

IMPAACT P1083

**A PHASE II/III TRIAL OF LOPINAVIR/RITONAVIR DOSED ACCORDING TO THE
WHO PEDIATRIC WEIGHT BAND DOSING GUIDELINES**

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

Sponsored by:

The National Institute of Allergy and Infectious Diseases (NIAID)

and

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

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- I. SCHEDULE OF EVALUATIONS
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- III. DAIDS SAMPLE INFORMED CONSENT
- IV. FACT SHEET AND TEMPLATE CONSENT FORM FOR SPECIMEN STORAGE AT REPOSITORIES FUNDED BY THE NATIONAL INSTITUTE OF CHILD HEALTH AND HUMAN DEVELOPMENT (NICHD) – PARENT FACT SHEET (Version 2.0, dated 11/29/05)

SCHEMA

A PHASE II/III TRIAL OF LOPINAVIR/RITONAVIR DOSED ACCORDING TO THE WHO
PEDIATRIC WEIGHT BAND DOSING GUIDELINES

- DESIGN: Phase II/III, intensive pharmacokinetic (PK) study.
- SAMPLE SIZE: Enroll 94 subjects to achieve a target of 85 evaluable infants and children
- POPULATION: HIV-infected infants and children ≥ 3 to < 25 kg (stratified by weight according to Table 1) initiating lopinavir/ritonavir (LPV/r) therapy at U.S. and non-U.S. IMPAACT sites.
- STRATIFICATION: Weight bands and formulations as described below:

Table 1: Number of Subjects to be Enrolled by Weight Band and Formulation*		
<i>Weight band (kg)</i>	<i>Liquid</i>	<i>Tablet</i>
3-4.9	11	-
5-6.9	11	-
7-9.9	17	-
10-16.9	11	22
17-19.9	--	11
20-24.9	--	11
Total	50	44

*numbers based on 10% loss to follow-up (final sample size estimate is 85 evaluable subjects)

- REGIMEN: LPV/r as heat-stable tablets (100/25 mg) or liquid formulation (80/20 mg/mL) when dosed according to the World Health Organization (WHO) pediatric weight band dosing guidelines plus two nucleoside reverse transcriptase inhibitors (NRTIs) chosen by clinical caregivers.
- TREATMENT DURATION: 24 weeks.

SCHEMA (Cont.)

OBJECTIVES:

Primary:

1. To determine if the weight band antiretroviral (ARV) dosing recommendations of the WHO provide safe and tolerable dosing of LPV/r when administered as the heat stable pediatric tablet or the liquid formulation as part of a combination ARV regimen in HIV-infected infants and children.
2. To delineate the pharmacokinetics of LPV/r when dosed according to the WHO ARV weight band dosing schedule in HIV-infected infants and children.

Secondary:

1. To explore the demographic and clinical factors which may impact LPV pharmacokinetics, LPV exposure, and LPV trough concentrations.
2. To evaluate adherence to the weight band dosing schema.
3. To evaluate the role of CYP3A4 (as well as ORM1 and SLCO1B1) genetic variants on alterations in PK that result in concentrations of LPV outside of target values.
4. To explore the association between viral suppressions and immune restoration and this dosing scheme.

1.0 INTRODUCTION

1.1 Background and Rationale

As access to antiretroviral (ARV) therapy for HIV-infected infants scales up in resource limited settings over the next years, the use of protease inhibitors, and especially LPV/r, in infants and young children will be increasing. WHO currently recommends that all infants under age 12 months with confirmed HIV infection begin antiretroviral therapy (1). A nevirapine-containing three drug regimen is recommended as the first-line therapy for HIV-infected infants except for those infants previously exposed to single-dose nevirapine or non-nucleoside reverse transcriptase-inhibitor-containing maternal antiretroviral therapy or preventive antiretroviral regimens. Since such infants have a high chance of harboring nevirapine resistant virus, they should start treatment with a protease-inhibitor-based triple antiretroviral combination (1). Given the widespread use of peripartum nevirapine (NVP), with or without prenatal short course maternal zidovudine (ZDV), for prevention of mother to child HIV transmission (PMTCT), many newly-diagnosed HIV-infected infants will have been previously exposed to NVP and will require a protease inhibitor (PI)-based first-line regimen (2). In addition, unavoidably some infants started on a NVP-based regimen will experience treatment failure and will require a PI-based regimen for second line therapy. As a result, there is a critical need for simple, reliable PI dosing regimens for infants and in particular for LPV/r, the most widely available PI with dosing formulations suitable for infants.

Current recommendations for LPV/r dosing in infants and children are complicated and questions remain as to whether they provide optimal LPV exposure in all age ranges. The manufacturer's recommended dosing for LPV/r in children is for 16/4 mg/kg or 300/75 mg/m² for infants age 14 days to 6 months, 12/3 mg/kg or 230/57.5 mg/m² for those over 6 months who are under 15 kg, and 10/2.5 mg/kg or 230/57.5 mg/m² for those children 15 to 40 kg (3). Independent investigators have noted that children treated with 230/57.5 mg/m² have plasma LPV concentrations roughly 67% of those seen in adults receiving standard LPV dosing (4;5). Increasing LPV/r doses to 300/75 mg/m² has been shown to maintain adequate LPV concentrations and the U.S. pediatric treatment guidelines suggest that initiating treatment with doses of 300/75 mg/m² may be preferred (4;6). LPV clearance is increased in young infants, who have reduced exposure when dosed with 230/57.5 mg/m², and dosing with 300/75 mg/m² has been shown to result in adequate LPV exposure in infants 6 weeks to 2 years of age (5;7;8). Infants under 6 weeks of age have reduced LPV exposure even with 300/75 mg/m² dosing, although virologic response was good despite the low LPV concentrations in a small group of infants (5). Treatment-experienced children may harbor antiretroviral-resistant viruses and some investigators have suggested

that they should receive even higher doses of 400/100 mg/m² (9;10). LPV/r has generally been well tolerated in all of these pediatric studies, including those using doses higher than those recommended by the manufacturer.

The formulations of LPV/r commonly available are 200/50 mg tablets, 100/25 tablets or a liquid formulation with 80/20 mg/mL. While liquid formulations work well in resource rich settings, tablet formulations are preferred in resource limited settings due to concerns with the volume of liquid that needs to be dispensed, problems with cleanliness of dosing equipment and need for refrigeration of liquid formulations. The development of solid, heat stable, affordable formulations of ARVs appropriate for pediatric use is essential to facilitate the scale up of HIV care for children in resource limited settings. The WHO Pediatric ARV Working Group (PAWG) (11) has included development of a smaller solid formulation of LPV/r in its urgent priority list of products. Abbott has recently released such a formulation - a lower strength LPV/r heat stable tablet (Kaletra or Aluvia) containing 100 mg of LPV and 25 mg of ritonavir intended for use in children.

The current recommended LPV/r dosing schedule for infants and children is too complicated to be practical in resource-limited settings where ARVs are provided in extremely busy clinics by staff that lack advanced pediatric training. Instead, the WHO-PAWG has recommended simplified ARV dosing based on weight bands for use in resource-limited settings (12). The purpose of pediatric weight band dosing is to make standardized ARV treatment practical in resource limited settings by simplifying drug delivery and reducing prescription errors. The WHO dosing schedule was based on weight bands to avoid the need for calculations associated with body surface area or per kilogram dosing. While the exact doses were selected with the goal of delivering at least 90% and no more than 125% of the recommend per kg or per m² dose, it was unavoidable that at some weights these dosing limits would be exceeded. The WHO ARV weight band dosing schedule for the Kaletra liquid and the new heat stable Aluvia or Kaletra tablet is presented in Table 2.

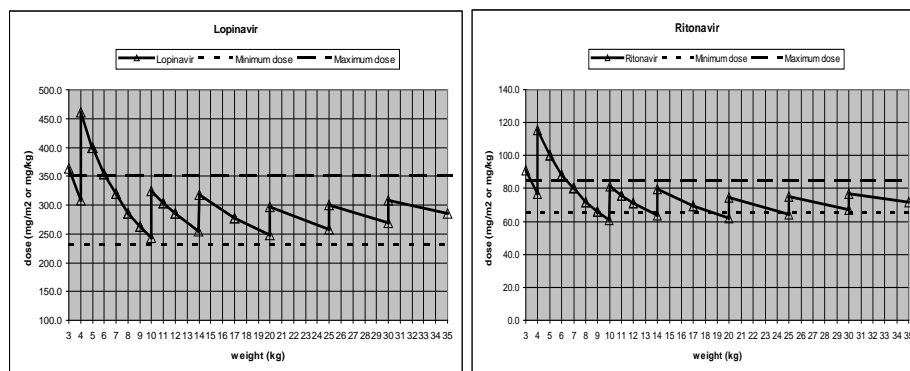
Table 2: WHO ARV Weight Band Dosing Schedule for LPV/r						
Weight range (kg)	Liquid	Dose (Volume of Liquid)		Tablet	Dose (# of Tablets)	
		AM	PM		AM	PM
3-3.9	80/20 mg/mL	1 mL	1 mL	-----	--	--
4-4.9	80/20 mg/mL	1.5 mL	1.5 mL	-----	--	--
5-5.9	80/20 mg/mL	1.5 mL	1.5 mL	-----	--	--
6-6.9	80/20 mg/mL	1.5 mL	1.5 mL	-----	--	--
7-7.9	80/20 mg/mL	1.5 mL	1.5 mL	-----	--	--
8-8.9	80/20 mg/mL	1.5 mL	1.5 mL	-----	--	--
9-9.9	80/20 mg/mL	1.5 mL	1.5 mL	-----	--	--
10-10.9	80/20 mg/mL	2 mL	2 mL	100/25 mg	2	1
11-11.9	80/20 mg/mL	2 mL	2 mL	100/25 mg	2	1
12-13.9	80/20 mg/mL	2 mL	2 mL	100/25 mg	2	1
14-16.9	80/20 mg/mL	2.5 mL	2.5 mL	100/25 mg	2	2
17-19.9	80/20 mg/mL	2.5 mL	2.5 mL	100/25 mg	2	2
20-24.9	80/20 mg/mL	3 mL	3 mL	100/25 mg	3	2

By definition, drug dosing with a weight band dosing regimen will be more granular, that is doses will change less frequently, than with an individualized per kg or per m² dosing regimen. Individual drug doses for children receiving weight band dosing will be greatest on a per kg or per m² basis for those children at the starting weight for each weight band and will be lowest for those children at the high end of each weight band, just before the transition to the next dose increment. In developing the WHO ARV weight band dosing schedule, prevention of antiretroviral resistance due to inadequate antiretroviral exposure was considered to be the first priority. As a result, the weight bands and doses were selected in order to minimize underdosing, while overdosing at the start of the weight bands was considered of less importance. A common practice in determining individualized size-based drug doses for children is to change doses when the child has increased in size by 10%. Following this practice, the doses in the weight band dosing schedule were selected to deliver at least 90% of the target dose to children at the end of each weight band. On the other hand, the limit of overdosing at the start of each weight band was set at no more than 125% of the recommended kg/m² dose. It was recognized that it was unavoidable that these dosing limits would be exceeded at some weights.

Figure 1 presents the actual per mg/m² LPV and ritonavir dose administered to children receiving LPV/r according to the above weight band dosing schedule. The horizontal dashed lines represent the target doses (not actual target drug

exposures) in mg/m^2 and the dashed line with triangles represents the administered LPV and ritonavir dose in mg/m^2 .

Figure 1:



As can be seen, children dosed according to the weight band dosing schedule generally stay within the 90% to 125% target dose ranges except for the smallest infants. A comparison of the WHO ARV weight band dosing recommendations with the actual dose received by infants less than 12 months of age enrolled in protocol P1030: Phase I/II Study of Lopinavir/ritonavir in HIV-1 Infected Infants <6 Months of Age, indicates that the WHO dosing recommendations can result in significant differences in LPV doses from those studied in P1030. If the WHO dosing was given to subjects in P1030, 76% of them would be within 25% of the dose they received in P1030 but 24% would receive a dose >25% higher with the WHO dosing than they received in P1030. As the above figures show, the highest doses will be received by the youngest infants. It is notable, however, that these infants also have the highest LPV clearance and, not surprisingly, the children in P1030 were significantly below the targeted area under the curve (AUC) for the study, but did meet the C_{\min} (5)

While the WHO ARV weight band dosing schedule is now the standard dosing regimen used in resource limited settings throughout the world, there are no data describing the plasma concentrations or safety profile of LPV and RTV in infants and children dosed in this way. Data describing both the pharmacokinetics and clinical safety and tolerance are crucial in order to evaluate the current WHO LPV/r weight band dosing recommendations. The goal of this protocol is to provide these data, which are critical for the safe and effective implementation of the current WHO recommendations to treat all HIV-infected infants as early as possible and to use LPV/r in those infants previously exposed to nevirapine and to safely treat older children who fail first line therapy.

1.2 Rationale for Pharmacogenetics

Considerable variability has been observed in the pharmacokinetics of LPV/r in adults and children treated with standard doses. Therefore, it is possible that there will be a broad range of exposure to LPV when children are dosed based on WHO weight band. We anticipate that for children who are identified as having LPV exposures below or above the expected ranges variations in genes that affect drug transport and/or metabolism will help to explain some of this variability. Because the LPV/r combination specifically uses ritonavir to boost concentrations of LPV through competition for CYP3A4, as a secondary objective, we will examine genetic variants of CYP3A4 to help understand PK profiles that fall outside of the desired drug targets. Although there is some controversy as to the role of CYP3A4 in LPV/r PK, no data are available in children. Additionally, the ritonavir boost is given specifically to alter CYP3A4 metabolism of LPV increasing the likelihood that changes in CYP3A4 expression will alter drug levels. In addition to CYP3A4 (rs6545984) genetic variants in ORM1 (ORM1*F1, ORM1*F2 and ORM1*S resulting from A to G transition at codons for aa position 20 in exon 1 and 156 in exon 5) and SLCO1B1 (rs4149056 and rs4149032) have been identified to alter LPV levels and PK (13).

Therefore, we believe that it will be important to examine variants in CYP3A4 as well as variants in ORM1 and SLCO1B1 in order to determine the potential impact of host genetics on LPV levels and expand the applicability of potentially using the WHO weight bands in developed as well as developing countries.

Recently, two abstracts have been presented suggesting that genetic variants within the OATP/SLCO family of polypeptide organic anion transporters may be associated with LPV pharmacokinetics. In one study, Kwan et al (14) found that LPV and other PIs are substrates for SLCO1B1 and SLCO1A2. In the second, Shallcross and colleagues (15) found that the SLCO1B1 521-T/C genetic variant was associated with plasma levels of LPV in a cohort of adults. These data suggest that the SLCO1B1 521-T/C genetic variant (now called OAT1B1 521-T/C) genotype may alter LPV pharmacokinetics in children and may be helpful in identifying children who experience unexpectedly high levels of LPV with the fixed-dose combination (FDC). Therefore, we propose to examine the OAT1B1 (SLCO1B1) 521-T/C genetic variant in children participating in the P1083 protocol using real-time PCR (14;15).

2.0 STUDY OBJECTIVES

2.1 Primary Objectives

- 2.11 To determine if the weight band ARV dosing recommendations of the WHO provide safe and tolerable dosing of LPV/r when administered as the heat stable pediatric tablet or the liquid formulation as part of a combination ARV regimen in HIV-infected infants and children.
- 2.12 To delineate the pharmacokinetics of LPV/r when dosed according to the WHO ARV weight band dosing schedule in HIV-infected infants and children.

2.2 Secondary Objectives

- 2.21 To explore the demographic and clinical factors which may impact LPV pharmacokinetics, LPV exposure, and LPV trough concentrations.
- 2.22 To evaluate adherence to the weight band dosing schema.
- 2.23 To evaluate the role of CYP3A4 (as well as ORM1 and SLCO1B1) genetic variants on alterations in PK that result in concentrations of LPV outside of target values.
- 2.24 To explore the association between viral suppressions and immune restoration and this dosing scheme.

3.0 STUDY DESIGN

This is a Phase II/III trial to assess the short-term pharmacokinetics, safety, tolerance, and virological effect of LPV/r in HIV-infected infants and children initiating LPV/r therapy who weigh ≥ 3 and < 25 kg and are dosed according to the WHO ARV weight band dosing guidelines. LPV/r will be administered as the heat-stable pediatric LPV/r 100/25 mg tablet in children who can swallow tablets or the liquid 80/20 mg/mL formulation in children who cannot swallow tablets. LPV/r will be dosed according to the WHO ARV weight band dosing schedule as part of a combination ARV regimen including two NRTIs as background therapy. The NRTI background will be prescribed by the health care provider according to local national and/or international guidelines for treatment of HIV-infected children. LPV/r will be provided as part of the study.

The study duration, on treatment, will be 24 weeks. Demonstrated ability to swallow tablets is a requirement for inclusion of children allocated to the solid formulations. This

can be assessed before inclusion (for example, a test trial with similar size solid tablet such as tic-tac). If adherence problems are detected while on study treatment, children should be managed as non-adherent (specified in Section 6.3). If the health care provider and protocol CMC agree that switching from the tablet formulation to the liquid formulation is a valid strategy to improve adherence, this switch may be considered on a case-by- case basis.

Baseline virology, immunology and safety/toxicity chemistry studies will be obtained at enrollment. Subjects will be started on LPV/r according to the WHO ARV weight band dosing schedule (Table 2). Adherence will be assessed at 2 week and after 4 weeks of therapy on a specific dose. Subjects will have a 12-hour intensive PK visit and laboratory safety evaluation scheduled. Children who outgrow their dose and switch to the next dosing increment, due to weight gain, during the initial 4 weeks of therapy will have their PK visit delayed until they have been on the increased dose for 4 weeks. Subjects who switch from the initial weight band dose to a larger dose will be contacted by study site personnel 2 weeks after the change to ensure tolerance of and adherence with the new dose followed by a 4 week post dose change visit which will consist of targeted history, physical exam, adherence assessment and blood chemistry test. Blood samples for safety/toxicity (see Appendix I), will be performed during the intensive PK visit.

In addition to the intensive 12-hour PK study, the safety, tolerability and virological effect of the new LPV/r FDC formulation and mode of administration will be evaluated along with demographic and clinical factors which may impact LPV exposure and the relationship between LPV exposure and concentration over the study timeframe.

Study subjects will be followed for 24 weeks and adherence will be assessed. A week 12 study visit will be scheduled to assess safety and tolerance of the study medication, adherence and to obtain a single post-dose PK sample (obtained 2-6 hours post dose). The end-of-study visit is at week 24 and will include safety, tolerance, adherence, and virologic assessments with a single post-dose PK sample (obtained 2-6 hours post dose) to compare drug exposure over time with the initial PK drug exposure.

Since the main toxicities of LPV/r involve GI side effects (especially nausea, vomiting, and diarrhea) and liver toxicity, visits to evaluate safety and toxicity will include questioning for the presence of GI side effects and blood sampling for liver function tests (LFTs).

If a child is not tolerating medication, contact the study team to discuss whether (or not) a switch in formulation will improve adherence/tolerability. If a subject's clinical caregiver determines that the subject is not tolerating the study medication, the subject will be removed from the study and will receive ARV therapy according to the local standard of care.

At the conclusion of the study, subjects will begin ARV therapy as prescribed by their health care providers. Unless LPV/r cannot be tolerated, it is expected that subjects will continue on LPV/r but using the standard formulation available locally for clinical care dosed according to local standard national or international guidelines.

Pharmacology: Intensive PK evaluations will be performed after 4 weeks (\pm 1 week) of LPV/r therapy. Children who outgrow their dose and switch to the next dosing increment, due to weight gain, during the initial 4 weeks of therapy will have their PK visit delayed until they have been on the increased dose for 4 weeks. Blood (1 mL) will be collected prior (pre-dose) to an observed dose; directly observed therapy (DOT) and at 2, 4, 6, 8 and 12 hours post dose (total 6 mL) for LPV and ritonavir plasma concentration determinations. Caregivers must report that the subjects have not missed any doses during the 72 hours prior to the intensive PK visit or the visit will be rescheduled. (See Section 9.0 for details). A telephone adherence assessment will be made on the day prior to the PK visit and the visit will be rescheduled if adherence requirements were not met.

Subjects receiving rifampicin-based TB therapy or any enzyme inducing antiepileptic drugs (such as phenobarbital, phenytoin, and carbamazepine), are not eligible (see Section 4.2).

The PK samples will be batched and shipped to the pharmacology laboratory to be assayed for LPV and RTV concentrations. PK results will be provided to investigators as soon as they are available. The 90% confidence interval of geometric mean (GM) for LPV AUC will be determined and compared to a target value defined on the basis of studies establishing safety and efficacy of LPV. The target GM (range) for LPV AUC₁₂ will be 80 (40-160) mcg*hr/mL.

HIV-1 viral load will be obtained at screening, study entry, week 4, week 12, week 24 and early discontinuation visits, according to current IMPAACT Laboratory guidelines. CD4 count will be obtained at study entry and at the end of study or early discontinuation visit (24 weeks). For the pharmacogenetic evaluations, DNA obtained from cells separated from plasma obtained for PK assays will be used to determine CYP3A4 (as well as ORM1 and SLCO1B1) genetic variants using real-time PCR. See Appendix I (SOE) and the Laboratory Processing Chart (LPC) for details concerning sample processing and shipping. See Appendix II for dried blood spot (DBS) collection procedures.

IMPAACT international and domestic sites which have demonstrated ability to perform pharmacokinetic (PK) studies will be eligible to participate in P1083. IMPAACT sites selected for participation in P1083 will be based on the demonstrated ability to perform intensive PK studies, potential enrollment, standard of care, and local use and availability of the study agent and NRTI backbone (as defined in section 5.11) in the host countries.

4.0 SELECTION AND ENROLLMENT OF SUBJECTS

4.1 Inclusion Criteria

- 4.11 Weight ≥ 3 and < 25 kg at the time of enrollment.
- 4.12 Past or current documentation of a confirmed diagnosis of HIV-1 infection defined as two positive assays from two different samples. At least one of the specified assays must be performed in an ACTG/IMPAACT certified laboratory. The two results may be in any combination of the following:
- at any age: DNA PCR or HIV culture
 - age > 4 weeks: p24 antigen detection or HIV-1 RNA viral load $> 5,000$ copies/mL plasma
 - age > 18 months: Reactive on two different manufacturers' licensed rapid tests based on a different antigen preparation and/or different test principal, or repeatedly reactive on a licensed EIA AND confirmed on a second sample by any one of the following assays: rapid test (a third manufacturer), licensed EIA, Western blot, chemiluminescence assay, or plasma RNA with a viral load $> 5,000$ cp/mL
- 4.13 LPV/r-treatment naïve and LPV/r-treatment eligible as defined by country-specific guidelines or the WHO pediatric treatment guidelines confirmed by investigator.
- 4.14 Willingness to take two NRTIs, in accordance with appropriate national or international treatment guidelines.
- 4.15 Demonstrated ability and willingness to swallow tablets for children > 10 kg.
- Note # 1: This can be assessed before inclusion (for example, a test trial with similar size solid tablet such as tic-tac).
- Note # 2: Subjects on the weight band 10-16.9 kg that are unable to swallow tablets will receive liquid formulation.
- 4.16 Parent or legal guardian able and willing to provide written informed consent.

4.2 Exclusion Criteria

- 4.21 Planned concurrent use of NNRTI, integrase inhibitors, or entry inhibitor.
- 4.22 Planned concurrent PI use, other than LPV/r.

- 4.23 Prior treatment with LPV/r (prior treatment with other PIs is allowed).
- 4.24 Any of the following laboratory tests within 30 days prior to study entry classified as \geq Grade 3 (see DAIDS Table for Grading the Severity of Adult and Pediatric Adverse Events, Version 1.0 [December 2004], Clarification August, 2009, <http://rcc.tech-res-intl.com>): neutrophil count, hemoglobin, platelets, AST, ALT, or serum creatinine.
- 4.25 A \geq Grade 2 lipase or clinical evidence of pancreatitis within 30 days prior to study entry.
- 4.26 Tuberculosis co-treatment with rifampicin-containing regimen.
- 4.27 Treatment with any enzyme-inducing antiepileptic drugs (such as phenobarbital, phenytoin or carbamazepine).
- 4.28 Clinical condition requiring the use of a prohibited medication (see 4.32)
- 4.29 Clinically unstable child requiring acute treatment for a serious opportunistic infection.
- 4.30 Chemotherapy for active malignancy.
- 4.310 Any clinically significant diseases (other than HIV-1 infection) or clinically significant findings during the screening medical history or physical examination that, in the investigator's opinion, would compromise participation in this study.
- 4.311 Treatment with experimental drugs for any indication within 30 days prior to study entry.
- 4.312 Known history of cardiac conduction abnormality and/or underlying structural heart disease, including congenital long QT.

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 (RCC) to obtain the most current information on drug interactions, contraindications, and precautions.

Concomitant administration with didanosine (ddI):

LPV/r tablets: may be administered with ddI without food.

LPV/r solution: ddI should be given one hour before or two hours after LPV/r solution (given with food).

Please contact the protocol team at actg.teamp1083@fstrf.org if treatment with any of these medications is necessary for clinical care.

4.32 Prohibited Medications

A complete list of current medications, including over-the counter and alternative/herbal medications will be taken at the screening/entry visit and prior to performing the intensive PK. Prohibited drugs are listed below:

- Any medication known to induce QT interval prolongation such as: chlorpheniramine, quinidine, erythromycin, clarithromycin
- HMG-CoA Reductase Inhibitors
- Rifabutin
- Rifampin
- Flecainide
- Propafenone
- Astemizole
- Terfenadine
- Dihydroergotamine
- Ergonovine
- Ergotamine
- Methylergonovine
- Cisapride
- Pimozide
- Midazolam*
- Triazolam
- St. Johns wort (*hypericum perforatum*)
- Sildenafil**

*midazolom (Versed) allowed if used only in a monitored setting for procedures.

**prohibited when used for the treatment of pulmonary arterial hypertension.

4.4 Enrollment Procedures

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

approved by the local Institutional Review Board (IRB) or Ethics Committee (EC) or other host-country agency, as applicable. Sites must be PK-certified. Upon receiving final approval, sites will submit all required protocol registration documents to the DAIDS Protocol Registration Office (DAIDS PRO) at the Regulatory Compliance Center (RCC). The DAIDS PRO will review the submitted protocol registration packet to ensure that all of the required documents have been received.

4.4.1 Initial Protocol Registration

Site-specific informed consent forms (ICFs) *WILL NOT* be reviewed or approved by the DAIDS PRO, and sites will receive an Initial Registration Notification when the DAIDS PRO receives a complete registration packet. Receipt of an Initial Registration Notification indicates successful completion of the protocol registration process. Sites will not receive any additional notifications from the DAIDS PRO for the initial protocol registration. A copy of the Initial Registration Notification should be retained in the site's regulatory files.

4.4.2 Amendment Protocol registration

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 RCC. 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.

4.5 Coenrollment Procedures

Co-enrollment in P1074: A Prospective Surveillance Study of Long-Term Outcomes in HIV-infected Infants, Children and Adolescents and other observational trials and non-ARV treatment trials is permitted. Co-enrollment is permitted except for protocols that would violate the exclusion criteria and/or local/country regulations. All co-enrollments require the assent of the protocol chairs of P1083 and the co-enrolled protocols.

5.0 STUDY TREATMENT

5.1 Drug Regimens, Administration and Duration

5.11 Treatment Regimen

Lopinavir/ritonavir (LPV/r) tablets PO BID
(For subjects within weight band ≥ 10 kg; dose based on Table 3)

OR

Lopinavir/ritonavir (LPV/r) solution PO BID
(For subjects within weight band < 17 kg; dose based on Table 4)

PLUS

Two NRTIs (not provided by this study, as approved by host country)

- LPV/r will be dosed according to WHO ARV weight band dosing schedule as indicated in Tables 3 and 4.
- For the purposes of this protocol, only LPV/r is considered to be a study drug. Other ARV agents used as part of a combination regimen, including NRTIs, will NOT be provided by the study and must be provided by prescription.
- Study clinicians, in conjunction with subjects, should determine the optimal HAART regimen for each subject. Secondary and subsequent regimens are not defined by this protocol, and should be determined at the discretion of the study clinicians.

Table 3: DOSING SCHEDULE FOR LPV/r TABLETS					
Weight Band Range: ≥ 10 kg					
Weight Band (kg)	Formulation	AM		PM	
		Total Dose	Tablets(n)	Total Dose	Tablets(n)
10 – 10.9	100/ 25 mg	200/ 50 mg	2	100/ 25 mg	1
11 – 11.9	100/ 25 mg	200/ 50 mg	2	100/ 25 mg	1
12 – 13.9	100/ 25 mg	200/ 50 mg	2	100/ 25 mg	1
14 – 16.9	100/ 25 mg	200/ 50 mg	2	200/ 50 mg	2
17 – 19.9	100/ 25 mg	200/ 50 mg	2	200/ 50 mg	2
20 – 24.9	100/ 25 mg	300/ 75 mg	3	200/ 50 mg	2

(Note: Subjects who reach the weight-band of 25 kg – 29.9 kg, should receive 300/ 75mg (administered as three 100/25 mg tablets) PO BID. This weight-band dosing is for informational purposes only and to be used only for those subjects already enrolled who reach this weight-band during the course of the study. Study enrollment into this weight-band is NOT permitted.)

Table 4: DOSING SCHEDULE FOR LPV/r SOLUTION					
Weight Band Range: < 17 kg					
Weight Band (kg)	Formulation	AM		PM	
		Total Dose	Volume	Total Dose	Volume
3 – 3.9	80/ 20 mg/mL	80/ 20 mg	1 mL	80/ 20 mg	1 mL
4 – 4.9	80/ 20 mg/mL	120/ 30 mg	1.5 mL	120/ 30 mg	1.5 mL
5 – 5.9	80/ 20 mg/mL	120/ 30 mg	1.5 mL	120/ 30 mg	1.5 mL
6 – 6.9	80/ 20 mg/mL	120/ 30 mg	1.5 mL	120/ 30 mg	1.5 mL
7 – 7.9	80/ 20 mg/mL	120/ 30 mg	1.5 mL	120/ 30 mg	1.5 mL
8 – 8.9	80/ 20 mg/mL	120/ 30 mg	1.5 mL	120/ 30 mg	1.5 mL
9 – 9.9	80/ 20 mg/mL	120/ 30 mg	1.5 mL	120/ 30 mg	1.5 mL
10 – 10.9	80/ 20 mg/mL	160/ 40 mg	2 mL	160/ 40 mg	2 mL
11 – 11.9	80/ 20 mg/mL	160/ 40 mg	2 mL	160/ 40 mg	2 mL
12 – 13.9	80/ 20 mg/mL	160/ 40 mg	2 mL	160/ 40 mg	2 mL
14 – 16.9	80/ 20 mg/mL	200/ 50 mg	2.5 mL	200/ 50 mg	2.5 mL

5.12 Administration and Duration

Doses of LPV/r should be administered orally approximately 12 hours apart and within two hours of the regularly scheduled time. Tablets may be taken with or without food, swallowed whole and not chewed, broken,

or crushed. Oral solution must be taken with food. Exact times of doses on the day prior to pharmacokinetic sampling must be recorded on the pharmacokinetic Case Report Forms (CRF). Study treatment duration is 24 weeks.

5.13 Dose/ Formulation Adjustments

Doses will not be modified for toxicity. In the event of toxicity, LPV/r will either be continued at protocol-specified doses or discontinued (see Section 6.1).

Site pharmacists must receive new prescriptions from an authorized prescriber if weight-based adjustments are required in subjects who outgrow their dose and are switched to the next dosing increment.

No switching of formulations is allowed, unless switching may improve adherence, as noted in Section 3.0. Site pharmacists must receive new prescriptions from an authorized prescriber if a formulation adjustment is required.

5.2 Drug Formulation

5.21 Lopinavir/ritonavir (LPV/r) pediatric tablets

Lopinavir 100 mg/ritonavir 25 mg will be available as heat stable, film-coated tablets. The tablet formulation may not be cut, chewed or crushed and will be used in study subjects weighing 10 kg or greater with a demonstrated ability and willingness to swallow study drugs.

Store lopinavir 100 mg/ritonavir 25 mg film-coated tablets at 20°C–25°C (68°F–77°F); excursions permitted to 15°C–30°C (59°F–86°F) until dispensed to subject. Exposure of this product to high humidity outside the original container or USP equivalent tight container for longer than 2 weeks is not recommended.

5.22 Lopinavir/ritonavir (LPV/r) oral solution

Lopinavir 80 mg/ritonavir 20 mg per milliliter oral solution contains 42.4% alcohol by volume.

Store lopinavir 80 mg/ritonavir 20 mg per milliliter oral solution at 2°C–8°C (36°F–46°F) until dispensed to subject. Avoid exposure to excessive heat. Refrigerated LPV 80 mg/ritonavir 20 mg oral solution remains stable until the stated expiration date. For subject use, if the LPV 80

mg/ritonavir 20 mg oral solution is stored at room temperature, 15°C-25°C (59°F-77°F), it should be used within 2 months. In settings where average room temperature exceeds 25°C, storage in a refrigerator at 2-8°C is required.

5.3 Drug Supply, Distribution and Pharmacy

5.31 Study Supply

Lopinavir 80 mg/ritonavir 20 mg per milliliter oral solution and lopinavir 100 mg/ritonavir 25 mg tablets will be supplied by Abbott Laboratories and will be available through the NIAID Clinical Research Products Management Center (CRPMC). The IMPAACT pharmacist can obtain the study agents for this protocol by following the instructions in the manual *Pharmacy Guidelines and Instructions for DAIDS Clinical Trials Networks* in the section on Study Product Management Responsibilities.

The NRTIs and any other ARV therapy will NOT be provided through this study. NRTI background will be prescribed by the health care provider according to local national and/or international guides for treatment of HIV-infected children and supplied from local pharmacies.

5.32 Study Agent Accountability

The IMPAACT pharmacist is required to maintain complete records of all study medication received from the NIAID CRPMC and subsequently dispensed. All unused study medication must be returned to the NIAID CRPMC after the study is completed or terminated. The procedures to be followed are given in the manual, *Pharmacy Guidelines and Instructions for DAIDS Clinical Trials Networks*, in the section on Study Product Management Responsibilities. Non-U.S. site pharmacists should contact the Protocol Pharmacist for further instructions before returning any study medication.

6.0 SUBJECT MANAGEMENT

6.1 Toxicity Management

The Division of AIDS Table for Grading the Severity of Adult and Pediatric Adverse Events (DAIDS AE Grading Table), Version 1.0, dated December 2004, clarification August 2009 must be used and is available on the RCC web site (<http://rcc.tech-res.com/>).

Management of adverse experiences will be according to the best clinical practice and the judgment of the site investigator. Alternate explanations for clinical and laboratory abnormalities must be sought.

Grading will be assigned based on the DAIDS AE Grading Table, Version 1.0, dated December 2004, clarification August 2009 (available on the RCC web site (<http://rcc.tech-res.com/>)) and laboratory normals will be based on the institutional values. However, if a site does not have an age-specific normal range/value for a particular lab, the site should use the latest edition of the Harriet Lane Handbook for normal ranges/values and document this for monitoring purposes. Abnormal clinical and laboratory findings should be followed until resolution to <Grade 2.

The toxicity management guidelines are for events for which a relationship to the study drug (LPV/r) and/or the NRTI backbone cannot be excluded. Any admission unrelated to an AE (e.g., for labor/delivery, cosmetic surgery, administrative or social admission for temporary placement for lack of a place to sleep) may not result in study drug interruption.

Study drug doses will not be modified for toxicity; the study drug will either be continued at protocol-specified doses or discontinued.

General toxicity management guidelines are provided below. The management of specific adverse events is detailed in Section 6.12 and supersedes the general guidelines.

Substitutions and dose modifications will be allowed within the NRTI backbone due to toxicity or intolerance.

6.11 General Toxicity Management Guidelines

All suspected adverse drug reactions (SADRs) should be recorded on CRFs at each visit. The protocol CMC team and RCC Safety Desk via DAERS system should be notified of any Grade ≥ 3 SADR (including death) within 72 hours of the site being aware of the event along with site investigator plan for clinical management and follow up of these events as appropriate.

Grade 1 Toxicity:

- Continue all ARVs (LPV/r and NRTI background agents).

Grade 2 Toxicity:

- Continue all ARVs.

Grade 3 Toxicity:

- LPV/r and NRTI background agents can be continued at the discretion of the site investigator/ health care provider for clinical events, or while awaiting a repeat assessment/ confirmation of an abnormal laboratory test as soon as possible (at most within 1 week).
- If repeat assessment confirms Grade 3 toxicity, the protocol CMC should be notified within 72 hours. If the health care provider and the P1083 CMC team decide that the toxicity is possibly, probably, or definitely related to LPV/r, hold all ARVs and follow abnormal laboratory values weekly and notify P1083 CMC team within 72 hours. Management of events where the toxicity is probably not related to study drug will be determined on a case by case basis at the discretion of the P1083 CMC team.
- If toxicity resolves to \leq Grade 2 within 21 days, LPV/r and NRTI background agents can be restarted.
- If Grade 3 toxicity persists for >21 days, or recurs to \geq Grade 3 after reintroduction of LPV/r and NRTI background agents, all ARVs must be permanently discontinued. The health care provider and the P1083 CMC team will consult on treatment options on a case-by-case basis.

Grade 4 Non-Life-Threatening Toxicity:

- LPV/r and the NRTI background agents should be held and the P1083 CMC team should be notified within 72 hours. For abnormal laboratory tests, repeat assessment/confirmation should be done as soon as possible (at most within 1 week).
- If repeat assessment confirms Grade 4 toxicity and the health care provider and P1083 CMC determine that the toxicity may be related to LPV/r, all ARVs should be permanently discontinued.
- If repeat assessment shows Grade 3 toxicity, continue to hold LPV/r and background NRTIs and follow abnormal laboratory values weekly and notify the P1083 CMC within 72 hours.
- If toxicity resolves to $<$ Grade 2 within 21 days, LPV/r and the background NRTIs can be restarted. If \geq Grade 3 toxicity recurs after reintroduction of LPV/r and the background NRTIs, all ARVs must be permanently discontinued.

Grade 4 Life-Threatening Toxicity:

- All ARVs (LPV/r and background NRTIs) should be permanently discontinued. The protocol CMC team should be notified immediately.

Subjects who prematurely discontinue study treatment will continue to be followed at scheduled study visits as indicated in the schedule of evaluations (SOE).

6.12 Special Toxicity Management Guidelines

6.1.2.1 Clinical Pancreatitis

If the subject develops nausea, vomiting, or abdominal pain of any grade associated with any elevation of serum fractionated pancreatic amylase or lipase, or develops a clinical syndrome that in the opinion of the subject's provider is classified as pancreatitis, all ARVs should be discontinued, and the protocol CMC team should be notified. Future consideration should be given to avoiding (didanosine) ddI or other drugs which potentially affect the pancreas.

6.1.2.2 Clinical Hepatitis or Hepatic Steatosis

- Subjects should be monitored for the development of non-specific prodromal signs or symptoms of hepatitis, such as fatigue, malaise, anorexia, nausea, jaundice, hyperbilirubinemia, acholic stools, liver tenderness or hepatomegaly, with or without initially abnormal serum transaminase levels per the DAIDS Table for Grading the Severity of Adult and Pediatric Adverse Events, Version 1.0 [December 2004], Clarification August, 2009, <http://rcc.tech-res-intl.com> Laboratory values (Version 1.0).
- Subjects with signs and symptoms of hepatitis must have LFTs performed.
- All study drugs must be permanently discontinued immediately if ALT or AST is even one grade higher than baseline. Possible alternative etiologies (e.g., acute viral hepatitis) should be sought but should not affect management of the subject as described in this section.
- Subjects who develop hepatic steatosis must immediately and permanently discontinue study treatment (LPV/r and all background NRTIs). Notify the protocol CMC team.

6.1.2.3 Hematologic Toxicity on a ZDV-Inclusive Regimen ONLY (subjects not receiving ZDV should follow general toxicity management guidelines in Section 6.11).

Grade 1 Toxicity:
Continue all ARVs.

Grade 2 Toxicity:
Continue all ARVs.

Grade 3 Toxicity defined as:

- Hgb <7.5 g/dL AND >1 g/dL below the baseline value;
- WBC <1,500/mm³;
- ANC <750/mm³;
- Platelets <50,000/mm³
- Continue all ARVs at the discretion of the site investigator/ health care provider while awaiting a repeat assessment/confirmation of the abnormal laboratory test as soon as possible (at most within 1 week). If repeat assessment confirms Grade 3 toxicity, the site investigator may replace ZDV with another NRTI at this point. Notify the P1083 Protocol CMC Team of the replacement. If Grade 3 toxicity persists for >21 days, or recurs to \geq Grade 3 despite NRTI substitution, LPV/r must be held.
- If trimethoprim/sulfamethoxazole (TMP/SMX) is being administered for PCP prophylaxis, and the site investigator considers TMP/SMX as a possible cause of Grade 3 hematologic toxicity and an alternate PCP prophylaxis regimen is readily available, the following drug management should be discussed with the protocol CMC team for approval before implementation: an alternative PCP prophylaxis regimen may be substituted while ARVs are being continued (at the discretion of the health care provider /investigator) and abnormal laboratory value(s) are being followed weekly. If Grade \geq 3 toxicity persists for >21 days, despite discontinuing TMP/SMX, LPV/r must be permanently discontinued. If toxicity resolves to Grade \leq 2 within 21 days, resume/continue ARVs and continue routine monitoring.

Grade 4 Hematologic Toxicity defined as:

- Hgb <6.5 g/dL;
- WBC <1,000/mm³;
- ANC <500/mm³;
- Platelets <25,000/mm³;
- All ARVs should be held.
- Repeat assessment should be done as soon as possible (at most within 72 hours).
- If repeat assessment confirms Grade 4 hematologic toxicity, LPV/r and background NRTIs should be permanently discontinued.
- If repeat assessment shows Grade 3 toxicity, follow management for Grade 3 toxicity.

6.1.2.4 Increases in Values for ALT and/or AST (without clinical symptoms attributed to hepatitis):

- Elevations in ALT and/or AST values should be managed based on the toxicity grade with the following exceptions:
- For all new Grade 2 ALT and/or AST values, monitor the subject every two weeks or more often until values return to Grade 1. Notify the protocol CMC team.
- In general, all new Grade 2 ALT and/or AST values or higher, should be reported to the P1083 protocol CMC team every other week.

6.1.2.5 Hyperlipasemia

For elevations of lipase in blood, follow this algorithm:

- For Grade 2 hyperlipasemia ($>1.5 \times \text{ULN}$), consider holding all ARVs, notify the protocol CMC team immediately, schedule follow-up visits every two weeks if necessary until toxicity resolves to Grade 1 or less.
- For any Grade 3 hyperlipasemia ($>3.0 \times \text{ULN}$), hold all ARVs until both lipase and pancreatic amylase are Grade 1 or less. Notify the protocol CMC team immediately.
- For Grade 4 hyperlipasemia ($>5.0 \times \text{ULN}$), all ARVs should be held and may be permanently discontinued. Do not restart until both lipase and pancreatic amylase are Grade 1 or less. Notify the protocol CMC team immediately to determine course of action. If hyperlipasemia recurs, discontinue all ARVs.

6.1.2.6 Hyperamylasemia

Management of this toxicity will be prompted for a Grade 3 or 4 hyperamylasemia.

Upon presentation of Grade 3 or 4 total amylase; the blood sample should be fractionated and the pancreatic fraction should then be used to determine the toxicity management. The toxicity grades for total amylase will be calculated using the local laboratory ULN and will be graded according to the table below:

LABORATORY				
PARAMETER	GRADE 1 MILD	GRADE 2 MODERATE	GRADE 3 SEVERE	GRADE 4 POTENTIALLY LIFE- THREATENING
CHEMISTRIES (Standard International Units as per Local Laboratory)				
Total amylase	>1.0-1.5 x ULN	>1.5-2 x ULN	>2.0-5.0 x ULN	> 5.0 x ULN

For purposes of this protocol the upper limit of normal (ULN) for pancreatic amylase is defined as 37% of the ULN for total amylase.

Pancreatic amylase will be graded according to the relationship to ULN (as determined above) and graded using the DAIDS Table for Grading the Severity of Adult and Pediatric Adverse Events, Version 1.0 [December 2004], Clarification August, 2009, <http://rcc.tech-res-intl.com> (see Laboratory section, pancreatic amylase parameter, pg. 19 of 20 of Version 1.0).

Additionally, a lipase should also be obtained and the following algorithm applied: (Remember that this is done as secondary assay to a Grade 3 or 4 hyperamylasemia. Hyperlipasemia alone must be managed as described in the previous section).

- If there is an elevation in lipase (\geq Grade 2), hold all study drugs until both pancreatic amylase and lipase are Grade 1 or less. Notify the protocol CMC team immediately.
- Pending the results of the fractionated amylase evaluation, if the lipase is normal, ARVs may be continued. Notify the protocol CMC team.
- Once available, fractionated pancreatic amylase elevations should be managed per the toxicity grade as described in Section 6.1.

6.1.2.7 Hyperglycemia

If non-fasting blood glucose is ≥ 250 mg/dL, then follow with a fasting glucose. If fasting blood glucose is ≥ 150 mg/dL, consider consulting an endocrinologist regarding possible new onset diabetes and notify the Protocol CMC team.

6.1.2.8 Hypertriglyceridemia

If triglycerides are > 750 mg/dL, obtain lipase and fasting triglycerides. Obtain all future triglyceride values in fasting state, and use fasting values for grading. Anti-hyperlipidemic agents may not be used.

NOTE: For infants < 6 months of age, draw blood immediately before the next feeding/meal (i.e., if the infant eats every three hours, draw blood at the third hour). Infants ≥ 6 months of age but < 12 months of age should fast for four hours prior to the blood draw. Infants ≥ 12 months of age should fast for six hours prior to the blood draw.

6.1.2.9 Elevated Cholesterol

If cholesterol is ≥ 500 mg/dL, obtain fasting cholesterol. Obtain all future cholesterol values in fasting state, and use fasting values for grading. Anti-hyperlipidemic agents may not be used.

NOTE: For infants < 6 months of age, draw blood immediately before the next feeding/meal (i.e., if the infant eats every three hours, draw blood at the third hour). Infants ≥ 6 months of age but < 12 months of age should fast for four hours prior to the blood draw. Infants ≥ 12 months of age should fast for six hours prior to the blood draw.

6.2 Subject Management

The following endpoints will be used for individual subject management and will be evaluated on bi-monthly conference calls.

6.2.1 Toxicity Endpoint

The subject will meet a toxicity endpoint for subject management purposes if the subject experiences any recurrent Grade 3 or non-life-threatening Grade 4 toxicity that is possibly, probably, or definitely related to treatment with the study drug, or a single life-threatening Grade 4

toxicity that is possibly, probably, or definitely related to treatment with the study drug. If therapy is permanently discontinued due to toxicity, the subject will be monitored in consultation with the protocol CMC team until the toxicity resolves to Grade ≤ 2 and the subject will then be taken off the study.

6.3 Subject Replacement Scenarios

- 6.31 Subject permanently discontinues study medications before week 4 PK evaluations:
- Replace for both PK and safety (if the subject has not experienced other treatment-related toxicities).
 - If the subject experienced any \geq Grade 3 treatment-related toxicities, the subject will not be replaced for safety but will count as a treatment failure.
- 6.32 Subject completes week 4 PK, but permanently discontinues study medications before week 12 safety evaluations:
- Replace for safety (if the subject has not experienced other treatment-related toxicities).
 - This subject's PK data will be included in the analysis.
- *Note that if the subject experienced any \geq Grade 3 treatment-related toxicities, the subject will count as failure, and will not be replaced for safety evaluations.
- 6.33 Subject discontinues treatment after completing week 4 PK evaluations and completes week 12 safety evaluation, but has to come off treatment after week 12:
- No replacement of subjects.
- 6.3.4 Subjects whose week 4 PK study is not evaluable (see Section 9.0) may repeat the intensive PK; if the repeat PK is still unevaluable, the subject will be replaced.
- 6.3.5 Subjects with incidence of TB after enrollment but before the first PK evaluation will be replaced.

6.4 Criteria for Treatment Discontinuation

- Treatment with disallowed medications.
- TB incidence after the subject has completed the initial PK.
- Drug toxicity that requires permanent study drug discontinuation as defined in Section 6.1.
- Non-adherence.

6.5 Criteria for Study Discontinuation

- The subject 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.
- Study is canceled at the discretion of IMPAACT, the IRB or EC, FDA, NIAID, NICHD, OHRP, Abbott Laboratories, or other country-specific governmental agencies.

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 RCC website at <http://rcc.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 RCC website: <http://rcc.tech-res.com/safetyandpharmacovigilance/>. For questions about EAE reporting, please contact the RCC (RCCSafetyOffice@tech-res.com).

7.2 Reporting Requirements for this Study

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

7.21 Study Agents for which expedited reporting are required are:

- lopinavir/ritonavir (LPV/r) tablets
- lopinavir/ritonavir (LPV/r) liquid

AEs due to background NRTIs do not require expedited reporting to DAIDS but should be reported to the study team and to the local IRB/Ethics Committee.

7.22 Grading Severity of Events

The Division of AIDS Table for Grading the Severity of Adult and Pediatric Adverse Events (DAIDS AE Grading Table), Version 1.0, dated December 2004, clarification August 2009 must be used and is available on the RCC web site (<http://rcc.tech-res.com/safetyandpharmacovigilance/>).

7.23 EAE 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).

Unexpected, serious, suspected adverse drug reactions related to study agent that occur at any time after the protocol-defined EAE reporting period should be reported, if the study staff become aware of the occurrence. These events include death, permanent disabilities, congenital abnormalities, hospitalizations, and life-threatening clinical events.

8.0 STATISTICAL CONSIDERATIONS

8.1 General Design Issues

This is a Phase II/III study to establish the pharmacokinetics, safety, tolerance, and virological effect of LPV/r in HIV-infected infants and children who weigh ≥ 3 to < 25 kg when dosed according to the WHO ARV weight band dosing schedule. This study will also determine the resulting frequency of sub-optimal

LPV exposures. Answers to these questions will provide the first data describing the actual plasma concentrations of LPV and ritonavir achieved when this simplified dosing schedule is used and whether the WHO ARV weight band dosing guidelines will provide LPV exposure that is appropriate, safe, well-tolerated and virologically potent.

8.2 Primary Endpoints and Outcome Measures

Subjects will meet a toxicity endpoint if the subject experiences any recurrent Grade 3 or non-life-threatening Grade 4 toxicity, or a single life-threatening Grade 4 toxicity related to study drug. If therapy is permanently discontinued due to toxicity, the subject will be monitored in consultation with the protocol CMC team until the toxicity resolves to Grade ≤ 2 and the subject will then be taken off the study.

The main PK exposure parameter of interest will be area under curve (AUC), as determined by a non-compartmental analysis of 12-hour PK sampling for LPV/r after 4 weeks of treatment. Maximum and minimum concentrations (C_{max} and C_{min}) will also be calculated. In addition, the proportion of subjects with an AUC of less than 10% for adults ($AUC < 52 \text{ mcg} \cdot \text{hr/mL}$) will be calculated. The outcome measures for safety and tolerance will be the number and percent of subjects with \geq Grade 3 adverse events. The outcome measure for adherence will be the proportion of doses taken. Viral loads will be used for clinical management purposes and will be a determinant of effectiveness of WHO dosing per 8.66. They will not be a specific outcome measure.

8.3 Randomization and Stratification

There will be no randomization of subjects. Subjects will be stratified by weight band and formulation as shown in Table 1 (SCHEMA).

8.4 Sample Size and Accrual

The study will enroll 94 subjects, with the goal of having 85 evaluable subjects (to account for an estimated 10% attrition): 50 receiving liquid formulation and 44 receiving solid formulation, stratified by weight band and formulation according to Table 1 (SCHEMA).

8.41 Area Under Curve (AUC)

In pediatric patients, Saez-Llorens (4) found a mean AUC of 72.6 with a coefficient of variation (CV) of 42%. Based on this, Table 5 shows the 90% confidence limits of estimates for the AUC for combinations of means and CVs surrounding those found by Saez-Llorens for a range of

sample sizes. A sample size of 85 subjects provides 90% confidence intervals where the lower and upper limits are all within 10% of the true AUC for a variety of plausible AUC/CV combinations.

Table 5: 90% Confidence limits on estimates of AUC with 85 subjects				
AUC	CV	90% Confidence Interval on AUC		
		N=75	N=85	N=95
60	30%	[57, 63]	[57, 63]	[57, 63]
	50%	[54, 66]	[55, 65]	[55, 65]
70	30%	[66,74]	[66, 74]	[66, 74]
	50%	[63, 77]	[64, 76]	[64, 76]
80	30%	[75, 85]	[76, 84]	[76, 84]
	50%	[72, 88]	[73, 87]	[63, 87]

8.42 Proportion of Subjects with Suboptimal LPV Exposure

If the AUC and CV are the same as those found by Saez-Llorens, the expected proportion of subjects with an AUC<52 is 25%. Table 6 shows the power to detect higher rates of subjects with AUC<52 given varying underlying true proportions for various sample sizes. For the planned sample size of 85, there is 80% power to detect the difference between the reference proportion of 25% and a true proportion of 38%.

Table 6: Power to detect proportion >.25 w/AUC <52			
N	True % with AUC<52	Power (one-sided, alpha=.05)	% for which have 80% power to detect %>.25
75	30%	0.22	39%
	35%	0.57	
	40%	0.86	
85	30%	0.24	38%
	35%	0.61	
	40%	0.89	
95	30%	0.25	37%
	35%	0.64	
	40%	0.91	

8.5 Monitoring

It is the responsibility of the protocol CMC team to interpret safety data, and make decisions regarding SADR 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 presenting 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 CMC team on conference calls held at every 2 weeks, or as needed. Data on accrual, pharmacokinetics, and toxicity will be reviewed.

Adverse events will be monitored throughout the follow-up period. If the protocol CMC 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 more than 6 out of the first 20 subjects or 30% of subjects thereafter have Grade 3 or greater toxicity determined to be anything other than not related to study drug.

Following temporary suspension of accrual, the protocol CMC 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 CMC team, including the study chair, the DAIDS medical officer of record, and Abbott representatives agree that the study drug is likely to be safe for additional subjects, they may allow accrual to resume. Regulatory agencies (IRB and Ethics Committee [EC]) will be notified of the event and the protocol CMC team's decision after this review of the safety data has taken place.

In the case of any life-threatening Suspected Adverse Drug Reaction (SADR) or any Grade 4 event that may not be judged to be life-threatening but is judged to be other than not attributable to the study medication, the CMC team will review the safety data within 48 hours of notification of event and determine whether it is appropriate to suspend accrual. Table 7 shows the probability of suspending accrual as a function of the true probability of Grade 3 or higher toxicity.

Table 7: Probability of suspending accrual as a function of the true probability of Grade 3 or higher toxicity

True prob. of Grade \geq 3 AE	Prob. of suspending accrual after:		
	20 subj.	30 subj.	40 subj.
0.1	0.2	0.05	0.01
0.2	8.7	6.1	4.3
0.3	39.2	41.1	42.3
0.4	75.0	82.4	87.1
0.5	94.2	97.9	99.2
0.6	99.4	99.9	>99.9

8.5.2 Accrual Rate Evaluation

Accrual to this study will be monitored by the IMPAACT leadership in accordance with standard operating procedures. Initially, the protocol CMC team will monitor site registration 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 from the time that the sites with likely the largest number of eligible subjects are able to begin enrollment (the Brazil sites are projected to have the highest enrollments). If these sites are open for enrollment for 6 months yet less than 1/2 of the subjects for the entire protocol or for a particular weight band enroll, the team may broaden the inclusion criteria via a Letter of Amendment (LOA) to include subjects who are lopinavir-experienced.

If the decision is made to broaden eligibility criteria it will occur by allowing the health care provider to enroll subjects who are otherwise eligible for the protocol yet with lopinavir experience per LOA substitution of eligibility criterion 4.14 with the following eligibility criterion 4.14A which will be:

4.14A LPV/r-treatment naïve or LPV/r treatment experienced and still LPV/r treatment appropriate using weight-band dosing in this protocol as determined by the HCP.

Notice of this change will be sent to sites via a Letter of Amendment (LOA) which will need to be submitted to each IRB or ethics committee

(EC) per each site's normal procedures. Any additional guidance issued by a site's IRB or EC will need to be followed by that site. If enrollment lags team predictions, the team will schedule an fyi with the DAIDS Clinical Science Review Committee (CSRC).

8.53 Discontinuation Rate Evaluation

The protocol team will monitor the rates of subject discontinuation of treatment for non-specific intolerance. In the case that 4 or more subjects in any weight band discontinue treatment, the protocol team will review the discontinuation data within one week to determine how to proceed.

8.6 Analyses

8.61 Primary Objective #1 (safety and tolerance):

Safety and tolerance of the study agent will be evaluated by summarizing the number and percent of subjects with documented Grade 3 or higher adverse events; each summary will be conducted overall and by formulation. The proportion of subjects experiencing Grade 3+ adverse events will be presented in aggregate and by formulation, with these proportions bounded by exact 95% confidence intervals; this will also be done for the proportions of subjects with Grade 3+ adverse events which have been judged to be at least possibly related to treatment.

8.62 Primary Objective #2 (PK LPV/r dosed by WHO ARV schedule):

Non-compartmental pharmacokinetic analysis will be performed using WinNonlin or a similar program. AUC will be determined using the trapezoidal method. C_{\min} , C_{\max} and t_{\max} will be taken from the observed data. The terminal slope λ_z will be determined from log-linear portion of the curve and half-life, $t^{1/2}$ calculated as $0.693/\lambda_z$. At least 5 of the 6 samples must be evaluable for the profile to be included in the non-compartmental analysis. Additional population analyses will be performed with the program NONMEM to determine compartmental PK parameters and their variance. These will be used as input to assess the weight band dosing with Monte Carlo simulations.

The PK samples will be batched and shipped to the pharmacology laboratory to be assayed for LPV concentration. PK results will be provided to investigators as soon as they are available. The 90% confidence interval of geometric mean (GM) for LPV AUC will be determined and compared to a target value defined on the basis of studies

establishing safety and efficacy of LPV. The target GM (range) for LPV AUC_{12} will be 80 (40-160) mcg*hr/mL.

The proportion of subjects with sub-optimal LPV exposure will be calculated for the entire sample, as well as for each formulation (liquid vs. solid). These response rates will be compared with the 25% rate expected if the PK parameters are the same as in the Saez-Llorens sample.

Body surface area (BSA) will be measured on all individuals, and the dose that would have been administered under the BSA-based dosing schedule will be calculated. The impact of adopting the weight-band based dosing schedule will be assessed by rescaling the weight-band based observations on AUC and C_{min} to the counterfactual BSA-based AUC and C_{min} by assuming linearity of pharmacokinetics over the ranges to be encountered in this study; for example, if the weight-based dose is 0.8 the usual BSA-based dose, then the observed AUC and C_{min} are expected to be 0.8 the AUC and C_{min} that would have occurred with BSA-based dosing.

8.63 Secondary Objective #1 (factors impacting LPV exposure):

The week 4, 12, and 24 PK samples will be combined to assess the potential impact of demographic variables and clinical variables on LPV pharmacokinetics, exposure and trough concentrations. This will be performed through a two stage model building process. The first stage will be an univariate screen of clinical factors added to the model and assess for ability to explain inter-subject variability. All factors identified in the first stage univariate screen will be included the second stage multivariate analysis which will be used to develop the final model that incorporates all relevant covariates.

8.64 Secondary Objective #2 (evaluate adherence to the weight band dosing schema):

Adherence will be evaluated by the proportion of doses taken.

8.65 Secondary Objective #3 (role of CYP3A4 genetic variants on PK):

Descriptive analysis of variants in CYP3A4 as well as variants in ORM1 and SLCO1B1. Chi-square tests will be used to examine the relationship between CYP3A4 genetic variants and having LPV/r concentrations within the target range.

8.66 Secondary Objective #4 (association between VL/immune restoration and dosing):

Effectiveness of the WHO dosing regimen will be evaluated by summarizing the percent of subjects achieving viral load <400 and CD4% \geq 25 both overall, by dose band, and by formulation, with these proportions bounded by exact 95% confidence intervals and compared with proportions at entry.

9.0 CLINICAL PHARMACOLOGY PLAN

9.1 Pharmacology Objectives

- 9.11 To delineate the pharmacokinetics of LPV/r when dosed according to the WHO ARV weight band dosing schedule in HIV-infected infants and children.
- 9.12 To explore the demographic and clinical factors which may impact LPV pharmacokinetics, LPV exposure and LPV trough concentration.

9.2 Primary and Secondary Data

Demographic data, recent LPV dosing history including food intake, and sample collection times will be obtained. Plasma drug concentrations collected prior to 2, 4, 6, 8, and 12 hours post dose at the week 4 visits will be used for the PK analysis. Alpha-1 acid glycoprotein and albumin concentrations will be determined from one of the pharmacokinetic samples.

9.21 Laboratory Analysis and Reporting

Site: Plasma pharmacokinetic samples collected at intensive PK will be sent to the IMPAACT Specialized Clinical Pharmacology Laboratory (PCPL) at UCSD and will be assayed for plasma concentration of LPV and ritonavir. Plasma samples from Thailand will be sent to and assayed at the IMPAACT-PHPT Pharmacology Laboratory at the Faculty of Associated Medical Science, Chiang Mai University. The alpha-1 acid glycoprotein and albumin concentration will be determined from one of the samples during the intensive PK visits.

Methods to be used: All assay methods will be standardized with a filed Methods Report, under Good Laboratory Practice (GLP) conditions currently used in the UCSD laboratory. The assay will be performed using high performance liquid chromatographic (HPLC) method or similar method approved by the NIAID Clinical Pharmacology Quality Assurance program.

Reporting of Assay Data: Assays will be batched in sufficient numbers to provide analysis by routine assays which will include at least 3 interim batches within 60 days of the laboratory receiving the first 3 quartiles of PK samples. All PK samples will be registered in the Lab Data Management System (LDMS) database.

9.3 Study Design, Modeling and Data Analysis

Intensive pharmacokinetic evaluations will be performed after 4 weeks (± 1 week) of LPV/r therapy. Blood (1 mL) will be collected prior (pre-dose) to an observed dose and at 2, 4, 6, 8, and 12 hours post dose for LPV and ritonavir plasma concentration determinations. Parents must report that the subjects have not missed any doses in the 72 hours prior to PK intensive visit or the visit will be rescheduled.

Non-compartmental pharmacokinetic analysis will be performed using WinNonlin or a similar program. The PK parameters determined will include:

- Area under the plasma concentration-time curve (AUC), estimated by the trapezoidal method.
- Maximum observed concentration of drug in plasma (C_{\max}) and time of the maximum observed concentration in plasma (T_{\max}).
- Minimum concentration of drug in plasma (C_{\min}).
- Half-life ($T_{1/2}$).

Pharmacokinetic parameters will be presented by weight group and by formulation with additional exploratory analysis performed as warranted by the data. AUC will be determined using the trapezoidal method. C_{\min} , C_{\max} and t_{\max} will be taken from the observed data. The terminal slope λz will be determined from log-linear portion of the curve and half-life calculated as $0.693/\lambda z$. At least 5 of the 6 samples must be evaluable for the profile to be included in the non-compartmental analysis. Evaluable samples are defined as samples with ample volume and integrity to generate accurate concentration results and their associated accurate dosing and sample times data.

The overall exposure observed will be compared to that seen in other populations. Specifically the geometric mean and 90% confidence interval for the AUC will be determined. It is expected that this will fall within the range 40 and 160 mcg*hr/mL, which represents approximately 50 and 200% of the values seen in adults with standard LPV 400 mg/ritonavir 100 mg dosing. In addition, the number of subjects that fall outside of this range will be tabulated.

A comparison will be made between the observed PK parameters with those expected from the alternative dosing strategy included in the FDA approved label

(16 mg/kg, 12 mg/kg or 10 mg/kg based on age and weight). This comparison will identify instances where subjects would be receiving different doses by the two dosing paradigms. The frequency of different dose recommendations will be determined and tabulated. The expected LPV exposure with FDA dosing will be estimated in those subjects where the doses differ. This estimation will be achieved by multiplying exposure parameters – AUC, C_{\min} and C_{\max} the ratio for the FDA recommended dose/WHO ARV weight band dose assuming linear pharmacokinetics. The geometric mean and 90% confidence interval will be determined for the expected AUC calculated from the FDA-recommended dosing paradigm.

Interim Pharmacokinetic Analyses

There will also be three interim pharmacokinetic analyses performed as the pharmacokinetic results are generated. These will include AUCs from the Week 4 intensive pharmacokinetic visit and occur following determination of lopinavir concentrations for each of the first three quartiles of samples. The AUCs will be categorized as <40, 40-160 or >160 mcg*hr/mL. If more than 20% of cumulative subjects fall outside the 40-160 mcg*hr/mL AUC range, the protocol team will hold a conference call to discuss the pharmacokinetic results in detail and determine if any modifications in the protocol are needed.

Population Pharmacokinetic Analysis

Population analyses will be performed on the intensive PK data and the 12 and 24 week single samples to determine compartmental PK parameters with the program NONMEM. The population pharmacokinetic analysis will also assess clinical factors (e.g., age, weight, etc.) that may be associated with LPV pharmacokinetic parameters. It will also be used to quantify the unexplained inter-subject variability. These parameters and their variability will be incorporated as the input model to assess the WHO ARV weight band dosing using Monte Carlo simulations.

9.4 Anticipated Outcomes

LPV exposure (AUC, C_{\min} , C_{\max}), following administration of heat stable pediatric tablets or the liquid formulation according to the WHO ARV weight band schedule. Relationships of these parameters with:

- Age and growth parameters.
- Albumin and alpha 1 acid glycoprotein concentrations, disease stage, concomitant medications, clinical chemistries and pharmacogenomic polymorphisms.

Performance of the weight band dosing to achieve target LPV exposure in comparison to the FDA (weight based) dosing recommendations for LPV/r.

10.0 HUMAN SUBJECTS

10.1 Institutional Review Board and Informed Consent

This protocol, the sample informed consent document (Appendix III), and any subsequent modifications must be reviewed and approved by the IRB or EC responsible for oversight of the study. Written informed consent must be obtained from the subject (or parents or legal guardians of subjects who cannot consent for themselves, such as those below the legal age). The subject's assent must also be obtained if he or she is able to understand the nature, significance, and risks of the study. Assent is determined by each site IRB and/or EC. The informed consent will describe the purpose of the study, the procedures to be followed, and the risks and benefits of participation. A copy of the consent form will be given to the subject (or parent or legal guardian).

Each site that receives U.S. 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. The plan should be documented and filed in the appropriate regulatory file at the site but not submitted to the Protocol Registration Office.

10.2 Subject Confidentiality

All laboratory specimens, evaluation forms, reports, and other records will be identified only by a coded number to maintain subject confidentiality. All records will be kept in a secured area. All computer entry and networking programs will be done with coded numbers only. Clinical information will not be released without written permission of the subject's parent or legal guardian, except as necessary for monitoring by the FDA, the Office for Human Research Protections (OHRP), the NIAID, NICHD, local IRB or Ethics Committee, or the pharmaceutical sponsor (Abbott).

10.3 Study Discontinuation

The study may be discontinued at any time by the IMPAACT Network, NIAID, NICHD, the FDA, the IRB or EC, OHRP, the pharmaceutical sponsor, or other country-specific 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 (CDC) and the National Institutes of Health (NIH).

All infectious specimens will be sent using packaging that meets the requirements specified by the International Air Transport Association Dangerous Goods Regulations for UN 3373, Biological Substances, Category B, and Packing Instruction 650. Please refer to individual carrier guidelines (e.g., Federal Express or Airborne).

13.0 REFERENCES

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Ref Type: Abstract

APPENDIX I
SCHEDULE OF EVALUATIONS (SOE)

EVALUATIONS	Screening ¹	Entry	Week 2* (± 1 week)	Week 4* (± 1 week)	Week 12* (± 2 weeks)	Post-Dose Change Evaluation**		Early D/C	Off Tx Follow Up ¹⁴	End of study Week 24 ¹⁵ (± 2 weeks)
						2-week	4-week			
CLINICAL										
Documentation of HIV	X									
Complete history ²	X	X								
Targeted history (Clinic) ^{3a}			X	X	X		X	X	X	X
Physical exam ⁴	X	X	X	X	X		X	X	X	X
Adherence Assessment ⁵			X	X	X		X	X		X
Targeted history (Phone Contact) ^{3b}						X				
LABORATORY										
Hematology ⁶	1 mL	1 mL		1 mL	1 mL			1 mL	1 mL	1 mL
Blood Chemistries ⁷	1 mL	1 mL		1 mL	1 mL		1 mL	1 mL	1 mL	1 mL
LFTs ^{7a}	X	X		X	X		X	X	X	X
<i>Virology</i>										
HIV-1 RNA PCR ⁸	1 mL	1 mL		1 mL	1 mL			1 mL		1 mL
<i>Immunology</i>										
Lymphocyte subsets ⁹	1 mL	1 mL						1 mL		1 mL
<i>Pharmacology</i>										
PK Reminder ¹⁰				X						
Intensive PK ¹¹				6 mL						
Single post-dose PK ¹²					1 mL					1 mL
Dried Blood Spot (for pharmacogenics) ¹³				X						
TOTAL BLOOD VOLUMES (maximum)	4 mL	4 mL		9 mL	4 mL		1 mL	4 mL	2 mL	5 mL

* Study visits must be scheduled on the weeks indicated in the SOE ± 1 week for visit weeks 2 and 4, then ± 2 weeks for visit weeks 12 and 24.

** Post dose change evaluations may occur anytime during the 0-24 week study period.

APPENDIX I (Cont.)

1. Screening evaluations must be performed within 30 days of Entry.
2. Complete history: diagnoses, signs & symptoms and WHO staging.
3. Targeted history- if the subject's weight-band and dose change during the study period
 - a. Clinic: Current diagnoses, signs & symptoms.
 - b. Phone: Self-reported signs & symptoms, adherence assessment.
4. Physical exam should include height, weight, head circumference, and vital signs.
5. Adherence Assessment: Adherence will be measured at each visit by questionnaire and pill counts or bottle measurements.
6. Hematology should include CBC with differential and platelet count.
7. Chemistries should include LFTs, serum creatinine, electrolytes, total amylase, glucose and lipids. See protocol section 6.1.2 for instructions on non-fasting versus fasting glucose and lipids.
 - a. LFTs: AST, ALT, total bilirubin
 - b. Electrolytes: bicarbonate (CO₂), phosphate (phosphorus), sodium, potassium, calcium, magnesium
8. HIV-1 PCR: Must be performed at DAIDS VQA-certified laboratory and per current IMPAACT Lab guidelines.
9. Lymphocyte subsets include CD4/CD8 counts and percentages. Must be performed at DAIDS IQA-certified laboratory.
10. PK reminder: A telephone (or in person contact) adherence assessment will be made on the day prior to the PK visit. If caregiver reports any missed doses within the past 72 hours, then visit should be rescheduled.
11. Intensive PK sampling time points are pre-dose and 2, 4, 6, 8, and 12 hours after an observed dose. Caregivers must report that the subjects have not missed any doses during the 72 hours prior to PK intensive visit or the visit will be rescheduled. The contents of the subject's last meal prior to intensive PK sampling will be recorded on the CRF.
 - a. Children who outgrow their dose and switch to the next dosing increment, due to weight gain, during the initial 4 weeks of therapy will have their PK visit delayed until they have been on the increased dose for 4 weeks.
12. Single dose PK sampling time point is 2-6 hours post-dose.
13. Dried blood spot: See Laboratory Processing Chart (LPC) and Appendix II for collection, processing, and shipping instructions.
14. Early discontinuation: Subjects who prematurely discontinue study treatment will continue to be followed at scheduled study visits, but only the evaluations listed in the Off Tx/Follow-up column are required.
15. End of study: Last visit-evaluations must be scheduled as indicated (study drugs will not be provided, after this visit) in the SOE \pm 2 weeks.

APPENDIX II
DRIED BLOOD SPOT (DBS) COLLECTION, PROCESSING AND STORAGE INSTRUCTIONS

I. General Instructions

The Dried Blood Spot (DBS) cards should be collected on Whatman Protein Saver Cards. DBS cards should be prepared from blood drawn in EDTA (purple top) tubes. Gloves must always be worn at all times when handling filter papers, *before and after* blood is applied.

The filter cards come with printed circles. Always apply blood to the inside of the circles. Fill the entire circle with blood (50 microliters). Apply blood to only one side of the filter paper (the side with the printing).

Avoid using capillary tubes to collect blood specimens. There exists considerable danger of infection for lab workers from puncture wounds resulting from the accidental breakage of the capillary tubes.

Shown: Picture representative of Whatman Protein Saver cards

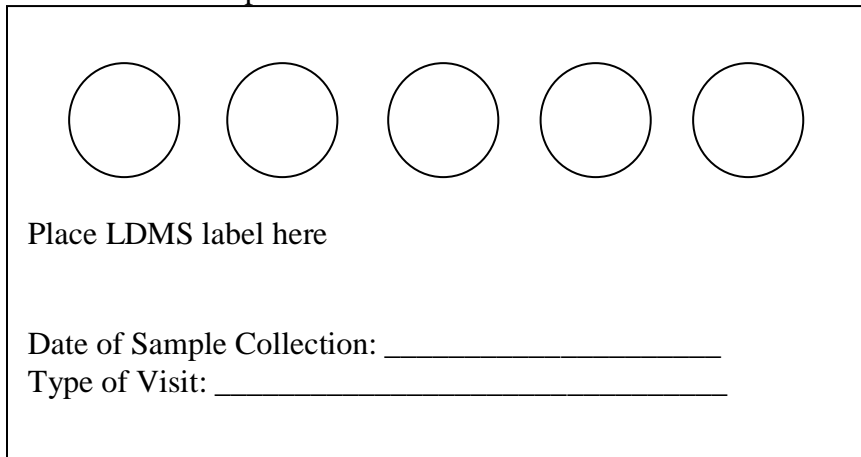


Figure 1: Dried Blood Spot Card



II. Biosafety

It is essential that universal precautions be taken while working with these specimens. Dried blood spots on filter paper are not considered to be a biohazard. However, you may want to double glove and wear a lab coat/gown at all times even with DBS to ensure safe handling of samples. If you should tear a glove, remove the torn one and replace it immediately. If a needle puncture should occur, notify the lab manager or project coordinator immediately and appropriate action will take place.

III. Preparation of DBS Using Fingerprick Specimen- for Children

Equipment Needed:

1. Unistick 2 device (depth of 1.8 mm)
2. Alcohol swab
3. Dry sterile gauze pad
4. Whatman Protein Saver Card (Whatman catalog number 10534612)
5. Gas impermeable storage bag
6. Indicator desiccant pack (such as Whatman catalog number WB100003)

Procedure:

Clean the area of the finger with an alcohol pad and allow the area to air dry. Prepare the Unistick 2 device by depressing the pink plunger until it clicks. Twist the plunger until it breaks off and remove it from the device. The Unistick 2 device is now ready for use. Do not touch the cleaned area or allow the finger to come into contact with any non-sterile item or surface.

Wipe away the first drop of blood using a dry sterile gauze pad. The blood is then allowed to flow to be collected on the dried blood spot card. To do this, gently touch the filter paper card to the blood drop. Allow the card to absorb the blood until the circle is FULL. You should be able to obtain 5 spots of blood on a card. You may need to squeeze the finger to obtain more blood; however, do not milk the finger as it mixes interstitial fluid with the blood. Once all 5 spots are obtained, gently press a sterile pad to the site until bleeding has stopped. The finger must then be monitored for bleeding. Placing a sterile pad will help prevent a hematoma from forming.

IV. Preparation of DBS Using Heelstick Specimen (for Whatman 903 Protein Saver cards)-for infants

Please make sure to indicate if this method was used in specimen collection directly on the card.

The area of the heel that is the safest to perform a heelstick is shown in Figure 1 and is identified by a line extending posteriorly from a point between the 4th and 5th toes and running parallel to the lateral aspect of the heel, and a line extending posteriorly from the middle of the great toe

running parallel to the medial aspect of the heel. (ZEBS manual taken from Lancet, 181 10:230-233,1979).

Equipment Needed:

1. Unistick 2 device
2. Alcohol swab
3. dry sterile gauze pad
4. Whatman Protein Saver Card (Whatman catalog number 10534612)
5. Gas impermeable storage bag
6. Desiccant pack (Whatman catalog number 10548234)
7. Whatman #903 Dry Rack (Whatman catalog number 10537173)

Figure 1. Heelstick Placement and Device



Procedure:

The Unistick 2 device has a penetration depth of 1.8 mm and a convex tip for accurate positioning that was designed to eliminate the risk of accidental needle stick injury or cross-infection as well as reduce the risk of osteomyelitis of the heel.

Preferably, the infant should be in a supine position with the knee at the edge of the table or the baby may be held in the mother's arms. This position allows for the foot to hang lower than the torso, thereby improving blood flow. Prepare the Unistick 2 device by depressing the pink plunger until it clicks. Twist the plunger until it breaks off and remove it from the device. The Unistick 2 device is now ready for use. When the baby is in an acceptable position for this procedure, clean the incision area of the heel with an alcohol pad and allow the heel to air dry.

Do not touch the incision site or allow the heel to come into contact with any non-sterile item or surface.

Wrap your index finger around the base of the heel and your thumb around the ankle. After the Unistick 2 heel-stick device is properly positioned against the heel and triggered wipe away the first drop of blood using a dry sterile gauze pad. The blood is then allowed to flow to be

collected on the dried blood spot card. To do this, gently touch the filter paper card to the blood drop. Allow the card to absorb the blood until the circle is full. You should be able to obtain 5 spots of blood on a card. You may need to squeeze the heel to obtain more blood; however, do not milk the heel as it mixes interstitial fluid with the blood. Once all 5 spots are obtained, gently press a sterile pad to the incision site until bleeding has ceased. The baby's heel must then be monitored for late bleeding and inflammation. Placing a sterile pad will help prevent a hematoma from forming. Note: Bandaging the baby's foot is a controversial issue because of skin sensitivity and potential bandage aspiration. However, the incision should be noted by the primary care nurse to ensure that the heel can be monitored for bleeding and inflammation. A bandage is not necessary as long as the bleeding has stopped before the child leaves the clinic. (ZEBS manual taken from Lancet, 181 10:230-233,1979).

Care should be taken to not touch the DBS circle once blood is applied. Place the blood spot card on the Whatman #903 dry rack to air dry in a clean dry place that is not exposed to direct sunlight and is protected from rodents or insects for at least 4 hours (overnight may be necessary in areas with higher humidity), and then place the card in a gas impermeable bag with a desiccant pack (see catalog number provided). Store no more than one card per bag. Once in the bag the blood spot cards can be stored at room temperature until shipped to the receiving laboratory. The protocol team will notify sites when to ship samples to the receiving laboratory.

V. Preparation of DBS using venous blood collected in EDTA tube (this can be used for both Protein Saver cards-please make sure to indicate if this method was used in specimen collection directly on the card).

Equipment Needed:

1. Vacutainer Evacuated Blood Collection Tubes – these tubes are designed to be filled with a predetermined volume of blood by vacuum. The rubber stoppers are color-coded according to the additive that the tube contains. Collect 1 EDTA (purple top) tube at each time point required- under no circumstances should these purple top tubes be placed in the refrigerator. Total volume required per card will be 250 microliters to fill five spots each at 50 microliters per spot.
2. Alcohol swab
3. Tourniquet
4. Bandage/Plaster
5. Vacutainer Needle
6. Vacutainer Needle Holder
7. Whatman Protein Saver Card (Whatman catalog number 10534612)
8. Gas impermeable storage bag
9. Indicator desiccant pack (such as Whatman catalog number WB100003)
10. Whatman #903 Dry Rack (Whatman 1 catalog number 0537173)

Procedure:

Standard procedures for labeling should be followed. The tubes should be labeled with the patient ID number, visit time point, and the date of collection. When recording date of collection, be sure to distinguish in your notes to the processing laboratory what orientation you are recording (Month/Day/Year or Day/Month/Year). Fill the blood collection tube to the recommended volume so the anticoagulant is at the proper dilution. Gently invert the tube (5-10 times) to mix thoroughly. After the blood is completely mixed, remove the cap, and take 50 microliters (μL) of the whole blood and apply to a single spot. Repeat four additional times to fill all five spots on the card. This transfer of blood should be performed with a pipette and a disposable tip.

VI. Handling and Storage of Dried Blood Spots

Care should be taken to not touch the DBS circle once blood is collected. Allow the blood spot to air dry in a clean, dry place overnight (protected from rodents and insects). The following day, place the DBS card in a gas impermeable bag with an indicator desiccant pack (see supplies suggestion). Store no more than one card per bag. Once in the bag, DBS should be stored at -20 degrees Celsius ($^{\circ}\text{C}$) until shipment to central laboratory. (For collection sites where -20°C storage is unavailable, the DBS card may be stored at room temperature for a maximum of two weeks before shipment to central laboratory).

DBS cards should be stored at -20°C at central laboratory until shipment to processing laboratory. DBS cards can be shipped at ambient temperature to processing laboratory. Once received at processing laboratory, samples should be then stored at -20°C . Care should be taken not to, under any circumstances, get the cards wet as this will affect the saturation of the cards

Figure 2: Storage of DBS



VII. Shipment of Dried Blood Spots

All of the individual dried blood spot cards in their corresponding gas impermeable storage bag with indicating desiccant are to be shipped together within a manila envelope. The whole blood is deemed non-infectious once dried on the filter cards; hence DO NOT USE a Biological Substance, Category B sticker for shipment.

APPENDIX III

DIVISION OF AIDS INTERNATIONAL MATERNAL PEDIATRIC ADOLESCENT AIDS CLINICAL TRIALS GROUP (IMPAACT)

SAMPLE INFORMED CONSENT

P1083: A Phase II/III Trial of Lopinavir/ritonavir Dosed According to the WHO Pediatric Weight Band Dosing Guidelines, Version 1.0, dated May 10, 2010

SHORT TITLE FOR THE STUDY: P1083: Lopinavir/ritonavir pharmacokinetic (PK) study

INTRODUCTION

Your child is being asked to take part in this research study because your child has HIV and your child's doctor feels that your child needs to start taking anti-HIV medications (antiretroviral drugs) to treat the HIV infection.

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?

The main purpose of this study is to measure the amount of lopinavir/ritonavir (two anti-HIV medications) in the blood. Results from this study will be compared to the levels of the drugs that have been found in other studies that showed that these medications were safe and effective.

This study will measure the amount of lopinavir/ritonavir (LPV/R) in your child's blood after your child has been taking the medication for four weeks. This study will look at a new tablet formulation to see if it is safe and works against HIV, when it is based on a weight range, instead of exact weight. Usually your doctor will measure and weigh your child at each visit and will calculate a specific dose for your child. The World Health Organization (WHO) has recently provided new directions which allow your child's doctor to determine dosing easily without any special calculations (WHO weight band dosing). In this study, your child will receive medication based on his/her weight only and the study will compare the blood level of the

medication in your child to blood levels other children have had when their doctors calculated their doses using both weight and height.

Lopinavir/ritonavir (LPV/R) has been approved by the Food and Drug Administration (FDA) for the treatment of HIV in adults and children, age 14 days and older.

As part of this study, special studies will be done using your child's blood samples, which will measure how your child's genes (DNA) may affect how his/her body handles these anti-HIV medication combinations. Please note that these tests are considered investigational (used for research) and are not used as part of routine clinical care.

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

Screening/Entry

If you decide that you want your child to join the study, we will do some screening tests followed by entry tests within a month to see if he/she is able to enroll:

- Each visit will take about 1-2 hours.
- We will get a medical history.
- Your child will have a physical exam.
- Your child will have about 1 teaspoon (about 5 mL) of blood drawn for blood tests to look at the amount of HIV in your blood, the amount of CD4+ cells (cells that fight HIV) in the blood, and to do routine safety tests (such as blood chemistry and liver function test) to make sure your child does not have any illnesses. You will be given the results of these tests as soon as they are available.

If your child is eligible to participate in the study, the study staff will determine if your child will take the liquid form of LPV/r or the tablet form. This decision will be based on whether your child can swallow the tablets or not. The amount of LPV/r your child takes will be based on how much he/she weighs.

This study will provide the LPV/r that your child will take during the study. Your child will also be required to take two other anti-HIV medications known as nucleoside reverse transcriptase inhibitors (NRTIs). This study will not provide the NRTIs that your child must take – these medicines must be obtained by a prescription from his/her doctor. Please ask your study staff or study pharmacist if you have any additional questions about these medicines.

If Your Child Does Not Enroll into the Study

If you decide not to have your child take part in this study or if your child does not meet the eligibility requirements, we will still use some of your information. As part of the screening visits, some demographic (e.g., age, gender, race), clinical (e.g., disease condition, diagnosis),

and laboratory (e.g., CD4+ cell count, viral load) data are being collected from your child so that IMPAACT researchers may help determine whether there are patterns or common reasons why people do not join a study.

There is no way this information would ever be associated with your child and is confidential.

Week 2 Study Visit

Two weeks after your child starts taking LPV/r, he/she will have a study visit:

- This study visit will take about 1-2 hours
- The staff at your site will ask you about how well your child is taking the study drugs.
- Your child will have a physical exam.

Week 4 Study Visit (PK Visit)

A PK visit is where we will measure the amount of drug in your child's body.

Four weeks after your child starts taking LPV/r, your child will have a study visit; your child will need to have taken all doses in the 72-hours prior to the PK visit or it will have to be rescheduled:

- The site staff will contact you (via your preferred method) on the day before this visit to remind you about this visit.
- This study visit will last about 12 hours. Your child will be required to stay at the hospital all day or possibly overnight.
- You will come to the clinic and will answer some questions about how well your child has been taking the medications in the past few days.
- Your child will have a physical exam.
- Your child will have about ½ teaspoon of blood drawn for blood tests to look at the amount of HIV in the blood, and to do routine safety tests. You will be given the results of these tests as soon as they are available.
- Your child will take a dose of LPV/r while at the clinic.
- Your child will have six blood samples drawn (about ¼ teaspoon each): pre-dose, 2, 4, 6, 8, and 12 hours after he/she takes the dose of medicine. A special needle may be inserted into your child's arm so that he/she may not have to be stuck by a needle multiple times. You will be given the results of these tests as soon as they are available.

Note: Week 4 visit will be postponed if your child's dose was increased due to weight during the first 4 weeks.

Week 12 Study Visit

Twelve weeks after your child starts taking LPV/r, your child will have a study visit. This visit needs to be timed to happen 2-6 hours after your child takes the day's medication:

- This visit will take about 1-2 hours

- The staff at your site will ask you about how well your child is taking the study drugs and if your child is having any problems with the medications.
- Your child will have a physical exam.
- Your child will have about ½ teaspoon of blood drawn for blood tests to look at the amount of HIV in the blood, and to do routine safety tests. You will be given the results of these tests as soon as they are available.
- Your child will have about ¼ teaspoon of blood drawn to determine how much LPV/r is in his/her blood.

Evaluation if the Dose of Your Child's Study Drug Changes

If your child gains weight during the study he/she may need to start taking more of the study drug (a higher dose). If this happens, the site staff will contact you by phone two weeks after your child starts taking the new dose to ensure that he/she is able to take the medication as prescribed and that he/she is not having any side effects from the new dose. Your child will also be required to come to the clinic after 4 weeks and have the following:

- about ½ teaspoon of blood drawn for routine safety tests.
- a physical exam.
- The staff at your site will ask you about how well your child is taking the study drugs and if your child is having any problems with the medications.
- This visit will take about 1-2 hours

Week 24 Study Visit (End of Study Visit)

Your child's study visit will occur twenty-four weeks after your child starts taking LPV/r. This visit needs to be timed to happen 2-6 hours after your child takes the day's medication:

- This visit will take about 1-2 hours
- The staff at your site will ask you about how well your child is taking the study drugs.
- Your child will have a physical exam.
- Your child will have about 1 teaspoon of blood drawn for blood tests to look at the amount of HIV and the amount of CD4+ cells in the blood, and to do routine safety tests. You will be given the results of these tests as soon as they are available.
- Your child will have about ¼ teaspoon of blood drawn to determine how much LPV/r is in your child's blood.

Early Discontinuation Visit

If your child leaves the study early, your child will be asked to return to the clinic for a final study visit:

- This visit will take about 1-2 hours
- The staff at your site will ask you about how well your child is taking the study drugs.
- Your child will have a physical exam.

- Your child will have about 1 teaspoon of blood drawn for blood tests to look at the amount of HIV and the amount of CD4+ cells in the blood, and to do routine safety tests. You will be given the results of these tests as soon as they are available.

FOR NICHD Sites:

If you agree, some of the blood specimens collected as part of this study will be stored for testing at a later date as part of this study. There is a separate consent form to explain this and get your consent.

For NIAID Sites:

Storage of Blood Samples

If you agree, what is left over from your child's blood after the lab tests are done will be stored (with usual protectors of identity) and used for future IMPAACT-approved, HIV-related research.

Your child's samples will be stored at a special laboratory facility in the U.S. called a repository. Only approved researchers will have access to them. People who work at the facility will also have access to your child's samples to keep track of them. These people won't have information that directly identifies you. Your child's samples will not be sold or directly used to produce commercial products. All proposed research studies using your child's samples will be reviewed by the National Institutes of Health (NIH). There is no time limit on how long your child's samples will be stored.

The researchers do not plan to contact your child's regular doctor with the results of studies done using your child's stored samples. This is because research studies are often done with experimental procedures. The results of such studies should not be used to make decisions about your child's medical care. If the researchers decide that the result of a certain study provides important information for your child's medical care, your child's study doctor will be notified. If you would like to be contacted with this sort of information, you must notify the study staff of any changes in your address or phone number.

You may decide that you do not want your child's samples stored for future research studies. Your child can still participate in this study even if you make this decision. You may withdraw your consent for the storage and use of your child's samples at any time. If you withdraw your consent, these stored samples will be destroyed.

Please read the following statement carefully and then mark your initials in the appropriate space provided.

I agree to allow my child's blood samples to be stored for use in future IMPAACT-approved, HIV-related research studies (please mark your initials):

_____ Yes _____ No _____ Date

OTHER INFORMATION

The information collected in this study may be used for other IMPAACT-approved HIV-related research.

HOW MANY PEOPLE WILL TAKE PART IN THIS STUDY?

About 94 children/infants will take part in this study

HOW LONG WILL MY CHILD BE IN THIS STUDY?

Your child will be in this study for about 6 months.

AFTER THE STUDY

After your child has finished study participation, the study will not be able to continue to provide your child with the study medicine. If continuing to take this medicine or if a similar medicine would be of benefit to your child, the study staff will discuss how you may be able to obtain **it** [sites insert local information here].

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:

- You cannot keep study appointments when you are supposed to;
- The study doctor determines that further participation could be harmful to your child's health or well-being;
- The study is stopped by the agency doing this study, the National Institute of Child Health and Human Development (NICHD) and the National Institutes of Health (NIH), your local Institutional Review Board (IRB) or Ethics Committee (EC), FDA, the Office for Human Research Protections (OHRP), the pharmaceutical sponsor (Abbott), or your country-specific governmental agencies.
- The study has to be stopped for other administrative reasons.

If you decide to take your child off the study early, your child's health information that has already been collected may be used or released as needed for this study or any follow-up activities related to the study. If your child is removed from the study or if you decided to take

your child off the study, the research staff will explain why your child was removed and also explain the alternatives that are available to your child.

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

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

If your child must stop taking the study drug before the study is over, the study doctor may ask you to continue to be part of the study and return for some study visits and procedures.

WHAT ARE THE RISKS OF THE STUDY?

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 the additional study drug side effects, please ask the medical staff at your site.

Use of Combination Antiretroviral (ARV) 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 ARV 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

Risks of Protease Inhibitors

The use of protease inhibitors (PIs) 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 (a bleeding/clotting disorder) who were treated with protease inhibitors. It is not known if protease inhibitors were the cause of these bleeding episodes.

Risks of Lopinavir/Ritonavir (LPV/r)

Abbott Laboratories

The following side effects are also associated with the use of LPV/r:

- Pancreatitis (inflammation of the pancreas), which may cause death. If you develop pancreatitis, you may have one or more of the following: stomach pain, nausea, vomiting or abnormal pancreatic function blood tests
- Abnormal bowel movements (stools), including loose or watery stools, upset stomach and stomach pain
- Vomiting
- Large increases in triglycerides (a type of fat) 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
- Feeling weak and tired
- Headache
- Rash (seen in children)
- Abnormal heart rhythm and electrocardiogram (EKG) changes. These changes can lead to serious heart problems. Your risk for these problems may be higher if you:
 - Already have a history of abnormal heart rhythm or other types of heart disease
 - Take other medicines that can affect your heart rhythm while you take lopinavir/ritonavirIf you develop abnormal heart rhythm you may experience lightheadedness, fainting spells or an abnormal heart beat.
- Rash, which may be severe

Risks of Drawing Blood

Your child may faint, feel lightheaded, or feel some discomfort when blood is drawn or a heparin lock is inserted for this study. Other risks include bleeding or bruising where the needle enters the body. A small blood clot may form where the needle enters the body, or swelling of the surrounding skin may occur. There is also a small risk of minor infection at the blood draw site.

ARE THERE BENEFITS TO TAKING PART IN THIS STUDY?

If your child takes part in this study, there may be a direct benefit to your child, but no guarantee can be made. Potential benefits for participation in this study include:

- a) The WHO weight band dosing schedule may be easier to use and may make it easier for you to follow the directions to use the medicine;
- b) Additional support to help you follow the directions to use the medicine is provided during the study duration;
- c) In some study locations, participation may result in more frequent medical check ups that may make it easier for early detection of complications related to the treatment.

It is also possible that your child may receive no benefit from being in this study. Information learned from this study may help others who have HIV.

WHAT OTHER CHOICES DO I HAVE BESIDES THIS STUDY?

Instead of being in this study you have the choice of:

- treatment with prescription drugs available to your child
- 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?

U.S. sites:

To help us protect your child's privacy, we have obtained a Certificate of Confidentiality from the National Institutes of Health. With this Certificate, the researchers cannot be forced to disclose information that may identify your child, even by a court subpoena, in any federal, state, or local civil, criminal, administrative, legislative, or other proceedings. The researchers will use the Certificate to resist any demands for information that would identify your child, except as explained below. The Certificate cannot be used to resist a demand for information from personnel of the United States Government that is used for auditing or evaluation of federally funded projects or for information that must be disclosed in order to meet the requirements of the federal Food and Drug Administration (FDA).

People who may review your child's records include the U.S. Food and Drug Administration, the site Institutional Review Board (IRB) (*insert name of site IRB*) or Ethics Committee, the National Institutes of Health (NIH), Office of Human Research Protections (OHRP), study staff, study monitors, drug companies supporting the study (Abbott), and their designees.

You should understand that a Certificate of Confidentiality does not prevent you or a member of your family from voluntarily releasing information about your child or your child's participation in this research. If an insurer, employer, or other person obtains your written consent to receive research information, then the researchers may not use the Certificate of Confidentiality to withhold that information.

Non-U.S. sites:

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

Your child's records may be reviewed by the U.S. Food and Drug Administration (FDA), (insert name of site) Institutional Review Board (IRB) or Ethics Committee (EC), National Institutes of Health (NIH), the Office for Human Research Protections (OHRP), study staff, study monitors, drug companies supporting this study (Abbott), or host country regulatory agencies.

WHAT ARE THE COSTS TO ME?

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.

[Enter any site-specific information]

WILL I RECEIVE ANY PAYMENT?

[Enter site-specific information about payment]

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 the 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 PARTICIPANT?

Taking part in this study is completely voluntary. You may choose not to have your child take part in this study or have your child leave the study at any time. 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. Your child will still be able to receive drugs to treat his/her HIV outside this study.

WILL I BE TOLD ABOUT NEW INFORMATION?

We will tell you about new information from this or other studies that may affect your child's health, welfare, or willingness to stay in this study. If you want the results of the study, let the study staff know.

WHAT DO I DO IF I HAVE QUESTIONS OR PROBLEMS?

For questions about this study or a research-related injury, contact:

- name of the investigator or other study staff
- telephone number of above

For questions about your/your child's rights as a research participant, 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 take part in this study, please sign your name below.

Participant's Name (print)

Participant's Signature and Date

Participant's Legal Guardian (print)
(As appropriate)

Legal Guardian's Signature and Date

Study Staff Conducting
Consent Discussion (print)

Study Staff Signature and Date

Witness' Name (print)
(As appropriate)

Witness's Signature and Date

Father's Name
(If father's consent is required)

Father's Signature and Date
(If father's consent is required)

APPENDIX IV

FACT SHEET and TEMPLATE CONSENT FORM for Specimen Storage at Repositories funded by the National Institute of Child Health and Human Development (NICHD)

PARENT FACT SHEET (Version 2.0 - 29 November 2005)

IMPAACT P1083 - A PHASE II TRIAL OF LOPINAVIR/RITONAVIR DOSED ACCORDING TO THE WHO PEDIATRIC WEIGHT BAND DOSING GUIDELINES

When your child joins this NICHD-sponsored study, you will be asked to give permission for having some specimens left over (after the lab tests are done) from what the doctor or nurse took from your child's body saved in a repository. (A repository is a special laboratory with freezers where specimens like blood or tissue cells and body fluids that are taken from you during a study are kept. Your child's name will not be on these specimens, only a special study number. Your child's samples will be stored at a special laboratory facility in the U.S. The people who run the repository laboratory will not know your child's name.)

WHY HAVE A REPOSITORY?

Researchers can learn a lot from a study but as time goes by the tests that they used get better or brand new tests are developed, and more can be learned with these better or new tests. When study volunteers consent to put specimens in the repository and consent to the researchers doing new tests on the specimens at some time in the future after their time in the study is ended, researchers can learn new information by being able to use the specimens. Your child's rights and privacy will be protected in any of these new studies.

HOW WILL MY CHILD'S PRIVACY BE PROTECTED?

The only record that your child participated in this NICHD sponsored study is at the clinic where it is kept separate from your child's health records and locked away.

Your child's specimens in the repository will not have your child's name on them. The specimens will have a special study code. It will be the same code that is on your child's information in the NICHD sponsored Study from your child's interviews and examinations. Again, none of this information will have your child's name on it.

HOW WOULD A RESEARCHER GET TO USE THE SPECIMENS IN THE REPOSITORY?

If a researcher wants to do a test on specimens from the NICHD sponsored repository in the future, he or she will write up the idea and it will have to be approved by a committee to make sure the research is worthwhile. If the idea is approved, then coded specimens and coded

information will be given to the researcher. The researcher will not know the names, addresses, or phone numbers of the people who gave the specimens to the repository.

WHY WOULDN'T I FIND OUT THE RESULTS OF THE RESEARCH USING MY CHILD'S SPECIMENS?

You will not receive the results of research done with your child's specimens. This is because research can take a long time and must use specimens from many people before results are known. Results from research using your child's specimens may not be ready for many years. Often when studies are first done, it is not always clear how to use the information from the study to change the health care that people receive. So none of these study results is likely to affect your child's care right now, but they may be helpful to people like your child in the future. Your child's specimens can last in the freezer for many years and there is no time limit to when studies could be done in the future.

WOULD I EVER BE CONTACTED IN THE FUTURE ABOUT RESEARCH USING MY CHILD'S SPECIMENS?

All of the studies to be done in the future on your child's specimens in the repository will be for the particular reasons that you agreed to. Every study that is planned to use specimens from your child and others from this NICHD Study has to be reviewed to make sure that what is planned is the same kind of study that you agreed to. If it is, then the research will go ahead since you would have agreed that these particular tests could be done without anyone contacting you to get your permission in the future.

If the study to be done is not like the kind of tests you agreed could be done, then the committee will decide if you need to be contacted to give permission for the new study.

I GAVE MY PERMISSION TO TESTING MY CHILD'S SPECIMENS IN THE REPOSITORY, BUT WHAT IF I CHANGE MY MIND?

People always have the right to stop participating in research. So if you decide that you do not want researchers to be able to use the specimens from your child in the repository, you can contact the clinic staff. They will tell the repository that the specimens with the study code number linked to your child's name in the clinic should not be studied. These specimens can be removed from the repository and destroyed if you tell us to do that.

WHAT TYPE OF RESEARCH WILL BE DONE WITH MY CHILD'S SPECIMENS?

Many different kinds of studies use specimens. Some researchers may develop new tests to find diseases. Others may develop new ways to treat or even cure diseases. In the future, some of the research may help to develop new products, such as tests and drugs. If this would happen and these tests or drugs make money, there are no plans to share that money with the people who gave the specimens.

As part of this study (A Phase II/III Trial of Lopinavir/ritonavir Dosed According to the WHO Pediatric Weight Band Dosing Guidelines), your child is being asked to have some blood samples taken. These specimens will go into the NICHD repository for research to be done at some time in the future so that more information can come from your child's time in this NICHD sponsored Study.

You do not have to agree to store your child's specimens for future tests for your child to take part in this study. Your child will not lose any benefits to which your child is entitled if you decide against storing your child's specimens.

You will also be asked to agree that these particular tests can be done without anyone contacting you to get your permission sometime in the future. No one doing these tests would know that these specimens came from your child and no one would contact you or your doctor or nurse with the results from these tests that might happen in the future.

TEMPLATE CONSENT FORM

WHAT ARE THE GENERAL HIV-RELATED STUDIES THAT CAN BE DONE WITH THE REPOSITORY SPECIMENS?

Researchers would like to store your child's specimens to understand how HIV causes disease and complications, and how best to treat or prevent HIV infection and its complications. They need specimens from people who have HIV and from those who do not. Sometimes, too, the specimens can be used to learn something about new problems that people with HIV have like liver disease, diabetes, and heart disease. These general studies would not include any genetic testing (looking at your child's DNA).

Benefits: There are no direct benefits to your child. Your child will be helping researchers learn more about how to help people with HIV or at risk of HIV infection.

Risks: The specimens would be collected as part of your child's study visits. (Insert text about collection procedures.) Once in the repository, there are few risks. Your child's name will not be available to the repository or to the scientists who may be doing any future test.

I give permission for the use of my child's stored specimens for the purposes stated in the preceding section (general HIV-related tests).

Parent or Legal Guardian Signature Witness Signature Date

I give my assent to the use of my stored specimens for the purposes stated in the preceding section (general HIV-related tests).

Participant Signature Witness Signature Date

WHAT ARE THE SPECIAL HIV-RELATED STUDIES THAT CAN BE DONE WITH THE REPOSITORY SPECIMENS?

Researchers in this study would also like to store your child's specimens to understand how HIV causes disease and complications, and how best to treat or prevent HIV infection and its complications through looking at how each person's genetic makeup (your child's DNA) either protects them or puts them at greater risk. It may be that researchers use some of your child's blood to make a "cell line". That means the blood cells can keep dividing and give an endless supply of your child's DNA for tests to be done in the future. This kind of information will be particularly important as scientists work toward a vaccine that could protect people from AIDS. They need specimens from people who have HIV and from those who do not.

Benefits: There are no direct benefits to your child. Your child will be helping researchers learn more about how to help people with HIV or at risk of HIV infection.

Risks: The specimens would be collected as part of your child's study visits. (Insert text about collection procedures.) Once in the repository, there are few risks. Your child's name will not be available to the repository or to the scientists who may be doing any future test. Since there are no plans to give participants the results of the tests performed on their stored specimens, you will not receive any information on your child's genetic makeup.

I give permission for the use of my child's stored specimens for the purposes stated in the preceding section (special HIV-related tests).

Parent or Legal Guardian Signature

Witness Signature

Date

I give my assent to the use of my stored specimens for the purposes stated in the preceding section (special HIV-related tests).

Participant Signature

Witness Signature

Date

WHAT IF I HAVE MORE QUESTIONS?

If you have any questions about the repository, about storage, or the use of your child's samples, contact (Study personnel) at (phone).

If you have questions about giving consent or your child's rights as a research volunteer, contact the (Name of Institution) Institutional Review Board at (phone).

I refuse to have any specimen collected from my child stored in the repository.

Parent or Legal Guardian Signature

Witness Signature

Date

TEMPLATE CONSENT/ASSENT FORM

WHAT ARE THE GENERAL HIV-RELATED STUDIES THAT CAN BE DONE WITH THE REPOSITORY SPECIMENS?

Researchers would like to store your specimens to understand how HIV causes disease and complications, and how best to treat or prevent HIV infection and its complications. They need specimens from people who have HIV and from those who do not. Sometimes, too, the specimens can be used to learn something about new problems that people with HIV have like liver disease, diabetes, and heart disease. These general studies would not include any genetic testing (looking at your DNA).

Benefits: There are no direct benefits to you. You will be helping researchers learn more about how to help people with HIV or at risk of HIV infection.

Risks: The specimens would be collected as part of your study visits. (Insert text about collection procedures.) Once in the repository, there are few risks. Your name will not be available to the repository or to the scientists who may be doing any future test.

I consent to the use of my stored specimens for the purposes stated in the preceding section (general HIV-related tests).

WHAT ARE THE SPECIAL HIV-RELATED STUDIES THAT CAN BE DONE WITH THE REPOSITORY SPECIMENS?

Researchers in this study would also like to store your specimens to understand how HIV causes disease and complications, and how best to treat or prevent HIV infection and its complications through looking at how each person's genetic makeup (your DNA) either protects them or puts them at greater risk. It may be that researchers use some of your blood to make a "cell line". That means the blood cells can keep dividing and give an endless supply of your DNA for tests to be done in the future. This kind of information will be particularly important as scientists work toward a vaccine that could protect people from AIDS. They need specimens from people who have HIV and from those who do not.

Benefits: There are no direct benefits to you. You will be helping researchers learn more about how to help people with HIV or at risk of HIV infection.

Risks: The specimens would be collected as part of your study visits. (Insert text about collection procedures.) Once in the repository, there are few risks. Your name will not be available to the repository or to the scientists who may be doing any future test. Since there are no plans to give

participants the results of the tests performed on their stored specimens, you will not receive any information on your genetic makeup.

I consent to the use of my stored specimens for the purposes stated in the preceding section (special HIV-related tests).

Participant Signature

Witness Signature

Date

WHAT IF I HAVE MORE QUESTIONS?

If you have any questions about the repository, about storage, or the use of your samples, contact (Study personnel) at (phone).

If you have questions about giving consent or your rights as a research volunteer, contact the (Name of Institution) Institutional Review Board at (phone).

I refuse to have any specimen collected for storage in the repository.

Participant Signature

Witness Signature

Date