, Study Outcomes; and Section 9.1, Pharmacology Objectives:

All original references to weeks following initiation of HAART are replaced with references to weeks following study entry.

3. In the Schema, Sample Size and Population:

50 (25 per cohort) to achieve 34 evaluable (17 per cohort)

Cohort 1: HIV-1-infected, antiretroviral naïve children ages ≥ 6 to ≤ 36 months ≥ 6 months to (≥ 180 days) < 36 months with severe malnutrition

Cohort 2: HIV-1-infected, antiretroviral naïve children ages ≥ 6 to ≤ 36 months ≥ 6 months (≥ 180 days) to < 36 months with normal nutrition-mild malnutrition

4. In Section 3.0, Study Design, first paragraph:

This is a Phase IV open label study to evaluate the pharmacokinetics (PK), safety, and tolerability of ZDV, 3TC, and LPV/r syrup in HIV-1-infected, ARV naïve infants and children aged 6-36 ≥ 6 months (≥ 180 days) to < 36 months with severe malnutrition and with normal nutrition-mild malnutrition. Two cohorts of children will be enrolled in the study: Cohort 1: 25 HIV-1-infected children who are severely malnourished and are eligible for HAART as defined by the WHO pediatric algorithm and Cohort 2: a control group of 25 HIV-1-infected children with normal nutrition-mild malnutrition who are also eligible for HAART. Children with severe malnutrition will undergo an approximate two week nutrition rehabilitation program before entering the study.
5. In Section 3.1, Stage 1: Pre-Entry/Screening, Cohort 1, last paragraph (deleted and replaced with text for Cohorts 1 and 2 per item C.7 below):

Seventy-two hours to 10 days after the day of admission to the nutrition rehabilitation unit, caregivers of the children identified as HIV infected will be told about the study and asked to allow their child to enroll. If consent is given, the caregiver will be asked to sign the screening consent form and bring the child to the clinic for a screening test to see if the child qualifies for the study. All screened children will be monitored and regularly evaluated for stabilization by hospital staff and caregivers of those found eligible for the study will be asked to sign a separate consent prior to study entry (enrollment to Stage 2).

6. In Section 3.1, Stage 1: Pre-Entry/Screening, Cohort 2, last paragraph (deleted and replaced with text for Cohorts 1 and 2 per item C.7 below):

Caregivers will be told about the study and asked to allow their child to enroll. If consent is given, the caregiver will be asked to sign the screening consent form and bring the child to the clinic for a screening test to see if the child qualifies for the study. If the child is eligible for the study the caregiver will be asked to sign a separate consent form prior to study entry (enrollment).

7. In Section 3.1, Stage 1: Pre-Entry/Screening, Cohort 1 and Cohort 2, added:

**Cohort 1 and Cohort 2**

Sites will identify severely malnourished children admitted to the nutrition rehabilitation unit and will identify children with normal nutrition or mild malnutrition from HIV treatment centers. For both cohorts, when a potentially eligible child is identified, the child’s parent or legal guardian will be informed about the study and asked to provide written informed consent for the child to be screened for eligibility. If informed consent is provided, the child will be assigned a participant identification number (PID) and a study-specific screening number will be obtained through the DMC Subject Enrollment System (SES). After informed consent is obtained, screening evaluations will be performed. Screening evaluations may be repeated during the screening period at the discretion of the site investigator, with the latest value used for eligibility determination. For children found to be eligible, the parent or legal guardian will be asked to provide written informed consent for study participation (refer to Section 3.2 for more information about the study enrollment process). For children found to be ineligible, or who do not enroll in the study for any reason, a CRF will be completed to record the screening outcome. Children who are not enrolled will be referred to the nutritional rehabilitation unit and/or non-study HIV treatment programs for ongoing care and treatment as needed.

8. In Section 3.2, Stage 2: Entry, first paragraph:

Stage 2 begins with the study entry visit and the initiation of the study HAART regimen. HAART may be initiated up to 3 days from date of enrollment.
9. In Section 3.2, Stage 2: Entry, Criteria for Stage 2 Entry, Cohort 1, first and second paragraphs (now combined in amended protocol):

For children with severe malnutrition who are found to be eligible, the entry visit will be conducted between entry into the study will occur after informed consent for study participation has been obtained and within 10-18 days after the day of admission to the nutritional rehabilitation unit. Before these severely malnourished children can advance to Stage 2, they must be judged by their clinician to have improved clinically and be eligible to begin the study HAART regimen. Clinical improvement is indicated by:

10. In Section 3.2, Stage 2: Entry, Criteria for Stage 2 Entry, Cohort 1, fourth bullet point, AND Entry, Cohort 2, first bullet point:

Normalized electrolytes (sodium and potassium) defined as severity grade 1 or lower.

11. In Section 3.2, Stage 2: Entry, Criteria for Stage 2 Entry, Cohort 1, sixth bullet point, AND Entry, Cohort 2, third bullet point:

No hypothermia or pyrexia - temperature stable at >35.0 to <38.0°C (non-axillary) or >34.4 to <37.4°C (axillary) Temperature stable - no hypothermia (≤35°C) or pyrexia (≥37.8°C)

12. In Section 3.2, Stage 2: Entry, Criteria for Stage 2 Entry, Cohort 1, last paragraph:

Children who are screened out, fail to show improvement after 10–18 days or choose not to enroll, will be referred back to the nutrition rehabilitation units under the national programs for follow up. They will also be referred to care programs for initiation of HAART.

13. In Section 3.2, Stage 2: Entry, Criteria for Stage 2 Entry, Cohort 2, first and second paragraphs (now combined in amended protocol):

For children with normal nutrition-mild malnutrition who are found to be eligible, entry into the study will occur after informed consent has been obtained and will be enrolled from HIV treatment centers and have the entry visit within 7-14 days from after screening. Before these children can advance to Stage 2, they must be judged by their clinician to be clinically stable and eligible to begin the study HAART regimen. Clinical stability will be indicated by:

14. In Section 3.2, Stage 2: Entry, Other Requirements for Cohort 1 and Cohort 2, added:

**Other Requirements for Cohort 1 and Cohort 2**

For children in both cohorts, entry evaluations are expected to be performed on the day of enrollment into the study, with enrollment defined as successful entry of required eligibility data into the SES. Successful entry into the SES will generate a study identification number (SID) and prescribing information for the study HAART regimen. The study HAART regimen should be initiated on the day of enrollment; however, if necessary, initiation of the study HAART regimen may be deferred up to 72 hours after enrollment. The P1092 Core Team should be notified of all instances in which the study HAART regimen is not initiated on the day of enrollment.
All eligible and enrolled children will initiate the study HAART regimen with doses prescribed based on weight bands. After HAART initiation, all severely malnourished children will remain inpatients until they stabilize on the ARVs.

At specified time points during the study, trough and intensive PK sampling will be performed, nutritional assessment, adherence assessment and adverse event monitoring will be carried out.

15. In Section 4.1, Inclusion Criterion 4.11:

Age ≥6 to <36 months (defined as ≥180 days) to <36 months at entry

16. In Section 4.1, Inclusion Criterion 4.12:

Documentation of HIV-1 infection defined as positive results from two samples collected at different time points. The same method may be used at both time points. All samples tested must be whole blood, serum or plasma using methods approved by the IMPAACT Laboratory Center.

Acceptable tests when subjects are ≤18 months of age
The first test may be any of the following:
• One HIV DNA PCR
• One HIV RNA (quantitative >5,000 copies/mL or qualitative)
• One HIV culture (prior to August 2009)
• One total HIV nucleic acid

If the first test(s) is positive, a second sample collected and tested using any of the tests listed above (except for qualitative RNA assays) in a laboratory participating in an appropriate external quality assurance program and NIH approved.

Acceptable tests when subjects are >18 months of age
The first test may be any of the following:
• Two rapid antibody tests from different manufacturers or based on different principles and epitopes
• One rapid antibody test AND one [enzyme immunoassay (EIA) OR Western blot (WB) OR immunofluorescence OR chemiluminescence]
• One EIA AND one [WB OR immunofluorescence OR chemiluminescence]
• One HIV DNA PCR
• One HIV RNA (quantitative >5,000 copies/mL or qualitative)
• One HIV culture (prior to August 2009)
• One total HIV nucleic acid

If the first test(s) is positive, a second sample collected and tested using any of the tests listed above (except for qualitative RNA assays) a laboratory participating in an appropriate external quality assurance program and either CAP/CLIA approved (for US laboratories) or NIH approved (for international laboratories).
For subjects less than 2 years of age or have not ceased breastfeeding for at least 4 weeks, Sample #1 and Sample #2 may be tested using any of the following:

- One HIV DNA PCR
- One quantitative HIV RNA PCR (above the limit of detection)
- One qualitative HIV RNA PCR
- One total HIV nucleic acid test

For these subjects, at least one of the two samples must be tested in the study site’s designated VQA-certified laboratory. For tests performed in other (non-VQA-certified) settings, adequate source documentation, including the date of specimen collection, date of testing, test performed, and test result, must be available.

For subjects 2 years of age and older who have ceased breastfeeding for at least 4 weeks, Sample #1 may be tested using any of the following:

- Two rapid antibody tests from different manufacturers or based on different principles and epitopes
- One EIA or Western Blot OR immunofluorescence OR chemiluminescence
- One HIV DNA PCR
- One quantitative HIV RNA PCR (above the limit of detection)
- One qualitative HIV RNA PCR
- One total HIV nucleic acid test

For subjects 2 years of age and older who have ceased breastfeeding for at least 4 weeks, Sample #2 may be tested using any of the following:

- Rapid antibody test. If this option is used in combination with two rapid tests for Sample #1, at least one of the three rapid tests must be FDA-approved and the third rapid test must be from a third manufacturer or based on a third principle or epitope.
- One EIA OR Western Blot OR immunofluorescence OR chemiluminescence
- One HIV DNA PCR
- One quantitative HIV RNA PCR (above the limit of detection)
- One qualitative HIV RNA PCR
- One total HIV nucleic acid test

For these subjects, if both samples are tested using antibody tests, at least one of the samples should be tested in a laboratory that operates according to GCLP guidelines and participates in an appropriate external quality assurance program. If nucleic acid testing is used, at least one test must be performed in the study site’s designated VQA-certified laboratory. For tests performed in other (non-VQA-certified or non-GCLP-compliant) settings, adequate source documentation, including the date of specimen collection, date of testing, test performed, and test result, must be available.

Note: HIV RNA PCR is a required screening evaluation that must be performed in a VQA-certified laboratory (refer to Appendix I). Assuming the result of this test is above the limit of detection of the assay, this test may serve as one of the two tests required for documentation of HIV infection.
17. In Section 4.1, Inclusion Criterion 4.14 (deleted):

Antiretroviral naïve except for ARVs used for prevention of mother-to-child transmission of HIV

18. In Section 4.1, Inclusion Criterion 4.15 (deleted; see Exclusion Criterion 4.25 in item C.27 below):

Children with acute serious infection must have been stabilized by at least five days on antimicrobials.

19. In Section 4.1, Inclusion Criterion 4.16, added:

Qualifying laboratory values obtained from specimens collected within the study-specific screening period:

Hematology testing indicates
- Hemoglobin ≤ Grade 2
- White blood cells ≤ Grade 2
- Neutrophils (absolute count) ≤ Grade 2
- Platelets ≤ Grade 1

Chemistry testing indicates
- AST ≤ Grade 2
- ALT ≤ Grade 2
- Creatinine ≤ Grade 1
- Sodium ≤ Grade 1
- Potassium ≤ Grade 1
- Bicarbonate ≤ Grade 1

20. In Section 4.1, Inclusion Criterion 4.18 (re-numbered as 4.17 in amended protocol):

For severely malnourished children: **An inpatient in a nutrition rehabilitation unit.** Clinical improvement after 10-18 days on nutrition rehabilitation defined as: Appetite returned and eating better - child shows interest in food even if does not complete amount given:

- No further weight loss  
  Weight gain of about 3.5gm/kg body weight/day for 1-2 days
- Normalized electrolytes (sodium and potassium) **defined as severity grade 1 or lower**
- No evidence of cardiac failure
- Loss of apathy and starting to play
- No hypothermia or pyrexia - temperature stable at >35.0 to <38.0°C (non-axillary) or >34.4 to <37.4°C (axillary) Temperature stable - no hypothermia or pyrexia

For children with normal – mild malnutrition, clinical stability will be indicated by:

- Good appetite
- Normalized electrolytes (sodium and potassium) **defined as severity grade 1 or lower**
- No hypothermia or pyrexia - temperature stable at >35.0 to <38.0°C (non-axillary) or >34.4 to <37.4°C (axillary) Temperature stable - no hypothermia (<35°C) or pyrexia (>37.8°C)
21. In Section 4.1, Inclusion Criterion 4.19 (deleted):

An inpatient in the nutrition rehabilitation unit

22. In Section 4.2, Exclusion Criterion 4.21:

Children with edematous malnutrition at the time of study entry

23. In Section 4.1, Inclusion Criterion 4.22 (deleted):

The following laboratory values within 30 days prior to entry:

- Any ≥ Grade 2 toxicity (except hemoglobin)
- Hemoglobin <7.5g/dL

24. In Section 4.2, Exclusion Criterion 4.23 (re-numbered as 4.22 in amended protocol):

≥ Grade 3 respiratory distress or presence of cardio respiratory compromise within 3 days of prior to entry

25. In Section 4.2, Exclusion Criterion 4.24 (re-numbered as 4.23 in amended protocol):

Chemotherapy for active malignancy

26. In Section 4.2, Exclusion Criterion 4.25 (re-numbered as 4.24 in amended protocol):

Children with an acute OI and on acute infection for which the child has received appropriate antimicrobial treatment for <5 days

27. In Section 4.2, Exclusion Criterion 4.26 (re-numbered as 4.25 in amended protocol):

Active Tuberculosis disease

28. In Section 4.2, Exclusion Criterion 4.27 (re-numbered as 4.26 in amended protocol):

Evidence of hepatitis demonstrated by either positive hepatitis B surface antigen or clinical hepatitis as evidenced by jaundice and hepatomegaly

29. In Section 4.4, Enrollment Procedures, sixth paragraph:

Written informed consent for study participation must be obtained before any study related procedures are performed. Informed consent will first be obtained for screening (prior to performing any study-specific screening procedures); for children found to be eligible, informed consent for study participation will be obtained separately (prior to performing any on-study procedures).

Minimum age at enrollment is six months (180 days). However, consent and screening evaluations may be performed up to 30-14 days (for children with normal nutrition to mild malnutrition) or 10-18 days (for children with severe malnutrition) prior to the six months (180 days) of age birthday, as long as the entry visit does not occur earlier than six months (180 days) of age.
Refer to Sections 3.1 and 3.2 for additional information on use of the DMC Subject Enrollment System (SES) for this study.

30. In Section 8.3, Randomization and Stratification, second sentence:

**Eligible** HIV-infected severely malnourished children and HIV-infected children with normal nutritional status–mild malnutrition will be enrolled into this study.

31. In Appendix I, Schedule of Evaluations (SoE), headings are added for Stage 1 and Stage 2; an indicator (X) is added for informed consent at Entry; a new row is added for Documentation of HIV Infection; footnote 1 is updated to clarify expectations for performing HIV testing; footnote 2 is updated to clarify the timing of study entry/enrollment and initiation of the study HAART regimen; footnote 3 is updated to clarify expectations for documenting use of ARVs and concomitant medications; and footnote 7 is updated to include testing of sodium and potassium levels.

32. In Appendix IV, Sample Informed Consent for Screening, WHAT WILL HAPPEN IF YOU AGREE TO HAVE YOUR CHILD SCREENED?, first paragraph:

If you are interested in allowing your child to join this research study, we will first do some screening tests to see if your child is eligible. **If requested by the study doctor, some screening tests may be performed more than once.**

33. In Appendix V, Sample Informed Consent for Enrollment, INTRODUCTION, first paragraph, first sentence:

You are being asked to allow your child to take part in this research study because your child is infected with Human Immunodeficiency Virus (HIV), the virus that causes AIDS (Acquired Immunodeficiency Syndrome) and you agreed to allow your child participate in the screening tests for this study and the screening tests show that your child is eligible for the able to join this study.

34. In Appendix V, Sample Informed Consent for Enrollment, WHAT DOES MY CHILD HAVE TO DO IF HE/SHE IS IN THIS STUDY?, Before the Study Starts and Entry Visit, first paragraph:

**Before the Study Starts:**
If your child is severely malnourished, your child must be eating better, showing an interest in food, gaining weight and able to start taking anti-HIV medications before your child can be in this study.

**If you agree to allow your child to take part in this study, we will first need to confirm that your child is eligible. For example, if your child is severely malnourished, he or she must be eating better, showing an interest in food, and gaining weight. Your child also must be able to start taking the anti-HIV medications given by the study before he or she can be in the study.**

**Entry Visit:**
If your child is eligible eating well and has not started taking anti-HIV medications, you will be asked to bring your child to the clinic for an entry visit. **If your child is hospitalized, the entry visit may be done in the hospital.** The following tests will be done:

35. In Appendix V, Sample Informed Consent for Enrollment, HOW LONG WILL MY CHILD BE IN THIS STUDY?:

Your child will be in this study for about 48 weeks after your child starts to take anti-HIV medication.
D. Updates of specimen collection volumes

1. In Appendix I, SoE, urinalysis is removed; blood draw volumes are added for hematology and chemistries at Weeks 4 and 8; blood draw volumes for HIV-1 RNA are updated to 1-3 mL; total blood draw volumes are updated; and a note is added below the numbered footnotes to confirm that NIH recommendations for maximum pediatric blood draw volumes will be followed in this study.

2. In Appendix IV, Sample Informed Consent for Screening, WHAT WILL HAPPEN IF YOU AGREE TO HAVE YOUR CHILD SCREENED?, fourth bullet point:

   - We will take a urine sample and draw 5-10 mL (1-2 one teaspoons) of blood for HIV testing and other routine tests. [Note to sites: add locally relevant description of blood volume]

3. In Appendix IV, Sample Informed Consent for Screening, WHAT ARE THE COSTS TO ME?:

   The screening tests (physical examination, blood and urine tests) will be done free of charge at no cost to you but you will not receive any payment for having the screening tests done on your child.

4. In Appendix V, Sample Informed Consent for Enrollment, WHAT DOES MY CHILD HAVE TO DO IF HE/SHE IS IN THIS STUDY?:

   Entry Visit, fourth bullet point
   - We take a urine sample and will draw 6-8 mL (about 1-2 teaspoons) of blood for routine tests and to check the amount of HIV in your child’s blood. [Note to sites: add locally relevant description of blood volume]

   On Study Visits, fifth bullet point:
   - We will draw blood for routine tests and to check how well your child’s immune system is working and the amount of HIV in your child’s blood. If the amount of HIV in your child’s blood is higher than expected, we will ask you to bring your child back to the clinic within 2-4 weeks for another test to confirm this result.

   On Study Visits, ninth bullet point
   - The total amount of blood drawn at the different study visits will vary from 1-3 2.3 mL to 12 14 mL (less than one teaspoon to 2 3 teaspoons) depending on the type of test and how much your child weighs. [Note to sites: add locally relevant description of blood volume]

   On Study Visits, last sentence (in paragraph below bullet points)
   The total amount of blood drawn at this visit will be 7-9 mL (about 1-5 less than 2 teaspoons). [Note to sites: add locally relevant description of blood volume]
E. Updates related to toxicity management, EAE reporting, and monitoring

1. In Section 6, a new subsection heading (Section 6.1) has been added for Team Communications, and all other subsections have been re-numbered:

6.1 Team Communications

Questions concerning clinical management of study subjects and all communication regarding adverse experiences should be addressed to the P1092 Core Team at impaact.corep1092@fstrf.org. Please include the subject’s PID when applicable. The appropriate team member will respond via e-mail, generally within 24 hours (Monday-Friday). actg.corep1092@fstrf.org. All other protocol-related communication should be addressed to the P1092 Protocol Team at actg.teamp1092@fstrf.org.

2. In Section 6.1 (re-numbered as Section 6.2 in amended protocol), Toxicity Management, first four paragraphs:

The Division of AIDS Table for Grading the Severity of Adult and Pediatric Adverse Events, (DAIDS AE Grading Table), Version 1.0, dated December 2004, Clarification August 2009 Version 2.0, dated November 2014, must be used for screening eligibility and for grading all adverse events, and is available on the RSC website (http://rsc.tech-res.com/safetyandpharmacovigilance/). The only exception to this requirement pertains to axillary-measured fever, which will be graded as follows:

Grade 1: 37.4 to < 38.0° C
Grade 2: 38.0 to < 38.7° C
Grade 3: 38.7 to < 39.4° C
Grade 4: ≥ 39.4° C

Management of AEs adverse experiences will be according to the best clinical practice and the judgment of the site investigator. Alternate explanations for clinical and laboratory abnormalities must be sought. Laboratory normals will be the institutional values. Abnormal clinical and laboratory findings should be followed until resolution to < Grade 2. For all grade 3 and 4 laboratory values, sites should attempt to repeat the test within 3 days and should notify the Core Team for exceptions (longer period of time needed) up to 7 days.

The toxicity management guidelines are for AEs events for which a relationship to study drugs cannot be excluded. Clinical or laboratory adverse events (AEs) that are definitely unrelated to study drug(s) may not result in study drug interruption.

Study drug doses will not be modified for toxicity; drugs will either be continued at protocol-specified doses or discontinued/replaced. Exceptions are for hematologic toxicity on a ZDV-inclusive regimen and ZDV intolerance (Section 6.12). The site investigator or designee must notify the core P1092 Core Team (actg.corep1092@fstrf.org). For hematologic toxicity on a ZDV-inclusive regimen and ZDV intolerance (Section 6.22), the site investigator or designee must notify the Core Team in the following situations:
ZDV may be replaced with ABC by d4T at the discretion of the site investigator/clinician in cases of ≥ Grade 3 hematologic toxicity on a ZDV-inclusive regimen or ZDV intolerance. Refer to Section 6.22. Notify Core Team within 3 business days. If ZDV is replaced with d4T, notify the protocol team within 5 working days.

| Grade 4 adverse events that are definitely not related to study drugs | Provide Notify Core Team with and provide management plan within 3 business days. |
| Study drug related Grade 4 adverse events | ZDV should be replaced with ABC. Notify Core Team and provide management plan within 3 business days. |

3. In Section 6.11 (re-numbered as Section 6.21 in amended protocol), Grade 3 and Grade 4 Toxicity:

**Grade 3 Toxicity:**

**Notify the Core Team within 3 business days.** Study drugs can be continued at the discretion of the site investigator/clinician for clinical events, or while awaiting a repeat assessment/confirmation of an abnormal laboratory test as soon as possible (at most within one week) except for hepatotoxicities (for Grade 3 hepatotoxicities, study drugs should be held as specified in Section 6.23 below). If repeat assessment confirms Grade 3 toxicity, hold all study drugs and follow abnormal laboratory values weekly. If toxicity resolves to ≤ Grade 2 within 14 days, all study drugs can be restarted. If Grade 3 toxicity persists for ≥14 days, or recurs to ≥ Grade 3 after reintroduction of study drugs, all study drugs must be permanently discontinued. **Alternatively, if the toxicity is clearly attributed to an individual study drug, that study drug may be permanently discontinued and replaced, with continuation of other drugs in the regimen.**

**Grade 4 Non-Life-Threatening Toxicity:**

All study drugs should be held and the Core Team should be notified within 3 business days. For abnormal laboratory test, repeat assessment/confirmation should be done as soon as possible (at most within 1 week). If repeat assessment confirms Grade 4 toxicity, all study drugs should be permanently discontinued. If repeat assessment shows Grade 3 toxicity, continue to hold all study drugs and follow abnormal laboratory values weekly. If toxicity resolves to ≤ Grade 2 within 14 days, all study drugs can be restarted after approval from the Core Team protocol team. If ≥ Grade 3 toxicity recurs after reintroduction of study drugs, all study drugs must be permanently discontinued.

**Grade 4 Life-Threatening Toxicity:**

All study drugs should be permanently discontinued and the Core Team should be notified within 3 business days.

4. In Section 6.12 (re-numbered as Section 6.22 in amended protocol), Hematologic Toxicity on a ZDV-Inclusive Regimen and ZDV Intolerance, Grade 3 Hematologic Toxicity, first and second paragraphs:

For Grade 3 hematologic toxicity — involving hemoglobin level, white blood cell count, absolute neutrophil count, or platelet count — on a ZDV-inclusive regimen, defined as:

- Hgb <7.5 g/dL;
- WBC <1,500/mm³;
- ANC <750/mm³;
- Platelets <50,000/mm³;
continue study drugs at the discretion of the site investigator/clinician while awaiting a repeat assessment/confirmation of the abnormal laboratory test as soon as possible (at most within 1 week). **Notify the Core Team within 3 business days.** If repeat assessment confirms Grade 3 toxicity, the site investigator/clinician may replace ZDV with ABC and restart study drugs at this point (if held). Notify the P1092 Core Team of the replacement within 5 days. **[paragraph continues]**

5. In Section 6.12 (re-numbered as Section 6.22 in amended protocol), Hematologic Toxicity on a ZDV-Inclusive Regimen and ZDV Intolerance, Grade 4 Hematologic Toxicity, first and second paragraphs:

For Grade 4 hematologic toxicity — **involving hemoglobin level, white blood cell count, absolute neutrophil count, or platelet count** — on a ZDV-inclusive regimen, defined as

- Hgb <6.5 g/dL;
- WBC <1,000/mm$^3$;
- ANC <500/mm$^3$;
- Platelets <25,000/mm$^3$;

ZDV should be discontinued and substituted with d4T ABC. **Notify the Core Team within 3 business days.** core P1092 Protocol Team of the replacement. **[paragraph continues]**

6. In Section 6.12 (re-numbered as Section 6.22 in amended protocol), Hematologic Toxicity on a ZDV-Inclusive Regimen and ZDV Intolerance, Grade 3 and Grade 4 management flow charts are replaced.

7. In Section 6.131 (re-numbered as Section 6.231 in amended protocol), Clinical (Symptomatic) Hepatitis:

Subjects taking study drug should be monitored for the development of a clinical hepatitis syndrome. Symptoms of hepatitis include the following: fatigue, malaise, anorexia, nausea, acholic stools, bilirubinuria, jaundice, liver tenderness, or hepatomegaly. Subjects with signs and symptoms suggestive of clinical hepatitis must seek medical attention immediately and have liver function tests (LFTs) and screening for hepatitis A and B performed. **Clinical hepatitis should be considered in subjects who have signs and symptoms of hepatitis even if LFTs are normal or alternative diagnoses are possible.** Subjects who develop clinical hepatitis will be screened for hepatitis A and B. Management of hepatitis will be managed according to grading of AST/ALT stipulated below.

8. In Section 6.132 (re-numbered as Section 6.232 in amended protocol), AST/ALT Elevations, first paragraph, added:

**If AST and ALT are of different severity grades, follow the management guidance for the higher of the two grades.**

9. In Section 6.132 (re-numbered as Section 6.232 in amended protocol), AST/ALT Elevations, Grade 1, text added before bullet points:

**If grade 1 at entry, no additional evaluation is required; if normal at entry, follow guidance in this section:**
10. In Section 6.132 (re-numbered as Section 6.232 in amended protocol), AST/ALT Elevations, Grade 2, text added before bullet points:

   If grade 2 at entry, no additional evaluation is required; if normal or Grade 1 at entry, follow guidance in this section:

11. In Section 6.132 (re-numbered as Section 6.232 in amended protocol), AST/ALT Elevations, Grades 3 and 4, second and third bullet points:

   • AST/ALT should be repeated as soon as possible (at most within 7 days) and then be followed weekly until levels are \( \leq \) Grade 1. Other LFTs also may be performed at the discretion of the site investigator if considered useful for diagnostic or clinical management purposes.
   • Notify the P1092 Core Team of Grades 3 or 4 asymptomatic hepatic toxicity within 3 business days.

12. In new Section 6.14 (re-numbered as Section 6.24 in amended protocol), Rash, added:

   **Grade 1 or 2, on Abacavir**
   Study drugs may need to be held depending on rash distribution and relatedness assessment.
   • If the rash is generalized and there is no specific alternative explanation for the rash:
     – Hold entire regimen,
     – Test ALT within 3 business days, and
     – Evaluate for symptoms of clinical hepatitis and hypersensitivity reaction.
   If any clinical symptoms of hepatitis or ALT elevation or hypersensitivity reaction, permanently discontinue abacavir and consult with the P1092 Core Team on alternative ARV regimens.
   • If the rash is not generalized or if there is a specific alternative explanation for the rash (e.g., varicella), study drugs — including abacavir — may be continued with no additional evaluation required.

   **Grade 1 or 2, Not on Abacavir**
   • Continue study drugs.
   • Rash may be treated symptomatically, but should be monitored closely by the site investigator.

   **Grade 3**
   • Hold entire regimen unless the rash is determined to be unrelated to study drug
   • Notify the Core Team within 3 business days.
   • If there is no specific alternative explanation for the rash (e.g., varicella), test ALT and manage per the ALT/AST guidelines in Section 6.23.
   • If on abacavir, permanently discontinue abacavir. When the rash resolves, study drug may be resumed with an alternate regimen that does not include abacavir; consult with the P1092 Core Team on alternative regimens.

   **Grade 4**
   • Hold entire regimen.
   • Notify and consult with the Core Team on alternative ARV regimens within 3 business days.

   Note: Abacavir should never be restarted following a hypersensitivity reaction.
13. In Section 6.24 (re-numbered as Section 6.4 in amended protocol), Criteria for Treatment Discontinuation, last two sentences, added:

Subjects who permanently discontinue all study drugs will remain in follow-up for the protocol-specified duration, however evaluations will be performed per the Off treatment/On study column of the Schedule of Evaluations. For these subjects, the site investigator/clinician may choose to continue the child on non-study HAART based on local treatment standards and the best interest of the child.

14. In Section 7.1, Adverse Event Reporting to DAIDS, third paragraph:

Where DAERS has not been implemented, sites will submit expedited AEs by documenting the information on the current DAIDS EAE Form. This form is available on the RSC website: http://rsc.tech-res.com/safetyandpharmacovigilance/. For questions about EAE reporting, please contact the RSC (DAIDSRSCSafetyOffice@tech-res.com or call 1-800-537-9979 or 301-897-1709 or fax 1-800-275-7619 or 301-897-1710).

15. In Section 7.2, Reporting Requirements for This Study, second and third paragraphs:

The study agents for which relationship assessments are required are zidovudine, lamivudine, and lopinavir/ritonavir. In addition, for subjects who may receive abacavir due to intolerance to zidovudine, relationship should also be assessed for abacavir.

In addition to reporting all SAE’s as defined above, other events that sites must report in an expedited fashion include all malignancies, seizures, and Grade 3 and 4 hepatotoxicities whether or not symptomatic or related to study drug, and all other Grade 3 or 4 related toxicities for which a relationship to study drug cannot be ruled out.

16. In Section 7.3, Grading Severity of Events:

The Division of AIDS Table for Grading the Severity of Adult and Pediatric Adverse Events (DAIDS AE Grading Table) Version 1.0, December 2004, Clarification August 2009 Version 2.0, dated November 2014, must be used and is available on the RSC website at http://rsc.tech-res.com/safetyandpharmacovigilance/

17. In Section 8.5, Monitoring:

Site investigators are responsible for close safety monitoring of all study participants, reporting of safety information at the participant level, and alerting the Core Team if unexpected concerns arise. Site investigators are also responsible for safety-related communications with their IRBs/ECs, per IRB/EC policies and procedures.

Site monitors under contract to the NIAID or NICHD may visit participating clinical research sites to review the individual participant records including consent forms, CRFs, supporting data, laboratory specimen records, and medical records (physicians’ progress notes, nurses’ notes, individuals’ hospital charts), to ensure protection of study participants, compliance with the protocol and accuracy and completeness of records. The monitors also will inspect sites’ regulatory files to ensure that regulatory requirements are being followed. The site investigator will make study documents readily available for inspection by the local IRB, site monitors, NIAID, NICHD, and the Office for Human Research Protections (OHRP).
It is the responsibility of the protocol team to interpret safety data, and make decisions regarding serious adverse events that are needed to protect subjects from undue risk. The safety and tolerability of the study agent will be monitored by means of adverse events reports and toxicity reports summarizing laboratory and clinical events. It is required that the data required for the toxicity reports be entered into the database within 48 hours of the time at which the results of the laboratory tests or clinical examinations become available. Reports compiled by the DMC will be reviewed and discussed by the protocol team on conference calls held at least every two to four weeks. Data on accrual, pharmacokinetics, and toxicity will be reviewed. The IMPAACT Study Monitoring Committee (SMC) will review the study regularly — at least annually — and on as more frequent or ad hoc basis for safety issues and any other concerns. Other study implementation issues, such as participant accrual, participant retention, and data quality, will also be monitored by the SMC.

If the protocol team identifies any potentially treatment-related toxicities, which may compromise subject safety, it will determine whether the study needs to be suspended or modified.

18. Section 8.51, Rules for Suspending Accrual to Assess Safety Following an Adverse Event, first bullet point:

- Any subject who has a life-threatening adverse event Suspected Adverse Drug Reaction (SADR) that is judged to be probably or definitely attributable to study drug medication.

19. In Appendix I, SoE, hematology and chemistries are added at Weeks 4 and 8; footnote 7 is updated to include additional chemistry analytes; footnote 8 is updated to clarify specimen collection requirements for “fasting” glucose levels; and a new footnote (#18) is added to clarify expectations for conducting Off Treatment/On Study Visits.

F. Updates related to pharmacokinetic evaluations:

1. In Section 1.12, Pharmacokinetics, last paragraph:

The overall goals of this study are to characterize the PK of ARVs (ZDV, 3TC, and LPV/r) in severely malnourished children following the initiation of nutritional rehabilitation and to compare results to normal – mildly malnourished children to determine if dosage adjustments in the severely malnourished child are warranted. Since PK is being studied at specific time points following HAART initiation study entry, PK results also will aid in determining if initiation of HAART early in SAM leads to adequate drug levels. It is hypothesized that children with severe acute malnutrition will have reduced absorption of antiretroviral drugs compared to those with normal nutrition–mild malnutrition.

2. In Section 3.3, Criteria for Continued Participation in Pharmacokinetics Testing, last sentence:

In addition, the subject’s most recent hemoglobin on the evening preceding the intensive PK study visit must be ≥ 7.5 g/dl. If any child’s parent/guardian withdraws consent for PK evaluations, the child will be discontinued from the PK component but continue on study/off study drug.
3. In Section 3.4, Pharmacokinetics:

At 1, 12 and 24 weeks after initiation of HAART, intensive PK sampling will be carried out in the context of a morning dose of ARVs. The caregiver will be asked to hold the child’s morning dose so that a pre-dose sample can be collected. Serial samples will be collected just prior to an observed morning dose and at 1, 2, 4, 8, and 12 hours post-dosing. To assure that the PK samples are collected under steady-state conditions, every effort will be made to assure doses are administered approximately every 12 hours for the 48 hours preceding the intensive sampling period.

For those in Cohort 1 (severely malnourished children), at week 1, intensive PK sampling is done as the child is an inpatient at 7–10 days following HAART initiation study entry, and the child’s inpatient providers will be asked to hold the child’s morning dose of ARVs so that a pre-dose sample can be collected. At weeks 12 and 24, children will return to the clinical research center in the morning or prior evening for intensive sampling. At weeks 12 and 24, the caregiver will be asked to hold the child’s morning dose of ARVs so that a pre-dose sample can be collected.

For those in Cohort 2, at weeks 1, 12 and 24, children will come to the clinical research center in the morning or prior evening for intensive sampling. The caregiver will be asked to hold the child’s morning dose of ARVs so that a pre-dose sample can be collected.

There will be standardization of food intake around the PK sampling at week 1 at all study sites. The meal will be similar to RUTF or F100 for children with normal–mild malnutrition.

For weeks 1, 12 and 24, an additional sample generating 1 mL of plasma will be collected at the 2 hour time point. This will be done to determine the free fraction of lopinavir at the time of the peak concentration.

At weeks 4, 8, 16, 36, 48, a trough PK sample will be collected for the ARVs just prior to the morning dose of drug. Again, caregivers are will be asked to hold the child’s morning dose of ARVs. These values will be analyzed in combination with trough samples collected just prior to dosing and as part of intensive sampling on weeks 1, 12 and 24.

In all cases for the PK visits, it is imperative that the precise time of the morning dose administration is recorded as well as the precise time for all samples collected. In the event that a child in Cohort 1 or 2 has diarrhea, intensive PK evaluations may be delayed for up to 5 days.

Refer to Appendix I, Schedule of Evaluations, for a complete description of the clinical and laboratory evaluations to be performed.

4. In new Section 6.5, Criteria for Deferral of PK Evaluations, added:

Intensive PK testing should be deferred (up to 5 days) if the subject:

- Missed any doses of study drug within the prior 72 hours. Intensive PK testing should be done as soon as all doses have been taken for 72 hours.
- Had a hemoglobin value < 7.5 g/dl at the most recent prior evaluation. Hemoglobin can be repeated and, if ≥7.5 g/dl, the intensive PK testing should be performed.
- Has diarrhea. Intensive PK testing should be done as soon as possible after the diarrhea has resolved.
For all of the above, if the intensive PK testing is not done within five days after the close of the allowable window for the evaluations, the evaluations will be considered missed for that visit.

As noted in Section 5.1, if a subject vomits within 30 minutes of dosing, he or she should be re-dosed one time to replace the vomited dose. If the vomiting occurs on a day of PK sampling, the sampling may proceed if the subject vomited within 30 minutes of the first dose and can be re-dosed with a full dose that is not subsequently vomited. Otherwise, the PK sampling should occur on the following day.

5. In new Section 6.6 (previously included in Section 6.25), re-titled as Criteria for Discontinuation of PK Evaluations:
   - Clinical deterioration during the study including development of edema. The subject should discontinue the PK component of the study.
   - Intensive PK testing should be deferred until the hemoglobin is > 7.5 g/dl. Hemoglobin can be repeated within 5 days and if still < 7.5 g/dl then the subject will defer the intensive PK evaluations at that visit.
   - Subject is non-adherent to study treatment and the investigator believes that adherence is unlikely to improve.

Subjects who have only one week of PK data will be replaced.

6. In Section 9.1, Pharmacology Objectives, first bullet point:
   - To compare the PK exposure (as estimated by the area under the plasma concentration versus time curve, AUC) and clearance of ZDV, 3TC, and LPV/r under steady-state conditions between severely malnourished children and children with normal nutrition-mild malnutrition at 1, 12 and 24 weeks following study entry (steady state is achieved or nearly achieved by 7 days of study drug initiation; therefore, the week 1 evaluations will be performed between days 7-10).

7. In Section 9.2, last paragraph:
   ZDV may be changed to ABC if hematologic toxicity dictates. In this case the subject may continue but analysis will be of LPV, 3TC and LPV/r.

8. In Appendix I, SoE:
   - Week 1 visit window in column heading, replaced +3 days

Footnotes 13 and 14, combined and now numbered in amended protocol as 13, replaced
Obtain the specified blood volume based on subject weight (0.8 mL for children ≥5kg, 0.3 mL for children <5 kg) for trough PK sampling prior to morning dose of ARVs. Caregivers will be asked to hold the child’s morning doses.

Footnote 17, now numbered in amended protocol as 16, replaced
Week 1 intensive PK must be completed 7-10 days following study entry (may defer up to day 15 if hemoglobin <7.5 g/dl or the child has diarrhea or the child missed ARV doses within the prior 72 hours).
Footnote 18, now numbered in amended protocol as 17, replaced
For children who permanently discontinue all study drugs, follow-up visits should be conducted per the schedule shown in the table above; however, evaluations performed should be limited to those indicated in the Off treatment/On study column of the table.

Note added below numbered footnotes
Note: For all PK evaluations, record the precise date, time, and amount of the prior ARV dose, as well as the precise date and time of each specimen collection.

9. In Appendix III, Pharmacokinetic Specimen Processing:

Processing of pharmacokinetic samples
Pharmacokinetic blood samples will be collected in spray-dried K-EDTA tubes and sent to the laboratory within 30 minutes of collection for processing. Samples will be centrifuged at 3000g for 10 minutes and stored in labeled polypropylene tubes at -80°C until analysis. Samples will be centrifuged at 1500 g for 10 minutes. Immediately after centrifugation, plasma is removed from cells and transferred to labeled screw cap cryovials and stored at -80°C until shipment for analysis, which is expected approximately every six months. All samples will be logged into the Laboratory Data Management System.

Determination of drug concentrations
Validated liquid chromatography–mass spectrometry (LC-MS) methods will be used to determine concentrations of LPV, RTV in plasma. High performance liquid chromatography (HPLC) will be used to measure ZDV and 3TC levels in plasma. Validated liquid chromatography mass spectrometry (LC-MS/MS) methods will be used to determine concentrations of LPV, RTV, ZDV and 3TC in plasma. These assays will be carried out within the designated IMPAACT-funded University of San Francisco Pharmacology Laboratory. The laboratory will perform testing and assay validation in accordance with the Clinical Pharmacology Quality Assurance procedures, which are based on the principles of Good Laboratory Practices and FDA guidelines.

10. In Appendix V, Sample Informed Consent Form for Enrollment, WHY IS THIS STUDY BEING DONE?, eighth sentence:

Your child’s blood will be sent to laboratory laboratories in South Africa and the United States for analysis.

11. In Appendix V, Sample Informed Consent Form for Enrollment, WHAT DOES MY CHILD HAVE TO DO IF HE/SHE IS IN THIS STUDY?, On Study Visits, seventh and eighth bullet points:

- For 5 of the visits less than one teaspoon of blood will be drawn right before your child takes the first dose of anti-HIV medications. [Note to sites: add locally relevant description of blood volume] You will be asked to hold your child’s first dose of anti-HIV medications on the days of these visits.
- For 3 of the visits, you will be asked to bring your child to the clinic to have blood drawn 6 times over 12 hours to measure the amount of anti-HIV medications in your child’s blood. The total amount of blood to be drawn for these tests will be a little more than one teaspoon if your child weighs 10 pounds or more and less than one teaspoon if your child weighs less than 10 pounds. [Note to sites: add locally relevant description of blood volume and weight] You will be asked to hold your child’s first dose of anti-HIV medications on the days of these visits.
12. In Appendix V, Sample Informed Consent Form for Enrollment, WHAT DOES MY CHILD HAVE TO DO IF HE/SHE IS IN THIS STUDY?, On Study Visits, paragraphs following bullet points:

It is important that you bring your child to the clinic for all study visits. If you do not come for a study visit, or if a test result comes back abnormal, we will contact you to find out how your child is doing. If your child becomes sick at any time, please contact the study nurse or doctor right away.

The tests that might affect your child’s healthcare will be done soon after your child’s blood is drawn, and you will be given the results as soon as possible, usually at the next visit. The tests of the amount of anti-HIV medications in your child’s blood will not be done right away; the blood will be kept for later testing and you will not be given the results of these tests.

On the days when your child has blood drawn over 12 hours, if your child vomits within 30 minutes after taking anti-HIV medications, we will try giving another dose of the medications. If your child cannot be given another dose, or vomits again, we will not do the blood draws that day. We will ask you to bring your child back to the clinic to try again the next day.

If you allow your child to take part in this study, but then later decide that you do not want your child to have the blood draws over 12 hours, your child will stop taking the anti-HIV medications that are given by the study. If your child stops taking the anti-HIV medications that are given by the study for this reason or other reasons before the study ends, you will be asked to continue to bring your child to the clinic for regular study visits until the study ends. At each of these visits, we will take a medical history, perform a physical exam, and draw blood for routine tests and to check how well your child’s immune system is working and the amount of HIV in your child’s blood. The total amount of blood drawn at this visit will be 7-9 mL (about 1.5- less than 2 teaspoons). [Note to sites: add locally relevant description of blood volume] If your child stops taking the anti-HIV medications that are given by the study, we will tell you about other options for treatment of your child’s HIV infection.

G. Updates of the protocol team roster and other protocol sections to enhance the clarity and precision of protocol specifications

1. On the protocol cover page and in the protocol team roster, team member listings are updated and study site representatives are added. The National Institute of Mental Health is added to the protocol cover page and all references to GlaxoSmithKline are replaced with references to Viiv Healthcare Ltd. The Core Team email address is updated to impaact.corep1092@fstrf.org.

2. On the protocol cover page, the study is identified as a non-IND study. Accordingly, all references to US Food and Drug Administration oversight of the study are removed.

3. The glossary, table of contents, and study flow chart are updated to reflect all other protocol sections.

4. In Section 1.2, Rationale, a numbered subsection heading (1.24) is added for Extended follow-up for 48 weeks and reference to adherence assessments is deleted from this subsection. Adherence questionnaires are deleted from Appendix I.
5. In Section 1.24 (re-numbered as Section 1.25 in amended protocol), Summary, first sentence:

The primary objectives of the study are to compare the pharmacokinetic characteristics of severely malnourished and normally nourished to mildly malnourished HIV-infected children starting lifelong antiretroviral therapy.

6. In Section 1.253 (re-numbered as Section 1.263 in amended protocol), Pediatric Experience with Lopinavir/Ritonavir, third paragraph:

In PACTG P1030, a Phase I/II study of LPV/r in HIV-1 infected infants < 6 months of age, infants are dosed with LPV/r 300/75 mg/m² BID. As of January 2004, 12 infants between the ages of two and five months have been enrolled. Average Cmax for LPV were 11.6 mg/L (range 4.8 – 20.4) and mean Ctrough concentrations were 4.0 mcg/L (range 1.4 – 5.6). HIV-1-infected infants less than 6 months of age were treated with LPV/r 300/75 mg/m² twice daily plus two nucleoside reverse transcriptase inhibitors (48). Results available at 24 weeks indicated that, although apparent clearance of LPV/r was slightly higher than in older children, the median area under the concentration-time curve 0-12 h (67.5μg.h/ml) was in the range reported from older children taking the recommended dose of 230/57.5 mg/m². Longer-term results indicated that, at 12 months of age, median LPV area under the curve was similar to older children and adults.


7. In new Section 7.5, CRF Recording Requirements for Laboratory Test Results, Signs, Symptoms, and Diagnoses, added:

The results of all laboratory tests performed at screening, entry, and post-entry must be recorded on CRFs, regardless of severity grade.

All abnormal (severity grade 1 and higher) signs, symptoms, and diagnoses occurring within 30 days prior to study entry must be recorded on CRFs. All abnormal (severity grade 1 and higher) signs, symptoms, and diagnoses occurring post-entry must also be recorded on CRFs at all visits.

8. In Section 8.52, Accrual Rate Evaluation, first paragraph, fourth and fifth sentences:

There may be 4 sites together (including South Africa). If Once 2 sites are activated, we would expect to enroll about 14-15 children per site and expect 7-8 children enrolled within 6 months and 10-15 by 12-18 months per site.

9. In Appendix IV, Sample Informed Consent Form for Screening, and in Appendix V, Sample Informed Consent Form for Enrollment, WHY IS THIS STUDY BEING DONE?, third sentence:

The reason for this study is to find out if the approved HIV medications for the treatment of HIV infection in children will give adequate drug levels in the blood when given to infected children with severe malnutrition and those as compared to children with mild to normal nutrition or mild malnutrition.