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

DAIDS ES #11689

This file contains the current IMPAACT P1092 protocol, which is comprised of the following documents, presented in reverse chronological order:

- Clarification Memorandum #4, dated 3 August 2017
- Clarification Memorandum #3, dated 25 August 2016
- Letter of Amendment #1, dated 12 April 2016
- Clarification Memorandum #2, dated 10 November 2015
- Clarification Memorandum #1, dated 24 April 2015
- Protocol Version 2.0, dated 11 February 2015

Clarification Memorandum #4 for:

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

Version 2.0, dated 11 February 2015

DAIDS ES #11689

Clarification Memorandum Date: 3 August 2017

Summary of Clarifications

This Clarification Memorandum (CM) clarifies the study evaluations in the protocol Schedule of Evaluations that are considered routine tests as referenced in the Sample Informed Consent form.

Implementation

This CM has been approved by the NIAID and NICHD Medical Officers. Institutional Review Board/Ethics Committee (IRB/EC) approval of this CM is not required by the study sponsor prior to implementation. However, sites may submit this CM to IRBs/ECs for their information or, if required by the IRBs/ECs, for their approval prior to implementation.

The content of this CM clarifies the study evaluations that are considered routine tests referenced in protocol Appendix V: Sample Informed Consent Form (ICF) for study participation. This CM does not modify the ICF and does not impact the benefit-to-risk ratio for study participants.

This CM should be maintained in each site's essential documents file for IMPAACT P1092. It is the responsibility of each site Investigator of Record to ensure that all study staff are made aware of this CM. The content of this CM will be incorporated into any future amendment of the IMPAACT P1092 protocol.

Clarification of study evaluations in the Schedule of Evaluations that are considered routine tests

This CM serves to clarify that the evaluations for hematology, chemistries, total protein/albumin, lipid profile, and the micronutrients: zinc and selenium in protocol Appendix I, Schedule of Evaluations, are considered routine tests for the study.

Clarification Memorandum #3 for:

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

Version 2.0, dated 11 February 2015

DAIDS ES #11689

Clarification Memorandum Date: 25 August 2016

Summary of Clarifications

This Clarification Memorandum (CM) clarifies expectations for evaluating lymphocyte subsets at study Week 36.

Implementation

This CM has been approved by the NIAID and NICHD Medical Officers. Institutional Review Board/Ethics Committee (IRB/EC) approval of this CM is not required by the study sponsor prior to implementation. However, sites may submit this CM to IRBs/ECs for their information or, if required by the IRBs/ECs, for their approval prior to implementation.

The content of the CM does not impact the sample informed consent forms for the study or the benefit-to-risk ratio for study participants.

This CM should be maintained in each site's essential documents file for IMPAACT P1092. It is the responsibility of each site Investigator of Record to ensure that all study staff are made aware of this CM. The content of this CM will be incorporated into any future amendment of the IMPAACT P1092 protocol.

Clarification of expectations for evaluating lymphocyte subsets at study Week 36

The IMPAACT P1092 Schedule of Evaluations (SoE), provided in protocol Appendix I, specifies that lymphocyte subsets (i.e., CD4 and CD8 cell counts and percentages), be evaluated at Screening; at Weeks 12, 24, 36, and 48; and at Off Treatment/On Study visits. The SoE also specifies that complete blood counts (CBCs) be evaluated at Screening; at Weeks 12, 24, and 48; and at Off Treatment/On Study visits; however, a CBC is not required per protocol at Week 36.

This CM serves to clarify that a CBC may be needed at some study sites to meet protocol requirements to evaluate CD4 and CD8 cell counts and percentages at Week 36. Specifically, at sites that utilize dual-platform lymphocyte testing methods, a CBC must be performed in order for both absolute counts and percentages to be obtained. At these sites, a CBC should be performed at Week 36 to permit evaluation of both absolute counts and percentages. The 1 mL of blood needed to perform a CBC at Week 36 does not exceed the blood draw volumes permitted in the sample informed consent form provided in protocol Appendix V. The results of any CBCs performed at Week 36 should be recorded on study case report forms.

Letter of Amendment #1 for:

IMPAACT P1092
Phase IV Evaluation of the Steady State Pharmacokinetics of Zidovudine, Lamivudine, and Lopinavir/Ritonavir in Severely Malnourished HIV-1-Infected Children
Version 2.0, dated 11 February 2015

DAIDS ES #11689

Letter of Amendment Date: 12 April 2016

Information/Instructions to Sites from the Division of AIDS

The information contained in this Letter of Amendment (LoA) impacts the oversight and management of the IMPAACT P1092 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. The information contained in this LoA does not impact the study informed consent forms or participant management at participating study sites. Nonetheless, IRB/EC approval of this LoA is required. 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, this LoA should be implemented immediately. 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.

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 IMPAACT P1092.

If the IMPAACT P1092 protocol is amended in the future, the contents of this LoA will be incorporated into the next version of the protocol.

Summary of Revisions and Rationale

In consultation with the IMPAACT Study Monitoring Committee (SMC), during a routine review of the study, the Protocol Team determined that protocol Section 8.51, Rules for Suspending Accrual to Assess Safety Following an Adverse Event, should be modified to allow for management of expected hematologic toxicities for participants on zidovudine per the toxicity management guidelines provided in protocol Section 6.22. This section of the protocol provides detailed guidance for the management of expected hematologic events, including substitution of abacavir for zidovudine when indicated. The modifications specified in this LoA will prevent unwarranted suspensions of participant accrual.

Implementation

Modifications of protocol Section 8.51, Rules for Suspending Accrual to Assess Safety Following an Adverse Event, are shown below, using strikethrough for deletions and bold type for additions.

8.51 Rules for Suspending Accrual to Assess Safety Following an Adverse Event

Accrual will be temporarily suspended***** if:

- Any subject has a life threatening adverse event that is judged to be probably or definitely attributable to study drug or Grade 4 event that may not be judged to be life-threatening but is judged to be probably or definitely attributable to study drug.
- Or if more than six out of the first 20 subjects or at least 30% of subjects thereafter have Grade 3 or greater toxicity that is judged to be definitely related to study drug.

***Grade 3/4 hematologic events that meet the above definitions may not require temporary suspension of accrual and this determination can be made by the DAIDS/NICHD Medical Officers. The SMC will be informed of all decisions.**

Following temporary suspension of accrual, the protocol team will further review the safety data within 48 hours of notification of the event to determine if continuation of accrual is appropriate. If the protocol team, including the study chair and the DAIDS medical officer of record agree that the study drug is likely to be safe for additional subjects, ~~they~~ **the DAIDS/NICHD Medical Officers** may allow accrual to resume**, and the SMC will be informed**. **If the protocol team, including the Medical Officers, determines that accrual should remain suspended for an ad hoc SMC review, the SMC will be notified.** Regulatory agencies (IRB/EC) will be notified of the event and the protocol team's decision after this review of the safety data has taken place.

Clarification Memorandum #2 for:

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

Version 2.0, dated 11 February 2015

DAIDS ES #11689

Clarification Memorandum Date: 10 November 2015

Summary of Clarifications

This Clarification Memorandum (CM) clarifies the required timing of Stage 2, Study Entry, for Cohort 2, in which children with normal nutrition to mild malnutrition will be enrolled. For children who are eligible for this cohort, entry must occur within 14 days after initiating the study screening process.

This CM also updates the Protocol Team Roster.

Implementation

This CM has been approved by the NIAID and NICHD Medical Officers. Institutional Review Board/Ethics Committee (IRB/EC) approval of this CM is not required by the study sponsor prior to implementation. However, sites may submit this CM to IRBs/ECs for their information or, if required by the IRBs/ECs, for their approval prior to implementation.

The content of the CM does not impact the sample informed consent forms for the study or the benefit-to-risk ratio for study participants.

This CM should be maintained in each site's essential documents file for IMPAACT P1092. It is the responsibility of each site Investigator of Record to ensure that all study staff are made aware of this CM. The content of this CM will be incorporated into any future amendment of the IMPAACT P1092 protocol.

Clarification of the required timing of Stage 2, Study Entry, for Cohort 2, children with normal nutrition to mild malnutrition

Protocol Sections 3.2 and 4.4, the Study Flow Chart, and Appendix I provide information about the timing of study entry for Cohort 2.

Prior to study entry, children screened for Cohort 2 must be assessed as clinically stable per eligibility criterion 4.17 and eligible for antiretroviral therapy per eligibility criterion 4.14. They must also meet all other eligibility requirements applicable to Cohort 2. "Within 7-14" days reflects the generally expected timeframe for completing the study screening and eligibility process for this cohort. **For children confirmed to meet all applicable eligibility criteria, entry into Cohort 2 may occur at any time within 14 days after initiating the study screening process.** This was the original intent for the protocol and is further clarified in the following protocol sections:

Section 3.2, Stage 2: Entry, Criteria for Stage 2 Entry
Cohort 2: Normal nutrition–mild malnutrition children
For children with normal nutrition-mild malnutrition who are found to be eligible, entry into the study will occur after written informed consent has been obtained and **within 14 days** after screening. *[paragraph continues]*

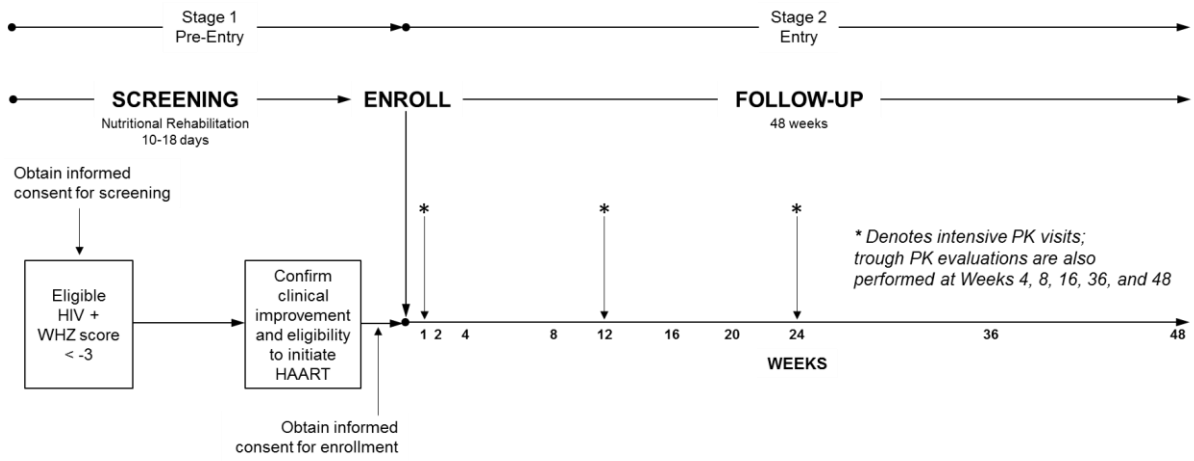
Section 4.4, Enrollment Procedures, seventh paragraph
Minimum age at enrollment is six months (180 days). However, screening evaluations may be performed **within 14 days** (for children with normal nutrition to mild malnutrition) or 10-18 days (for children with severe malnutrition) prior to six months (180 days) of age, as long as the entry visit does not occur earlier than six months (180 days) of age.

In the Study Flow Chart, Panel Cohort 2
SCREENING
within 14 days

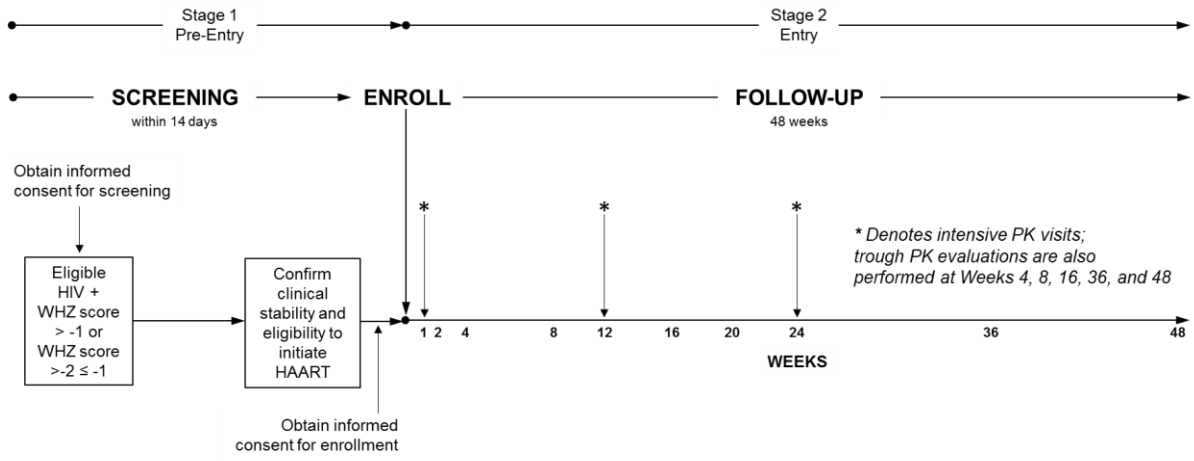
In addition to the above, the labeling of each panel in the chart is corrected; for ease of reference, the clarified version of the chart is provided in its entirety on page 3 of this CM.

Study Flow Chart:

Cohort 1: Severe Malnutrition



Cohort 2: Normal Nutrition-Mild Malnutrition



Update of Protocol Team Roster

Contact information for the NICHD Medical Officer is updated as follows:

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Clarification Memorandum #1 for:

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

Version 2.0, dated 11 February 2015

DAIDS ES #11689

Clarification Memorandum Date: 24 April 2015

Summary of Clarifications and Implementation

The purpose of this Clarification Memorandum (CM) is to update the listing of study sites and site investigators in the IMPAACT P1092 protocol team roster. The name and number of the site in Harare, Zimbabwe, are updated and sites in Blantyre and Lilongwe, Malawi, are added. In addition, other listings in the protocol team roster are updated to reflect current team membership and contact details.

This CM has been approved by the NIAID and NICHD Medical Officers. Institutional Review Board/Ethics Committee (IRB/EC) approval of this CM is not required by the study sponsor prior to implementation. However, sites may submit this CM to IRBs/ECs for their information or, if required by the IRBs/ECs, for their approval prior to implementation.

The content of the CM does not impact the sample informed consent forms for the study or the benefit-to-risk ratio for study participants.

This CM should be maintained in each site's essential documents file for IMPAACT P1092. It is the responsibility of each site Investigator of Record to ensure that all study staff are made aware of this CM. The content of this CM will be incorporated into any future amendment of the IMPAACT P1092 protocol.

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IMPAACT P1092

PHASE IV EVALUATION OF THE STEADY STATE PHARMACOKINETICS OF ZIDOVUDINE, LAMIVUDINE, AND LOPINAVIR/RITONAVIR IN SEVERELY MALNOURISHED HIV-1-INFECTED CHILDREN

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

Sponsored by:

The National Institute of Allergy and Infectious Diseases (NIAID),
the Eunice Kennedy Shriver National Institute of Child Health
and Human Development (NICHD), and
the National Institute of Mental Health (NIMH)

Pharmaceutical Support Provided by:

ViiV Healthcare Ltd
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Non-IND Study
DAIDS ES #11689

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FINAL VERSION 2.0
11 February 2015

IMPAACT P1092 PROTOCOL TEAM ROSTER

Please refer to the Manual of Procedures for guidance on study-related communications with protocol team members. Contact details for subject management are also provided in Section 6 of this protocol.

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TABLE OF CONTENTS

APPENDICES:

GLOSSARY

3TC	Lamivudine, Epivir
AAG	Alpha -1 acid glycoprotein
ABC	Abacavir
AE	Adverse Event
ALT	Alanine aminotransferase
ART	Antiretroviral therapy
ARV	Antiretroviral
AST	Aspartate aminotransferase
AUC	Area under the curve
BID	Twice a day
BLQ	Below the limit of quantification
BMI	Body Mass Index
C_{max}	Peak plasma concentration
C_{trough}	Minimum concentration
CBC	Complete blood count
CHER	Children with Early HIV Antiretroviral Therapy
CL/F	Clearance
CLIA	Clinical Laboratory Improvement Amendments
CI	Confidence Interval
CRF	Case report form
CRPMC	NIAID Clinical Research Products Management Center
CYP	Cytochrome
DAERS	DAIDS Adverse Experience Reporting System
DAIDS	Division of AIDS
DAIDS PRO	DAIDS Protocol Registration Office
DMC	Data Management Center
DNA	Deoxyribonucleic Acid
EAE	Expedited Adverse Event
EC	Ethics Committee
EIA	Enzyme immunoassay
EKG	Electrocardiogram
F75	High energy milk (75 kilocalories/100ml)
F100	High energy milk (100 kilocalories/100ml)
FDA	Food and Drug Administration
HAART	Highly active antiretroviral therapy
HIV/AIDS	Human Immunodeficiency Virus/ Acquired Immunodeficiency Syndrome
ICF	Informed consent form
IMPAACT	International Maternal Pediatric Adolescent AIDS Clinical Trials Network
IRB	Institutional review board
LAR	Legally authorized representative
LC-MS	Liquid chromatography-Mass spectroscopy
LFT	Liver function test
LTFU	Loss to follow-up
LPV/r	Lopinavir/ritonavir, Kaletra

MUAC	Middle upper arm circumference
NIAID	National Institute of Allergy and Infectious Diseases
NICHD	National Institute of Child Health and Development
NIH	National Institutes of Health
NNRTI	Non-nucleoside reverse transcriptase inhibitor
NRTI	Nucleoside reverse transcriptase inhibitor
NVP	Nevirapine, Viramune
OHRP	Office for Human Research Protections
PACTG	Pediatric AIDS Clinical Trials Group
PCR	Polymerase chain reaction
PENTA	Pediatric European Network for Treatment of AIDS
PI	Protease inhibitor
PID	Participant identification number
PK	Pharmacokinetic
RNA	Ribonucleic Acid
RSC	Regulatory Support Center
RTV	Ritonavir
RUTF	Ready to use therapeutic feed
SAE	Serious adverse event
SAM	Severe acute malnutrition
SES	Subject Enrollment System
SID	Study identification number
SMC	Study Monitoring Committee
SUSAR	Suspected unexpected serious adverse reactions
TID	Three times a day
T_{max}	Time to reach C_{max}
US HHS	United States Department of Health and Human Services
WHO	World Health Organization
WHZ	Weight for height z score
ZDV	Zidovudine, Retrovir

SCHEMA

PHASE IV EVALUATION OF THE STEADY STATE PHARMACOKINETICS OF ZIDOVUDINE, LAMIVUDINE, AND LOPINAVIR/RITONAVIR IN SEVERELY MALNOURISHED HIV-1-INFECTED CHILDREN

DESIGN:	Phase IV, multicenter, open-label, intervention pharmacokinetic trial
SAMPLE SIZE:	50 (25 per cohort) to achieve 34 evaluable (17 per cohort)
POPULATION:	Cohort 1: HIV-1-infected children ages ≥6 months (≥180 days) to <36 months with severe malnutrition Cohort 2: HIV-1-infected children ages ≥6 months (≥180 days) to <36 months with normal nutrition–mild malnutrition
STRATIFICATION:	Two strata: Age <18 months and ≥18 months
REGIMEN:	Cohort 1 (severe malnutrition) Arm A: <18 months: ZDV+3TC+LPV/r Arm B: ≥18 months: ZDV+3TC+LPV/r Cohort 2 (normal nutrition/mild malnutrition) Arm C: <18 months: ZDV+3TC+LPV/r Arm D: ≥18 months: ZDV+3TC+LPV/r
TREATMENT DURATION:	48 weeks after initiation of HAART

PRIMARY OBJECTIVES:

1. 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.

2. To evaluate the safety and tolerability of ZDV, 3TC, and LPV/r in severely malnourished children and children with normal nutrition – mild malnutrition at 24 weeks following study entry.

SECONDARY OBJECTIVES:

1. To compare the minimum concentration (C_{trough}) of LPV/r between severely malnourished children and children with normal nutrition – mild malnutrition at 1, 4, 8, 12,16, 24, 36 and 48 weeks following study entry.

2. To investigate the impact of malnutrition on LPV protein binding by comparing the free fraction of LPV in severely malnourished children and children with normal nutrition – mild malnutrition at 1, 12 and 24 weeks following study entry.

3. To compare the viral loads between severely malnourished children and children with normal nutrition – mild malnutrition at baseline, 12, 24, 36 and 48 weeks following study entry.

4. To compare CD4 cell percent between severely malnourished children and children with normal nutrition – mild malnutrition at baseline, 12, 24, 36 and 48 weeks following study entry.

5. To describe the recovery of lean body mass and linear growth in severe acute malnutrition at 24 and 48 weeks following study entry.

1.0 INTRODUCTION

1.1 Background

1.11 Severe Acute Malnutrition (SAM)

Malnutrition is a major problem of children living in resource-limited settings and is responsible for over one million deaths per year in children under five years of age (1). Severe malnutrition remains one of the most common presentations of HIV infection in African infants and children, with wasting being recognized as a risk factor for mortality (2, 3). Lean body mass has been closely associated with, and predictive of survival in both adults and children living with HIV even when on antiretroviral therapy. 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 less than -3 Z score using the WHO growth standards, or a mid-upper arm circumference (MUAC) less than 115mm (11.5cm), or any degree of bilateral edema (4). A systematic review and meta-analysis of children presenting with SAM in sub-Saharan Africa reported an average HIV seroprevalence of 29%, with an urban large referral hospital having the highest burden of disease (5). The urban nutritional treatment centers had HIV prevalence rates as high as 50%, with mortality of 30% in HIV-infected children.

The clinical presentation of severe acute malnutrition includes severe visible wasting (marasmus), nutritional edema (kwashiorkor) or a mixed picture (marasmic–kwashiorkor). In sub-Saharan Africa, marasmus occurs more commonly than kwashiorkor in HIV-infected children (6). It is unclear why HIV-infected children are more prone to marasmus than to kwashiorkor. In the earlier years of the HIV epidemic in North America, HIV- infected children also presented with HIV-related wasting that was associated with profound anorexia and weight loss. In African settings, it is generally not possible to differentiate clinically between HIV-related wasting and marasmus that affects HIV uninfected children from the same communities. Both HIV-infected and uninfected children presenting with SAM suffer recurrent infectious diseases, persistent diarrhea (usually due to villous atrophy and disaccharide or even monosaccharide intolerance) and oral candidiasis which contributes to anorexia and poor oral intake. Micronutrient deficiencies are common and may contribute to growth failure and disease progression. However micronutrient supplements alone do not necessarily restore body stores or result in improved weight gain or linear growth. While vitamin A supplements have been shown to reduce all-cause mortality in HIV-infected children, systematic reviews have not concluded that micronutrient supplements improve survival in HIV-infected children or adults although these reviews have not disaggregated outcomes by nutritional status such as severe malnutrition.

Among HIV-infected children with SAM mortality has been reported to be three times higher than in those without HIV infection (5). HIV-infected children with SAM are often admitted with multiple complex pathologies such as persistent diarrhea, tuberculosis, septicemia and oral thrush which make it more difficult to respond to the standard nutritional rehabilitation. Severely malnourished HIV-infected children generally have a prolonged hospital stay with inadequate and slow weight gain and increased risk of death especially in the first two weeks of admission. In Uganda, Bachou et al reported a mortality of 24% in a cohort of 220 children admitted with SAM and the majority of deaths occurred within the first week of admission (7). However, there have been some reports of HIV-infected children who survive having similar weight gain following nutritional rehabilitation when compared to the HIV-uninfected children with SAM (8).

In any child suffering severe malnutrition, normal physiological mechanisms adapt to low food intake in a process called reductive adaptation. These changes affect every physiological function in the body to decrease energy and nutrient demands and mobilize energy and nutrients from other reserves; adaptations include reduced cardiac output, glomerular filtration and hepatic perfusion. This is initially beneficial but eventually becomes detrimental to the child as the body is unable to handle stress and control normal physiological functions leading to poor homeostasis and serious infections.

Complicated SAM is associated with important biochemical and electrolyte abnormalities, including hypoglycemia, hypokalemia, hyponatremia, and micronutrient deficiencies such as zinc, magnesium and phosphate. Immune function even in HIV-uninfected children is also compromised in SAM and has given rise to the term “nutrition acquired immunodeficiency”. HIV-infected children with SAM have lower total white cell counts, lymphocyte counts and CD4 cell counts and impaired cell mediated immunity with additional risk of miliary tuberculosis, invasive salmonellosis and candidiasis. Bacteremia occurs in 20% of children admitted with SAM and is more common in those with SAM and HIV and is associated with higher mortality. The majority of the pathogens are Gram-negative enteric bacteria probably due to the break down in the intestinal barrier (7,9).

Nutritional Rehabilitation

The World Health Organization recommends a ten step approach to the management of SAM which is described in Appendix II (10). This involves a stabilization and rehabilitation phase. The stabilization phase which usually lasts up to two weeks includes feeding with management of the acute medical conditions and initiation of therapeutic feeding (high energy milk F75 and F100). This involves providing standard antibiotic coverage for bacterial infections, prevention of and treatment for hypoglycemia, hypothermia and dehydration if present. Electrolyte and micronutrient deficiencies are managed by supplementing potassium and magnesium, while multivitamins, zinc and folic acid are added to the feeds. Iron is replaced only in the rehabilitation phase because of the pro-oxidative effects and potential complication of worsening infections.

1.12 Pharmacokinetics

In recent years, there has been increased access to highly active antiretroviral therapy (HAART) for HIV-infected children with improved morbidity and mortality outcomes (11). The goal of antiretroviral therapy is to sustain immunologic health by achieving a sustained control of viral replication which is dependent upon adequate drug exposure.

Multiple factors significantly influence pharmacokinetic (PK) processes of drugs including disease states like malnutrition, age, sex, genetic variations and variations in physiological processes such as absorption and drug metabolism (12). In the general population, variations in gastric pH, emptying time, integrity of gut absorptive surface area and permeability have been determined to influence absorption while variations in body composition, total body water, fat content, body mass and levels of binding protein have been found to influence distribution of drugs within the body compartments (12).

Any disease state that disrupts drug absorption and metabolism will also affect the PK of drugs. Malnourishment has been associated with villous atrophy of the gut, reduced gastric acidity, prolonged emptying time and reduced binding of some drugs due to reduced albumin levels causing PK changes in the malnourished children (13,14). Decreased gastric acidity (higher gastric pH) associated with malnutrition can result in increased absorption of acid labile drugs and decreased absorption of drugs requiring lower gastric pH for stability (15). The protease inhibitors [PIs, e.g. LPV/r (lopinavir/ritonavir)] and the non-nucleoside reverse transcriptase inhibitors [NNRTIs, e.g. nevirapine (NVP)] prefer an acidic environment for absorption and thus, may exhibit diminished absorption in the malnourished child (16). In contrast, the nucleoside reverse transcriptase inhibitors [NRTIs, e.g. zidovudine (ZDV) and lamivudine (3TC)] are acid

labile and thus may exhibit increased absorption with the increase in gastric pH consistent with malnutrition.

Malnutrition may also affect drug metabolism. Drugs like antipyrine, anti-tuberculosis drugs and antibiotics exhibit altered metabolism in severely malnourished children due to altered hepatic oxidative drug biotransformation via the cytochrome P450 (CYP) enzymatic system. In early animal studies, it was shown that as protein was restricted in the diet, the microsomal P450 content and activity was lowered which was confirmed using several drugs as substrates. Diminished metabolism, reduced elimination of conjugates and reduced elimination of renally excreted drugs seemingly increases the risk of toxicity in malnourished children (17,18). The protease inhibitors and non-nucleoside reverse transcriptase inhibitors undergo CYP metabolism by the isozymes CYP3A4 and CYP2B6 and thus may exhibit diminished metabolism in the context of malnourishment.

While the PK of several drugs has been studied in the malnourished child, very few studies have investigated the effect of severe malnutrition on the PK of ARVs. Ellis et al found an independent association between lower NVP concentrations and lower height-for-age (indicating stunting, p=0.05) and higher body mass index (BMI) for age (indicating lack of wasting, p=0.03) (19). This study conducted in 56 Zambian and 71 Malawian children was designed to investigate the PK of NVP in subjects receiving fixed-dose generic agents. In another study in Malawi, children with moderate malnutrition had a trend toward lower NVP levels. This study also measured unbound NVP and reported no apparent change in the percentage of unbound NVP, a finding expected since NVP is only 60% bound to plasma proteins (while changes in the binding of LPV/r which is 98-99% bound are more likely). Younger children independent of nutrition status had an increased risk of sub-therapeutic NVP concentrations (20).

In general, PK of ARV drugs in children is less predictable than adults. For several ARVs, age-dependent PK parameters have been reported (21, 22). Furthermore, high inter-individual variability in PK of ARV drugs may occur within age brackets. Variations in weight among children may affect drug disposition as shown in the Zambian study where children ≥6 kg exhibited appropriate concentrations of NVP with Triomune® junior and baby formulations. However, more information as to appropriateness of dosing was needed for children < 6kg (23).

When ARVs are administered orally, they are absorbed from the intestinal epithelial cells into the systemic circulation. They are then distributed into tissues depending on their affinity for the tissues relative to plasma proteins. ARVs are variably bound to plasma proteins (<5% to >99%) (24). NRTIs are not highly protein bound with binding ≤40% in most

cases. Protease inhibitors, with the exception of indinavir, are >90% protein bound, mainly to α1-acid glycoprotein (AAG). In particular, lopinavir is highly protein bound in plasma (98-99%); mainly to AAG for which it has the highest affinity, and albumin. Since malnutrition may lead to lower plasma albumin and AAG levels, the fraction of lopinavir that is unbound (pharmacological active) may be increased (25). The actual concentration of unbound drug is unlikely to change at steady-state; however, the fraction of unbound drug (relative to total drug) may change. Thus, an estimate of the fraction of unbound drug for highly bound drugs in the malnourished state is helpful for interpreting the results for total drug levels generated in this study. In other words, if a difference in total drug exposure is detected in the severely malnourished child compared to a child that is not severely malnourished, this change should be interpreted in the context of any change in fraction unbound. For example, a 40% decrease in total drug exposure may be partially offset by an increase in the fraction unbound.

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 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.

1.2 Rationale

1.21 Pharmacokinetics in severe malnutrition

Severe malnutrition that is not responding to nutritional rehabilitation (WHO clinical stage IV) is an indication to initiate HAART. A PK study of adult Triomune® given to children with mild to moderate malnutrition in Malawi revealed antiretroviral therapy (ART) dosing in the children was too low, but did not detect an effect of malnutrition on total drug exposure or the unbound fraction of NVP. In severe malnutrition, however, metabolic and or gut structural derangement may lead to inadequate ARV absorption and or erratic drug levels. The greater surface area to weight ratio in these children also could place them at higher risk of under dosing compared to the group with mild to moderate malnutrition. The paucity of ARV PK data in these vulnerable, severely malnourished children speaks to the need to determine the PK of ARVs in this group with the aim of informing future dosing guidelines for this particular group of patients.

1.22 Pharmacokinetics in moderate malnutrition

In Malawi, HIV-1-infected children initiated on HAART using a FDC Triomune® 30 had similar total AUC0-12hr in the mild to moderately malnourished children (70-85% weight for height) compared to children of normal nutritional status (> 85% weight for height). Mean (90% CI) AUC0-12hr in malnourished children (n=12) was 60,082 (35,328 - 166,629) ng*h/mL compared to 79,861 (43922-146376) ng*h/mL in the normal group (n=25) [p=0.17]. However there was a trend towards lower total nevirapine C_{max} (29%) in the malnourished children [6719 (3401 - 18947) ng/mL] versus the normal children [9483 (5099 – 22453) ng/mL] (p=0.089). There was no difference in C_{trough} (p=0.327). Age and dose were the main predictors of achieving a therapeutic C_{trough} in the univariate model and, in the multivariate model, age was found to be independent of dose. The authors' conclusion was that malnutrition did not seem to have a significant impact on NVP PK (26). However, children with acute severe malnutrition were not included in this study (4).

The current study will utilize the recommended weight band dosing which simplifies dosing in resource limited settings and is the approach used in the WHO pediatric ARV dosing guidelines. It will also use pediatric formulations which have not been studied before in severely malnourished children.

1.23 Virology and immunology

Children who acquired HIV infection through mother-to-child transmission develop high peak levels of circulating virus within the first six months of life with a plateau and slow decline over the next 18 months. Complete viral suppression is critical to effective treatment and survival. HAART has been shown to reduce HIV-1 RNA levels dramatically with the most rapid reduction in viremia occurring during the first two weeks with a slower decline thereafter. Adequate ARV drug levels ensure complete viral suppression and delay emergence of HIV-1 resistant mutations. By measuring HIV-1 RNA levels at baseline and at 12 and 24 weeks after initiating dosing, it will be possible to ascertain whether the study drug levels achieved as measured by pharmacokinetics are effective in reducing viremia.

HIV-1-infected children presenting with severe malnutrition are at a high risk of mortality during nutritional rehabilitation - 35% mortality in a study in Malawi (8). In a study of severely malnourished Zambian children, CD4 percentages were lower among HIV-1-infected children compared to uninfected children, with 46% of the HIV-1-infected children having a CD4 percent <15% (27). The difference in CD4 percent is even more pronounced in children with SAM and lacking edema, with approximately 80% having CD4 < 15%. Despite successful nutritional

rehabilitation among those children who survived, CD4 percent did not increase. On the contrary, at the time of complete nutritional recovery, an increased proportion of the children (85%) had CD4 percent <15% (27). This observation argues for initiation of ART since nutritional treatment alone did not result in CD4 recovery. However, studies demonstrating the effect of ART and nutritional rehabilitation on CD4 parameters are lacking. It is not known whether severely malnourished children will have CD4 recovery similar to those with more normal nutrition. A study of adults in Singapore examined the CD4 count increases following ART initiation (28). The study did not demonstrate a significant difference between adults presenting with a BMI <17 vs. higher BMI. However this study was performed in adults and the degree of malnutrition was not detailed. In children production of naïve cells by the thymus is thought to be an important contributor to CD4 recovery with ART. Severe malnutrition results in thymic atrophy (29). It is possible that HIV-infected children with severe malnutrition will have greater thymic compromise which might lead to delayed or inadequate increases in CD4 parameters. Therefore a secondary objective of this study will investigate the hypothesis that change from baseline for CD4 percent at 12 and 24 weeks will be lower for the cohort with severe malnutrition at baseline.

1.24 Extended follow-up to 48 weeks

The primary objectives of the study are to compare the pharmacokinetic characteristics of severely malnourished and normally nourished HIV-infected children starting lifelong antiretroviral therapy. However, there is very limited well-documented, comparative, clinical data about these groups of children, and hence there would be significant benefit in monitoring the outcomes of study children for a period of 48 weeks total. While the sample size would not be predicated on answering other clinical questions, valuable observational data could be derived on differences in the two groups of children on:

- Recovery of lean body mass (proxy = weight for height and middle upper arm circumference (MUAC)
- Linear growth
- Rate of metabolic complications

Such information, even if not definitive, would contribute to the emerging body of knowledge about how to manage these children and the benefits of doing so, and may serve as preliminary data for subsequent research proposals.

Outcomes to be monitored over 48 weeks of follow-up:

- Vital status
- Weight, height and MUAC
- Glucose and lipid profile
- Skin fold thickness
- Viral load and CD4 count

1.25 Summary

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. Whether or not it is better to wait for some nutritional recovery before initiation of ART is not known. There is the potential for the ARVs to cause adverse events in a child who is metabolically unstable, has reduced hepatocellullar function and has low antioxidant capacity. However, slow weight gain and recovery associated with high mortality makes it difficult to wait for complete nutritional recovery before initiating HAART. Therefore developing a better understanding of the PK in these severely malnourished children will better inform future research as to the best timing of HAART initiation in severely malnourished children.

Furthermore, the findings of this study will provide information on the PK of HAART in severely malnourished children compared to children with normal nutrition–mild malnutrition. It will inform us whether or not current recommended doses are optimum for treating severely malnourished children. Results from this study will also have important implications for how best to administer new ARVs to severely malnourished children as new ARVs become available.

1.26 Pediatric Antiretroviral Drug Regimens

1.261 Zidovudine (ZDV, Retrovir®)

Zidovudine, a nucleoside analog, is an FDA-approved antiretroviral agent for the treatment of HIV infection (initially approved in March 1987). It is indicated for treatment of HIV-infected adults and children who have impaired immunity. Separate placebo-controlled studies evaluated zidovudine therapy in adults with asymptomatic HIV infection, early symptomatic disease and advanced symptomatic disease (30-32). In patients with advanced HIV disease, zidovudine therapy provided significant benefits in terms of reduced morbidity and decreased mortality. In those with less advanced HIV disease, zidovudine therapy was associated with a decrease in the rate of disease progression. Moderate antiviral activity has been documented for all stages of HIV disease.

Zidovudine is also indicated for the treatment of children with symptomatic HIV disease or those with laboratory evidence of significant immune deficiency. Zidovudine is commonly used as one of two "backbone" NRTI agents within HAART. The WHO currently recommends lopinavir/ritonavir plus an NRTI backbone of either zidovudine or abacavir (ABC) paired with lamivudine as the first line regimen for children less than three years of age. HIV-infected infants have a high mortality regardless of CD4 cell count, and this also was confirmed by the CHER study of HIV-infected children who received late HAART (33). Therefore the new WHO guidelines recommend that all HIV-infected infants should be initiated on HAART regardless of CD4 cell count or clinical state (4). PACTG 076 demonstrated that zidovudine therapy, initiated during the second or third trimester of pregnancy, can reduce the risk of perinatal transmission of HIV by approximately two-thirds.

In general, the frequency and severity of adverse events associated with the use of zidovudine are greater in patients with advanced disease at the time of initiation of therapy. The most frequently reported adverse events are hematologic abnormalities including anemia and granulocytopenia. Some investigators are concerned that an increased incidence of anemia may occur among ZDV-treated infants and children in resource-poor settings where malnutrition and multiple infections may so predispose them. For this reason, hematology values will be monitored frequently. In placebo-controlled trials, the clinical side effects reported more by zidovudine than placebo recipients were nausea, insomnia, myalgia, severe headache, asthenia, dyspepsia, vomiting, anorexia, malaise, dizziness and constipation. The development of myositis, with and without elevated CPK levels, has been reported for some patients with advanced HIV disease receiving long-term zidovudine therapy.

Twice daily ZDV dosing is a common clinical practice for ease of administration and to promote adherence (34). Current WHO pediatric treatment guidelines for resource-limiting settings also recommend BID dosing. In a small pharmacokinetic study of six HIV-infected children, ZDV plasma pharmacokinetic parameters (AUC0-24 and C_{max}) were not significantly different when comparing BID vs. TID dosing (35).

Please refer to the Retrovir® package insert for complete prescribing information.

1.262 Lamivudine (3TC, Epivir®)

Lamivudine (3TC) was approved in November 1995 for use in infants greater than 3 months of age and in children based on efficacy studies in adults in conjunction with safety and PK studies in children. 3TC is the negative enantiomer of a synthetic cytidine analogue. 3TC requires intracellular phosphorylation to become active and does so preferentially, like ddI and zalcitabine (ddC), in resting cells. 3TC has activity against HIV-1 and HIV-2, as well as Hepatitis B virus (36). The CSF/plasma ratio in children is relatively low (0.11) compared with that of ZDV (0.25), but higher than that of ddI (0.05) (37). The bioavailability is approximately 66% in children and 86% in adolescents and adults. Its plasma half-life is 2 hours and its intracellular half-life is 10-15 hours, allowing for twice daily dosing.

When 3TC is administered as monotherapy, resistance emerges rapidly and is associated with a single genotypic mutation at codon 184. Resistance also develops rapidly (within weeks) when 3TC is used in non-suppressive combination antiretroviral regimens, such as dual NRTI therapy with ZDV/3TC (38). Therefore, optimal use of 3TC is within a combination of at least three ARV medications capable of providing full suppression of viral replication. 3TC-resistant virus may be partially cross-resistant to ddI and ddC. In vitro, development of the codon 184 3TC resistance mutation is associated with increased fidelity of the viral RT enzyme for its substrate (39). It is speculated that this could influence the evolution of the virus and may prevent or delay the generation of drug resistant variants. For example, the 184 mutation is reported to suppress ZDV resistance in vitro and when introduced into the background of a ZDV-resistant reverse transcriptase gene to suppress the effect of some ZDV resistance mutations (40). Additionally, the M184V mutation is associated with diminished viral replicative fitness (41).
Pediatric Experience

A phase I/II study of 3TC showed that the agent could decrease viral burden by 0.77 logs when used as monotherapy (37). In PACTG 300, children receiving ZDV and 3TC had a lower risk of HIV disease progression or death than those receiving ddI alone (42). In the European PENTA-4 double-blind, randomized trial of the addition of 3TC or placebo to NRTI therapy in pediatric patients with advanced disease, 3TC was well-tolerated when coupled with ZDV, ddI or ZDV plus ddC (43). In PACTG 338, 42% of previously treated children receiving triple combination ZDV, 3TC plus RTV had undetectable HIV-RNA at week 48 compared with 27% receiving a single NRTI plus RTV (44).

Adverse Effects

3TC is very well-tolerated. The major reported toxicities are pancreatitis and peripheral neuropathy (37). Headache, fatigue and gastrointestinal upset also have been described. Lactic acidosis and severe hepatomegaly with steatosis, including fatal cases, have been reported with the use of nucleoside analogues alone or in combination, including 3TC.

In 175 pediatric patients treated with 3TC, 10 cases of clinical pancreatitis and six cases of chemical pancreatitis have been reported. Patients have ranged from 29 months to 18 years of age. Total daily dose ranged from 64 mg to 350 mg and duration of treatment prior to the event varied from five weeks to 13 months. In 14 of these cases, causality was judged possibly related to 3TC or unknown. Ten of these 14 cases have possibly confounding factors including previous pancreatitis, cholecystitis/cholelithiasis, recent mumps vaccine, hemophilia, mycobacterium infection, and HIV progression. Concomitant medications listed for these patients that also may be linked to pancreatitis are cotrimoxazole, ddI, pentamidine, and ZDV. Only one patient had never received prior ART. None of the 16 patients died as a result of the pancreatitis (42,43).

Please refer to the Epivir® package insert for complete prescribing information.

1.263 Lopinavir/ritonavir (LPV/r, Kaletra®)

LPV/r is a fixed combination of LPV (133.3 mg) plus RTV (33.3 mg). LPV/r received FDA approval in 2000 for combination with other antiretroviral agents for the treatment of HIV-1 infection in adults and pediatric patients age six months and older. It is available in both liquid and solid formulations. Like other PIs, LPV/r is metabolized by the hepatic cytochrome P450 system and multiple drug interactions are possible (45). Administration of LPV/r with food increases plasma concentrations; to enhance bioavailability and minimize PK variability, LPV/r should be taken with food. Resistance to LPV/r has been associated with genotypic mutations at 11 positions of the protease enzyme including codons 10, 20, 24, 46, 53, 54, 63, 71, 82, 84, and 90. Importantly, high-level resistance generally requires at least six mutations. Cross-resistance among PIs is likely.

Pediatric Experience

The use of dual protease inhibitors that include RTV have been studied in adults. In these combinations, rather than being used for its ARV activity, RTV acts as a PK enhancer by inhibiting the metabolism of other PIs and therefore increasing its plasma concentrations. RTV inhibits the metabolism of LPV and thus increases its plasma concentration. Data on combination PIs in children is more limited. Abbott Study M98-940 is a phase I/II open-label study that evaluated the PK profile, tolerability, safety, and efficacy of LPV/r oral solution and either two NRTIs or NVP plus up to two NRTIs in 100 pediatric patients aged six months to 12 years of age at two doses, 230/57.5 mg/m^2 BID and 300/75 mg/m^2 BID. Treatment-naïve subjects also were taking d4T and 3TC and treatment-experienced subjects also were taking NVP and one to two NRTIs. PK profiles at study week three indicated that both the 230/57.5 mg/m^2 BID dose given without enzyme-inducing NVP and the 300/75 mg/m^2 BID dose given with NVP approximated adult exposures observed in the M98-720 study. Consequently, the dose for all subjects was changed to 300/75 mg/m^2 BID (46).

Children receiving LPV/r 300/75 mg/m^2 in combination with NVP and one or two NRTIs yielded a C_{trough} of 5.6 μg/mL (+/-3.3). Through 24 weeks of therapy, the proportion of patients with HIV RNA <400 copies/mL was 82% for antiretroviral-naïve patients and 66% for antiretroviral-experienced patients. Follow-up at 60 weeks was 77% and 70% for naïve and experienced patients, respectively (47). The mean increase from baseline in CD4+ cell count was 328 cells/mm^3 for antiretroviral-naïve and 335 cells/mm^3 for antiretroviral-experienced patients treated through 24 weeks. This increased to 404 cells/mm^3 for naïve patients and 238 cells/mm^3 for treatment-experienced patients at week 60.

In PACTG P1030, HIV-1-infected infants less than 6 months of age were treated with LPV/r 300/75 mg/m^2 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/m^2. Longer-term results indicated that, at 12 months of age, median LPV area under the curve was similar to older children and adults.

Adverse Effects

The most common side effects associated with LPV/r have been diarrhea, asthenia, and triglyceride and cholesterol elevations. Pancreatitis has been reported in adult patients taking LPV/r. High triglyceride levels may be a risk factor for pancreatitis to develop. As with all agents in this class, new onset diabetes mellitus, exacerbation of pre-existing diabetes mellitus, hyperglycemia, and diabetic ketoacidosis may occur. In the phase I/II Abbott Study M98-940, only one subject discontinued therapy due to a study drug-related adverse event (pancreatitis). Grade 3 or higher clinical adverse events included vomiting (1%) and rash (2%) (47).

Please refer to the Kaletra® package insert for complete prescribing information.

2.0 STUDY OBJECTIVES

2.1 Primary Objectives

2.11 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

2.12 To evaluate the safety and tolerability of ZDV, 3TC, and LPV/r in severely malnourished children and children with normal nutrition-mild malnutrition at 24 weeks following study entry

2.2 Secondary Objectives

2.21 To compare the minimum concentration (C_{trough}) of LPV/r between severely malnourished children and children with normal nutrition - mild malnutrition at 1, 4, 8, 12, 16, 24, 36 and 48 weeks following study entry

2.22 To investigate the impact of malnutrition on LPV protein binding by comparing the free fraction of LPV in severely malnourished children and children with normal nutrition – mild malnutrition at 1, 12 and 24 weeks following study entry

2.23 To compare the viral loads between severely malnourished children and children with normal nutrition – mild malnutrition at baseline, 12, 24, 36 and 48 weeks following study entry

2.24 To compare CD4 cell percent between severely malnourished children and children with normal nutrition – mild malnutrition at baseline, 12, 24, 36 and 48 weeks following study entry

2.25 To describe the recovery of lean body mass and linear growth in severe acute malnutrition at 24 and 48 weeks following study entry

3.0 STUDY DESIGN

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 infants and children aged ≥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.

Children in each cohort will be assigned to receive ZDV+3TC+ LPV/r. All subjects will continue on treatment and on study for 48 weeks after the initiation of HAART. Post study access to study HAART regimen: once the study is over, all children will be referred to their country national care program where they will be eligible to receive the standard of care in their country.

The study will be conducted in two stages.

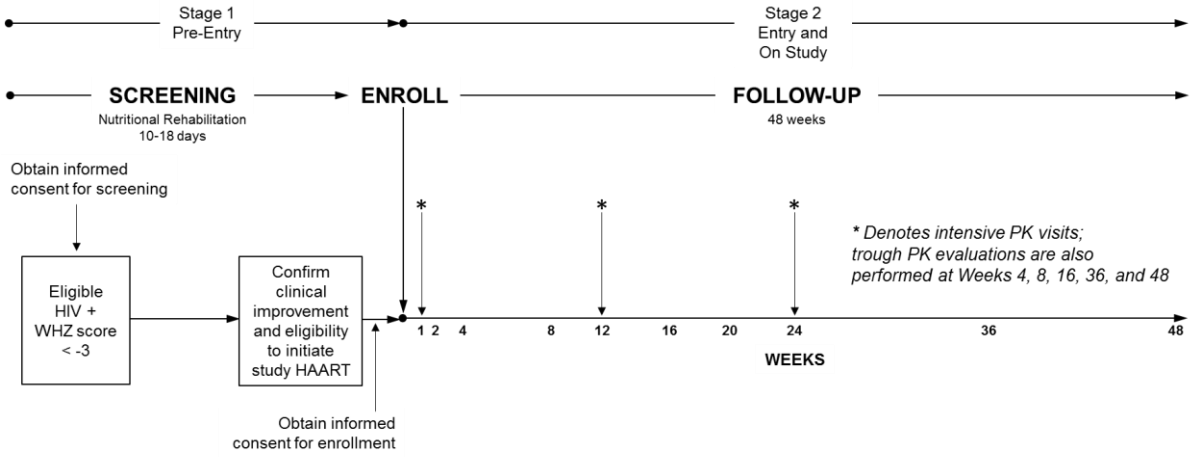
3.1 Stage 1: Pre-Entry/Screening

Cohort 1: Severely malnourished children
Severe acute malnutrition (SAM) in children age 6-59 months is defined by WHO (2013) as a weight-for-height less than -3 Z score using the WHO growth standards or a MUAC less than 115 mm (11.5 cm), or any degree of bilateral edema (49).

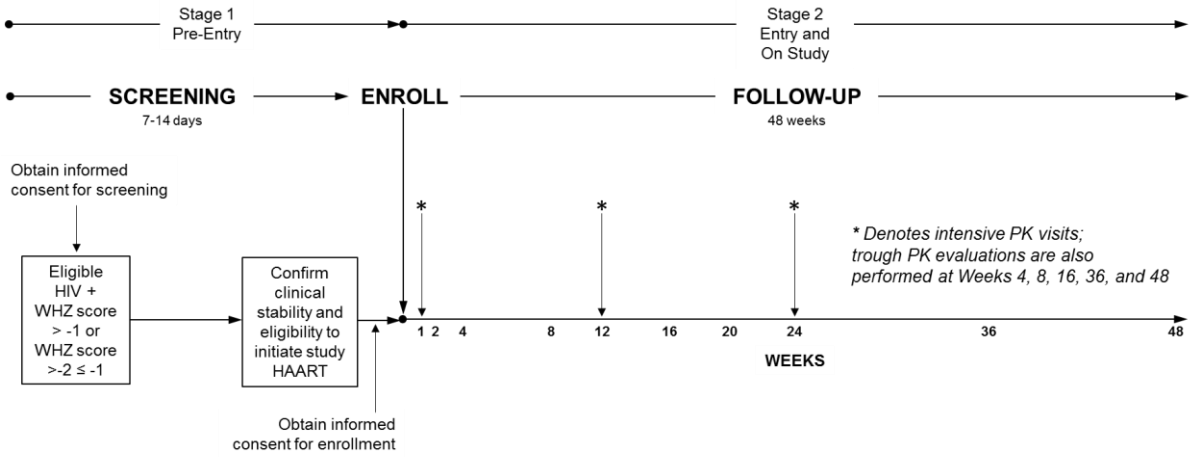
Sites will identify severely malnourished children admitted to the nutrition rehabilitation unit; however, children with edematous malnutrition will not be included in this study. All sites will manage these children according to WHO (2013) guidelines on managing children with severe malnutrition.

Study Flow Chart:

Normal Nutrition-Mild Malnutrition



Severe Malnutrition



Nutritional Rehabilitation

The World Health Organization recommends a ten step approach to the management of SAM as described in Table 1 (10). This involves a stabilization and rehabilitation phase. The stabilization phase which usually lasts up to two weeks includes feeding with management of the acute medical conditions and initiation of therapeutic feeding. This involves providing standard antibiotic coverage for bacterial infections, prevention of and treatment for hypoglycemia, hypothermia and dehydration if present. Electrolyte and micronutrient deficiencies are managed by supplementing potassium and magnesium, while multi-vitamins, zinc and folic acid are added to the feeds. Iron is replaced only in the rehabilitation phase because of the pro-oxidative effects and potential complication of worsening infections.

The initial feeds are small and frequent given every 2 to 3 hours and provide total of about 100kcal/kg/day. The World Health Organization recommends local hospitals to prepare milk referred to as F75 that is fortified with vitamins, electrolytes and micronutrients and contains 75 kcal/100ml and 0.9g of protein.

Children with SAM 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, 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.

Children will be carefully monitored throughout the stabilization phase as they are particularly susceptible to fluid overload and cardiac failure. Monitoring will include:

- Respiratory rate
- Vomiting
- Temperature
- Glucose level
- Stool frequency and consistency
- Amount of feed offered and left over. Note: while feeds need to be started in the stabilization phase, significant weight gain is not expected until underlying sepsis and electrolyte disturbances are treated and resolved.
- Weight gain

If children survive the immediate stabilization phase, the focus of care and management is to initiate and sustain catch up growth. However, full recovery and reaching expected weight-for-height will take about 6-8 weeks and therapeutic feeds therefore need to be continued at home.

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 children are stabilized and have appetite, they are ready to move into the rehabilitation phase, and should be transitioned from F75 to another milk formulation called F100 or an equivalent 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.

- F100 is a milk-based preparation with added vitamins and trace elements which has 100kcal/100 ml and 2.9g protein per 100ml. The volume of milk is increased to about 130ml/kg day while other foods are introduced and increased
- RUTF is an energy dense food usually containing peanut butter, milk powder, oil, sugar and micronutrients with an equivalent nutritional content to F100. The major advantage of RUTF over milk F100 is that it can be given to the mother to take and safely use at home whereas F100, being a milk preparation that is easily contaminated unless prepared in hygienic conditions, is reserved for hospital use only.
- In the rehabilitation phase, children recovering from SAM will consume about 200-230 kcal/kg/day and between 5-7gm protein/kg/day.
- Expected daily weight gain of HIV uninfected children in rehabilitation phase of Severe Acute Malnutrition:
  - Poor: < 5g/kg/day
  - Moderate: 5-10 g/kg/day
  - Good: > 10g/kg/day

HIV-infected children with SAM should be managed with the same therapeutic feeding approaches as children who are HIV-uninfected. 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.

Discharge criteria
Readiness for discharge from hospital 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

Play and emotional stimulation are also essential elements of management in this phase as these can directly influence clinical outcomes including growth. Attending to maternal needs and preparing her to look after her child once discharged are similarly important.

Table 1. The WHO ten-step approach to management of severe malnutrition

Treat/Prevent hypoglycaemia
Treat/Prevent hypothermia
Treat/Prevent dehydration
Correct electrolyte imbalance
Treat/Prevent infection
Correct micro deficiencies
Initiate refeeding
Facilitate catch up growth
Provide sensory stimulation and emotional support
Prepare for follow up and recovery

Stage 1: Pre-Entry/Screening (continued)

Cohort 2: Normal nutrition–mild malnutrition children

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

Normal nutrition = WHZ score >-1
Mild malnutrition =WHZ score >-2 ≤-1

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 case report form (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.

3.2 Stage 2: Entry

Stage 2 begins with the study entry visit and initiation of the study HAART regimen.

Criteria for Stage 2 Entry:

Cohort 1: Severely malnourished children

For children with severe malnutrition who are found to be eligible, 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 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 will be indicated by:

- Appetite returned and eating better - child shows interest in food even if does not complete amount given
- No edema and no recurrence of edema
- No recurrence of diarrhea (if present earlier)
- Normalized sodium and potassium defined as severity grade 1 or lower
- No evidence of cardiac failure
- No hypothermia or pyrexia - temperature stable at >35.0 to <38.0° C (non-axillary) or >34.4 to <37.4° C (axillary)
- Ideally, HIV-infected children will show weight gain of about 3-5gm/kg body weight/day for 1-2 days as expected among recovering HIV- uninfected children. However, HIV-infected children will still be enrolled as long as the criteria above are fulfilled and there is no further weight loss.

Cohort 2: Normal nutrition–mild malnutrition children

For children with normal nutrition-mild malnutrition who are found to be eligible, entry into the study will occur after written informed consent has been obtained and within 7-14 days 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:

- Normalized sodium and potassium defined as severity grade 1 or lower
- No evidence of cardiac failure
- No hypothermia or pyrexia - temperature stable at >35.0 to <38.0° C (non-axillary) or >34.4 to <37.4° C (axillary)

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.

Eligible and enrolled children will initiate the study HAART regimen with doses prescribed based on weight bands. 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, and adverse event monitoring will be carried out.

3.3 Criteria for Continued Participation in Pharmacokinetics Testing

Prior to conducting the intensive pharmacokinetic measurements at 1, 12 and 24 weeks, the severely malnourished children must be judged by their clinician to be nutritionally and clinically improved. If a child's condition is not improving or if there are signs of clinical deterioration including weight loss or development of edema at any time during the study period, the child should be readmitted and managed according to WHO guidelines. **All children who develop edema during the course of the study will be discontinued from the PK component but continue on study/off study drug.** Those with only weight loss, but no edema will have their PK evaluations done but blood volumes drawn will be according to their current weight. In addition, the subject's most recent hemoglobin 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.

3.4 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 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 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.

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

4.0 SELECTION AND ENROLLMENT OF SUBJECTS

4.1 Inclusion Criteria

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

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

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.

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

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

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

4.15 Parent or legal guardian able and willing to provide signed informed consent, remain within the study area during the study period and agree to have subject followed at the clinical site

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

<u>Hematology testing indicates</u>

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

<u>Chemistry testing indicates</u>

- AST ≤ Grade 2
- ALT ≤ Grade 2
- Creatinine ≤ Grade 1
- Sodium ≤ Grade 1
- Potassium ≤ Grade 1
- Bicarbonate ≤ Grade 1

4.17 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
- Normalized 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)

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

- Good appetite
- Normalized 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)

4.2 Exclusion Criteria

4.21 Edematous malnutrition at the time of study entry

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

4.23 Chemotherapy for malignancy

4.24 Acute infection for which the child has received appropriate antimicrobial treatment for <5 days

4.25 Tuberculosis disease

4.26 Clinical hepatitis as evidenced by jaundice and hepatomegaly

4.27 Taking any disallowed medications (see Section 4.32)

4.28 Any condition, situation, or clinical finding that in the opinion of the investigator would place the child at an unacceptable level of risk for injury, or render the child/caregiver(s) unable to meet the requirements of the study, interfere with study participation, or in the interpretation of study results.

4.3 Concomitant Medication Guidelines

4.31 Precautionary Medications

Please refer to the study medications' most recent package inserts, Investigator's Brochures, or updated information from DAIDS (RSC) to obtain the most current information on drug interactions, contraindications, and precautions.

4.32 Disallowed Medications

The following medications are disallowed while on study:

- Use of known inducers or inhibitors of cytochrome P450, such as rifampicin, ketoconazole, anticonvulsants
- Herbal medications
- Antihyperlipidemic agents
- Rifabutin
- Flecainamide
- Propafenone
- Astemizole
- Terfenadine
- Diydroergotamine
- Ergonovine
- Ergotamine
- Methylergonovine
- Cisapride
- Pimozide
- Midazolam (allowed if used in a monitored setting for procedures)
- Triazolam

4.4 Enrollment Procedures

Prior to implementation of this protocol, and any subsequent full version amendments, each site must have the protocol and the protocol informed 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 is required from each site participating in the study. The plan must be submitted to the Protocol Team for review and approval before protocol registration can occur.

Written informed consent 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, screening evaluations may be performed 7-14 days (for children with normal nutrition to mild malnutrition) or 10-18 days (for children with severe malnutrition) prior to six months (180 days) of age, 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.

4.5 Co-enrollment Procedures

Co-enrollment into other studies will be considered on a case by case basis and requires the approval of the protocol chairs of P1092 and the co-enrollment protocols.

5.0 STUDY TREATMENT

5.1 Drug Regimens, Administration and Duration

For purposes of this study, LPV/r, ZDV and 3TC are all considered to be study drugs.

All children will receive the same starting regimen: a LPV/r-based regimen, with ZDV/3TC as the backbone. 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.

Arms A, B, C, D
Day 0-Week 48
Lopinavir/Ritonavir two times daily orally at the WHO weight band dose
Zidovudine two times daily orally at the WHO weight band dose
Lamivudine two times daily orally at the WHO weight band dose

Lopinavir/Ritonavir Administration
Administer lopinavir/ritonavir every 12 hours according to weight band dosing. Lopinavir/ritonavir must be taken with food. The Dosing Table presents dosing guidelines for zidovudine, lamivudine, and lopinavir/ritonavir oral solution based on body weight.

All liquid doses should be administered using a calibrated dosing syringe. Contact the protocol pharmacist for information regarding purchasing calibrated dosing syringes.

Dosing Table

Drug	Strength	Dose Volume by Weight Band for Study-Supplied LIQUID Formulations *(twice daily)*				
		3.0-5.9 kg	6.0-9.9 kg	10.0-13.9 kg	14.0-19.9 kg	20.0-24.9 kg
ZDV	10 mg/mL	6 mL	9 mL	12 mL	15 mL	18 mL
3TC	10 mg/mL	3 mL	4 mL	6 mL	8 mL	10 mL
LPV/r	80/20 mg/mL	1 mL	1.5 mL	2 mL	2.5 mL	3 mL

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.

5.2 Drug Formulation and Storage

This protocol will use pediatric liquid formulations.

Zidovudine
Zidovudine (ZDV, Retrovir®) will be available as a strawberry-flavored clear colorless to pale yellow syrup in a glycerin/sucrose base at a concentration of 10 mg/ml. The ZDV syrup will be supplied in opaque plastic bottles with child resistant closures. Store at room temperature, 15°-25°C (59°-77°F).

Lamivudine
Lamivudine oral solution (Epivir®, 3TC) is for oral administration. One milliliter (1 mL) of lamivudine oral solution contains 10 mg of lamivudine (10 mg/mL) in an aqueous solution and the inactive ingredients artificial strawberry and banana flavors, citric acid (anhydrous), methylparaben, propylene glycol, propylparaben, sodium citrate (dihydrate), and sucrose. Store in tightly closed bottles at 25°C (77°F). See USP Controlled Room Temperature.

Lopinavir/ritonavir
Lopinavir 80 mg/ritonavir 20 mg per milliliter oral solution (Kaletra®, LPV/r) contains 42.4% alcohol by volume. Inactive ingredients: acesulfame potassium, alcohol, artificial cotton candy flavor, citric acid, glycerin, high fructose corn syrup, Magnasweet-110 flavor, menthol, natural and artificial vanilla flavor, peppermint oil, polyoxyl 40 hydrogenated castor oil, povidone, propylene glycol, saccharin sodium, sodium chloride, sodium citrate, and water.

Store lopinavir 80 mg/ritonavir 20 mg oral solution at 2°- 8°C (36°-46°F) until dispensed to subject. Avoid exposure to excessive heat. Refrigerated lopinavir 80 mg/ritonavir 20 mg oral solution remains stable until the stated expiration date. For subject use, if the lopinavir 80 mg/ritonavir 20 mg oral solution is stored at room temperature, up to 25°C (77°F), it should be used within 2 months.

5.3 Drug Supply, Distribution and Pharmacy

Zidovudine 10 mg/mL syrup and lamivudine 10 mg/mL oral solution will be supplied by ViiV Healthcare Ltd. Lopinavir 80 mg/ritonavir 20 mg per milliliter oral solution will be supplied by Abbott Laboratories.

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 provided 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.

		Dose Volume by Weight Band for LIQUID Formulation *(twice daily)*				
Drug	**Strength**	**3.0-5.9 kg**	**6.0-9.9 kg**	**10.0-13.9 kg**	**14.0-19.9 kg**	**20.0-24.9 kg**
ABC	**20 mg/mL**	**3 mL**	**4 mL**	**6 mL**	**—**	**—**

		Number of Tablets by Weight Band for DISPERSIBLE TABLET Formulation *(twice daily)*				
Drug	**Strength**	**3.0-5.9 kg**	**6.0-9.9 kg**	**10.0-13.9 kg**	**14.0-19.9 kg**	**20.0-24.9 kg**
ABC	**60 mg**	**1**	**1.5**	**2**	**2.5**	**3**

6.0 SUBJECT MANAGEMENT

6.1 Team Communications

Questions concerning clinical management of study subjects and all communication regarding adverse events (AEs) should be addressed to the P1092 Core Team at impaact.corep1092@fstrf.org. Include the subject's PID when applicable. The appropriate team member will respond via e-mail, generally within 24 hours (Monday-Friday).

6.2 Toxicity Management

The Division of AIDS Table for Grading the Severity of Adult and Pediatric Adverse Events, (DAIDS AE Grading Table), 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 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 for which a relationship to study drugs cannot be excluded. Clinical or laboratory 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. 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 replacement with ABC	ZDV may be replaced with ABC 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.
Grade 4 adverse events that are definitely not related to study drugs	Notify Core Team 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.

DMC-generated reports of all Grade 2 LFTs, and Grade 3 and 4 AEs for which a relationship to study drugs cannot be excluded will be reviewed by the P1092 Core Team on a regular basis.

Subjects who prematurely discontinue study treatment will be placed in an off drug/on study category and continue to be followed for the duration of the study.

6.21 General Toxicity Management Guidelines

Grade 1 Toxicity:
Continue study drugs.

Grade 2 Toxicity:
Continue study drugs.

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. 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.

6.22 Hematologic Toxicity on a ZDV-Inclusive Regimen and ZDV Intolerance

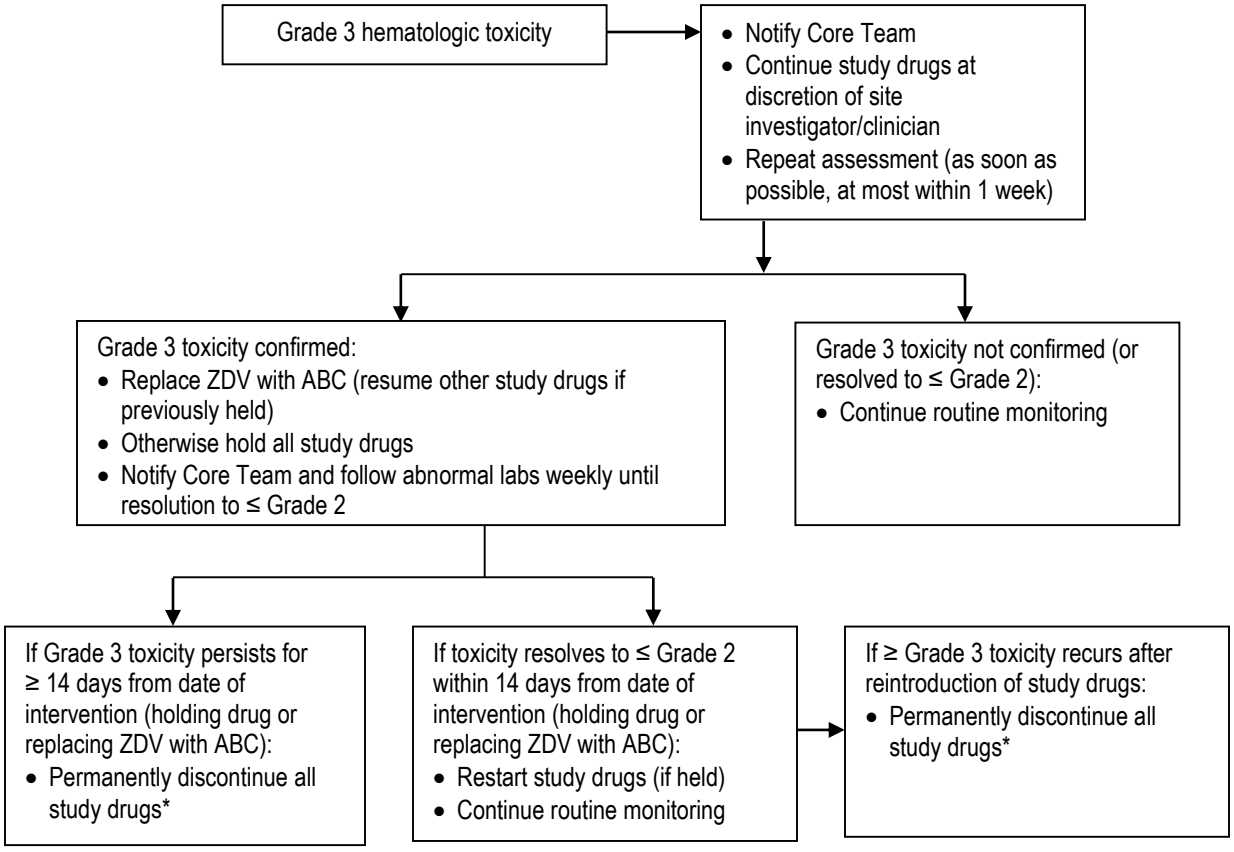
NOTE: For subjects not receiving ZDV, follow general toxicity management guidelines in Section 6.11.

Grade 1 Hematologic Toxicity
Continue study drugs.

Grade 2 Hematologic Toxicity
Continue study drugs.

Grade 3 Hematologic Toxicity

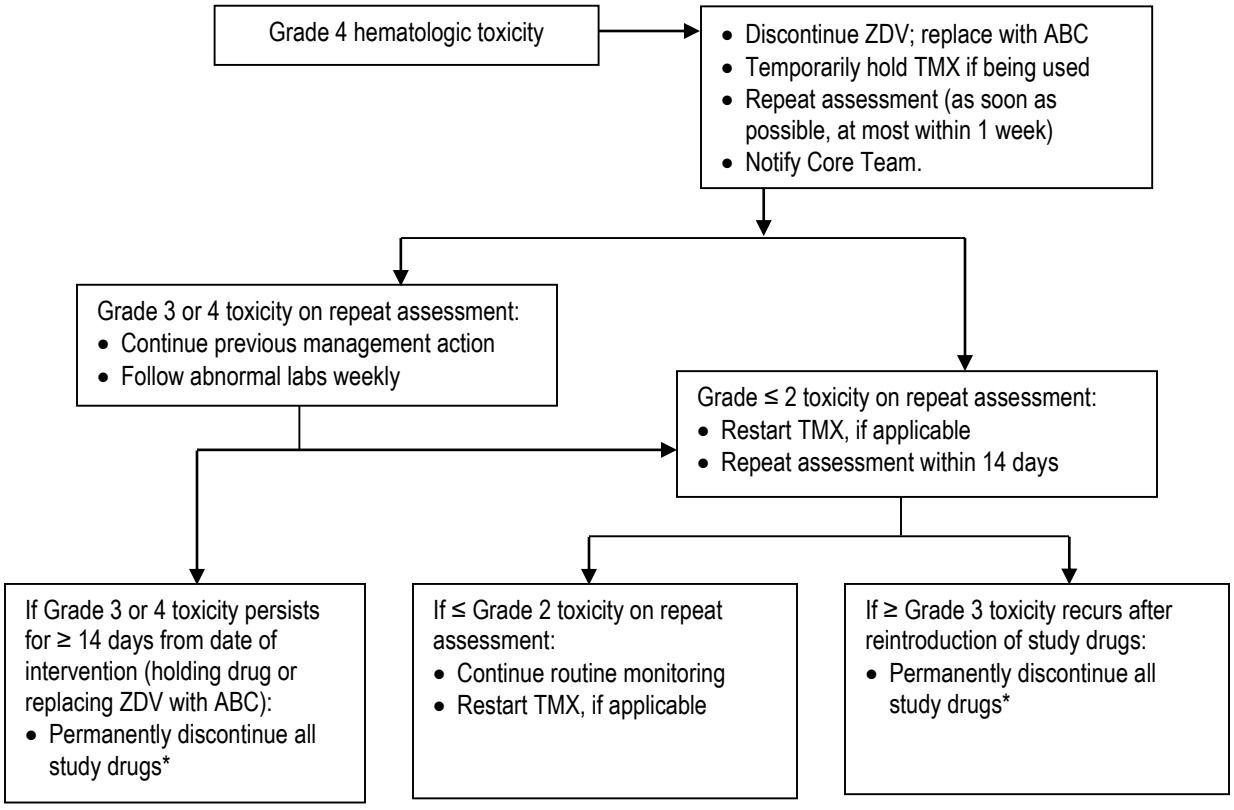
For Grade 3 hematologic toxicity — involving hemoglobin level, white blood cell count, absolute neutrophil count, or platelet count — on a ZDV-inclusive regimen, continue study drugs at the discretion of the site investigator/clinician while awaiting a repeat assessment/confirmation of the abnormal laboratory 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). Abnormal laboratory value(s) should be followed weekly until resolution to ≤ Grade 2. If trimethoprim/sulfamethoxazole is being administered for prophylaxis, the site investigator/clinician may decide to continue or discontinue this in the presence of Grade 3 hematologic toxicity.



*Site clinician may choose to continue the child on non-study HAART based on local treatment standards and the best interest of the child.

Grade 4 Hematologic Toxicity

For Grade 4 hematologic toxicity — involving hemoglobin level, white blood cell count, absolute neutrophil count, or platelet count — on a ZDV-inclusive regimen, ZDV should be discontinued and substituted with ABC. Notify the Core Team within 3 business days. If trimethoprim/sulfamethoxazole is being administered for prophylaxis, it should be temporarily held. Repeat assessment should be done as soon as possible (at most within one week). If repeat assessment confirms Grade 4 non-life threatening hematologic toxicity and this persists for more than 14 days, study drugs should be permanently discontinued. Abnormal laboratory value(s) should be followed weekly. The child may remain on study drugs/on study if the toxicity resolves to ≤ Grade 2 within 14 days. If resolution to ≤ Grade 2 does not occur within 14 days or ≥ Grade 3 toxicity recurs, all study drugs must be permanently discontinued.



*Site clinician may choose to continue the child on non-study HAART based on local treatment standards and the best interest of the child.

6.23 Symptomatic and Asymptomatic Hepatitis in Subjects on Study Drug

6.231 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. Management of hepatitis will be according to the grading of AST/ALT stipulated below.

6.232 AST/ALT Elevations

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

Grade 1

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

- AST and ALT must be repeated as soon as possible (at most within one week).
- Study drugs may be continued while repeating AST and ALT as long as the subject is asymptomatic. Subjects with a confirmed Grade 1 AST or ALT who are asymptomatic may continue study drugs with continued close observation.
- For study subjects with Grade 0 AST and/or ALT at study entry, an increase to Grade 1 AST and/or ALT even in an asymptomatic subject may be of concern.
- Subjects should be evaluated for a cause of the LFT abnormality, and should be observed for worsening LFT elevation or development of clinical hepatitis. Careful assessments should be undertaken for non-study drug-related toxicity, the lactic acidosis syndrome, and viral hepatitis as the cause of the transaminase elevation.

Grade 2

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

- AST/ALT must be repeated as soon as possible (at most within one week) and then be followed weekly until levels are $\leq$ Grade 1.

- Study drugs may be continued while repeating AST and ALT as long as the subject is asymptomatic. Subjects with a confirmed Grade 2 AST or ALT who are asymptomatic may continue study drugs with continued close observation.
- Subjects should be evaluated for a cause of the LFT abnormality, and should be observed for worsening LFT elevation or development of clinical hepatitis. Careful assessments should be undertaken for non-study drug-related toxicity, the lactic acidosis syndrome, and viral hepatitis as the cause of the transaminase elevation.
- If the AST/ALT elevation is considered most likely due to concomitant illness or medication, then standard management, including discontinuation of the likely causative medication, should be undertaken.

Grades 3 and 4

- Hold study drugs while awaiting a repeat assessment/confirmation of the abnormal laboratory test as soon as possible but at most within 7 days.
- 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 toxicity within 3 business days.
- If the AST/ALT elevation does not improve to $\leq$ Grade 2 within two weeks of discontinuing study drug, all study drugs should be permanently discontinued.
- If an alternate cause of the AST/ALT elevation can be established (i.e. confirmed diagnosis Hepatitis A) Study drugs may be restarted after resolution of AST/ALT to $\leq$ Grade 2 and within 21 days of the initial elevation. If the AST/ALT does not resolve to $\leq$ Grade 2 within 21 days, all study drugs must be permanently discontinued. If $\geq$ Grade 3 elevation in AST/ALT recurs after reintroduction of study drugs, all study drugs must be permanently discontinued. The protocol team will be notified to discuss further management.
- Subjects should be evaluated for development of clinical hepatitis. Careful assessments should be undertaken for non-study drug-related toxicity, the lactic acidosis syndrome, and viral hepatitis as the cause of the transaminase elevation.

6.24 Rash

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 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 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.

6.3 Endpoints

6.31 Toxicity Endpoints

Any one of the following constitutes a toxicity endpoint:

- Persistent (lasting ≥ 14 days) or recurrent treatment-related Grade 3 toxicity
- Persistent (lasting ≥14 days), non-life-threatening, treatment-related Grade 4 toxicity (confirmed within 7 days) or recurrence to Grade ≥ 3
- EXCEPTION: in the setting of ZDV and Grade 4 hematologic toxicity - persistent (lasting ≥ 14 days) treatment-related Grade 4 toxicity
- Single, treatment-related, life-threatening Grade 4 toxicity

Subjects who achieve any of the above toxicity endpoints will be placed in an off drug/on study category and continue to be followed for the duration of the study.

6.32 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.

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 >1000 copies/ml, the site investigator will intensify work with the subject's family to ensure adherence and if need be effect a change in ARV therapy.

6.33 Pharmacokinetic Endpoint

The primary pharmacokinetic endpoint is the area under the plasma concentration time curve from 0-12 hrs ($AUC_{0\text{-}12h}$) of 100 micrograms*hr/mL which will be estimated under steady-state conditions and PK trough of > 1 micrograms/mL

Additional parameters to be investigated include plasma clearance (CL/F), C_{trough} (collected just prior to the morning ARV dose), C_{max} (peak plasma concentration) and T_{max} (the time to reach C_{max}).

6.4 Criteria for Treatment Discontinuation

- Treatment with disallowed medications as described in Section 4.32.
- Drug toxicity that requires permanent study drug discontinuation as defined in Section 6.0

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.

6.5 Criteria for Deferral of PK Evaluations

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.

6.6 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.
- 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.

6.7 Criteria for Study Discontinuation

- The parent or legal guardian refuses further treatment and/or follow-up evaluations.
- The investigator determines that further participation would be detrimental to the subject's health or well-being.
- The subject fails to comply with the study requirements so as to cause harm to him/herself or seriously interfere with the validity of the study results

7.0 EXPEDITED ADVERSE EVENT REPORTING

7.1 Adverse Event Reporting to DAIDS

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

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

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).

7.2 Reporting Requirements for this Study

The SAE Reporting Category, as defined in Version 2.0 of the DAIDS EAE Manual, will be used for this study.

The study agents for which 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 SAEs 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.

The death of any subject after enrollment or within 30 days of study completion, regardless of the cause, must be reported within three business days of first becoming aware of the death. If an autopsy is performed, the report must be provided. Reports of all deaths must be communicated as soon as possible to the appropriate IRB or EC and/or reported in accordance with local law and regulations.

For all SAEs submitted to RSC, sites must file an updated SAE report to RSC with the final or stable outcome (Status Code p. 5 of the EAE form) unless the SAE reported in the initial EAE form already had a final or stable outcome.

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 2.0, dated November 2014, must be used and is available on the RSC website at http://rsc.tech-res.com/safetyandpharmacovigilance/

7.4 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).

After the protocol-defined reporting period, unless otherwise noted, only SUSARS as defined in Version 2.0 of the EAE Manual will be reported to DAIDS if the study staff become aware of the events on a passive basis (from publicly available information).

7.5 CRF Recording Requirements for Laboratory Test Results, Signs, Symptoms, and Diagnoses

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.

8.0 STATISTICAL CONSIDERATIONS

8.1 General Design Issues

This is a Phase IV, multicenter, open label, intervention pharmacokinetic study to compare the pharmacokinetics, safety and tolerance of ZDV+3TC+LPV/r in severely malnourished and normal – mildly malnourished children. Two cohorts will be formed (severely malnourished and normal – mildly malnourished) and age-based strata (threshold 18 months of age) will be formed within each cohort. Within each stratum in each cohort, patients will be assigned to ZDV+3TC+LPV/r. Because it is desired that the two cohorts have comparable age distributions, upper bounds on stratum arm enrollments will be established, as described in section 8.3.

8.2 Outcome Measures

All components of treatment regimens will be evaluated in six conditions (two initial nutritional states and three follow-up times: 1, 12 and 24 weeks following study entry).

Primary Outcome Measures

- Steady-state AUC and plasma clearance (CL/F) for ZDV, 3TC, and LPV/r
- Safety and tolerability measures, which include numbers and percent of subjects with at least Grade 3 adverse events related to study drugs and at least Grade 3 adverse events regardless of the relationship to study drugs.

Secondary outcome measures include:

- The minimum concentration ("trough") of LPV/r in the two cohorts, at Weeks 1, 4, 8, 12, 16, 36 and 48
- The measures of LPV protein binding in the two cohorts at weeks 1, 12 and 24
- The HIV-RNA load and CD4 percent in the two cohorts at study entry and Weeks 12, 24, 36 and 48
- Description of the recovery of the lean body mass by assessment of weight to height z-score (WHZ) and mid-upper arm circumference (MUAC) in children in severe acute malnutrition at Weeks 24 and 48
- Assessment of height and change in height over time in severe acute malnutrition.

8.3 Randomization and Stratification

There will be no randomization in this study. Eligible HIV-infected severely malnourished children and HIV-infected children with normal nutritional status–mild malnutrition will be enrolled into this study. Children with severe malnutrition will be enrolled to Cohort 1, and children with normal – mild malnutrition will be enrolled to Cohort 2. Within cohorts, age strata will be defined with threshold 18 months, and children will be assigned to LPV/r-containing arms with common ZDV+3TC backbone. An initial upper bound of 13 patients per stratum arm combination will be established. Once this bound is reached, no more patients will be enrolled to that study cell. If, as the study matures and 2 of 4 cells have reached capacity, the team may reevaluate the values of upper bounds, recognizing that PK analysis can accommodate imbalances of approximately 20% between groups without sacrificing interpretability.

8.4 Sample Size and Accrual

The primary objective is to compare severely malnourished and normal–mildly malnourished children on HAART with respect to pharmacokinetic exposures quantified as concentration AUCs. The coefficient of variation of AUC for LPV was estimated to be approximately 0.40 in similarly aged children (50). The protocol team considers a 40% difference between groups with respect to LPV AUC to be clinically important. A parallel-

arm study with two groups would require N=17 patients per group to detect a 40% difference between groups in the LPV AUC with 80% power and a two-sided Type I error of 5% for a CV of 0.4. In addition, a 10% LTFU and 20% mortality rate (current mortality rate in the malnutrition unit) is considered for the estimate. This yields a necessary sample size of 17 children + 30% for a total of 23 children required per treatment group. Because of uncertainties in the estimation of AUC CV and possible heterogeneity in variance associated with differential malnutrition status, we suggest a further 10% inflation to 25 children per nutrition status stratified by age.

The following table gives the 90% confidence intervals (CI) associated with various potential rates. This will provide 95% confidence that the rate of severe adverse effects is not greater than the upper limit of the CI. These intervals are computed for a sample of 17 evaluable subjects per group. Because of the small sample sizes, these intervals will be calculated using exact methods, rather than normal distribution approximations.

Table 2: 90% Confidence Intervals for Potential Rates of Severe Adverse Events

Proportion of Subjects with Severe Adverse Events	90% Confidence Limits	
	Lower	Upper
0.000 (0/17)	0.000	0.162
0.059 (1/17)	0.003	0.250
0.118 (2/17)	0.021	0.326
0.176 (3/17)	0.050	0.396
0.235 (4/17)	0.085	0.461
0.294 (5/17)	0.124	0.522
0.353 (6/17)	0.166	0.580
0.412 (7/17)	0.212	0.636
0.471 (8/17)	0.260	0.689
0.529 (9/17)	0.311	0.740
0.588 (10/17)	0.364	0.788
0.647 (11/17)	0.420	0.834
0.706 (12/17)	0.478	0.876
0.765 (13/17)	0.539	0.915
0.824 (14/17)	0.604	0.950
0.882 (15/17)	0.674	0.979
0.941 (16/17)	0.750	0.997
1.000 (17/17)	0.838	1.000

This table shows that if 4 of 17 subjects (23.5%) in a group experience adverse events, with 95% confidence the true rate in the population represented by this sample is very likely no greater than 0.461. The relatively wide range in the confidence interval reflects imprecision due to the small sample size.

An N of 25 is our best guess of the number needed to get 17 evaluable; if because of the unusual nature of this population a greater loss to follow-up is encountered or data is deemed unevaluable enrollment may be extended beyond 25 to reach 17 evaluable.

Therefore, a total of 50 children, (25 severely malnourished and 25 normal nutrition–mildly malnourished) are required for study completion.

Evaluable participants: The goal of the study is to have all subjects have intensive PK parameters available for weeks 1, 12 and 24 following initiation of HAART. Therefore, in order for a subject to be evaluable, the subject must have results for the week 1 intense PK evaluations and either week 12 or 24 intense PK results.

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 a 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.

8.51 Rules for Suspending Accrual to Assess Safety Following an Adverse Event

Accrual will be temporarily suspended if:

- Any subject has a life-threatening adverse event that is judged to be probably or definitely attributable to study drug or Grade 4 event that may not be judged to be life-threatening but is judged to be probably or definitely attributable to study drug.
- Or if more than six out of the first 20 subjects or at least 30% of subjects thereafter have Grade 3 or greater toxicity that is judged to be definitely related to study drug.

Following temporary suspension of accrual, the protocol team will further review the safety data within 48 hours of notification of the event to determine if continuation of accrual is appropriate. If the protocol team, including the study chair and the DAIDS medical officer of record agree that the study drug is likely to be safe for additional subjects, they may allow accrual to resume. Regulatory agencies (IRB/EC) will be notified of the event and the protocol team's decision after this review of the safety data has taken place.

8.52 Accrual Rate Evaluation

Accrual to this study will be monitored by the IMPAACT leadership in accordance with standard operating procedures. Initially, the protocol team will monitor site registration and site activation monthly to ensure that an adequate number of sites have registered to complete the protocol. The expected period of enrollment will be over 12 months, but should allow up 18 months since the malnourished may be hard to accrue quickly. 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.

Monthly conference calls will be held by the study team to assess accrual of both severely malnourished and normal–mildly malnourished subjects, and follow-up statistics will be reported to the team by the data management group on a monthly basis. Rate of enrollment will be closely monitored with input provided from team members and participating sites. If any group has not accrued half of its subjects within 12 months after opening of the protocol, the team will identify the reasons for lack of accrual and take corrective actions to speed enrollment if needed.

8.6 Analyses

Details on pharmacokinetic analyses are given in sections 9.1 and 9.3 below. Analysis of safety and tolerability data will take the form of detailed tabulation of all adverse events and computation of confidence intervals for incidence of severe adverse events by month of study follow-up.

Comparison of LPV protein binding characteristics and HIV RNA viral load and CD4 percent will occur through standard two-sample analyses. Pre-specified null hypotheses will be tested individually at the 0.05 level of significance. Ad hoc analysis of data within subgroups will be presented with caveats and attention to multiple testing corrections.

9.0 CLINICAL PHARMACOLOGY PLAN

9.1 Pharmacology Objectives

- 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).
- To compare the minimum concentration (C_{trough}) of LPV/r between severely malnourished children and children with normal nutrition - mild malnutrition at 1, 4, 8, 12, 16, 36 and 48 weeks following study entry.
- To investigate the impact of malnutrition on LPV protein binding by comparing the free fraction of LPV in severely malnourished children and children with normal nutrition – mild malnutrition at 1, 12 and 24 weeks following study entry.

9.2 Primary and Secondary Data

Primary objectives concern: PK AUCs to be analyzed. Non-compartmental analysis will be performed for individual PK estimates via the linear up-log down trapezoidal rule in conjunction with an oral input model using WinNonlin 5.0.1 (Pharsight Corporation, Mountain View, USA). Safety and tolerability analysis will consist of summaries of numbers of adverse and severe adverse events encountered in all strata with exact testing of hypotheses of equal rates of adverse events and rates of treatment cessation due to tolerability concerns. Secondary objectives include comparison of C_{trough} values of LPV/r at 1, 4, 8, 12, 16, 24, 36 and 48 weeks, albumin concentrations, CD4 and HIV RNA viral load measures at baseline, 12, 24, 36 and 48 weeks and linear growth at 24 and 48 weeks. Week 1, 12 and 24 week trough measurements will be collected as part of the intensive PK assessments. Full descriptive statistics and appropriate tests of relationships between malnutrition status, drug exposure, and distributions of these clinical parameters will be provided.

ZDV may be changed to ABC if hematologic toxicity dictates. In this case the subject may continue but analysis will be of 3TC and LPV/r.

9.3 Study Design, Modeling and Data Analysis

Plasma PK data from intensive sampling visit will be analysed using non-compartmental analysis to determine the following PK measures for ZDV, 3TC, LPV and RTV. C_{trough} (pre-dose sample concentration), C_{max} (peak plasma concentration) and T_{max} (the time to reach C_{max} after drug ingestion) will be determined by inspection of the results. Drug concentrations below the limit of quantification (BLQ) will be handled using standard pharmacokinetic methods (e.g., 50% BLQ or ‘0’ value) to assure all data are handled in a consistent manner.

Population PK analysis will be carried out utilizing the intensive PK data coupled with the trough measurements carried out throughout the 48 week study period.

Protein binding and albumin: Lopinavir free drug measurements will be carried out during the intensive PK sampling weeks when children are malnourished (week 1) and after they begin to improve nutritionally (weeks 12 and 24). Due to limitations for blood collection volumes, markers for malnutrition such as albumin will be collected at different study weeks (e.g baseline), but should still represent the child's overall nutritional status at the time of PK collections (week 1). Exploratory analysis relating malnutrition markers and the fraction of lopinavir binding will be carried out.

Target PK- The trough measurements collected in children will be compared to published measurements for lopinavir trough of >1 ng/mL. This latter trough estimate will be considered the target trough concentration for these children.

9.4 Anticipated Outcomes

The overall goal of the study aims is to determine if current dosing guidelines for LPV/r based HAART are optimum for severely malnourished children by comparing PK data generated in severely malnourished children to PK data generated in children with normal nutrition-mild malnutrition. The results from this study will also aid in determining appropriate timing of HAART initiation during nutritional rehabilitation in the severely malnourished children.

10.0 HUMAN SUBJECTS

10.1 Institutional Review Board and Informed Consent

This protocol, the informed consent documents (Appendices IV and V), and any subsequent modifications must be reviewed and approved by the Institutional Review Board (IRB) or Ethics Committee (EC) responsible for oversight of the study. Written informed consent must be obtained from the parents or legal guardians of subjects who cannot consent for themselves, such as those below the legal age. The informed consent will describe the purpose of the study, the procedures to be followed, and the risks and benefits of participation. A copy of the consent form will be given to the 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 programs will be done with coded numbers only. Clinical information will not be released without written permission of the subject's parent or Legally Authorized Representative, except as necessary for monitoring by the Office for Human Research Protections (OHRP), the NIAID or other authorized governmental agencies, or the local IRB/EC.

10.3 Study Discontinuation

The study may be discontinued at any time by IMPAACT, the NIAID, the IRB/EC, ViiV Healthcare Ltd, Abbott Laboratories, local regulatory authorities, the OHRP, or other governmental 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. Any presentation, abstract, or manuscript will be made available for review by the pharmaceutical sponsors prior to submission.

12.0 BIOHAZARD CONTAINMENT

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

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.

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APPENDIX I
SCHEDULE OF EVALUATIONS

	Stage 1	Stage 2											
	Screening[1]	Entry[2]	Week 1[17] (+ 3 days)	Week 2 (± 2 days)	Week 4 (± 7 days)	Week 8 (± 7 days)	Week 12 (± 7 days)	Week 16 (± 7 days)	Week 20 (± 7 days)	Week 24 (± 7 days)	Week 36 (±14 days)	Week 48 (±14 days)	Off treatment/ On study[18]
Informed Consent	X	X											
History[3]	X	X	X	X	X	X	X	X	X	X	X	X	X
Physical exam[4]	X	X	X	X	X	X	X	X	X	X	X	X	X
Nutrition assessment[5]	X	X	X	X	X	X	X	X	X	X	X	X	X
Hematology[6]	1mL		1mL		1mL	1mL	1mL			1mL		1mL	1mL
Chemistries[7]	2mL		2mL		2mL	2mL				2mL			2mL
Total protein/albumin		2mL				2mL		2mL				2mL	2mL
Glucose					1mL							1mL[8]	
Lipid profile[9]		1mL						1mL				1mL	
Micronutrients[10]		2mL										2mL	
Documentation of HIV infection[1]	0-3mL												
HIV-1 RNA [11]	1-3mL	1-3mL					1-3mL			1-3mL	1-3mL	1-3mL	1-3mL
Lymphocyte subsets[12]	1mL						1mL			1mL	1mL	1mL	1mL
Trough PK for weight ≥5kg[13]					0.8mL	0.8mL		0.8mL			0.8mL	0.8mL	
Trough PK for weight <5kg[13]					0.3mL	0.3mL		0.3mL			0.3mL	0.3mL	
Intensive PK for weight ≥5kg [14,16]			7 mL				7mL			7mL			
Intensive PK for weight <5kg[15,16]			1.8 mL				1.8 mL			1.8 mL			
TOTAL BLOOD	5-10mL	6-8mL	4.8-10 mL	-	4.3-4.8mL	5.3-5.8mL	4.8-12mL	3.3-3.8mL	-	6.8-14mL	2.3-4.8mL	9.3-11.8mL	7-9mL

Appendix I Footnotes:

1. Screening evaluations must be performed within 18 days prior to entry for Cohort 1 and within 14 days prior to entry for Cohort 2. For purposes of documentation of HIV infection for eligibility determination, if adequate documentation is available to fulfill the requirements of inclusion criterion 4.12, no HIV testing is required at Screening. If testing is required to fulfill the requirements of inclusion criterion 4.12, the HIV RNA PCR required at Screening may serve as one of the two required tests, and additional blood (1-3 mL) may be collected as Sample #1 and/or Sample #2.
2. Entry may occur when the subject is nutritionally stable. Eligible subjects will be considered enrolled in the study upon successful entry into the DMC's Subject Enrollment System (date of subject enrollment = day 0 for determining the target dates of all follow-up visits). The study HAART regimen must be initiated within 72 hours of enrollment/entry.
3. A complete history is required to be source documented at screening and at all follow-up visits; see Section 7.5 for CRF recording requirements for signs, symptoms, and diagnoses. All ARVs and concomitant medications taken within 30 days prior to study entry and throughout follow-up will be source documented and recorded on CRFs.
4. Physical exam includes length, weight, head circumference, and vital signs (temperature, heart rate, respiratory rate). Skin fold thickness (triceps) will be at entry, weeks 24 and 48.
5. Nutritional assessment includes mid upper arm circumference.
6. Hematology includes CBC with differential and platelet count.
7. Chemistries include AST, ALT, creatinine, sodium, potassium, chloride, and bicarbonate.
8. Obtain fasting if the subject is clinically stable. For subjects 6-24 months, collect specimen at least 3 hours after last meal; for subjects >24 months, collect specimen at least six hours after last meal.
9. Lipid profile includes triglycerides and total cholesterol.
10. Micronutrients include zinc and selenium to be processed and stored until shipping to the central laboratory for testing.
11. Must be performed at DAIDS VQA-certified laboratory.
12. Lymphocyte subsets include CD3/CD4/and CD3/CD8 absolute counts and percentages. Must be performed at DAIDS IQA/UK NEQAS-certified laboratory.
13. 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.*
14. For children weighing ≥5kg, obtain 0.8mL of blood at the following intensive PK sampling time points: pre-dose and 1, 2, 4, 8 and 12 hours post-dose. An additional sample of 2.2 mL whole blood (generating 1 mL of plasma) will be collected at the 2 hour time point to determine the free fraction of lopinavir at the time of the peak concentration.
15. For children weighing <5kg, obtain 0.3mL of blood at the following intensive PK sampling time points: pre-dose and 1, 2, 4, 8 and 12 hours post-dose.
16. Obtain intensive PK sampling if hemoglobin is ≥7.5 g/dl at the most recent prior evaluation, the child does not have diarrhea, and the child has not missed any ARV doses within the prior 72 hours.
17. 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).
18. 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: NIH recommendations for maximum pediatric blood draw volumes will be followed in this study. The volume of blood drawn at any study visit should not exceed 5 mL/kg in a single day and 9.5 mL/kg over any eight-week period. Priority of draw should be as follows: (1) Hematology, (2) Chemistries, (3) Pharmacokinetics, (4) HIV RNA, (5) Lymphocyte subsets.

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.

APPENDIX II
WORLD HEALTH ORGANIZATION (2013) APPROACH TO THE MANAGEMENT OF SEVERE ACUTE MALNUTRITION

The World Health Organization recommends local hospitals to prepare a milk referred to as F75 that is fortified with vitamins, electrolytes and micronutrients and contains 75 kcal/100ml and 0.9g of protein. The initial feeds are small and frequent given every 2 to 3 hours and provide a total of about 100kcal/kg/day.

Children with severe acute malnutrition (SAM) may also require vitamin A, zinc, and antibiotics. Children with SAM should be provided with about 5000 IU vitamin A daily, either as an integral part of therapeutic foods or as part of a multi-micronutrient formulation. Children with SAM do not require a high dose of vitamin A as a supplement if they are receiving F75, F100 or ready-to-use therapeutic food that comply with WHO specifications (and therefore already contain sufficient vitamin A), or vitamin A is part of other daily supplements. Children with SAM should be given a high dose of vitamin A (50 000 IU, 100 000 IU or 200 000 IU, depending on age) on admission, only if they are given therapeutic foods that are not fortified as recommended in WHO specifications and vitamin A is not part of other daily supplements. 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.

Children with HIV and severe acute malnutrition should be given the same antiretroviral drug treatment regimen as HIV-infected children without severe acute malnutrition. HIV-infected children with severe acute malnutrition should also be given the same therapeutic feeding as children with severe acute malnutrition that are not HIV-infected.

Children need to be carefully monitored throughout the stabilization phase as they are particularly susceptible to fluid overload and cardiac failure. Monitoring should include:

- Respiratory rate
- Vomiting
- Temperature
- Glucose level
- Stool frequency and consistency
- Amount of feed offered and left over. Note: while feeds need to be started in the stabilization phase, significant weight gain is not expected until underlying sepsis and electrolyte disturbances are treated and resolved.

If children survive the immediate stabilization phase, the focus of care and management is to initiate and sustain catch up growth. However, full recovery and reaching expected weight-for-height will take about 6-8 weeks and therapeutic feeds therefore need to be continued at home.

Increase in appetite is one of the most important signs indicating that the child is entering the rehabilitation phase. Once children are stabilized, have appetite and reduced edema, they are ready to move into the rehabilitation phase, and should be transitioned from F75 to another milk formulation called F100 or an equivalent 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.

- F100 is a milk-based preparation with added vitamins and trace elements which has 100kcal/100 ml and 2.9g protein per 100ml. The volume of milk is increased to about 130ml/kg day while other foods are introduced and increased
- RUTF is an energy dense food usually containing peanut butter, milk powder, oil, sugar and micronutrients with an equivalent nutritional content to F100. The major advantage of RUTF over milk F100 is that it can be given to the mother to take home whereas F100, being a milk preparation that is easily contaminated unless prepared in hygienic conditions, is usually reserved for hospital use.
- In the rehabilitation phase, children recovering from SAM will consume about 200-230 kcal/kg/day and between 5-7gm protein/kg/day.
- Expected daily weight gain:
  - Poor: < 5g/kg/day
  - Moderate: 5-10 g/kg/day
  - Good: > 10g/kg/day

Readiness for discharge from hospital 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

Play and emotional stimulation are also essential elements of management in this phase as these can directly influence clinical outcomes including growth. Attending to maternal needs and preparing her to look after her child once discharged are similarly important.

The WHO ten-step approach to management of severe malnutrition

Treat/Prevent hypoglycaemia
Treat/Prevent hypothermia
Treat/Prevent dehydration
Correct electrolyte imbalance
Treat/Prevent infection
Correct micro deficiencies
Initiate refeeding
Facilitate catch up growth
Provide sensory stimulation and emotional support
Prepare for follow up and recovery

APPENDIX III
PHARMACOKINETIC SPECIMEN PROCESSING

Processing of pharmacokinetic samples

Pharmacokinetic blood samples will be sent to the laboratory within 30 minutes of collection for processing. 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^{o} 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/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 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.

APPENDIX IV

DIVISION OF AIDS
INTERNATIONAL MATERNAL PEDIATRIC ADOLESCENT AIDS CLINICAL TRIALS GROUP (IMPAACT)
SAMPLE INFORMED CONSENT – SCREENING

For protocol:

PHASE IV EVALUATION OF THE STEADY STATE PHARMACOKINETICS OF ZIDOVUDINE, LAMIVUDINE AND LOPINAVIR/RITONAVIR IN SEVERELY MALNOURISHED HIV-1 INFECTED CHILDREN
VERSION 2.0, DATED 11 FEBRUARY 2015

INTRODUCTION

You are being asked to allow your child to take part in screening tests to see if your child will be able to take part in the research study named above because your child is infected with Human Immunodeficiency Virus (HIV), the virus that causes AIDS (Acquired Immunodeficiency Syndrome). This study is sponsored by the National Institutes of Health (NIH). The doctor in charge of this study at this site is: (insert name of Principal Investigator). Before you decide if you want your child to participate in the screening tests, we want you to know about the study.

This is a consent form that gives you information about the screening tests. The study staff will talk with you about this information. You are free to ask questions at any time. If you agree to allow your child to take part in screening tests, you will be asked to sign this consent form. You will get a copy to keep.

WHAT SHOULD YOU KNOW ABOUT SCREENING FOR THIS STUDY?

- Your permission to allow your child to participate in the screening is entirely voluntary.
- You may decide not to allow your child to participate in the screening tests or to withdraw from the screening at any time without losing the benefits of your child's standard medical care.
- Even if you have agreed to allow your child to participate in the screening, it does not mean that you have agreed to allow your child to be in the research study.
- If you consent to allow your child to be screened, you are saying that you are interested in allowing your child to be in this research study but you can change your mind before actually agreeing to allow your child to join the study.
- If you decide not to allow your child to participate in the screening, your child cannot participate in this research study, but your child can join another research study later if one is available and your child qualifies.

WHY IS THIS STUDY BEING DONE?

There are currently approved anti-HIV medicines and doses to treat HIV infection in children. Based on strong data, children with severe malnutrition are expected to have differences in the levels of these anti-HIV drugs in their blood. 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 as compared to children with normal nutrition or mild malnutrition. The information from the study will be used in the future to recommend if the same dose or a different dose should be used in children with severe malnutrition who are starting a similar anti-HIV medicine. No changes will be made to your child's doses based on these results. In addition, the study will also find out how well the children take these drugs and if they are safe for the children. The purpose of this screening is to see if your child will be able to be in this research study.

WHAT WILL HAPPEN IF YOU AGREE TO HAVE YOUR CHILD SCREENED?

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.

- We will ask about your child's medical history including questions about your child's health and what symptoms, medications, and illnesses your child has had.
- We will do a physical exam including length, weight, mid upper arm measurement, head measurement, and vital signs (temperature, heart rate and respiratory rate).
- We will ask you questions about what you are feeding your child and how well your child is eating, playing and behaving.
- We will draw 5-10 mL (1-2 teaspoons) of blood for HIV testing and other routine tests. *[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]*

You will be asked to return to the clinic to get the results of these tests. If the screening tests show that your child is able to join the research study, you will be given more detailed information about the research study and be asked to sign another consent form to allow your child to participate in the research study.

WHY WOULD THE DOCTOR STOP MY CHILD'S SCREENING TESTS EARLY?

Your child will be withdrawn from the screening if at any time the screening tests show that your child will not be able to be in the research study. Your child may also be withdrawn from the screening if the study is cancelled or stopped.

WHAT ARE THE RISKS STUDY SCREENING?

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 also a small risk of inflammation or infection of the vein. If your child is screened for this study, some hospital staff and study staff will know that your child has HIV. The study doctors and staff will protect information about your child's participation in these screening tests to the best of their ability. On your child's screening records, a code will be used instead of your child's name. Only the study staff will know the code. Study staff will make every possible effort to be sure that others do not learn your child's HIV status. However, sometimes if your child receives special treatment or attends a special clinic, it may make others wonder if your child has HIV.

ARE THERE BENEFITS TO TAKING PART IN SCREENING TESTS?

The screening tests may or may not be of direct benefit to your child. The results of the screening tests will be shared with you and the medical staff providing your child's care and may help them know more about what care your child needs.

WHAT ABOUT CONFIDENTIALITY?

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

Your child's records may be reviewed by the [*insert name of site]* IRB/EC, National Institutes of Health (NIH), Office for Human Research Protections (OHRP), study staff, study monitors, ViiV Healthcare Ltd, Abbott Laboratories, IMPAACT, and local regulatory authorities. An IRB protects the rights and well-being of people in research.

WHAT ARE THE COSTS TO ME?

The screening tests (physical examination, blood 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.

WHAT DO I DO IF I HAVE QUESTIONS OR PROBLEMS?

For questions about screening for this study or a screening-related injury, contact:
- *[name of the investigator or other study staff]*
- *[telephone number of above]*

For questions about your child's rights as a research subject, contact:
- *[name or title of person on the Institutional Review Board (IRB), Ethics Committee (EC) or other organization appropriate for the site]*
- *[telephone number of above]*

SIGNATURE PAGE

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

Participant's Name (print)		
Parent or Legal Guardian Name (print)	Parent or Legal Guardian Signature	Date
Study Staff Conducting Consent Process Name (print)	Study Staff Signature	Date
Witness Name	Witness Signature	Date

APPENDIX V

DIVISION OF AIDS
INTERNATIONAL MATERNAL PEDIATRIC ADOLESCENT AIDS CLINICAL TRIALS GROUP (IMPAACT)
SAMPLE INFORMED CONSENT - ENROLLMENT
For protocol:

PHASE IV EVALUATION OF THE STEADY STATE PHARMACOKINETICS OF ZIDOVUDINE, LAMIVUDINE AND LOPINAVIR/RITONAVIR IN SEVERELY MALNOURISHED HIV-1 INFECTED CHILDREN
VERSION 2.0, DATED 11 FEBRUARY 2015

INTRODUCTION

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 the screening tests show that your child is eligible for the study. This study is sponsored by the National Institutes of Health (NIH). The doctor in charge of this study at this site is: (insert name of Principal Investigator). Before you decide if you want your child to be a part of this study, we want you to know about the study.

This is a consent form. It gives you information about this study. The study staff will talk with you about this information. You are free to ask questions about this study at any time. If you agree to allow your child 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?

There are currently approved anti-HIV medicines and doses to treat HIV infection in children. Based on strong data, children with severe malnutrition are expected to have differences in the levels of these anti-HIV drugs in their blood. 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 as compared to children with normal nutrition or mild malnutrition. The information from the study will be used in the future to recommend if the same dose or a different dose should be used in children with severe malnutrition who are starting a similar anti-HIV medicine. No changes will be made to your child's doses based on these results. In addition, the study will also find out how well the children take these drugs and if they are safe for the children. We will do this by measuring how much anti-HIV medicine is in your child's blood. Your child's blood will be sent to laboratories in South Africa and the United States for analysis. Two groups of children will be enrolled in this study; a group of severely malnourished children and a group of children with normal nutrition or who are mildly malnourished.

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

Before the Study Starts:
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, 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:

- We will ask more questions about your child's medical history including questions about your child's health and what symptoms, medications, and illnesses your child has had.
- We will do a physical exam including length, weight, mid upper arm measurement, head measurement, and vital signs (temperature, heart rate and respiratory rate).
- We will ask you questions about what you are feeding your child and how well your child is eating, playing and behaving.
- We will draw 6-8 mL (about 1-2 teaspoon) 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]*
- If your child can start taking anti-HIV medications, your child will be started on zidovudine + lamivudine + lopinavir/ritonavir. Your child will take zidovudine two times daily + lamivudine two times daily + lopinavir/ritonavir two times daily by mouth for 48 weeks.
- 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 child to the clinic at least 10 times over 48 weeks. The visits will be at the beginning of the study (weeks 1, 2, and 4) and will then spread out to every 4 weeks (weeks 8, 12, 16, 20, 24) and then to every 12 weeks (weeks 36 and 48).
- Most of these visits will take about ___ hours to complete. *[Note to sites: add locally relevant length of study visit]*
- At each visit, we will take a medical history, perform a physical exam, and ask you how well your child is eating.
- At 5 of these visits, we will ask you how well your child is taking his/her anti-HIV medications.

- 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.
- For 2 of these visits, less than one teaspoon of blood will be drawn for a glucose test (to see if there is sugar in the blood). At one of these visits, your child may be ask to fast (not eat or drink) before the test.
- 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.
- A small plastic catheter (a needle that is placed in a vein for an extended period of time, so that blood can be drawn multiple times, without having to stick your child with a needle each time) will be placed in your child's arm to draw these blood samples. The needle will stay in place during the visit until all of the blood samples are drawn.
- The total amount of blood drawn at the different study visits will vary from 2.3 mL to 14 mL (less than one teaspoon to 3 teaspoons) depending on the type of test and how much your child weighs. *[Note to sites: add locally relevant description of blood volume]*

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 (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.

HOW MANY CHILDREN WILL TAKE PART IN THIS STUDY?

About 50 children will take part in this study; 25 children with severe malnutrition and 25 children with normal nutrition/mild malnutrition.

HOW LONG WILL MY CHILD BE IN THIS STUDY?

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

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

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

- The study is cancelled by the National Institutes of Health (NIH), ViiV Healthcare Ltd, Abbott Laboratories, IMPAACT, and local regulatory authorities, the Office for Human Research Protections (OHRP), or the site's Institutional Review Board (IRB) or Ethics Committee (EC). An IRB/EC is a committee that watches over the safety and rights of research subjects.
- Your child is not able to attend the study visits as required by the study.

The study doctor may also need to take your child off the study drug(s) without your permission if:

- Continuing certain study procedures may be harmful to your child.
- Your child needs a treatment that your child may not take while on the study.
- Your child is not able to take certain study drugs as required by the study.

WHAT ARE THE RISKS OF THE STUDY?

Taking part in this study may involve some risks and discomfort. These include risks of study procedures, risks of study medicine and risks to your child's privacy.

Risks of Study Procedures:

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 also a small risk of inflammation or infection of the vein. Because your child is small, infected with HIV and severely malnourished, these risks from drawing blood are greater than in children who are older or do not have these problems.

Risks of Study Medicines:

We are asking your child to participate in this study because we don't know if young severely malnourished children with HIV are getting the best doses of anti-HIV medicine. If the dose of the treatment is not correct, treatment could fail, the HIV could become resistant to the medicines, or your child could be more likely to have serious side effects from the treatment. This study will help make sure that other young children in the future who are severely malnourished and infected with HIV get the best possible anti-HIV treatment.

The drugs used in this study may have side effects, some of which are listed below. Please note that these lists do not include all the side effects seen with these drugs. These lists include the more serious or common side effects with a known or possible relationship. If you have questions concerning additional study drug side effects please ask the medical staff at your site.

Use of Combination Antiretroviral Drugs

Immune Reconstitution Syndrome: In some people with advanced HIV infection, signs and symptoms of inflammation from other infections may occur soon after anti-HIV treatment is started.

The use of potent antiretroviral drug combinations may be associated with an abnormal placement of body fat and wasting. Some of the body changes include:

- Increase in fat around the waist and stomach area
- Increase in fat on the back of the neck
- Thinning of the face, legs, and arms
- Breast enlargement

Nucleoside Reverse Transcriptase Inhibitor

Lactic acidosis and severe hepatomegaly (enlarged liver) with steatosis (fatty liver) that may result in liver failure, other complications and death have been reported with the use of antiretroviral nucleoside analogues alone or in combination. The liver complications and death have been seen more often in women on these drug regimens. Some

nonspecific symptoms that might indicate lactic acidosis include: unexplained weight loss, stomach discomfort, nausea, vomiting, fatigue, weakness, and shortness of breath.
Zidovudine (RETROVIR®)
ViiV Healthcare Ltd

The following side effects have been associated with use of zidovudine:

- Decrease in the number of white blood cells that help fight infection
- Decrease in the number of red blood cells that may cause weakness, dizziness, and fatigue
- Muscle aches, weakness, and wasting
- Headache
- Upset stomach
- Vomiting
- Decrease in appetite
- Vague overall feeling of discomfort
- Lack of energy
- Feeling tired
- Sleeplessness
- Heartburn

Lamivudine (3TC, EPIVIR®)
ViiV Healthcare Ltd

The following side effects have also been associated with use of lamivudine:
If your child is infected with both Hepatitis B and HIV, you should be aware that your child's liver function tests may increase, and symptoms associated with hepatitis (an acute inflammation of the liver) may worsen if lamivudine is stopped. Although most of these cases have resolved without treatment, some deaths have been reported.

- Headache
- Feeling tired
- Dizziness
- Numbness, tingling, and pain in the hands or feet
- Depression
- Trouble sleeping
- Rash
- Upset stomach, vomiting, nausea, loose or watery stools
- Pancreatitis (inflammation of the pancreas), which may cause death. If your child develop pancreatitis, your child may have one or more of the following: stomach pain, nausea, and vomiting.
- Abnormal pancreatic and liver function blood tests

Protease Inhibitors

The use of protease inhibitors may be associated with the following:

- Increases in the amount of triglycerides and/or cholesterol in the blood
- Development of diabetes or the worsening of high blood sugar

There have been reports of increased bleeding in HIV-infected persons with hemophilia who were treated with protease inhibitors. It is not known if protease inhibitors were the cause of these bleeding episodes.

Lopinavir/Ritonavir (LPV/r, KALETRA™)
Abbott Laboratories

The following serious side effects are associated with the use of lopinavir/ritonavir:

- Abnormal heart rhythm and electrocardiogram (EKG) changes. These changes can lead to serious heart problems. Your child's risk for these problems may be higher if your child :
  - Already has a history of abnormal heart rhythm or other types of heart disease
  - Takes other medicines that can affect your child's heart rhythm while your child takes lopinavir/ritonavir

If your child develops abnormal heart rhythm your child may experience lightheadedness, fainting spells or an abnormal heart beat.

Pancreatitis (inflammation of the pancreas), which may cause death. If your child develops pancreatitis, your child may have one or more of the following:

- Stomach pain, nausea, vomiting or abnormal pancreatic function blood tests
- Large increases in triglycerides and cholesterol in the blood

Liver problems and worsening liver disease, which may result in death. People with these conditions may have abnormal liver function blood tests. If your child is developing liver problems, your child may have one or more of the following: yellowing of the skin or whites of the eyes, dark urine, pain on the right side of your stomach, loss of appetite, upset stomach or vomiting, pale colored stools, itchy skin. Additional side effects may include:

- Abnormal bowel movements (stools), including loose or watery stools, upset stomach and stomach pain
- Feeling weak and tired
- Headache
- Rash which could blister and may be severe or life-threatening. Contact your health care provider if your child develops a rash.

Risks When 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 also a small risk of inflammation or infection of the vein.

Risks of Resistance

All anti-HIV medicines can cause resistance. When resistance occurs, a medicine no longer works against HIV, which can limit the choices of medicines a person can take against HIV in the future. To avoid resistance, it is important to take anti- HIV medicines as instructed and not to miss doses.

Other Risks

If your child joins this study, some hospital staff and all study staff will know that your child has HIV. These workers are very serious about your privacy. Study staff will make every possible effort to be sure that others do not learn your child's HIV status. However, sometimes if your child receives special treatment or attends a special clinic, it may make others wonder if your child has HIV.

ARE THERE BENEFITS TO TAKING PART IN THIS STUDY?

If your child takes part in this study, there is no guarantee of direct benefit to your child since the levels of drug in your child's body will not be done immediately after your child takes it. The information learned from this study may help other children who have HIV. Your child's participation would benefit others by allowing access to anti-HIV medications that are not currently available as first line treatment for children starting anti-HIV medications.

WHAT OTHER CHOICES DOES MY CHILD HAVE BESIDES THIS STUDY?

Instead of being in this study your child has the choice of:

- treatment with prescription drugs available to your child in care programs
- treatment with experimental drugs, if your child qualifies
- no treatment

Please talk to your doctor about these and other choices available to your child. Your doctor will explain the risks and benefits of these choices.

WHAT ABOUT CONFIDENTIALITY?

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

Your child's records may be reviewed by the *[insert name of site]* IRB/EC, National Institutes of Health (NIH), Office for Human Research Protections (OHRP), study staff, study monitors, and drug companies supporting this study.

WHAT ARE THE COSTS TO ME?

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 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.]*

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 child is taking part in a research study. *[Note to sites: Language related to insurance can be deleted if it is not relevant to your site.]*

WHAT HAPPENS IF MY CHILD IS INJURED?

If your child is injured as a result of being in this study, your child will be given immediate treatment for his/her injuries. The cost for this treatment will be charged to you or your insurance company. There is no program for compensation either through this institution or the National Institutes of Health (NIH). You will not be giving up any of your legal rights by signing this consent form.

WHAT ARE MY CHILD'S RIGHTS AS A RESEARCH SUBJECT?

Taking part in this study is completely voluntary. You may choose not to allow your child to take part in this study or take your child out of the study at any time. Your child will be treated the same no matter what you decide. Your decision will not have any impact on your child's participation in other studies conducted by NIH and will not result in any penalty or loss of benefits to which your child is otherwise entitled.

We will tell you about new information from this or other studies that may affect your child's health, welfare or your willingness to allow your child 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 child'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 child to take part in this study, please sign your name below.

Participant's Name (print)		
Parent or Legal Guardian Name (print)	Parent or Legal Guardian Signature	Date
Study Staff Conducting Consent Process Name (print)	Study Staff Signature	Date
Witness Name	Witness Signature	Date