IMPAACT P1110
(DAIDS Document ID 11891)

A PHASE I TRIAL TO EVALUATE THE SAFETY AND PHARMACOKINETICS OF RALTEGRAVIR IN HIV-1-EXPOSED NEONATES AT RISK OF ACQUIRING HIV-1 INFECTION

A Multicenter, US Domestic and International Trial of the
International Maternal Pediatric Adolescent AIDS Clinical Trials Network
(IMPAACT)

**This file contains the current IMPAACT P1110 protocol,
which is comprised of the following documents,
presented in reverse chronological order:**

Letter of Amendment #1, dated 6 September 2018
Clarification Memorandum #2, dated 15 June 2017
Clarification Memorandum #1, dated 08 February 2017
Protocol Version 2.0, dated 18 January 2017

IMPAACT P1110
A PHASE I TRIAL TO EVALUATE THE SAFETY AND PHARMACOKINETICS OF RALTEGRAVIR IN HIV-1-EXPOSED NEONATES AT RISK OF ACQUIRING HIV-1 INFECTION

LoA # 1 to Version 2.0, dated 18 January 2017

DAIDS ID # 11891
IND # 77,787 Held By DAIDS

Letter of Amendment Date: 6 September 2018

Information/Instructions to Study Sites from the Division of AIDS

The information contained in this Letter of Amendment (LoA) impacts the IMPAACT P1110 study Version 2.0 and must be submitted to site Institutional Review Boards and/or Ethics Committees (IRBs/ECs) as soon as possible for their review and approval. The LoA serves to clarify the correct interpretation of eligibility criteria with respect to participants with known vs. newly discovered HIV status. While most working from 2.0 have interpreted Section 4.0 of the protocol as the team intended and as training slides further explained, this LOA serves to reinforce the correct understanding of Section 4.0 of the protocol, independent of protocol training. Approval must also be obtained from site regulatory entities if applicable per the policies and procedures of the regulatory entities. All IRB/EC and regulatory entity requirements must be followed.

Upon obtaining IRB/EC approval and any other applicable regulatory entity approvals, each site should immediately begin implementing this LoA. Sites are required to submit a LoA registration packet to the DAIDS Protocol Registration Office (DAIDS PRO) at the Regulatory Support Center (RSC). Sites will receive a registration notification for the LoA after the DAIDS PRO verifies that all required registration documents have been received and are complete. Sites should not await this notification before implementing this LoA.

Please file this LoA, all associated IRB/EC and regulatory entity correspondence, and all correspondence with the DAIDS PRO in your essential documents files for IMPAACT P1110. If the IMPAACT P1110 protocol is amended in the future, the contents of this LoA will be incorporated into the next version of the protocol.

IMPAACT P1110
A PHASE I TRIAL TO EVALUATE THE SAFETY AND PHARMACOKINETICS OF RALTEGRAVIR IN HIV-1-EXPOSED NEONATES AT RISK OF ACQUIRING HIV-1 INFECTION

LoA # 1 to Version 2.0, dated 18 January 2017
(DAIDS Document ID 11891)

Dated 6 September 2018

Letter of Amendment Signature Page

I will conduct this study in accordance with the provisions of this protocol, including this Letter of Amendment, and all applicable protocol-related documents. I agree to conduct this study in compliance with United States (US) Health and Human Service regulations (45 CFR 46); applicable US Food and Drug Administration regulations; standards of the International Conference on Harmonization Guideline for Good Clinical Practice (E6); Institutional Review Board/Ethics Committee determinations; all applicable in-country, state, and local laws and regulations; and other applicable requirements (e.g., US National Institutes of Health, Division of AIDS) and institutional policies.

_____ _____

Signature of Investigator of Record Date

_____

Name of Investigator of Record
(printed)

Summary of Modifications and Rationale

The purpose of this LoA is to:

1. Provide background, clarify maternal inclusion criterion 4.11 and to define the terms used.

   Background: In designing P1110, the team recognized that in some countries mothers with a history of HIV infection could present in labor at delivery sites separate from where they received their routine HIV care. At some research sites, mothers travel to delivery sites with Prenatal Cards that serve as medical records for their prenatal history, laboratory tests results, documentation of antiretroviral treatment, and overall delivery of health care. Mothers with HIV infection may be referred to another location for delivery by referring health care providers.

   Clarification of Maternal Inclusion Criterion 4.11: To be eligible to enroll in IMPAACT P1110, participating infants had to be enrolled within 48 hours of birth. The protocol team recognized that source documentation of past HIV test results might not be available at the delivery site and that there might be difficulty in obtaining this documentation within the infant enrollment window of 48 hours after delivery. For this reason, the team included the stipulation in the protocol section 4.11 that HIV test results "documented in the clinical record from past testing may be used to satisfy the criteria for documentation of HIV-1 infection." Documentation in the medical record that the diagnosis of HIV infection had previously been done using in-country standard of care diagnostic tests could be used to document HIV infection, qualifying the mother as "known to be HIV infected," and therefore additional HIV testing as part of study procedures would not be required. An additional pragmatic factor, which further made the medical record documentation of past HIV positive test results an inclusion criterion was the situation that for women known to be HIV positive for some duration of time and on cART, they might have such low viral load that test results from re-confirming HIV infection could take longer than 48 hours, making it either impossible to enroll the infant or making maternal test results of no usefulness, being obtained after the baby is already on dosing. The algorithm for newly diagnosing HIV would be the less useful approach for a woman known to be HIV positive and medically managed for a period of time prior to study entry.

   Definitions
   "Known" to be HIV infected: can be documented in the medical clinic file at the research site and may include the following: 1) maternal subject is documented to be HIV positive in the medical record per the usual designation at the site, either on or starting prescribed treatment with cART (combination Anti-Retroviral Treatment) for the current pregnancy; 2) based on available medical records, or per her history obtained at the research site , from a referring clinic documented by mail (electronic or other), or phone contact with the referring prescribing healthcare provider.

   "Medical record" can include: Mobile paperwork carried throughout the pregnancy as a mother gets treatment in one or more clinics; patient file hard-copy or electronic copy in the research clinic or from another clinic which notes the HIV status of the mother; or other medical record that is normally accepted by the research site.

   "HIV test results" documented in the clinical record for "known" HIV positive women: the standard method of designation will be confirmed by the research site. This may include the designation of RVD positive=Retroviral Disease Positive. This designation is routinely used in some countries to document positive HIV test on the Prenatal Cards. This is done to protect the confidentiality of the HIV status of women where stigma and discrimination are potential barriers to their health care.

In summary, "HIV testing documentation required for mothers known to be HIV-infected": For mothers known to be HIV-infected (as defined above), testing obtained and documented per the local in-country health department standard of care applicable to the research site (e.g. SOC using 2 separate tests and samples, without naming them) are sufficient for meeting the requirement of HIV-1 testing documentation in the medical record as clarified under part (i) in Section 4.11. After noting the HIV positive designation in the maternal medical record, per the health department guidelines for the site, if two samples and two timepoints are used, no further HIV testing is needed for enrollment. The HIV testing documentation algorithm only applies for mothers identified as HIV infected at the time of labor or in the immediate postpartum period, as clarified under part (ii) in Section 4.11.

Implementation

The modification included in this Letter of Amendment will be incorporated into the next protocol amendment as specified below. Additions to the text are indicated in bold; deletions are indicated by strike-through.

1. *Section 4.11, Maternal Inclusion Criteria, is clarified regarding the required source documentation for mothers known to be HIV infected versus mothers diagnosed at the time of labor or in the immediate postpartum period. Additions to the text are indicated in bold. Furthermore, formatting changes have been made separating the first paragraph after "Documentation of HIV infection" into three paragraphs with added text shown in bold. The first paragraph applies to both groups of mothers, whereas the second paragraph is clarified as only applying to mothers who are known to be HIV infected (clarified under i). The third paragraph (newly added) and all remaining text under Section 4.11 is clarified as only applying to mothers who are diagnosed at the time of labor or in the immediate postpartum period (clarified under ii).*

   4.11 Mother is either **i)** known to be HIV-1 infected prior to labor **(testing obtained and designated per local SOC in the medical record and either on or recently started CART prior to delivery** or **ii)** identified as HIV-1 infected at the time of labor or in the immediate postpartum period.

   Documentation of HIV infection **for (i) and (ii)**:

   Documentation of HIV-1 infection is defined as positive results from <u>two</u> samples (whole blood, serum, or plasma) collected at <u>different</u> time points. **This can occur at enrollment or can be historical and documented by a notation of HIV positivity in the maternal medical record for women known to be HIV positive before delivery.**

   (i): Results documented in the clinical record from past testing may be used to satisfy the criteria for documentation of HIV-1 infection. **No further testing for HIV is needed for this group of mothers.**

   (ii): For mothers identified as HIV-1 infected at the time of labor or in the immediate postpartum period the following testing algorithm should be applied.

   If both samples are tested using antibody tests, at least one of the samples must be tested in a laboratory that operates according to Good Clinical Laboratory Practice (GCLP) guidelines and participates in an appropriate external quality assurance program. If nucleic acid testing is used, at least one test must be performed in a CLIA-certified (US sites) or VQA-certified (non-US) laboratory. For tests performed in other (non-GCLP-compliant or non-VQA-certified) settings,

adequate source documentation including the date of specimen collection, date of testing, test performed, and test result must be available.

Sample #1 must be tested using any of the following:

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

Note: Confirmatory testing (Sample #2) may be pending at the time of enrollment of the mother-infant pair. If maternal confirmatory testing is negative, the infant will be removed from active dosing but will be followed for safety as part of the study.

Sample #2 must be tested using any of the following:

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

Clarification Memorandum #2 for:

IMPAACT P1110
A Phase I Trial to Evaluate the Safety and Pharmacokinetics of Raltegravir in HIV-1-Exposed Neonates at Risk of Acquiring HIV-1 Infection

Version 2.0, dated 18 January 2017
IND # 77,787
DAIDS ES # 11891

Clarification Memorandum Date: 15 June 2017

Summary of Clarifications

This Clarification Memorandum (CM) clarifies that infant exclusion criterion 4.43 applies to all infant participants, including Cohort 2 RAL-exposed participants as well as Cohort 1 RAL-naïve, Cohort 1 RAL-exposed, and Cohort 2 RAL-naïve. The specification of RAL-naïve was a typo in Version 2.0, and inconsistent with the intention of Section 4.5 Disallowed Medications.

Implementation

Institutional Review Board/Ethics Committee (IRB/EC) approval of this CM is not required by the study sponsor prior to implementation; however, sites may submit it to IRBs/ECs for their information or, if required by the IRBs/ECs, for their approval prior to implementation. The clarifications included in this memorandum will be incorporated into the next full protocol amendment. Modifications are shown below, using strikethrough for deletions and bold type for additions.

Section 4.4, Infant Exclusion Criteria, page 34, is clarified to emphasize that the infant exclusion criteria apply to all infants.

4.43 For Cohort 2 ~~RAL naïve~~ and Cohort 1 (RAL-naive and RAL-exposed): Receipt of disallowed medications (phenytoin, phenobarbital, rifampin)

Clarification Memorandum #1 for:

IMPAACT P1110
A Phase I Trial to Evaluate the Safety and Pharmacokinetics of Raltegravir in HIV-1-Exposed Neonates at Risk of Acquiring HIV-1 Infection

Version 2.0, dated 18 January 2017
IND # 77,787
DAIDS ES # 11891

Clarification Memorandum Date: 08 February 2017

Summary of Clarifications

This Clarification Memorandum (CM) removes the pre-dose monitoring call and the post-dose monitoring call from the Early Discontinuation visit for Cohort 2, as participants at this visit will be off study drug and no longer being dosed.

This CM also clarifies that Appendix V-A, Sample Informed Consent for Cohort 1 (Closed), will not be used in P1110 Version 2.0, as Cohort 1 is closed to accrual, all Cohort 1 participants are no longer in follow-up and have exited the study.

Implementation

Institutional Review Board/Ethics Committee (IRB/EC) approval of this CM is not required by the study sponsor prior to implementation; however, sites may submit it to IRBs/ECs for their information or, if required by the IRBs/ECs, for their approval prior to implementation. The clarifications included in this memorandum will be incorporated into the next full protocol amendment.

In Appendix II-B: Infant Schedule of Evaluations for Cohort 2, Column for Early Discontinuation Visit, Rows for Pre-dose monitoring and Post-dose monitoring:

Pre-dose monitoring	~~X~~
Post-dose monitoring	~~X~~

IMPAACT P1110

A Phase I Trial to Evaluate the Safety and Pharmacokinetics of Raltegravir in HIV-1-Exposed Neonates at Risk of Acquiring HIV-1 Infection

A Study of the International Maternal Pediatric Adolescent
AIDS Clinical Trials Network (IMPAACT)

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

Pharmaceutical Support Provided by:
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DAIDS ES 11891
IND # 77,787 held by NIAID

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Version 2.0
18 January 2017

IMPAACT P1110 PROTOCOL TEAM ROSTER

All questions concerning this protocol should be sent via e-mail to impaact.teamp1110@fstrf.org. Remember to include the participant's PID when applicable. The appropriate team member will respond to questions via e-mail with a "cc" to impaact.teamp1110@fstrf.org. A response should generally be received within 24 hours (Monday - Friday). For protocol registration questions, e-mail protocol@tech-res.com or call 301-897-1707. Protocol registration material can be sent electronically to epr@tech-res.com or by fax at 1-800-418-3544 or 301-897-1701. For EAE questions, e-mail DAIDSRSCsafetyoffice@tech-res.com or call 1-800-537-9979 or 301-897-1709 or fax 1-800-275-7619 or 301-897-1710. For enrollment questions, contact the Data Management Center at 716-834-0900 or by e-mail at sdac.random.desk@fstrf.org .

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TABLE OF CONTENTS

GLOSSARY

3TC	Lamivudine
ALT	Alanine aminotransferase
ARV	Antiretroviral
AST	Aspartate aminotransferase
AUC	Area under the curve
BID	Twice a day
cART	Combination antiretroviral therapy
CI	Confidence interval
DAIDS PRO	Division of AIDS Protocol Registration Office
DMC	Data Management Center
DNA	Deoxyribonucleic Acid
EAE	Expedited adverse event
EC	Ethics Committee
FTC	Emtricitabine
GCLP	Good Clinical Laboratory Practice
GM	Geometric mean
HAART	Highly active antiretroviral therapy
HIV	Human immunodeficiency virus
IMPAACT	International Maternal Pediatric Adolescent AIDS Clinical Trials Network
IRB	Institutional Review Board
LAR	Legally authorized representative
LDMS	Laboratory Data Management System
NAT	Nucleic acid test
NFV	Nelfinavir
NVP	Nevirapine
OHRP	Office for Human Research Protections
PID	Patient Identification Number
PK	Pharmacokinetic
PMTCT	Prevention of Mother-to-Child Transmission
RAL	Raltegravir
RE	Regulatory entity
RNA	Ribonucleic Acid
RSC	Regulatory Support Center
SES	Subject enrollment system
SID	Study Identification Number
UDP	Uridine diphosphate
UGT	Uridine diphosphate glucuronyl transferase
ZDV	Zidovudine

SCHEMA

A Phase I Trial to Evaluate the Safety and Pharmacokinetics of Raltegravir in HIV-1-Exposed Neonates at Risk of Acquiring HIV-1 Infection

DESIGN: Phase I, open label, non-comparative dose-finding study

SAMPLE SIZE: Approximately 50 infants in order to accrue a minimum of 32 pharmacokinetic (PK) evaluable HIV-1-exposed infants, and their mothers. Cohort 1 will enroll a minimum of 12 PK evaluable infants and Cohort 2 will enroll a minimum of 20 PK evaluable infants.

Note: Cohort 1 RAL-naïve, Cohort 1 RAL-exposed, and Cohort 2 RAL-naïve groups were fully accrued under protocol Version 1.0. Cohort 2 RAL-exposed group will be opened to accrual under protocol Version 2.0 and will enroll a minimum of 8 PK evaluable infants.

POPULATION: HIV-1 exposed full-term infants (aged ≤48 hours in protocol Version 1.0 and ≤ 60 hours in protocol Version 2.0) assessed as risk of acquiring HIV-1 infection and their mothers. Two groups of infants will be enrolled in each Cohort according to infant *in-utero* exposure to maternal raltegravir (RAL):

- RAL–naïve (infants born to mothers not receiving RAL prior to delivery) and
- RAL–exposed (infants born to mothers who received at least one dose of RAL within 2 – 24 hours prior to delivery).

REGIMEN: Cohort 1: Raltegravir as oral granules for suspension administered at two time points: as a single dose within 48 hours of birth in addition to standard of care ARV for PMTCT prophylaxis, with a second single dose administered at 7-10 days of life.

Cohort 2: Raltegravir as oral granules for suspension initiated in RAL–naive infants within 48 hours of birth and in RAL–exposed infants between 12 and 60 hours of birth, as outlined below, in addition to standard of care ARV for PMTCT prophylaxis.

- 1.5 mg/kg once daily during Days 1–7 of life (week 1)
- 3.0 mg/kg twice daily during Days 8-28 of life (weeks 2-4)
- 6.0 mg/kg twice daily during Days 29-42 of life (weeks 5-6)

Based on ongoing interim analysis of pharmacokinetic data and safety information, raltegravir dosing may be modified in the range of 1.5 mg/kg to 6 mg/kg per dose. Dosing frequency may also be modified from once to twice daily, reaching a maximum daily dose of 12 mg/kg/day.

STUDY DURATION: Infants will be followed for 24 weeks after birth. Women will be followed until discharge from the labor and delivery unit.

PRIMARY OBJECTIVES:

1. To evaluate the safety and tolerability through 6 weeks of life of raltegravir oral granules for suspension when administered during the first 6 weeks of life with standard PMTCT ARV prophylaxis to infants exposed to HIV-1 assessed at risk of infection.

2. To evaluate the pharmacokinetics of raltegravir oral granules for suspension during the first 6 weeks of life along with standard PMTCT ARV prophylaxis.

3. To determine an appropriate dose of raltegravir oral granules for suspension for use in neonates and infants during the first 6 weeks of life.

SECONDARY OBJECTIVES:

1. To assess safety and tolerability of raltegravir oral granules for suspension through 24 weeks of life when administered during the first 6 weeks of life with standard PMTCT ARV prophylaxis to infants exposed to HIV-1 assessed at risk of infection.

2. To investigate the relationship between neonatal raltegravir elimination and UGT1A1 genotype, and whether there is an association of UGT1A1 (**28/*28*) and SLCO1B3 (rs2117032-C/T) with hyperbilirubinemia.

1.0 INTRODUCTION

1.1 Background and Rationale

Although significant progress has been made in identifying strategies to prevent perinatal of HIV transmission by administering antiretroviral drugs to pregnant women with HIV infection and their infants, new pediatric HIV infections continue, with an estimated 370,000 infant infections in 2009 [1-3]. It is estimated that only 35% of pregnant women with HIV infection in low-resource countries received antiretroviral prophylaxis for prevention of mother-to-child HIV transmission [1]. When the diagnosis of HIV infection in a pregnant woman goes unrecognized and antiretrovirals have not been used during pregnancy and labor, infant prophylaxis with zidovudine and either nelfinavir plus lamivudine or nevirapine can reduce the risk of HIV transmission by 44% compared with the use of zidovudine alone [4]. In HIV endemic settings up to 3-10% of pregnant women become infected during pregnancy placing their infants at even higher risk for acquiring HIV infection [5].

It is critically important to develop new and potentially more effective regimens for postnatal prophylaxis for perinatal transmission in high-risk settings. Use of integrase inhibitors as part of neonatal prophylaxis may further reduce transmission risk as these agents block integration of viral DNA into the host cell, a critical step in the virus lifecycle required for productive infection to occur. Integrase inhibitors as part of postnatal infant prophylaxis also have a potential role in the setting of high-risk pregnancies or maternal infection with drug-resistant HIV.

In addition, integrase inhibitors have theoretical advantages as part of early highly active antiretroviral therapy for neonates with HIV infection. Neonates with HIV infection can be identified in the first few weeks of life, allowing for immediate or early initiation of HAART. Early therapy is now standard of care for infants with HIV infection globally due to the survival benefit conferred, but limited antiretroviral agents are available for this purpose [6]. As such, there is a critical need for additional potent antiretroviral drugs for the treatment of pediatric HIV infection. Studies such as P1115 involving strategies for early treatment of newborns infected with HIV with more intensive antiretroviral drug regimens are being conducted, with the goal of either improving clearance of HIV-infected cells that contribute to prolonged second-phase decay in plasma viremia during HAART in infants, or even potentially to eradicate or lower HIV reservoirs throughout the body of the infant with HIV infection. In a recent study, time to undetectable plasma viremia in infants treated with a lopinavir-based HAART regimen (PACTG P1030) was strongly correlated with resting CD4+ T cell latent reservoir size at two years of age [7]. This relationship suggests that more rapid clearance of plasma viremia during HAART may reduce viral reservoir seeding in infants with HIV infection and antiretroviral drugs that block viral integration may have a role to play in accelerating the rate of viral decay.

There are limited safety and dosing information for ARVs in neonates. Only zidovudine (ZDV), lamivudine (3TC), emtricitabine (FTC), nevirapine (NVP), and stavudine (d4T) are approved for use in neonates < 14 days of age. Nelfinavir (NFV) pharmacokinetics and safety have been studied in neonates and used as part of a prophylaxis regimen in the recently reported HPTN/NICHD 040 trial [8], but its use is not approved in children less than 2 years

old. The three-drug ARV regimen with the greatest experience in neonates for prophylaxis and treatment is ZDV/3TC/NVP. Of the protease inhibitors, only NFV has pharmacokinetic data available for neonates, but these data demonstrate highly variable plasma concentrations and the optimal dosing regimen remains uncertain [9, 10]. Lopinavir/ritonavir, the protease inhibitor used most commonly to treat HIV infection in infants, is available as a pediatric solution, but dosing is uncertain in the first weeks of life. The solution contains 15% propylene glycol and 42% ethanol, and its use in the first two weeks of life is not recommended after several cases of life-threatening brady-arrhythmias and cardiac dysfunction were identified in preterm infants [11, 12]. Evaluation of the pharmacokinetics and safety of additional antiretroviral drugs for use in neonates for prevention or treatment of HIV infection is vitally important.

Raltegravir has the potential to play an important role in both prophylaxis and treatment of infants at high risk of HIV-1 infection. Raltegravir, an integrase inhibitor, has a unique mechanism of action, is effective in rapidly clearing plasma virus, and is well tolerated in children and adults. Overall, the currently available preclinical and clinical data support the evaluation of this highly promising antiretroviral agent in neonates exposed to HIV who are at risk of becoming infected. The primary goal of this protocol is to define the pharmacokinetics of raltegravir in at risk infants less than 6 weeks of age in order to develop an appropriate raltegravir dosing regimen for prophylaxis and or treatment of HIV in exposed neonates. This current study will evaluate the safety and pharmacokinetics of raltegravir in neonates at risk of acquiring HIV-1 infection and determine the appropriate dose that can be administered to infants. It is also hoped that a multi-dose regimen will be established for subsequent use for treatment in order to examine the effects of early neonatal therapy with integrase inhibitors towards eliminating widespread establishment of HIV reservoirs.

1.2 Raltegravir

Raltegravir (Isentress™) is a potent and selective HIV-1 integrase inhibitor. Integrase, one of three HIV-1 enzymes required for viral replication, catalyzes the stepwise process which results in the integration of the HIV-1 DNA into the genome of the host cell. Raltegravir inhibits HIV-1 replication by interfering with this process of integration. The drug is well tolerated and has demonstrated potent HIV-1 suppression in treatment naïve and experienced adults and treatment experienced infants and children at least 4 weeks of age [13-20].

1.21 Raltegravir Pharmacokinetics in Adults

There is considerable variability in the pharmacokinetics of raltegravir. In adults raltegravir has an initial (α) t ½ of approximately 1 hour and a terminal elimination (β) t ½ of approximately 7 to 12 hours [21]. In normal adults, approximately 7-14% of an administered raltegravir dose is excreted unchanged in urine. The primary route of raltegravir elimination is hepatic metabolism by UDP (uridine diphosphate)-glucuronosyltransferases (UGT), primarily UGT1A1 but with minor contributions from UGT1A3 and UGT1A9, followed by excretion of raltegravir-glucuronide via stool and urine [22].

Extrinsic and intrinsic factors have been evaluated in adults. Gender, age, body mass index, race, and HIV status had no clinically meaningful effect on raltegravir pharmacokinetics. Moderate hepatic insufficiency and severe renal insufficiency also had no clinically meaningful effect on raltegravir pharmacokinetics [23].

1.22 Summary of Raltegravir Drug-Drug Interactions

The potential for raltegravir drug-drug interactions was investigated in a series of clinical studies in uninfected adults. A summary of drug interaction studies appears below.

Table 1
Comparison of Drug-Drug Interactions of Raltegravir Plasma Pharmacokinetic Parameter: Mean % Effect on Raltegravir

Antiretroviral	C12h	AUC †	Cmax
Atazanavir (ATV) ‡	↑ 100%	↑ 73%	↑ 53%
ATV/RTV ‡ §	↑ 77%	↑ 41%	↑ 24%
Ritonavir (RTV) ‡	↓ 1%	↓ 16%	↓ 24%
Efavirenz ‡	↓ 21%	↓ 36%	↓ 36%
Tipranavir/RTV ‡ §	↓ 55%	↓ 24%	↓ 18%
Rifampin (400 mg RAL) ‡	↓ 61%	↓ 40%	↓ 38%
Rifampin (800 mg RAL) §, ‖	↓ 53%	↑ 27%	↓ 62%
Tenofovir ‡ §	↑ 3%	↑ 49%	↑ 64%
Etravirine	↓34%	↓10%	↓11%

† $AUC_{0-\infty}$ for SD raltegravir ; AUC_{0-12h} for MD raltegravir
‡ Multiple doses of concomitant medication plus single dose (SD) of raltegravir
§ Multiple doses of concomitant medication plus multiple doses (MD) of raltegravir
‖ 800 mg BID raltegravir + 600 mg QD rifampin compared to 400 mg BID raltegravir alone.

Raltegravir was shown not to be an inducer or inhibitor of CYP3A4, as demonstrated in the midazolam interaction study, suggesting that raltegravir will not impact the pharmacokinetics of drugs metabolized by CYP3A4 [21]. Raltegravir is approximately 83% bound to plasma proteins.

1.23 Raltegravir in Pregnancy for Prevention of Perinatal Transmission of HIV

In the United States, while transmission has been significantly reduced, perinatal transmission of HIV continues to occur. The Centers for Disease Control and Prevention conducts Enhanced Perinatal Surveillance in 15 U.S. jurisdictions. In a study evaluating transmission risk in 2005-2008 in 8,054 births to mothers with HIV infection, 179 infants (2.2%) were diagnosed with HIV infection [24]. The odds of having an infant with HIV

infection were higher among women with HIV infection who were tested late, had no antiretroviral (ARV) medications, abused illicit substances, breastfed, or had lower CD4 cell counts. In another report of nearly 8,600 births to women with HIV infection reported to the CDC, 8% of women did not receive prenatal care; of those with prenatal care, 3% did not receive HIV testing during pregnancy; of those with HIV testing, 6% did not receive ARV prophylaxis or treatment during pregnancy; of those who received antenatal therapy, 5% did not receive ARV drugs during labor and delivery [25]. In a study of 707 women receiving HAART during pregnancy, overall transmission was 1.6%; MTCT was directly correlated with HIV viral load nearest delivery and duration of HAART during pregnancy and CD4 count near delivery were correlated with viral load [26]. A number of studies have demonstrated that duration of ARV prophylaxis during pregnancy is significantly associated with the risk of MTCT [27], [28]; in the European Collaborative Study, MTCT was significantly related to insufficient antenatal HAART, defined as no or <13 days of HAART [27]. An additional important risk factor for transmission in the U.S. is acute HIV infection during pregnancy in women with initially negative HIV tests, who therefore initiate ARV late and have high levels of viremia [29]. Perinatal transmission with multi-class drug resistant virus despite antiretroviral prophylaxis, even with viral suppression, has been described [30]. Finally, the number of women with HIV infection giving birth in the U.S. has increased by approximately 30% since the year 2000 to approximately 9,000 annually, which can result in increased perinatal transmission secondary to these missed opportunities for prevention [25]. Thus, infants born to mothers with late diagnosis of HIV, receiving no antiretroviral drugs or short duration of HAART, have multi-class drug-resistant virus, or detectable viral load at delivery, are at particularly high risk of HIV transmission in the U.S. as well as in developing countries.

Raltegravir is now included in the list of recommended regimens for use in pregnant women[31]. Raltegravir pharmacokinetics (PK) were evaluated in 42 women during pregnancy in the IMPAACT P1026s study. Raltegravir PKs in these women showed extensive variability as seen in non-pregnant individuals. Median raltegravir area under the curve was reduced by approximately 50% during pregnancy. No significant difference was seen between the third trimester and postpartum trough concentrations. Plasma HIV RNA levels were under 400 copies/mL in 92% of women at delivery. Given the high rates of virologic suppression and the lack of clear relationship between raltegravir concentration and virologic effect in non-pregnant adults, no change in dosing was recommended during pregnancy [32]. In a study of 22 women with paired third-trimester and postpartum data from the PANNA Network, the geometric mean ratios of third trimester/postpartum values were AUC0-12hr 0.71 (0.53–0.96), Cmax 0.82 (0.55–1.253), and C12hr 0.64 (0.34–1.22). One patient was below the target C12hr in the third trimester and none were below the threshold postpartum. No change in dosing during pregnancy was recommended based on these data [33].

In the P1026s Study and the PANNA study, raltegravir was well tolerated, with no treatment-related serious adverse events in pregnant women, and all infants were at least 36 weeks' gestation at delivery [32, 33]. Raltegravir has been shown to induce a rapid decline in viral load and could be beneficial in women who present late in pregnancy with detectable virus [34]. In multiple case reports and case series of 4, 5, and 14

pregnant women treated with raltegravir in combination with 2 or 3 other antiretroviral drugs because of persistent viremia or late presentation, the drug was well tolerated and led to rapid reduction in HIV RNA levels [35-40].

1.24 Raltegravir in Children

IMPAACT P1066, conducted by the International Maternal, Pediatric, Adolescent AIDS Clinical Trials (IMPAACT) Group and entitled "A Phase I/II, Multicenter, Open-Label, Noncomparative Study to Evaluate the Safety, Tolerability, Pharmacokinetics, and Antiretroviral Activity of Raltegravir (Isentress™, MK-0518) in HIV-1 Infected Children and Adolescents," evaluated the safety, tolerability, pharmacokinetic parameters, and efficacy of three raltegravir formulations across the pediatric age range of 4 weeks to 18 years. Patients were stratified by age, enrolling adolescents first (Cohort I) and then successively younger children. Patients received the film-coated tablet formulation (Cohorts I and IIA; 6 through 18 years of age); or the chewable tablet formulation (Cohorts IIB and III; 2 through 11 years of age); or the granules for oral suspension (Cohorts IV and V; 4 weeks through 2 years of age). Raltegravir was administered with an optimized background regimen.

The initial dose-finding stage included intensive pharmacokinetic evaluation. Dose selection for each cohort (see Table 2, Cohorts I, IIA, IIB and III and Table 4, Cohorts IV and V) was based upon achieving similar raltegravir plasma exposure and trough concentration as seen in adults, with a specific goal to maintain both a geometric mean (GM) $AUC_{0\text{-}12hr}$ between 14 and 25 uM*hr and a GM C_{12hr} greater than 33 nM (the *in vitro* IC_{95} for antiviral activity), and acceptable short term safety. After dose selection, additional patients were enrolled for evaluation of long term safety, tolerability, and efficacy.

2 to 18 Years of Age

As shown in Table 2, for Cohorts I-III, the targeted PK parameters (area under the curve [AUC]0-12hr and C12hr) were achieved for each cohort allowing for dose selection.

Table 2
Raltegravir Pharmacokinetic Parameters Following
Administration of Recommended Pediatric Doses in IMPAACT P1066
Cohorts I - III

Age	Formulation	Mean Dose mg/kg	N†	Geometric Mean *(%CV)* AUC $_{0\text{-}12hr}$ (μM●hr)	Geometric Mean *(%CV)* C_{12hr} (nM)
12 to < 19 years	400 mg tablet ‡	9.3	11	15.7 (98)	333 (*78*)
6 to < 12 years	400 mg tablet	13.5	11	15.8 (*120*)	246 (*221*)
6 to < 12 years	Chewable tablet	6.5	10	22.6 (*34*)	130 (88)
2 to < 6 years	Chewable tablet	6.2	12	18.0 (*59*)	71 (55)

† Number of patients with intensive pharmacokinetic (PK) results at the final recommended dose.
‡ Patients in this age group received approximately 8 mg/kg dose at time of intensive PK which met PK and safety targets. Based on review of the individual profiles and receipt of a mean dose of 390 mg, 400 mg b.i.d was selected as the recommended dose for this age group.

Of the 126 children and adolescents enrolled (All Treated population), 96 patients received only the recommended dose of raltegravir (Final Dose population). In the 96 patients who received the recommended dose of raltegravir, the frequency, type, and severity of drug related adverse reactions through Week 24 were comparable to those observed in adults [41-45]. One patient experienced drug related clinical adverse reactions of Grade 3 psychomotor hyperactivity, abnormal behavior and insomnia; one patient experienced a Grade 2 serious drug related allergic rash. One patient experienced drug related laboratory abnormalities, Grade 4 AST and Grade 3 ALT, which were considered serious. These adverse events did not result in discontinuation.

Ninety-one (94.8%) patients 2 through 18 years of age completed 48 weeks of treatment. At Week 48, 78.9% achieved ≥1 $\log_{10}$ HIV RNA drop from baseline or <400 copies/mL; 56.7% achieved HIV RNA <50 copies/mL. The mean CD4 count (percent) increase from baseline to Week 48 was 155.7 cells/mm^3 (4.6%).

In December 2011, based on review of complete Week 24 and partial Week 48 data from this study, the United States Food and Drug Administration (US FDA) approved the use of raltegravir (as chewable or 400 mg film-coated tablet) in combination with other antiretroviral agents in pediatric patients 2 through 18 years of age.

- 12 years of age and older: One 400 mg film-coated tablet twice daily, orally
- 6 through 11 years of age (2 dosing options):
    - Film-coated tablet: One 400 mg tablet twice daily, orally (if at least 25 kg in weight) OR
    - Chewable tablets: weight based to maximum dose 300 mg, twice daily, as specified in Table 3.
- 2 through 5 years of age (and at least 10 kg in weight):
    - Chewable tablets: weight based to maximum dose 300 mg, twice daily, as specified in Table 3.

Table 3
Recommended Dose for Raltegravir Chewable Tablets in
Pediatric Patients 2 through 11 Years of Age

Body Weight (kg)	Body Weight (lbs)	Dose	Number of Chewable Tablets per dose
10 to < 14	22 to < 31	75 mg twice daily	3 x 25 mg
14 to < 20	31 to < 44	100 mg twice daily	1 x 100 mg
20 to < 28	44 to < 62	150 mg twice daily	1.5 x 100 mg[†]
28 to < 40	62 to < 88	200 mg twice daily	2 x 100 mg
at least 40	at least 88	300 mg twice daily	3 x 100 mg
[†] The 100 mg chewable tablet can be divided into equal halves.			

4 Weeks to < 2 Years of Age

As shown in Table 4, the targeted PK parameters (area under the curve [AUC]0-12hr and C12hr) were achieved for Cohort IV and V, allowing for dose selection.

Table 4
Raltegravir Pharmacokinetic Parameters Following
Administration of Recommended Pediatric Doses in IMPAACT P1066
Cohorts IV and V

Age	Formulation	Mean Dose mg/kg	N[†]	Geometric Mean *(%CV)* $AUC_{0\text{-}12hr}$ (μM●hr)	Geometric Mean *(%CV)* C_{12hr} (nM)
6 months to < 2 years	Granule Suspension	5.9	8	19.8 (34)	108.2 (52)
4 weeks to < 6 months	Granule Suspension	5.7	11	22.3 (40)	116.6 (68)
[†] Number of patients with intensive pharmacokinetic (PK) results at the final recommended dose.					

Twenty-six enrolled and were treated in Cohorts IV (6 months to < 2 years) and V (4 weeks to < 6 months) [20]. All 26 patients were included in the safety analysis. Through Week 48, there were 10 patients with Grade 3+ AEs. Two were judged related to study drug. There was 1 discontinuation due to an AE of skin rash, 1 event of immune reconstitution syndrome, and no drug-related deaths.

Of the 26 patients treated, 23 patients were included in the efficacy analysis. At Week 48, for Cohorts IV and V, 87.5% of patients achieved virologic success and 45.5% had HIV RNA <50 copies/mL. At Week 48, gains in CD4 cells of 527.6 cells/mm(3) and 7.3% were observed. A total of 6 mg/kg per dose twice daily of RAL for oral suspension was well tolerated and showed favorable virologic and immunologic responses.

Based upon these data, US FDA in December 2013 approved the use of raltegravir (as granules for oral suspension) in combination with other antiretroviral agents in pediatric patients 4 weeks to 2 years of age. During review of this data, the raltegravir pediatric dosing and administration (D&A) was restructured to a weight-based rather than age based cut-off approach. Table 5 displays PK data from IMPAACT P1066 based on the new weight-based dosing scheme without age categories.

The current pediatric doses recommended for each formulation, based on the United States Product Circular (USPC), are as follows:

- *If at least 25 kg*: One 400 mg film-coated tablet orally, twice daily.
- If unable to swallow a tablet, consider the chewable tablet, as specified in Table 5.

Table 5
Alternative Dose* with ISENTRESS Chewable Tablets for Pediatric Patients Weighing at Least 25 kg

Body Weight	Dose	Number of Chewable
25 to less than 28	150 mg twice daily	1.5 x 100 mg† twice daily
28 to less than 40	200 mg twice daily	2 x 100 mg twice daily
At least 40	300 mg twice daily	3 x 100 mg twice daily
*The weight-based dosing recommendation for the chewable tablet is based on approximately 6 mg/kg/dose twice daily. †The 100 mg chewable tablet can be divided into equal halves.		

- If at least 4 weeks of age and weighing at least 3 kg to less than 25 kg: Weight based dosing, as specified in Table 6.
- For patients weighing between 11 and 20 kg, either the chewable tablet or oral suspension can be used, as specified in Table 7. Patients can remain on the oral suspension as long as their weight is below 20 kg.

Table 6
Recommended Dose* for ISENTRESS For Oral Suspension and Chewable Tablets in Pediatric Patients Weighing Less than 25 kg

Body Weight (kg)	Volume (Dose) of Suspension to be Administered	Number of Chewable Tablets
3 to less than 4	1 mL (20 mg) twice daily	
4 to less than 6	1.5 mL (30 mg) twice daily	
6 to less than 8	2 mL (40 mg) twice daily	
8 to less than 11	3 mL (60 mg) twice daily	
11 to less than 14†	4 mL (80 mg) twice daily	3 x 25 mg twice daily
14 to less than 20†	5 mL (100 mg) twice daily	1 x 100 mg twice daily
20 to less than 25		1.5 x 100 mg‡ twice daily
*The weight-based dosing recommendation for the chewable tablet and oral suspension is based on approximately 6 mg/kg/dose twice daily *[see Clinical Pharmacology (12.3)]*. †For weight between 11 and 20 kg either formulation can be used. Note: The chewable tablets are available as 25 mg and 100 mg tablets. ‡The 100 mg chewable tablet can be divided into equal halves. Note: Oral suspension reconstituted to 20 mg/mL		

Table 7
Raltegravir Steady State Pharmacokinetic Parameters in Pediatric Patients Following Administration of Recommended Doses

Body Weight	Formulation	Dose	N	Geometric Mean (%CV)** $AUC_{0\text{-}12hr}$ (uM*hr)	Geometric Mean (%CV)** C_{12hr} (nM)
≥25 kg	Film-coated tablet	400 mg twice daily	18	14.1 (121%)	233 (157%)
≥25 kg	Chewable tablet	Weight based dosing, see [Table 5]	9	22.1 (36%)	113 (80%)
11 to less than 25 kg	Chewable tablet	Weight based dosing, see [Table 6]	13	18.6 (68%)	82 (123%)
3 to less than 20 kg	Oral Suspension	Weight based dosing, see [Table 6]	19	24.5 (43%)	113 (69%)

*Number of patients with intensive pharmacokinetic (PK) results at the final recommended dose.
**Geometric coefficient of variation.

1.25 Relative Bioavailability of Raltegravir Formulations

Protocol 068 provides relevant biocomparison data in adults for the current approved pediatric formulations oral granules for suspension) and/or approved and chewable tablets. The data provided below indicate that both oral granules for suspension and the chewable tablet formulations have somewhat greater bioavailability than the adult, film-coated tablet. Protocol 068 was an open label, 4-period, randomized, crossover study in healthy, adult, male and female subjects. Twelve (12) subjects each received 4 treatments (Treatments A, B, C, and D) randomized in a balanced, crossover design in Periods 1 through 4. Treatment A consisted of a single oral dose of 400 mg raltegravir adult formulation tablet. Treatment B consisted of a single oral dose of 400 mg raltegravir ethylcellulose pediatric chewable tablet formulation (administered as 4 x 100 mg tablets). Treatment C consisted of a single oral dose of 400 mg raltegravir oral granules in a liquid suspension. Treatment D consisted of a single oral dose of 400 mg raltegravir ethylcellulose pediatric chewable tablet formulation (as 4 x 100 mg tablets) administered following a high fat meal. Treatments A-C were administered in the fasted state. All doses of raltegravir, regardless of formulation, were administered under supervision and retention of drug in the mouth was not permitted. There was a minimum of 4 days of washout between the single doses in each treatment period.

The geometric mean pharmacokinetic parameter values for the raltegravir pediatric chewable tablet and oral granules for suspension formulations were estimated and compared to the corresponding values for the adult tablet, all following single dose administration of 400 mg in the fasted state, with results shown in Table 8. The geometric mean C_{12hr} values were similar for all formulations, while $AUC_{0\text{-}\infty}$ and C_{max} values were higher for both the pediatric chewable tablet and the oral granules formulation compared to the adult tablet. For the oral granules formulation, $AUC_{0\text{-}\infty}$ and C_{max} were moderately higher (2.6- and 4.6-fold) than those obtained with the adult tablet and slightly higher (1.5- and 1.4-fold) than those obtained with the pediatric chewable tablet. Both the pediatric chewable tablet and oral granules formulations had earlier median T_{max} values

compared with the adult tablet (0.5 and 1.0 hours for the chewable tablet and oral granules, respectively, compared to 4.0 hours for the adult tablet). Half-life values for both the initial (α) and terminal (β) phases were similar for all formulations. The results were consistent with some difference in the absorption portion of the pharmacokinetic profile among the formulations, but little difference in the later part of the profile. Mean plasma concentration–time profiles for all formulations are shown in Figure 1.

The higher $AUC_{0-\infty}$ and C_{max} values for the oral granules formulation are not expected to have any meaningful clinical consequences. The pharmacokinetic properties of the two pediatric formulations are similar to the raltegravir Phase I lactose formulation which was well tolerated in adults. To date in the development program for raltegravir, there have been no acute safety findings that were temporally associated with peak concentrations, and raltegravir has been found to be generally well tolerated in the clinical program with no dose-related toxicities. Based on the lack of a statistically significant difference in trough values, and the otherwise moderate dissimilarities in the other pharmacokinetic parameters, these results supported continued clinical development of both the chewable tablet and oral granules for suspension pediatric formulations in IMPAACT P1066. Acceptable pharmacokinetic, efficacy, and safety profiles for the chewable tablet and oral granules for suspension formulations have been observed in pediatric patients in IMPAACT P1066 to date [46, 47].

Table 8
Comparison of Raltegravir Plasma Pharmacokinetics Following Single-Dose Administration of the Raltegravir Adult Tablet, Pediatric Chewable Tablet (Fasted or Fed), and Raltegravir Oral Granules in a Liquid Suspension to Healthy, Adult, Male and Female Subjects (Protocol 068)

Pharmacokinetic Parameter (Units)	N	A† GM	B† GM	C† GM	D† GM	Comparison Treatment X/ Treatment Y	GMR (90% CI)
C_{12hr} (nM)§	12	149	134	162	387	C / A	1.09 (0.84 , 1.41)
						C / B	1.20 (0.92 , 1.56)
						D/ B	2.88 (2.21 , 3.75)
						B/ A	0.90 (0.70 , 1.18)
$AUC_{0-\infty}$ (μM•hr)§	12	19.2	34.2	50.4	32.3	C / A	2.62 (2.17 , 3.17)
						C / B	1.47 (1.22 , 1.78)
						D/ B	0.94 (0.78 , 1.14)
						B/ A	1.78 (1.47 , 2.15)
C_{max} (μM)§	12	5.00	16.1	23.2	6.14	C / A	4.64 (3.41 , 6.30)
						C / B	1.44 (1.06 , 1.95)
						D/ B	0.38 (0.28 , 0.52)
						B/ A	3.22 (2.37 , 4.38)
T_{max} (hr)⍰	12	4.0	0.5	1.0	1.0		
$t_{1/2I}$ (hr)¶		1.5 (0.3)	1.7 (0.2)	1.6 (0.3)	2.0 (0.6)		
$t_{1/2T}$ (hr)¶	12	9.0 (5.9)	9.3 (5.1)	10.0 (3.2)	9.2 (3.8)		

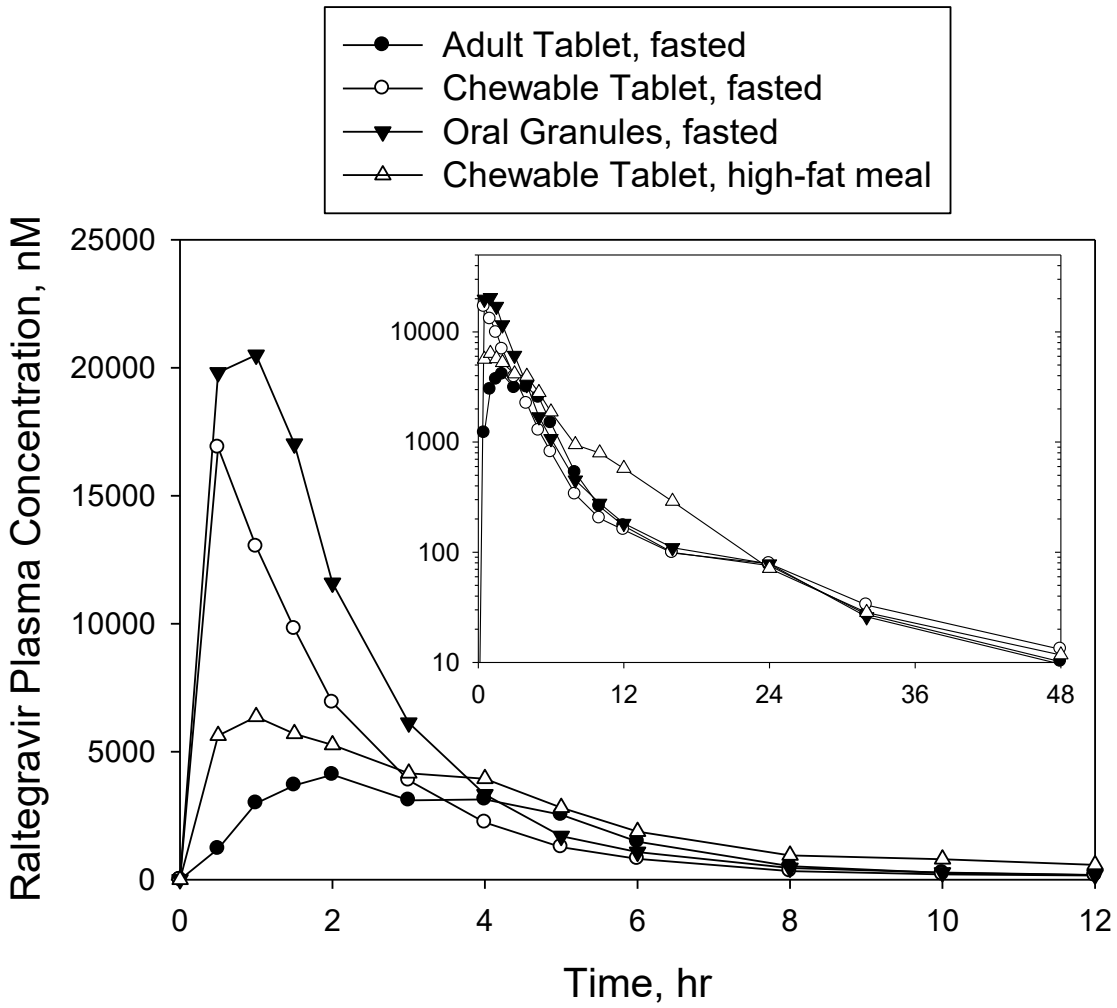
† Treatment A = 400 mg raltegravir, adult tablet (administered fasted).
Treatment B = 400 mg raltegravir, chewable tablet (administered fasted).
Treatment C = 400 mg raltegravir, oral granules in a liquid suspension (administered fasted).
Treatment D = 400 mg raltegravir, chewable tablet (administered with a high-fat meal).

§ Back-transformed least squares mean and confidence interval from mixed effects model performed on the natural log-transformed values.

⍰ Median values presented for T_{max}.

¶ Harmonic mean (jack-knife standard deviation) values presented for $t_{1/2I}$ and $t_{1/2T}$. For $t_{1/2I}$, the N's for Treatments A, B, C, and D are 11, 12, 12, and 10, respectively.

Figure 1
Arithmetic Mean Raltegravir Plasma Concentration-Time Profiles Following Single-Dose Administration of the Raltegravir Adult Tablet, Pediatric Chewable Tablet (Fasted or Fed), and Oral Granules in a Liquid Suspension to Healthy, Adult, Male and Female Participants (N=12; inset = semilog scale)



1.26 Raltegravir Resistance

The mutations observed in the HIV-1 integrase coding sequence associated with phenotypic resistance to raltegravir include the following amino acid substitutions: at either Q148H/K/R, N155H, or Y143C/H/R) plus one or more additional substitutions. In the raltegravir clinical development program, virologic failure was associated with emergent integrase signature mutations (at amino acids 143, 148, and 155) in 66% of treatment-experienced adults and 44% of treatment-naïve adults failing raltegravir therapy.

In IMPAACT P1066, the emergence of raltegravir-resistant viruses was monitored by isolating viral RNA from all patients displaying virologic failure and determining the

amino acid sequences of the HIV integrase gene, the reverse transcriptase (RT) gene, and the protease inhibitor (PI) gene if the HIV RNA plasma level was >1000 copies/mL, the approximate limit of the resistance assay, and adequate sample was available for testing. In Cohorts I, II, and III (N=126), a total of 27 (21.4%) patients were considered virologic failures by Week 24 and 36 (28.6%) patients were virologic failures by Week 48. Of the 33 Cohort I-III patients for whom genotypic data were available, viruses from 12 (36.4%) displayed signature resistance mutations as follows: 1 at AA 143, 7 at AA 148, and 8 at AA155, which is consistent with observations in adults**.** In Cohort IV, no patients failed by Week 24 and 4 patients failed by Week 48. No patients in Cohort V met virologic failure criteria by Week 24 or 48. Because of limited blood volume obtained, only 2 of the 4 patients with virologic failure had genotypic data available. One patient had a mutation at AA155 (without other raltegravir associated resistance mutations), and one patient had no known raltegravir mutations detected during study treatment.

1.27 Special Concerns for the Use of Raltegravir in the Neonate

UGT1A1, the enzyme primarily responsible for raltegravir metabolism, is also the only enzyme that contributes to bilirubin glucuronidation in human hepatocytes, and as such is essential for the biliary elimination of bilirubin from the body [48]. Glucuronidation activity is low in fetuses and in the newborn immediately after birth but increases exponentially over the first weeks and months of life. Hepatic UGT activity in liver samples is very low in samples from 2nd trimester fetuses, and increases roughly 10 fold during the 3rd trimester and then another 100-fold during the first 3 months following a full term delivery [49]. The low level of hepatic UGT activity at birth plays a major role in the elevations of bilirubin routinely seen in the newborn, referred to as physiologic jaundice.

In adults, decreased UGT1A1 activity has been shown to result in increased plasma concentrations of both bilirubin and raltegravir. Atazanavir, an HIV protease inhibitor, is also an inhibitor of UGT1A1 and elevation of direct bilirubin is a very common side effect of atazanavir use in HIV infected adults. When raltegravir and atazanavir are co-administered, raltegravir AUC increases on average by 41% and C_{max} by 77% [50]. Similarly, the *UGT1A1 *28/*28* genotype, one of the common genotypes found in individuals with Gilbert's Syndrome, is characterized by a roughly 30% decrease in UGT1A1 activity and increased serum bilirubin concentrations [51, 52]. Following standard dosing with raltegravir, individuals with the *UGT1A1 *28/*28* genotype have on average an increase of 40% in raltegravir AUC and C_{max} and of 90% in trough concentration compared to individuals with wild type *UGT1A1*. Raltegravir elimination t ½ was not prolonged in the *UGT1A1 *28/*28* individuals, suggesting that increased raltegravir bioavailability due to decreased hepatic first pass metabolism may play a major role in the increase in raltegravir plasma concentrations seen in these individuals [53].

Administration of an exogenous drug that is eliminated by glucuronidation poses special risks in the newborn. Low UGT activity that results in decreased elimination of endogenous bilirubin and physiologic jaundice will also result in decreased metabolism

of an exogenous drug whose major elimination pathway is glucuronidation. A neonatal dosing regimen for such a drug extrapolated from older infants or children may result in accumulation of unexpectedly high and potentially toxic plasma drug concentrations [54]. Chloramphenicol, a drug metabolized predominantly by glucuronidation that causes cardiovascular collapse at elevated plasma concentrations, provides the classic example of the harm that may result from using a drug in the newborn without an adequate understanding of its pharmacology in this population. When chloramphenicol was first administered to neonates in the 1950s, the use of neonatal doses extrapolated from those used in older infants and children in ignorance of the low level of neonatal glucuronidation activity led to the accumulation of chloramphenicol to toxic concentrations and the clinical syndrome of fatal cardiovascular collapse known as gray baby syndrome [55]. More recently, elimination of zidovudine, which is also metabolized by hepatic glucuronidation, has been shown to be decreased in neonates, necessitating use of reduced doses during the first months of life in both term and preterm infants [56, 57]. The reduction in neonatal zidovudine glucuronidation was associated not only with reduced clearance but also with higher bioavailability, consistent with decreased first pass metabolism [58].

Another potential risk posed by neonatal administration of a drug metabolized by UGT1A1 is an increase in neonatal bilirubin levels. Since both the drug and bilirubin share the same elimination pathway via UGT1A1 metabolism, the drug may compete with bilirubin for UGT binding sites, leading to a further reduction in bilirubin clearance and an increase in total serum bilirubin. This is unlikely to be a problem for raltegravir, which has a Km for UGT1A1 of 99 μM and binds much less avidly to UGT than does bilirubin, which has a Km of 5 μM for UGT1A1 [22]. Km, the Michaelis constant, is the substrate concentration at which an enzymatic reaction rate is at half its maximum speed. A low Km value indicates high affinity between substrate and enzyme, while a high Km value indicates low affinity.

Competition for neonatal albumin binding sites between bilirubin and an exogenous drug may also present a significant risk to the infant. Under normal circumstances, most circulating bilirubin in the newborn is in the unconjugated (indirect) form rather than the glucuronidated (conjugated or direct) form. Unconjugated bilirubin bound by albumin and other plasma proteins is unable to cross the blood-brain barrier. If the concentration of circulating unconjugated bilirubin exceeds the capacity of albumin for bilirubin binding, then the excess bilirubin will be unbound or “free”, with the potential to cross the blood-brain barrier and cause kernicterus [59]. In the newborn when bilirubin concentrations are high, a drug that displaces bilirubin from albumin binding sites may place the infant at increased risk of kernicterus and death, as was the case when sulfisoxazole was first used in premature neonates [60]. However, raltegravir is unlikely to cause a significant problem by displacement of bilirubin from albumin. The typical concentration of albumin in the healthy newborn ranges from about 3.5 to 4.5 g/dL, or 529 to 680 μmol/L [61]. After factoring in raltegravir protein binding of 83%, raltegravir should occupy approximately 2% of albumin under normal physiologic conditions, which should not increase kernicterus risk significantly. By comparison, kernicterus developed in premature infants when sulfisoxazole concentrations exceeded 205 μmol/L [62].

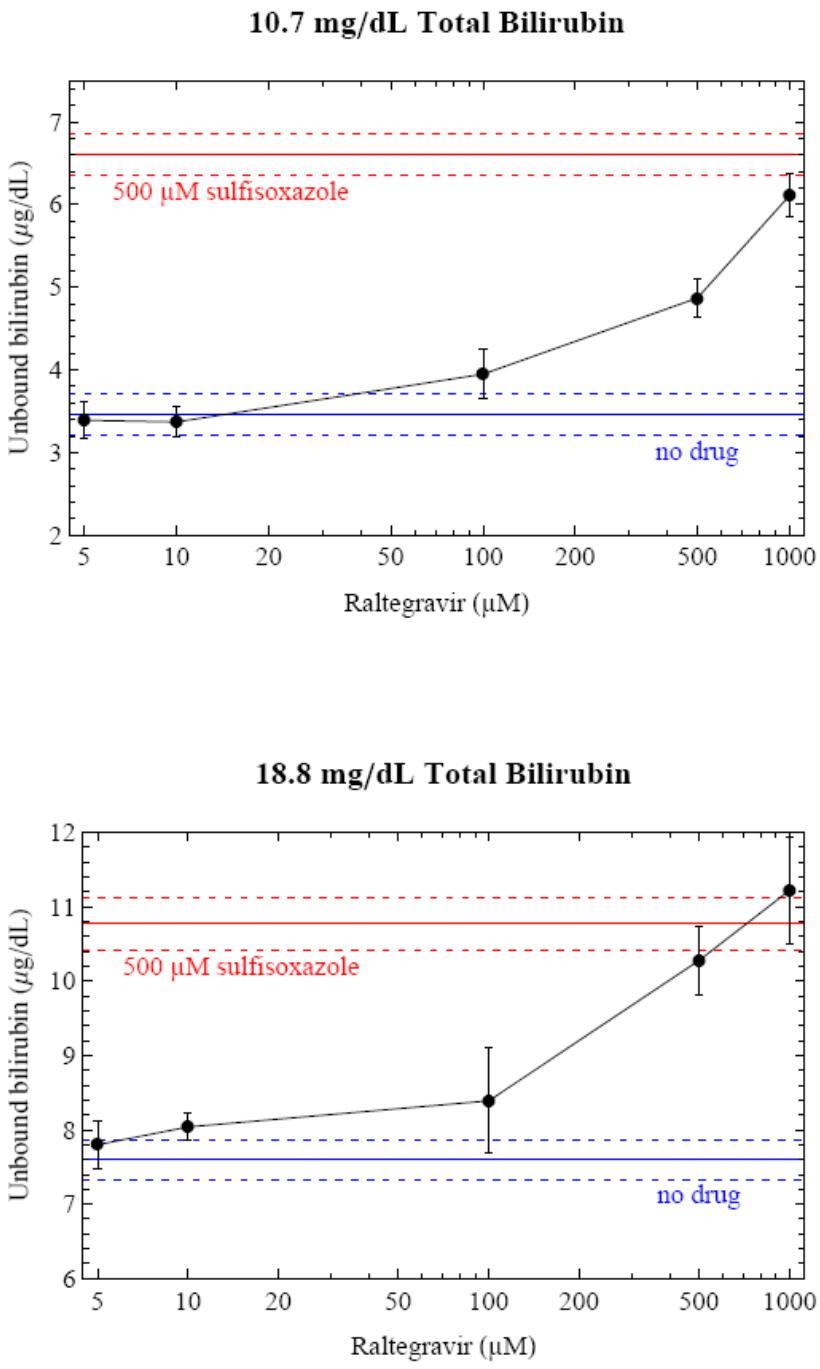
In vitro evaluation of the effect of raltegravir on bilirubin-albumin binding was performed in pooled neonatal serum using the peroxidase method [59, 61, 62]. Raltegravir had minimal effect on bilirubin-albumin binding at concentrations of 5 and 10 μM, caused a small, but statistically significant, increase in unbound bilirubin at 100 μM and potentially harmful increases at 500 and 1000 μM. The effect of raltegravir on neonatal bilirubin binding is unlikely to be clinically significant unless concentrations exceed typical peak concentrations of 10 μM (4440 ng/mL) by 50–100-fold [63]

Recently a genetic variant in the *SLCO13 gene* (rs2117032-C/T) was found to have a strong association with bilirubin levels in neonates [64]
In order to try to identify potential predisposing factors that might be associated with elevated bilirubin levels in the study population, the UGT1A1 and *SLCO1B3* (rs2117032) genetic variant will be evaluated at the end of the study.

Table 9:
Mean (SD) unbound bilirubin concentrations (μg/dL) with no additional drug or in presence of varying concentrations of raltegravir or sulfisoxazole.
*Significantly greater than no drug ($p \leq 0.05$)

Total Bilirubin	No Drug	Raltegravir (μM)					Sulfisoxazole (μM)	
		5	10	100	500	1000	500	1000
10.7 mg/dL	3.46	3.39	3.37	3.95	4.87	6.11	6.60	8.64
	(0.25)	(0.22)	(0.18)	(0.30)*	(0.24)*	(0.26)*	(0.25)*	(0.17)*
18.8 mg/dL	7.60	7.80	8.04	8.39	10.28	11.22	10.77	-----
	(0.27)	(0.32)	(0.18)*	(0.71)*	(0.46)*	(0.72)*	(0.36)*	

Figure 2
Mean (SD) unbound bilirubin concentrations (µg/dL) with no additional drug or in presence of varying concentrations of raltegravir or sulfisoxazole.



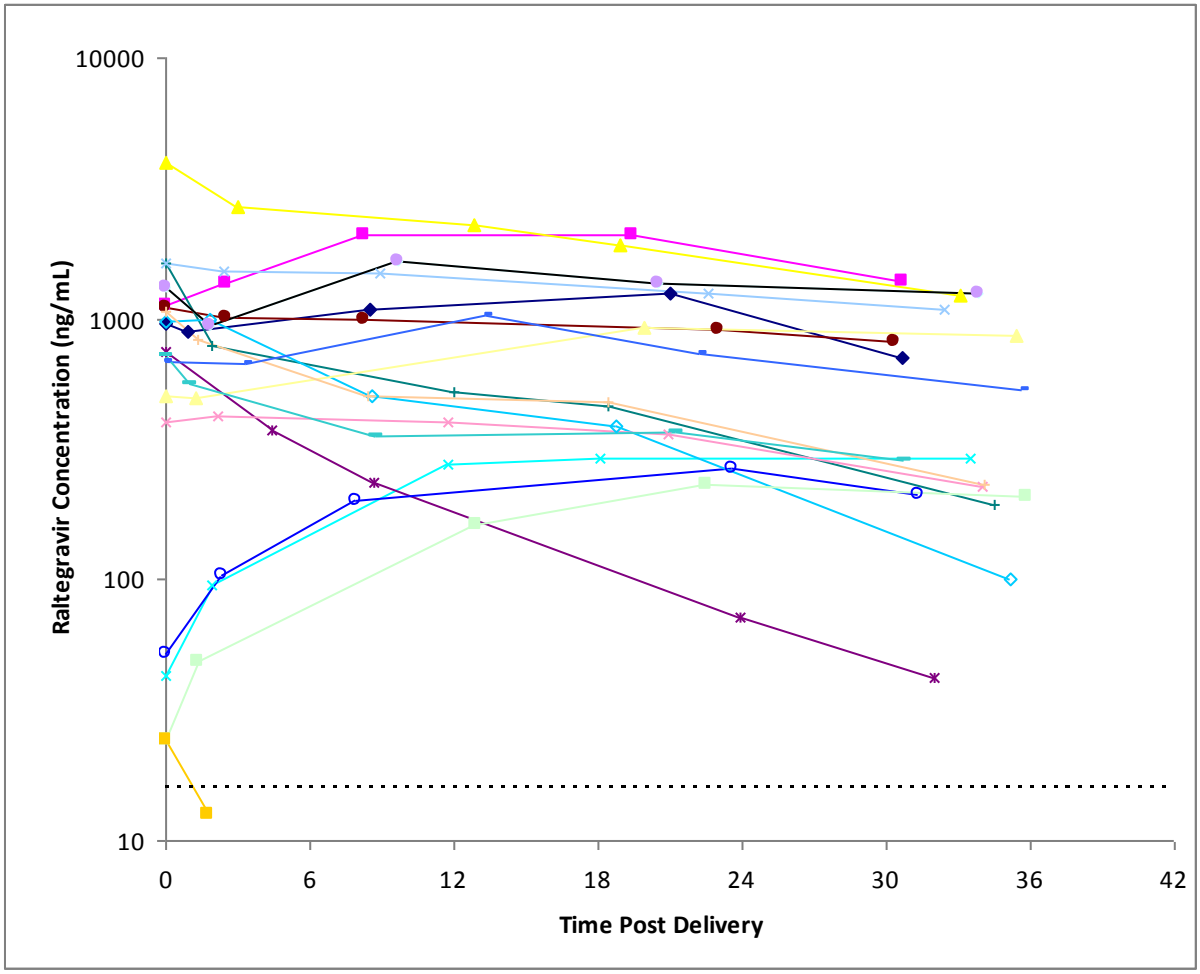
1.28 P1097: Raltegravir Washout PK Results

IMPAACT P1097 is an ongoing multicenter trial to determine the washout PK and safety of *in utero*/intrapartum exposure to RAL in both low birth weight (≤ 2500 grams) and full-term infants born to pregnant women with HIV infection receiving RAL at the FDA approved adult dose of 400 mg twice daily as part of their cART regimen. Cord blood and a single maternal blood sample are collected at delivery. In Version 1, which enrolled full term infants has been completed [65]. In full term infants, blood samples were collected at 1-5, 8-14, 18-24, and 30-36 hours after birth. In version 2, which is currently enrolling low birth weight infants, blood samples are collected at 1-6, 12-24, 36-48, 72-84, and 108-132 hours after birth. RAL concentrations are measured using a validated HPLC-MS-MS method. Infant t ½ is estimated using terminal 2 or 3 concentration-time points for each infant. Safety of *in utero*/intrapartum exposure to RAL has been evaluated in the full-term infants for up to 6 months of age.

In full-term infants, twenty-two mother-infant pairs were enrolled: 59% of the mothers were African American, 36% were Hispanic. Evaluable PK data were obtained from 19 mother-infant pairs (Figure 3). Median (range) ng/mL RAL plasma concentration values were: maternal at delivery: 540 (12-5809); cord blood 957 (24-3974); ratio of cord/maternal blood: 1.48 (0.32-4.33); initial infant plasma: 671 (13-2672); and infant plasma at 30-36 hours: 291 (<10-1402). Median infant apparent t ½ of RAL was 26.6 (9.3-184) hours. Infant washout RAL concentrations initially increased before decreasing in 9 of 19 (47%) evaluable infants. All infants tolerated RAL exposure well with 20 week follow-up evaluations completed with no unexpected adverse events or transmission of HIV infection [66].

Raltegravir readily crosses the placenta. The plasma t ½ of RAL in neonates is highly variable suggesting potential roles for developmental aspects of neonatal UGT1A1 enzyme activity, redistribution and/or enterohepatic recirculation of RAL. Understanding the features of RAL PK in neonates will be critical for development of a neonatal dosing regimen. P1097 version 2 includes LBW infants and is currently enrolling at both sites in the United States and internationally. It is anticipated that LBW infants will have delayed elimination of RAL as UGT1A1 activity is extremely low in this patient population.

Figure 3
P1097 Washout PK Full term infants
RAL Infant Concentration Time Plot (n=19)



1.29 P1110 Cohort 1: Raltegravir Pharmacokinetic Results

P1110 Cohort 1 infants received RAL administered as a single oral dose within 48 hours of birth in addition to standard of care antiretroviral agents (ARVs) for prevention of perinatal transmission, and a second dose administered at 7- 10 days of life. The initial dose was RAL 3 mg/kg and doses were adjusted on a rolling basis. RAL-exposed infants (infants born to mothers receiving RAL prior to and during delivery) were excluded initially but later were allowed to enroll and received a lower initial dose of 1.5 mg/kg.

Sixteen mother-infant pairs enrolled: 10 RAL- naïve infants (born to mothers who did not receive RAL during pregnancy and delivery) and 6 RAL-exposed infants. There were 8 females and 8 males; the median (range) gestational age was 38.7 (37-40) weeks; and the

median birth weight (range) was 3.02 (2.32-4.20) kg. Evaluable PK results were available for 15 of 16 infants. The first 6 RAL naïve infants received 3 mg/kg initial doses. While none of the 6 infants exceeded the Cmax upper limit, there were 3 out of 6 infants who exceeded the AUC12 upper limit of 28 mg*h/L. The initial dose was reduced after interim analysis and for subsequent enrollments RAL-naïve infants received a 2 mg/kg dose while RAL-exposed infants received a 1.5 mg/kg for the initial dose. All infants, regardless of maternal RAL usage, received 3 mg/kg for the second dose at 7-10 days of life.

P1110 Cohort 1 (RAL-naïve): Raltegravir Pharmacokinetic Preliminary Results

PK results from Cohort 1 [67-69] were combined with that from older infants and children receiving daily dosing in a population PK model and simulations performed to develop a daily RAL dosing regimen to be evaluated in 20 infants in Cohort 2 [70-72]. The RAL dosing regimen studied in Cohort 2 for infants unexposed to RAL in utero is: 1.5 mg/kg daily starting within 48 hours of life through day 7; 3 mg/kg twice daily on days 8-28 of life; 6 mg/kg twice daily after 4 weeks of age [71, 72].

PK results and 6 week safety data were presented for the first 10 RAL-naïve infants who received the dose under study: 1.5 mg/kg daily through day 7; 3 mg/kg twice daily on days 8-28 of life; 6 mg/kg twice daily after 4 weeks of age [69, 73, 74]. After the first dose of 1.5 mg/kg, geometric mean RAL AUC_{24} was 38.9 mgxh/L (range18.6-78.3 mgxh/L). On 3 mg/kg twice daily the geometric mean for RAL AUC_{12} was 12.1 mgxh/L (range 4.7-24.5 mgxh/L) and C_{min} estimated to be 120.4 ng/mL. Sparse sampling confirmed that RAL plasma concentrations were within the expected range.

There have been no safety concerns associated with daily RAL administration based on safety data through 6 weeks of life. Daily RAL has been well tolerated in the infants receiving this regimen during the first 6 weeks of life. The PK targets and the safety guidelines have been met for the RAL-naive infants in cohort 2.

2.0 STUDY OBJECTIVES

2.1 Primary Objectives

2.11 To evaluate the safety and tolerability through 6 weeks of life of raltegravir oral granules for suspension when administered during the first 6 weeks of life with standard PMTCT ARV prophylaxis to infants exposed to HIV-1 assessed at risk of infection.

2.12 To evaluate the pharmacokinetics of raltegravir oral granules for suspension during the first 6 weeks of life along with standard PMTCT ARV prophylaxis.

2.13 To determine an appropriate dose of raltegravir oral granules for suspension for use in neonates and infants during the first 6 weeks of life.

2.2 Secondary Objectives

2.21 To assess safety and tolerability of raltegravir oral granules for suspension through 24 weeks of life when administered during the first 6 weeks of life with standard PMTCT ARV prophylaxis to infants exposed to HIV-1 assessed at risk of infection.

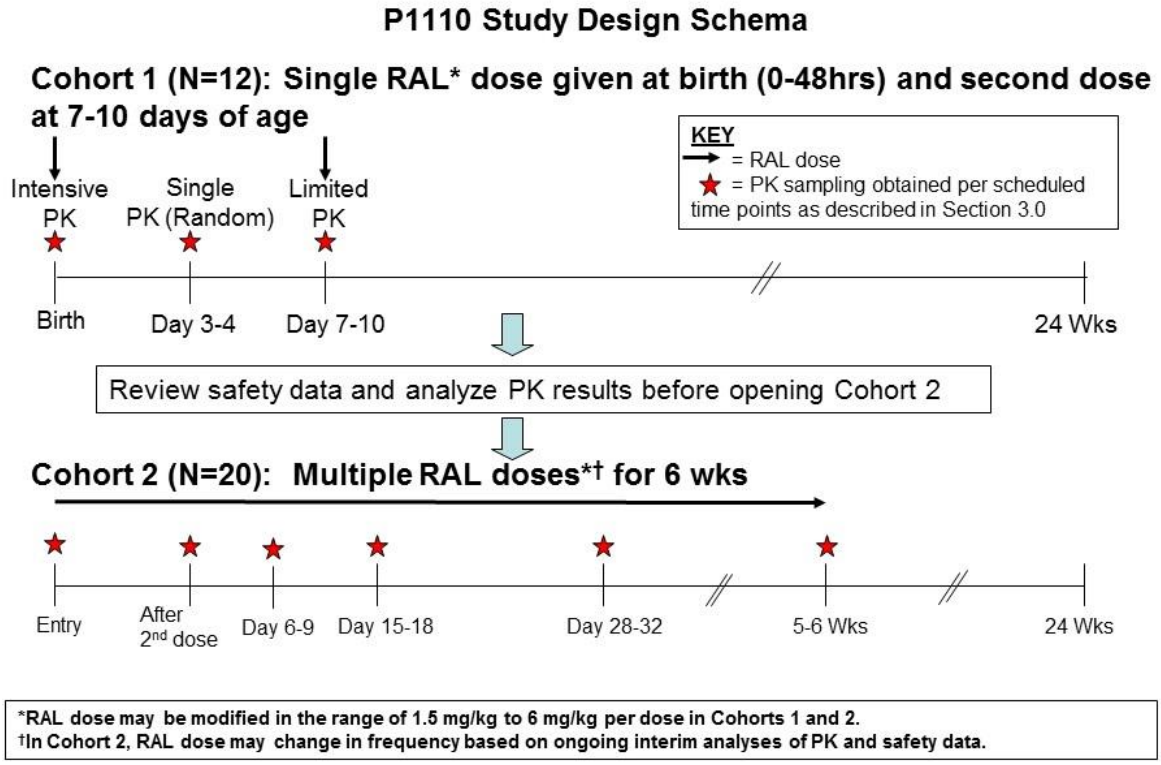
2.22 To investigate the relationship between neonatal raltegravir elimination and UGT1A1 genotype and whether there is an association of UGT1A1 (*28/*28) and SLCO1B3 (rs2117032-C/T) with hyperbilirubinemia.

3.0 STUDY DESIGN

This is a Phase I multi-center, open label, non-comparative study to evaluate the safety and pharmacokinetics (PK) of raltegravir (RAL) administered to HIV-1-exposed neonates at risk of acquiring HIV-1 infection. The goal is to determine the appropriate dosing regimen of RAL oral granules for suspension that can be safely administered to neonates and infants in the first 6 weeks of life.

The study will enroll approximately 50 mother-infant pairs in order to accrue a minimum of 32 PK evaluable HIV-1-exposed infants.

Mother-infant pairs will enroll at the time of delivery/birth (up to 48 hours of life under protocol Version 1.0 and up to 60 hours of life under protocol Version 2.0). Pregnant women who are expected to have a full term uncomplicated delivery will be identified prior to delivery. The informed consent process will typically be conducted during the 2nd or 3rd trimester; however, the consent process may be conducted in whole or in part after infant birth. Women will be followed until discharge from the labor and delivery unit. Infants will be followed on study for 24 weeks after birth.



Cohort 1:

A minimum of 12 neonates will be enrolled into Cohort 1 to provide data for 12 PK evaluable neonates. All neonates enrolled in Cohort 1 will receive RAL 2 mg/kg as oral granules for suspension administered as single dose within 48 hours of birth, in addition to standard of care ARV for PMTCT prophylaxis, and a second dose administered at 7 to 10 days of life.

The primary purpose of Cohort 1 is generation of PK data that will help inform RAL dose selection for Cohort 2. As this is the first time neonates will be actively dosed with RAL, the extent to which PK may differ from older infants with respect to absorption and metabolism is unknown. The first dose (<48 hours) will provide PK data when infant glucuronidation is known to be at its nadir, and the second dose (7-10 days) will provide information about changes in metabolism in Week 2. The 2 mg/kg single starting dose of RAL is 25% of the total daily dose (6 mg/kg BID) that was studied in infants with HIV infection 4 weeks to < 6 months of age in IMPAACT P1066. Since RAL clearance is substantially lower in the first days of life, based on interim data from IMPAACT P1097, the 3 mg/kg single dose was selected as a conservative first dose to minimize potential safety concerns and still provide informative PK data.

RAL dosing in Cohort 1 may be modified in the range of 1.5 mg/kg to 6 mg/kg per dose. The PK results and safety will be assessed through regular team monitoring (done at least every 4 weeks) and at full cohort accrual to ensure that the individual RAL concentrations are in the target range (not exceeding C_{max} of 19.63 µM and not exceeding an AUC12 of 63.05 µM-hr) and that there

are no life-threatening toxicities probably or definitely related to RAL administration. Based on team assessment of the PK data and review of safety information, the dose may be modified within the stated range for the subsequent participants entering into Cohort 1.

All Cohort 1 infants will have a history, physical examination, and hematology and chemistry laboratory evaluations performed at the time of dosing for each of the two doses, and follow-up visits at 2 weeks, 6 weeks and 24 weeks of life.

Pharmacokinetic sampling for infants in Cohort 1 will include the following:

Dose 1 (within 48 hours of birth) Intensive PK: Pre-dose, 1-2 hours post-dose, 4-8 hours post-dose, 12 (±1) hours post-dose, and 24 (±1) hours post-dose.

Day 3-4 Single Random PK: One random PK sample will be obtained with laboratory evaluations on Day 3-4 of life.

Dose 2 (7-10 days of life) Limited PK: Pre-dose, 1-2 hours post-dose and 24 (±1) hours post-dose.

*Note: For the 12 and 24 hour PK sampling time points, it is necessary to collect blood samples within the window of ±1 hour for the accurate calculations of PK parameters of raltegravir. However, in the event that a sample collection in this window is not possible, the sample should be obtained within ±2 hours and this deviation from the sampling instructions should be recorded.

Cohort 2:

A minimum of 20 evaluable infants will be enrolled into Cohort 2 to receive raltegravir for 6 weeks in addition to standard of care ARV for PMTCT prophylaxis. Cohort 2 dosing has been determined based upon modeling and simulation analyses, which included data generated from IMPAACT P1097, P1066 (Cohorts IV and V), P1026s, and P1110 Cohort 1 and incorporated information about UGT1A1 ontogeny to inform the development of neonate metabolic pathways. RAL-naïve infants in Cohort 2 will receive RAL at a dose of 1.5 mg/kg daily as oral granules for suspension starting within 48 hours of birth. RAL-exposed infants in Cohort 2 will receive RAL at a dose of 1.5 mg/kg daily as oral granules for suspension starting within 12 to 60 hours of birth. Additionally, RAL dosing in Cohort 2 may be modified based on ongoing interim analysis of pharmacokinetic data and safety information.

All Cohort 2 infants will have a history, physical examination, and hematology (except for the After Second Dose visit) and chemistry laboratory evaluations performed at all study visits. Additional repeat total and direct bilirubin will be done on day 2-4 of life (after the second dose). Follow-up visits will occur at Day 6-9, Day 15-18, Day 28-32, and 5-6 weeks, 8-10 weeks and 24 weeks of life.

Note: Cohort 1 (RAL-exposed and RAL-naïve groups) and Cohort 2 (RAL-naïve group) were fully enrolled under protocol Version 1.0 and the results of Cohort 1 were used to inform the dosing regimen for Cohort 2, see protocol Section 1.29 for a summary of these results.

Pharmacokinetic sampling for infants in Cohort 2 will include the following:

*Note: PK sampling will ideally be scheduled after RAL has reached steady state (approximately 7-10 days after the dose increase). For example, the Day 15-18 PK sampling collection visit should ideally be scheduled 7-10 days after the infant received his/her RAL dose regimen increased from 1.5 mg/kg once daily to 3 mg/kg twice daily.

Entry with first dose: within 1 hour pre-dose, and 1-2 hours, 6-10 hours, 20-24 hours post-dose.

After second dose: PK sample obtained 3-6 hours post-dose with laboratory evaluations.

Day 6-9 of life: within 1 hour pre-dose of initiating 3mg/kg twice daily. A physical exam will also be conducted at this visit.

Day 15-18 of life: within 1 hour pre-dose, and 1-2 hours post-dose, 4-6 hours post-dose, and 8-12 hours post-dose.

Day 28-32 of life: within 1-hour pre-dose of initiating 6 mg/kg twice daily.

Week 5-6 of life (33-42 Days of life): within 1 hour pre-dose, and 3-6 hours post-dose.

See Section 6.21 for Cohort 1 and Cohort 2 PK target exposures**.**

3.1 Evidence of HIV infection and resistance testing (Cohorts 1 and 2):

All infants will receive appropriate testing for evidence of HIV-1 infection within 60 hours of birth (if not done as per standard of care), and at 6 and 24 weeks of life. If any study participant is found to be HIV-1 infected during the course of the study, blood samples for viral resistance testing to raltegravir and ARVs will be collected as soon as possible after confirmation of vertical transmission. Infants who become HIV infected will have hematology, chemistry, lymphocyte subsets, and HIV viral load laboratory evaluations performed every 3 months up to 24 weeks of life.

3.2 Optional genotyping (Cohorts 1 and 2):

Optional genotyping for UGT1A1 and SLCO1B1 polymorphisms will be performed in infants undergoing PK sampling to determine how polymorphisms, such as UGT1A1*28/*28 genotype, associated with decreased UGT1A1 activity impact RAL elimination in the neonate. UGT1A1 activity is reduced in all neonates at birth but increases rapidly over the first weeks of life, and the effect of UGT1A1 polymorphisms on the metabolism of RAL during this period of time is unknown.

3.3 Raltegravir Compassionate Use (Cohorts 1 and 2):

Raltegravir will be provided to infants through the protocol for the duration of the study as part of combination antiretroviral therapy (cART), but the choice of the ARV regimen will be left to the discretion of the site investigator. At the end of the study, infants with HIV infection who are receiving the RAL granules as part of their cART regimen at sites where the RAL granules are either 1) not commercially available in that country for the caregiver to purchase, or 2) the caregiver cannot gain access to the granules via a government program, then Merck will arrange for access to the granules through the local Merck subsidiary at no cost to the patient.

See Appendix I, Maternal Schedule of Evaluations, Appendix II-A, Infant Schedule of valuations for Cohort 1, Appendix II-B, Infant Schedule of Evaluations for Cohort 2, and Appendix II-C, Schedule of Evaluations for Infants Who Become HIV Infected, for a complete description of the procedures to be performed.

4.0 SELECTION AND ENROLLMENT OF PARTICIPANTS

4.1 Maternal Inclusion Criteria

4.11 Mother is either known to be HIV-1 infected prior to labor or identified as HIV-1 infected at the time of labor or in the immediate postpartum period.

Documentation of HIV infection:

Documentation of HIV-1 infection is defined as positive results from <u>two</u> samples (whole blood, serum, or plasma) collected at <u>different</u> time points. Results documented in the clinical record from past testing may be used to satisfy the criteria for documentation of HIV-1 infection.

If both samples are tested using antibody tests, at least one of the samples must be tested in a laboratory that operates according to Good Clinical Laboratory Practice (GCLP) guidelines and participates in an appropriate external quality assurance program. If nucleic acid testing is used, at least one test must be performed in a CLIA-certified (US sites) or VQA-certified (non-US) laboratory. For tests performed in other (non-GCLP-compliant or non-VQA-certified) settings, adequate source documentation including the date of specimen collection, date of testing, test performed, and test result must be available.

Sample #1 must be tested using any of the following:

- Up to two rapid antibody tests from different manufacturers or based on different principles and epitopes.
- One EIA OR Western Blot OR immunofluorescence OR chemiluminescence
- One quantitative HIV RNA PCR (above the limit of detection of the assay)
- One HIV DNA PCR

- One qualitative HIV RNA PCR
- One total HIV nucleic acid test

Note: Confirmatory testing (Sample #2) may be pending at the time of enrollment of the mother-infant pair. If maternal confirmatory testing is negative, the infant will be removed from active dosing but will be followed for safety as part of the study.

Sample #2 must be tested using any of the following:

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

4.12 For Cohort 1 and Cohort 2 (RAL-naive): Mother is at high-risk of transmitting HIV to infant as evidenced by any of the following:

1) Mother has not received any antiretroviral therapy during the current pregnancy prior to the onset of labor and delivery;

2) HIV RNA > 1000 copies/mL within 4 weeks (28 days) prior to delivery

3) Receipt of ARV for < 4 weeks (28 days) before delivery

4) On ARVs for ≥ 4 weeks but has not taken any ARV for > 7 days prior to delivery

5) Mother has documented drug resistant virus to at least one class of ARV drugs

Note: Mothers may have received prenatal and/or intrapartum antiretrovirals.

Note: For Cohort 2 RAL-exposed, there is no requirement that the mother be determined 'high-risk' of transmitting HIV to her infant.

4.13 Maternal written informed consent for study participation.

4.2 Maternal Exclusion Criteria

4.21 Known maternal-fetal blood group incompatibility as evidenced by the presence of an unexpected clinically significant maternal red cell antibody that is known to be capable of causing hemolytic disease of the fetus/newborn.

4.22 Mother receiving RAL as part of her cART regimen after delivery and intending to breastfeed her infant.

4.23 For Cohort 1 (up to 6 mothers only) and Cohort 2 RAL-naïve: Mother who received RAL prior to and through delivery.

4.3 Infant Inclusion Criteria

4.31 For Cohort 1 and Cohort 2 (RAL-naive): Full-term infants exposed to HIV aged ≤48 hours. Infant may have received up to 48 hours of standard of care ARV prophylaxis before enrollment.

For Cohort 2 (RAL-exposed): Full-term infants exposed to HIV aged ≤ 60 hours. Infant may have received standard of care ARV prophylaxis/ treatment before enrollment.

4.32 Infant gestational age at birth at least 37 weeks.

4.33 No known severe congenital malformation or other medical condition not compatible with life or that would interfere with study participation or interpretation, as judged by the examining clinician.

4.34 Birth weight ≥2 kg.

4.35 Able to take oral medications.

4.36 Parent or legal guardian able and willing to provide signed informed consent.

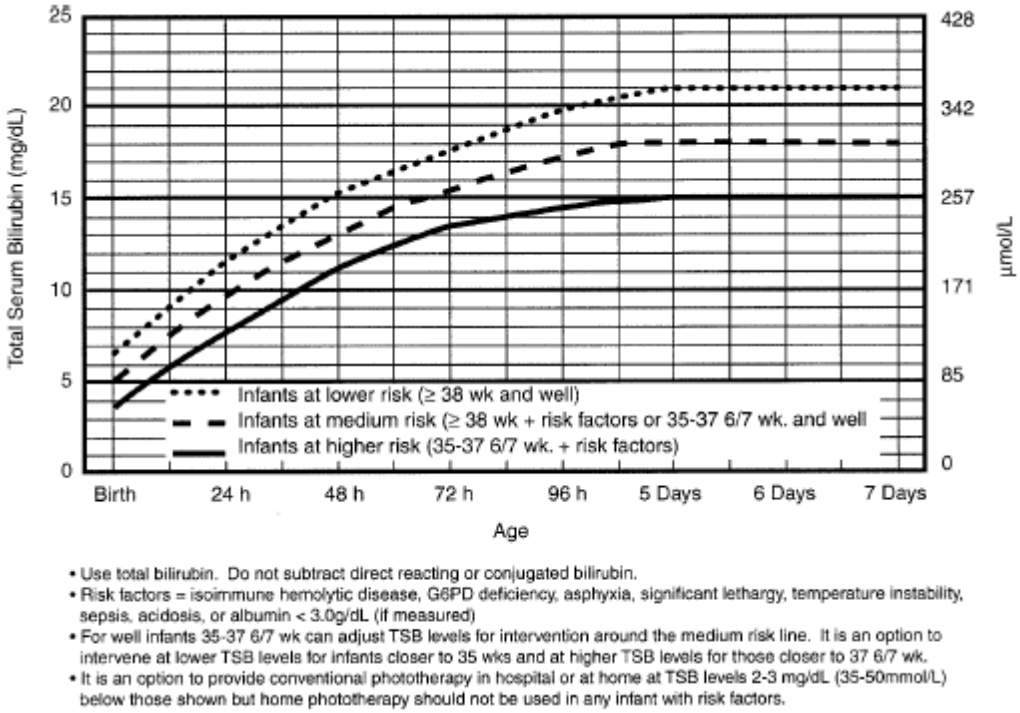
4.37 For Cohort 2 RAL-exposed Group
Infants born to a mother who received at least one dose of raltegravir (RAL) within 2 to 24 hours of delivery

Note: Based on mother's self-report and confirmed by medical records if available.

Note: For Cohort 1 RAL-exposed Group infants were born to mothers receiving RAL as part of their ARV regimen.

4.4 Infant Exclusion Criteria

4.41 Infant with bilirubin exceeding the American Academy of Pediatrics guidelines for phototherapy, using the infant's gestational age and risk factors as described below [75].



- Use total bilirubin. Do not subtract direct reacting or conjugated bilirubin.
- Risk factors = isoimmune hemolytic disease, G6PD deficiency, asphyxia, significant lethargy, temperature instability, sepsis, acidosis, or albumin < 3.0g/dL (if measured)
- For well infants 35-37 6/7 wk can adjust TSB levels for intervention around the medium risk line. It is an option to intervene at lower TSB levels for infants closer to 35 wks and at higher TSB levels for those closer to 37 6/7 wk.
- It is an option to provide conventional phototherapy in hospital or at home at TSB levels 2-3 mg/dL (35-50mmol/L) below those shown but home phototherapy should not be used in any infant with risk factors.

4.42 Clinical evidence of renal disease such as edema, ascites, or encephalopathy.

4.43 For Cohort 2 RAL naïve, and Cohort 1 (RAL-naive and RAL-exposed): Receipt of disallowed medications (phenytoin, phenobarbital, rifampin)

4.5 Disallowed Medications

Phenytoin, phenobarbital, rifampin: RAL is eliminated mainly via a UDP glucuronosyltransferase UGT1A1-mediated glucuronidation pathway and may be subject to drug-drug interactions when co-administered with drugs that are known to be UGT1A1 inducers or inhibitors. However, RAL is not anticipated to affect the metabolic clearance of drugs metabolized by UGT1A1 given its low UGT1A1 inhibitory (IC_{50} for the inhibition of UGT1A1 >50 µM) and induction potential. Since RAL is neither an inducer nor inhibitor of cytochrome P-450 enzymes, RAL is not expected to result in metabolic drug interactions with substrates of cytochrome P-450.

4.6 Enrollment Procedures

Prior to implementation of this protocol, and any subsequent full version amendments, each site must have the protocol and the protocol informed consent form(s) approved, as appropriate, by their local institutional review board (IRB)/ethics committee (EC) and any other applicable regulatory entity (RE). Upon receiving final approval, sites will submit all

required protocol registration documents to the DAIDS Protocol Registration Office (DAIDS PRO) at the Regulatory Support Center (RSC). The DAIDS PRO will review the submitted protocol registration packet to ensure that all of the required documents have been received.

Site-specific informed consent forms (ICFs) WILL be reviewed and approved by the DAIDS PRO and sites will receive an Initial Registration Notification from the DAIDS PRO that indicates successful completion of the protocol registration process. A copy of the Initial Registration Notification should be retained in the site's regulatory files.

Upon receiving final IRB/EC and any other applicable RE approval(s) for an amendment, sites should implement the amendment immediately. Sites are required to submit an amendment registration packet to the DAIDS PRO at the RSC. The DAIDS PRO will review the submitted protocol registration packet to ensure that all the required documents have been received. Site-specific ICF(s) *WILL NOT* be reviewed and approved by the DAIDS PRO and sites will receive an Amendment Registration Notification when the DAIDS PRO receives a complete registration packet. A copy of the Amendment Registration Notification should be retained in the site's regulatory files.

For additional information on the protocol registration process and specific documents required for initial and amendment registrations, refer to the current version of the DAIDS Protocol Registration Manual.

Enrollment of participants onto the study will be done through the Subject Enrollment System (SES) on the DMC website (at https://www.frontierscience.org) under the Systems heading.

4.7 Co-enrollment Procedures

Co- enrollment in P1081 is allowed as long as blood draw limitations are not exceeded. NIH and local restrictions apply.

Co-enrollment in other research protocols will require the consent of the protocol chair(s) of P1110 and the other research protocol.

5.0 STUDY TREATMENT

Study treatment is defined as Raltegravir (Isentress®, RAL) oral granules for suspension.

5.1 Drug Regimens, Administration, and Duration

5.11 Regimen

Cohort 1: HIV-1 exposed full-term infants

For RAL-naïve (unexposed) infants: RAL 2 mg/kg oral granules for suspension as a single dose within 48 hours of birth in addition to standard of care ARV for PMTCT prophylaxis (refer to *Appendix III, Raltegravir Weight Band Dosing Table for Oral Granules for Suspension*).

For RAL-exposed infants: RAL 1.5 mg/kg oral granules for suspension as a single dose within 48 hours of birth in addition to standard of care ARV for PMTCT prophylaxis (refer to *Appendix III, Raltegravir Weight Band Dosing Table for Oral Granules for Suspension*).

For all Cohort 1 infants (RAL-naïve and RAL-exposed infants): Administer a second single dose of RAL 3 mg/kg oral granules for suspension in addition to standard of care ARV for PMTCT prophylaxis (refer to tables in Appendix III) on day 7 to 10 of life.

Cohort 2: HIV-1 exposed full-term infants

For RAL-naïve (unexposed) infants: RAL oral granules for suspension, provided as follows in addition to standard of care ARV for PMTCT prophylaxis (refer to tables in Appendix III): First Dose to be administered within 48 hours of life:

- 1.5 mg/kg once daily during Days 1-7 of life (week 1)
- 3.0 mg/kg twice daily during Days 8-28 of life (weeks 2-4)
- 6.0 mg/kg twice daily during Days 29-42 of life (weeks 5-6)

For RAL-exposed infants. First dose to be administered between 12 and 60 hours of life (refer to tables in Appendix III):

- 1.5 mg/kg once daily during Days 1-7 of life (week 1)
- 3.0 mg/kg twice daily during Days 8-28 of life (weeks 2-4)
- 6.0 mg/kg twice daily during Days 29-42 of life (weeks 5-6)

The reference weight to be used for each dose, and throughout the duration of that dose, is shown in the Table 10 below. The doses are calculated at 3 time points during the 6 weeks:

1. Initial dose based on birth weight;
2. At day 6-9 of life study visit; and
3. At day 28-32 of life study visit.

Note: Intent is to minimize the number of dose adjustments while receiving study treatment.

Table 10
Weight for Weight Bands (Cohort 2 RAL-exposed) in Appendix III

RAL dose regimen	Weight to be used for Appendix III weight bands
1.5 mg/kg once daily	Birth Weight Note: First dose administered between 12 and 60 hours of life
3.0 mg/kg twice daily	Weight on Day 6-9 of Life Study Visit (Note: if infant has lost weight during first week of life, use birth weight for dose calculation)
6.0 mg/kg twice daily	Weight on Day 28-32 of Life Study Visit

NOTE: If dose adjustment is required for Cohort 1 and Cohort 2 based on pharmacokinetic data, this will be communicated by the protocol team to sites. A new prescription will be required for the site pharmacist. Refer to Appendix III for dosing tables of RAL oral granules for suspension based on 1.5, 2, 3, 4, 5, and 6mg/kg Daily or Twice Daily.

5.12 Administration

Cohort 1: The first single dose given within 48 hours of birth and the second single dose given on day 7 to 10 of life will be prepared by the study staff. Clinic Staff will provide phone call follow up prior to visit days for dosing and after dosing visits to review side effects to watch for, and to confirm no problems with tolerability.

Cohort 2: The initial dose administered while the participant is in the hospital will be prepared and administered by the study staff. The initial dose will be administered in RAL–naive infants between 0 to 48 hours of birth and in RAL–exposed infants between 12 and 60 hours of birth. Prior to discharge from the hospital, the site staff will instruct the parent or caregiver how to properly prepare and administer the doses to the infant. Subsequent doses can be prepared and administered by caregivers as part of the teaching process. Clinic staff will call the participant's home prior to PK sampling days to confirm adherence, understanding of dosing, and no intercurrent illnesses that might preclude PK sampling. If correct dosing for 48 hours prior to PK sampling is not confirmed, PK sampling will be rescheduled.

Competency of the parent or caregiver to both properly prepare and administer the doses to the participant must by documented in the participants chart by site staff prior to discharge from the hospital.

See Appendix IV, Diagram and Caregiver Instructions for Preparing and Administering Raltegravir Oral Granules for Suspension 10 mg/mL, for directions on the preparation and dosing of raltegravir oral granules for suspension.

5.13 Duration

Cohort 1 will receive two single observed doses of RAL oral granules that are prepared by site staff in addition to standard of care ARV for PMTCT prophylaxis. The first dose should be within 48 hours of birth and the second single dose at 7 to 10 days of life.

Cohort 2 will receive 6 weeks of RAL oral granules in addition to standard of care ARV for PMTCT prophylaxis.

Participants will be followed for 24 weeks after birth.

5.2 Study Drug Formulation and Storage

5.21 Description of Formulation of Raltegravir (Isentress®, RAL)

Raltegravir oral granules for suspension will be provided in foil pouches with each pouch containing 100 mg of study drug. Raltegravir oral granules are for suspension in water only. After reconstitution the final concentration is 10 mg/mL.

Note: Final concentration was changed from 20 mg/mL to 10 mg/mL in v.1 LOA#3.

The oral granules for suspension formulation has a banana flavor, and contains the following: raltegravir, hydroxypropylcellulose, ethylcellulose, Opadry I film coat blend, sucralose, monoammonium glycyrrhizinate, natural banana flavor, crospovidone, mannitol, Avicel Cl-611, and magnesium stearate.

5.22 Storage Instructions

Stability studies for the oral granules formulation are ongoing. Raltegravir oral granules pouches should be securely stored in a dry place between 15 to 30°C (59 to 86°F). Do not refrigerate, freeze, or put on ice. The foil pouches should remain sealed until used. Refer to Appendix IV for instructions for the caregiver.

5.3 Drug Supply, Distribution, and Pharmacy

5.31 Study Product Acquisition/Distribution

RAL oral granules will be supplied by Merck Research Laboratories. RAL 100 mg sachets of oral granules for suspension will be available through the Clinical Research Products Management Center (CRPMC). The site pharmacist can obtain the study product for this study by following the instructions in the manual *Pharmacy Guidelines and Instructions for DAIDS Clinical Trials Networks* in the section: Study Product Management Responsibilities.

Ancillary supply kits that include mixing cups, spatulas, and syringes for preparation and administration of the oral granules for suspension as well as dosing and disposal instructions are also available through the CRPMC.

The other components of the antiretroviral (ARV) regimen will not be supplied by the study and should be initiated per local standard of care. ARV regimen must be obtained outside of this study.

5.32 Study Product Accountability

The site pharmacist is required to maintain complete records of all study products received from the NIAID CRPMC and subsequently dispensed. All unused study product must be returned to the NIAID CRPMC (or as otherwise directed by the sponsor) after the study is completed or terminated. The procedures to be followed are provided in the manual Pharmacy Guidelines and Instructions for DAIDS Clinical Trials Networks in the section Study Product Management Responsibilities.

6.0 PARTICIPANT MANAGEMENT

6.1 Toxicity Management

The DAIDS Table for Grading the Severity of Adult and Pediatric Adverse Events (DAIDS AE Grading Table), Version 1.0, December 2004, Clarification August 2009, which is available on the RSC website at http://rsc.tech-res.com/safetyandpharmacovigilance will be used for screening eligibility and for grading toxicities when specifically noted below. Alternate explanations for clinical or laboratory abnormalities that may at first appear to be related to the study agents(s) must be explored. Expedited Adverse Event (EAE) reporting must be done according to Section 7.1

*NOTE: SPECIAL MANAGEMENT PROCEDURES FOR BILIRUBIN WILL BE USED ACCORDING TO SECTION 6.13

6.11 Reporting of Suspected Adverse Drug Reactions (for bilirubin management, see Section 6.13)

A suspected adverse drug reaction (SADR) is an adverse event that could potentially have a causal relationship to the study agent (definitely, probably, or possibly related). General guidelines for study drug suspected adverse drug reactions SADRs are provided below.

- Grade 1 - All study drug SADRs should be recorded on Case Report Forms (CRFs) at each visit.
- Grade 2 - All study drug SADRs should be recorded on CRFs at each visit. Inform team monthly whether toxicity has resolved or not.
- Grade 3 or 4 -
    - The protocol team must be notified of study drug SADRs within 24 hours at impaact.teamp1110@fstrf.org.
    - The investigator should confirm all Grade 3 and 4 study drug SADR laboratory test results as soon as possible but always within 72 hours.
    - Expedited Adverse Event (EAE) reporting must be done according to Section 7.1.

6.12 Management of RAL toxicity (for bilirubin management, see Section 6.13)

Cohort 1:

Grade 1 - The second RAL dose can be administered; routine monitoring.
Grade 2 - The second RAL dose can be administered; monitor closely with more frequent visits; as per site PI, and work-up to exclude other causes.
Grade 3 - The second RAL dose should be withheld while awaiting confirmatory results; other PMTCT antiretroviral prophylaxis may be continued. If Grade 3 abnormalities are confirmed, contact the study team and the second RAL dose should be withheld until the abnormalities are Grade 2 or below unless the clinician, with the approval of the study team and medical officer, believes that the event is unlikely related to RAL administration and that antiretroviral therapy (including RAL) should be continued.
Grade 4 - The second RAL dose should be withheld and concomitant antiretrovirals used for PMTCT should also be held and the study team contacted awaiting results of the confirmatory test unless the clinician, with the approval of the study team and medical officer, believes that withholding antiretroviral prophylaxis (including or excluding RAL) would be harmful to the participant and that continuing them would pose little additional risk. If the Grade 4 abnormality is confirmed but the adverse event is determined to be unrelated to RAL, the investigator should contact the team to determine if and when the second RAL dose should be administered; other antiretroviral drugs used for PMTCT prophylaxis can be restarted when abnormalities are Grade 2 or below unless the clinician, with the approval of the study team and medical officer, believes that the event is unlikely related to PMTCT prophylaxis. If the Grade 4 abnormality is confirmed and

thought to be related to RAL the second RAL dose should not be given and the investigator should contact the study team for further instructions.

Attempt to confirm any unexpected laboratory results as soon as possible, but always within 72 hours of the recognition of the event. The protocol team should be notified of the results at impaact.teamp1110@fstrf.org

*NOTE: In the event of treatment discontinuation, participants will be asked to continue to be followed until the 24 week visit.

Cohort 2:

Grade 1 - Continue RAL; routine monitoring.
Grade 2 - Continue RAL; monitor closely with more frequent visits; as per site PI, work-up to exclude other causes.
Grade 3 - Continue RAL while awaiting confirmatory results unless the clinician believes that remaining on RAL would be unsafe. Other PMTCT antiretroviral prophylaxis may be continued pending confirmatory testing.
If Grade 3 abnormalities are confirmed, contact the study team, and the RAL should be withheld and other antiretroviral drugs used for PMTCT prophylaxis should be held until the abnormalities are Grade 2 or below unless the clinician, with the approval of the study team and medical officer, believes that the event is unlikely related to RAL administration and/or that PMTCT prophylaxis should be continued.
Grade 4 – Contact the study team. Hold RAL and concomitant antiretrovirals used for PMTCT immediately unless the clinician, with the approval of the study team and medical officer, believes that withholding antiretroviral prophylaxis (including RAL) would be harmful to the patient and that continuing them would pose little additional risk. Attempt to confirm any unexpected laboratory results as soon as possible, within 72 hours of awareness of the event. The protocol team should be notified of the results at impaact.teamp1110@fstrf.org.

For confirmed drug related Grade 4 SADRs, RAL should be permanently discontinued. For Grade 4 adverse events that are determined to be unrelated to study drug, the investigator should contact the team to determine when RAL may be safely resumed.

*NOTE: In the event of treatment discontinuation, participants will be asked to continue to be followed until the 24 week visit.

6.13 Bilirubin Management

Due to the potential for interactions between RAL and bilirubin affecting RAL pharmacokinetics and bilirubin elimination and toxicity (see Section 1.27) special management procedures for bilirubin will be used. Bilirubin concentrations and interventions to lower bilirubin (such as phototherapy and exchange transfusion) will be recorded but bilirubin will be graded according to the DAIDS Toxicity Table and

managed according to the schema described below. Hyperbilirubinemia will be managed by clinical caregivers according to local standards of care. If total bilirubin is >16.0 mg/dL or an exchange transfusion is performed, no further RAL doses will be administered but participants will continue to be followed for safety assessments. Participants who receive phototherapy may continue to receive study drug as long as total bilirubin concentration ≤16.0 mg/dL.

The protocol team must be notified if study drug is held due to elevated bilirubin or of Grade 3 or 4 hyperbilirubinemia determined to be at least possibly related within 24 hours of site awareness at impaact.teamp1110@fstrf.org.

6.14 Follow-up of Abnormal Events and Laboratory Values

All abnormal clinical events and laboratory values, not related or probably not related (non-SADR events), occurring in enrolled participants will be followed closely until resolution. The urgency and frequency of repeat evaluations will depend on the clinical significance of the specific abnormality. Study clinicians will provide appropriate clinical management of adverse events according to their best medical judgment and local practice. For any persistent Grade 3 or 4 clinical or laboratory study drug SADRs, evaluations should be repeated approximately weekly (or more frequently if necessary) until toxicity falls to Grade 2 or below and as appropriate thereafter. Alternate explanations will be sought for all clinical and laboratory abnormalities.

6.2 Study Management Plan

The Data Management Center (DMC) will maintain a web page informing sites as to the availability of enrollment slots per cohort. The protocol team, including the co-chairs, medical officers, pharmacist, and pharmacologist, will respond to sites who contact the team with questions regarding toxicity management, dosing, or other issues within one business day. Team responses will include the entire team.

Sites will be given 7 days to respond to queries to allow the team to meet Merck data delivery requirements. Sites will be contacted by the protocol data manager or co-chairs regarding any query responses or data issues that are outstanding after 7 days.

All RAL dose modifications will be recommended by the protocol team. See Section 6.21 for information on dose modifications for Cohorts 1 and 2. The protocol team will review the PK data for each participant as part of an on-going evaluation of the dosing regimen to determine whether a dose adjustment is required. The study team will conduct an extensive review of the data obtained from participants enrolled in Cohort 1 before opening enrollment for Cohort 2. Dose recommendations for Cohort 2, and supporting dose finding data from Cohort 1, must be approved by the Medical Officers, IMPAACT representatives and Merck representatives. If all agree, Cohort 2 opens to enrollment. If there is disagreement among IMPAACT, Merck and/or the study team, a Study Monitoring Committee (SMC) will be

appointed to review the data understanding that Cohort 2 will not open without Merck approval. See Section 8.51 for more details on SMC monitoring of study data and progress.

The P1110 team will notify sites of any change in dose and/or dosing frequency through an appropriate mechanism. Dosing tables found in Appendix III will be used for dosing changes and are based on weight bands.

6.21 Cohort Dosing Management

Cohort 1
A minimum of 12 neonates will be enrolled into Cohort 1 to provide data for 12 PK evaluable neonates. All neonates enrolled in Cohort 1 will receive, per Section 5.11, oral granules for suspension as two separated single doses, the first given within 48 hours of birth and a second dose administered at 7 to 10 days of life, with PK assessed after each dose. The PK results and safety will be assessed through the regular team monitoring (done at least every 4 weeks) and at full cohort accrual to ensure that the RAL concentrations in each individual do not exceed a C_{max} of 19,630 nM (8,720 ng/mL) and do not exceed an AUC12 of 63,050 nM-hr (28,000 ngxh/mL), and that no life-threatening toxicities probably related to RAL administration have occurred.

Based on the team assessment of the PK data and review of safety information, the dose may be modified for the subsequent participants receiving the 2 doses in Cohort 1, in which RAL dosing may be modified in the range of 1.5 mg/kg to 6 mg/kg per dose.

Cohort 2
After enrollment of participants into Cohort 1 RAL-exposed or RAL-naïve group is completed with acceptable safety and an appropriate multiple dose regimen from birth to 6 weeks is determined, Cohort 2 will open for the respective group. The initial multiple dose regimen for Cohort 2 may be determined based on results from P1097, P1110 Cohort 1, P1066 (Cohorts IV and V), P1026s, and PK modeling and simulation. The PK targets for Cohort 2 are geometric mean target exposures for:

- once-daily dosing of AUC24 of 28-90 µMxhr (12-40 mgxh/L) and an approximate GM trough (C24hr) > 75nM (33ng/mL)
- twice-daily dosing of AUC12 of 14-45 µMxhr (6-20 mgxh/L) and an approximate GM trough (C12hr) > 75nM (33ng/mL)

A minimum of 20 neonates will be enrolled into Cohort 2 to provide data for 20 PK evaluable infants. The dosing for RAL is further detailed in Section 5.11 of this protocol.

Cohort 2 dosing may be modified based on observed pharmacokinetic data coupled with modeling and simulation to determine the optimal multiple dose regimen capable of meeting the selected PK targets: If the minimum targets above are not achieved, the dose will be increased in linear fashion.

6.3 Criteria for Treatment Discontinuation

The participant will have study drug discontinued for the following reasons:

6.31 The participant requires treatment with medications that are disallowed while on this study.

6.32 The participant experiences dose limiting or intolerable drug toxicity as defined in Section 6.1.

6.33 New data become available that indicate treatment should be discontinued.

6.34 It is determined by the study team or the treating healthcare providers that continued study treatment with RAL is not in the best interest of the participant and the participant will be followed off study treatment on study.

6.4 Permanent Study Discontinuation

The participant will be discontinued from the study for the following reasons:

6.41 The parent or legal guardian refuses further treatment and/or follow-up evaluations.

6.42 The investigator determines that further participation would be detrimental to the participant's health or well-being.

6.43 The parent or legal guardian fails to comply with the study requirements so as to cause harm to the participant or seriously interfere with the validity of the study results.

The study may be discontinued at any time by the IMPAACT network, the Office for Human Research Protections (OHRP), the National Institutes of Health (NIH), the local IRB or EC, U.S. Food and Drug Administration (FDA), the pharmaceutical sponsors, or other 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 RSC website at http://rsc.tech-res.com/clinical-research-sites/safety-reporting/manual.

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 NIAID CRMS Support at CRMSSupport@niaid.nih.gov. Site queries may also be sent from within the DAERS application itself.

Where DAERS has not been implemented, sites will submit expedited AEs by documenting the information on the current DAIDS EAE Form. This form is available on the RSC website: http://rsc.tech-res.com/clinical-research-sites/safety-reporting/manual. For questions about EAE reporting, please contact the RSC (DAIDSRSCSafetyOffice@tech-res.com).

7.2 Reporting Requirements for this Study

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

The study agent for which relationship assessments are required is raltegravir.

In addition to reporting all SAEs as defined above, other events that sites must report in an expedited fashion include bilirubin concentrations >16.0 mg/dL, exchange transfusions for hyperbilirubinemia, all malignancies, seizures, IRIS events, and hepatotoxicities whether or not symptomatic or related to study drug, and all other Grade 3 or 4 related toxicities for which a relationship to study drug cannot be ruled out.

Over doses will be reported on a quarterly basis to the pharmaceutical sponsor.

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

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

7.3 Grading Severity of Events

The Division of AIDS Table for Grading the Severity of Adult and Pediatric Adverse Events (DAIDS AE Grading Table), Version 1.0, December 2004, Clarification August 2009, must be used and is available on the RSC website at http://rsc.tech-res.com/clinical-research-sites/safety-reporting/daids-grading-tables

7.4 Expedited AE Reporting Period

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

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

8.0 STATISTICAL CONSIDERATIONS

8.1 General Design Issues

This is a Phase I multi-center, open label, non-comparative study to assess the safety and pharmacokinetics of raltegravir administered to full-term neonates, aged ≤ 48 hours (protocol Version 1.0) and ≤ 60 hours (protocol Version 2.), at risk of acquiring HIV-1 infection. The goal is to determine a dose of raltegravir, that is safe, well-tolerated and meets PK targets, administered as an oral granules suspension to neonates and infants in the first 6 weeks of life. Both the mother and the infant will be enrolled, with the mother having only a study entry visit and the infant followed through 24 weeks of life.

Safety data will include signs/symptoms, diagnoses and laboratory test results, which will include results of evaluations specified in the protocol and results from the infant's clinical care. Infants will be evaluable for safety analysis if they received at least one dose of raltegravir. For CRF reporting and analysis of safety data, the sites' assessments of AE relationship to raltegravir will be used. However, with regards to participant safety and PK evaluations which will support the selection of a dose for a given cohort, the protocol team will also have input as to the causality and drug relation of specific adverse experiences. Regular monitoring of RAL safety, which could result in dose or study modification, described in detail in Section 8.5.

Approximately 50 infants and their mothers will be enrolled in order to have a minimum of 12 and 20 PK evaluable participants in Cohorts 1 and 2, respectively. If a participant has unevaluable PK data, which reflects uncertainty about appropriate exposure to the study medication then the participant will be excluded from PK analyses and will be replaced.

The study design consists of two cohorts with the following dosing regimens of raltegravir in addition to standard PMTCT:

<u>Cohort 1</u>:

Raltegravir as oral granules for suspension, per Section 5.11 administered as a single dose within 48 hours of birth, with a second dose administered at 7-10 days of life

Cohort 2:

Raltegravir as oral granules for suspension, per Section 5.11 administered as daily dosing through 6 weeks of life with first dose given within 48 hours of birth for RAL-naïve infants and between 12 and 60 hours of birth for RAL-exposed infants.

Study accrual will initially be for Cohort 1 only with accrual to Cohort 2 contingent upon neonates in Cohort 1 successfully meeting the safety criteria and providing adequate information for Cohort 2 initial dosing. Initial dosing for Cohort 2 RAL-naïve and RAL-exposed groups will be determined using modeling and simulation analyses based on P1110 available data and data from IMPAACT P1097, P1066 (Cohorts IV and V) and P1026s.

Criteria for defining PK evaluable neonates, along with descriptions of PK parameters and analyses can be found in Section 9.

8.2 Outcome Measures

(Outcome Measures are for infants only; maternal data are to be used as covariates, not as outcomes)

8.21 Primary Endpoints for Cohorts 1 and 2

Toxicity Endpoints: Toxicity from study entry through 6 weeks of life

- Adverse events of Grade 3 or 4 severity or death (primary safety endpoint for final analysis)
- Suspected adverse drug reaction (SADR) of Grade 3 or 4 severity or death (primary safety endpoint for dose finding guidelines described in Section 8.52) but secondary safety endpoint for the analyses described in Section 8.71)

Pharmacokinetic Endpoints: (See Section 9.0: Clinical Pharmacology Plan)

8.22 Primary Response Variables for Cohorts 1 and 2 Pharmacokinetic parameters (See Section 9.0)

8.23 Secondary toxicity endpoints for Cohorts 1 and 2: Toxicity from study entry weeks through 24 weeks of age

- Adverse events of Grade 3 or 4 severity or death
- Suspected adverse drug reaction (SADR) of Grade 3 or 4 severity or death

8.24 Secondary Response Variables for Cohorts 1 and 2

- UGT1A1 genotype(presence or absence of *28/*28 genetic variant)
- SLCO1B3 (rs2117032-C/T) genotype
- Hyperbilirubinemia defined as total bilirubin exceeding 16.0 mg/dL or infant receiving phototherapy, or transfusion therapy, or other therapies for hyperbilirubinemia

8.3 Randomization and Stratification

There will be no randomization. The infant's RAL exposure in utero will be an accrual and an analysis stratification factor.

8.4 Sample Size and Accrual

Under Protocol Version 1.0, the study target enrollment was approximately 50 infants and their mothers in order to accrue minimum of 12 and 20 PK evaluable neonates in Cohorts 1 and 2, respectively. These sample sizes have been determined on the basis of data needed for the PK analysis. The team estimated it will take 4 years to accrue 32 evaluable participants.

To date, Cohort 1 RAL-naïve, Cohort 1 RAL-exposed, and Cohort 2 RAL-naïve groups were fully accrued under protocol Version 1.0. Cohort 2 RAL-exposed group will open to accrual under protocol Version 2.0 with a minimum accrual of 8 infants. The team estimates it will take 1 year to accrue 8 evaluable participants.

8.5 Monitoring and Safety Guidelines

The team will assess safety on routine monitoring conference calls which will occur at least every 4 weeks for Cohorts 1 and 2. Safety analyses will be performed at full accrual to Cohort 1, at interim analysis when 8 participants have been accrued to Cohort 2 and at full accrual to Cohort 2, evaluating whether the safety guidelines specified in Section 8.52 have been met. For dose finding purposes, infants who have been excluded from the PK analyses, due to evidence of problematic exposure to the study medication, will also be excluded from evaluation of the safety guidelines.

The attribution of relationship of serious adverse events to study drug for the purposes of employing the start, stop and pause rules will be by consensus among the site investigator, study team (which includes representatives from Merck) and DAIDS medical officer; if unanimous agreement between them cannot be established, the attribution made by the majority of these 3 persons or entities will be used. Gradation of relationship will use the following terminology: Not related, probably not related, possibly related, probably related or definitely related.

8.51 Monitoring of Safety Data by the Protocol Team and the Study Monitoring Committee (SMC)

Since Phase I studies are not routinely reviewed by a Data and Safety Monitoring Board (DSMB), it is the responsibility of the protocol team to interpret safety data, and make decisions regarding SADRs that are needed to protect participants 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 72 hours of the time at which the results of the laboratory tests or clinical examinations become available.

Reports compiled by the Data Management Center (DMC) will be reviewed and discussed by the Protocol Team on conference calls held at least every 4 weeks. Data on accrual, pharmacokinetics and toxicity will be reviewed.

In addition, an independent IMPAACT Study Monitoring Committee (SMC) will review this study regularly, following policies described in the IMPAACT Manual of Procedures. The composition of the SMC will include the SMC Chair; IMPAACT Chair or Vice Chair; IMPAACT Treatment Scientific Committee Chair or Vice Chair; representatives of the IMPAACT Operations Center, Statistical and Data Management Center, and Laboratory Center; and representatives of NIAID and NICHD.

SMC reviews will occur at least annually and on a more frequent or *ad hoc* basis if any safety issues or concerns arise. *Ad hoc* reviews may also be triggered by temporary suspension of accrual or pausing administration of study product due to safety concerns, as outlined in Section 8.52 below. Based on any of its reviews, the SMC may recommend that the study proceed as currently designed, proceed with design modifications, or be discontinued. The SMC may also provide operational recommendations to help address any study implementation challenges that may be identified during their reviews.

The SMC will monitor study progress (see Section 8.6), quality of study conduct, and participant safety. The SMC will generally review the same types of data reports as the Protocol Team. For *ad hoc* or triggered safety reviews, more limited data may be reviewed, focusing on the events that triggered the reviews.

8.52 Guidelines for the Evaluation of Safety Data (See Section 9.0 for Pharmacokinetic Guidelines)

Accrual to Cohort 1 will be temporarily suspended if:

- any participant has a new life threatening event or death judged to be a Suspected Adverse Drug Reaction (SADR) or if any of the participants has a new Grade 4 event that may not be judged to be life-threatening but is judged to be probably or definitely attributable to the study medication;

OR

- at least 4 of the participants have had treatment discontinuation due to non-life threatening Grade 3 or 4 severity SADR, judged to be at least possibly treatment related.

Accrual to Cohort 2 will be temporarily suspended if:

- any participant has a new life threatening event or death judged to be an SADR or if any of the participants has a new Grade 4 event that may not be judged to be life-threatening but is judged to be probably or definitely attributable to the study medication;

OR

- at least 3 of the first 8 participants to be included in the Cohort 2 RAL-unexposed group interim analysis have had treatment discontinuation due to non-life threatening Grade 3 or 4 severity SADR, judged to be at least possibly treatment related;

OR

- if after the Cohort 2 RAL-unexposed group interim analysis,
  - there was no dose adjustment and at least 6 of 20 participants to be included in Cohort 2 final analysis have had treatment discontinuation due to non-life threatening Grade 3 or 4 severity SADR, judged to be at least possibly treatment related; or
  - there was a dose adjustment and at least 4 of the 12 participants on the final dose for Cohort 2 have had treatment discontinuation due to non-life threatening Grade 3 or 4 severity SADR, judged to be at least possibly treatment related.

Following any temporary suspension of accrual, the 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 team, including the study chair, the DAIDS medical officer of record and Merck representatives, agrees that the study drug is likely to be safe for additional participants, they may decide to allow accrual to resume. However, the P1110 SMC will be informed of this decision, and the study will not reopen without the approval of this committee. The SMC may ask for any data it may want to review before making its decision. Regulatory agencies will be notified of the event and the team's and SMC's decision.

8.521 Final Evaluation of Cohort 1 Safety Data

At final evaluation of the Cohort 1 RAL-exposed or RAL- naïve groups, safety guidelines will be assessed on infants on the final dose for each group in Cohort 1 using safety data through week 6 of life. If none of the participants has experienced a new life-threatening event or death judged to be an SADR or a new Grade 4 event that is probably or definitely attributable to the study medication; and no more than 25% of the participants have had treatment discontinuation due to non-life threatening Grade 3 or 4 severity SADR at least possibly related to the study drug, then final dose in Cohort 1 has passed the safety guidelines. Otherwise the team will review the

safety data and will consult with the P1110 SMC to determine whether it is safe to proceed to Cohort 2 and under what conditions this will be allowed to occur.

8.522 Interim Evaluation of Cohort 2 RAL-naïve Group Safety Data

The safety and PK of the starting dose for Cohort 2 will be assessed on the first 8 participants based on safety data through 6 weeks of life, for the purpose of determining whether accrual to the full cohort can proceed and determining if any adjustment in dosing may be necessary (see Section 9.0 for PK evaluation.). Accrual will be stopped while this interim analysis is being performed. Dosing decisions will depend upon severity of adverse events, attribution of these events to the study drug and PK data.

If none of the 8 participants has experienced a new life-threatening event or death judged to be an SADR or a new Grade 4 event that is probably or definitely attributable to the study medication; and no more than 2 of the participants have had treatment discontinuation due to non-life threatening Grade 3 or 4 severity SADR at least possibly treatment related to the study drug, then full accrual to Cohort 2 can proceed. Otherwise the team will review the safety data and will consult with the P1110 SMC to determine whether it is safe to complete full enrollment into Cohort 2 and under what conditions this will be allowed to occur.

8.523 Final Evaluation of Cohort 2 Safety Data

The safety guidelines will be assessed on the final dose for each group in Cohort 2 based on safety data through week 6 of life. If none of the participants has experienced a new life-threatening event or death judged to be an SADR or a new Grade 4 event that is probably or definitely attributable to the study medication and no more than 25% of the participants on the final dose for Cohort 2 have had treatment discontinuation due to non-life threatening Grade 3 or 4 severity SADR at least possibly treatment related to the study drug, then final dose in Cohort 2 has passed the safety guidelines.

8.53 Probabilities of Failing the Safety Guidelines

The safety guidelines will be assessed at final analysis of Cohort 1, at interim analysis of Cohort 2 and at final analysis of Cohort 2, based on safety data through 6 weeks of life on samples of 12, 8, and maximum of 20 infants, respectively. Given these small sample sizes, the information available for safety decisions will be imperfect. Two types of sampling errors are possible:

1) In a group where the true rate of toxicity is too high to warrant increased exposure to the current starting dose of the medication, the sample data may pass the safety guidelines;

2) In a group where the true rate of toxicity is low enough that further exposure to the current starting dose is warranted, the sample data may fail the guidelines.

The extent to which the safety guidelines protect against the errors described above can be assessed by examining various hypothetical rates of "true toxicity" which could occur, if the study medication were used extensively among the participant population at the dose level under question. The hypothetical situations presented in Tables 11,12, and 13 are for the sample sizes of the 12 participants in Cohort 1, the first 8 participants for the interim analysis for Cohort 2, and 20 participants for final analysis of Cohort 2, respectively. Should there be a dose change following the interim analysis of Cohort 2, then only the 12 remaining participants will be exposed to the new dose; in that case the probabilities presented in Table 11 will apply. Tables 11,12 and 13 show the probabilities of failing the safety guidelines for a range of conditions under which a given dose level would cause a high incidence of severe and life threatening SADRs to conditions under which severe SADRs would be relatively rare and would not be life threatening. For each of these hypothetical situations, we assume that the sample is drawn from the participant population and that the safety guidelines for Cohort 1 (Section 8.521), interim analysis for Cohort 2 (8.522) and final analysis for Cohort 2 (Section 8.523) are followed.

Table 11.
Probability of Failing Safety Guidelines for a Sample of 12 Participants for Final Analysis of Cohort 1 Under Potential Rates of True Toxicity

True Toxicity Rates		Probability of Failing Safety Guidelines
Non-life threatening SADR that would result in treatment discontinuation, excluding Grade 4 events probably or definitely attributable to study medication	Death or life-threatening SADR or Grade 4 events probably or definitely attributable to study medication	
0.50	0.00	0.93
0.50	0.05	0.97
0.50	0.25	1.00
0.25	0.00	0.35
0.25	0.05	0.67
0.25	0.25	0.99
0.05	0.00	0.00
0.05	0.05	0.46
0.05	0.25	0.97
0.00	0.05	0.46
0.00	0.25	0.97

Table 12.
Probability of Failing Safety Guidelines for a Sample of 8 Participants for Interim Analysis of Cohort 2 under Potential Rates of True Toxicity

True Toxicity Rates		
Non-life threatening SADR that would result in treatment discontinuation, excluding Grade 4 events probably or definitely attributable to study medication	Death or life-threating SADR or Grade 4 events probably or definitely attributable to study medication	Probability of Failing Safety Guidelines
0.50	0.00	0.86
0.50	0.05	0.93
0.50	0.25	1.00
0.25	0.00	0.32
0.25	0.05	0.57
0.25	0.25	0.95
0.05	0.00	0.01
0.05	0.05	0.34
0.05	0.25	0.90
0.00	0.05	0.34
0.00	0.25	0.90

Table 13.
Probability of Failing Safety Guidelines for a Sample of 20 Participants for Final Analysis of Cohort 2 Under Potential Rates of True Toxicity

True Toxicity Rates		Probability of Failing Safety Guidelines
Non-life threatening SADR that would result in treatment discontinuation, excluding Grade 4 events probably or definitely attributable to study medication	Death or life-threatening SADR or Grade 4 events probably or definitely attributable to study medication	
0.50	0.00	0.98
0.50	0.05	1.00
0.50	0.25	1.00
0.25	0.00	0.38
0.25	0.05	0.80
0.25	0.25	1.00
0.05	0.00	0.00
0.05	0.05	0.64
0.05	0.25	1.00
0.00	0.05	0.64
0.00	0.25	1.00

For example, Table 11 shows that for a sample of size 12, there is a 97% chance of failing the safety guidelines under conditions in which the true rate of life-threatening toxicity is 5% and the rate of non-life threatening SADR is 50%. Assuming that it would be undesirable to accrue additional participants at a dose that had these true rates of adverse events, the 3% chance of NOT failing the safety guidelines would represent the probability of error.

8.6 Accrual Rate Evaluation

Accrual to this study will be monitored by the IMPAACT leadership in accordance with standard operating procedures. The team monitored site registration and accrual to Cohort 1 RAL-naïve, Cohort 1 RAL-exposed groups, and Cohort 2 RAL-naïve group as specified in protocol Version 1.0. For Cohort 2 RAL-exposed group, if less than 4 infants have been accrued after 8 months of this study group opening, the team will re-assess the reasons for low accrual, and will possibly amend or close the protocol accordingly.

8.7 Analyses

8.71 Primary and Secondary Safety Analyses of the Primary Safety Endpoints

To evaluate the safety and tolerability of RAL through 6 weeks of life, descriptive statistics will be calculated summarizing the safety data from study entry through 6 weeks of life from all safety evaluable infants in the four study groups: (i) Cohort 1 RAL-naïve, (ii) Cohort 1 RAL-exposed, (iii) Cohort 2 RAL-naïve, and (iv) Cohort 2 RAL-exposed infants. Overall summary statistics for the cohort will be provided if the data suggests that there is no difference between RAL-naïve and RAL-exposed infants within that cohort. The primary safety analysis will be the calculation of the point and 2-sided 90% confidence interval (CI) using the Clopper-Pearson exact method estimates of the proportion of infants meeting the primary toxicity endpoint of adverse event Grade 3 or 4 severity or death. Secondary safety analyses will include point and 90% CI estimates of infants with a SADR of Grade 3 or 4 severity or death. Table 14 shows the precision with which confidence intervals around proportions of serious adverse events can be estimated, for the 12 participants in Cohort 1 and for the 8 and 20 participants in the interim and final analyses for Cohort 2.

Table 14
90% Confidence Intervals Around Potential Proportions of Infants Meeting a toxicity Endpoint[a]

Number of participants	Proportion of participants meeting toxicity endpoint	Clopper-Pearson 90% CI
8	0.00	(0.00, 0.37)
	0.25	(0.03, 0.65)
	0.50	(0.16, 0.84)
12	0.00	(0.00, 0.26)
	0.25	(0.05, 0.57)
	0.50	(0.21, 0.79)
20	0.00	(0.00, 0.17)
	0.10	(0.01, 0.32)
	0.20	(0.06, 0.44)
	0.50	(0.27, 0.73)

[a] *Clopper-Pearson exact confidence interval estimates using SAS Version 9.2.*

The primary safety analyses population will include all infants who have had at least one dose of raltegravir. For Cohort 2 RAL-naïve group, if there was dose adjustment after the interim analysis, a sensitivity analysis will be performed on infants who were enrolled after dose adjustment and only took the adjusted dose. Patients who had an idiosyncratic dose adjustment, based on extreme PK data, will be included in the primary analysis.

However, this adjustment will be acknowledged in the narrative part of the report where these results are described.

8.711 Secondary Analyses

To assess the safety and tolerability of RAL through 24 weeks of life, descriptive statistics will be calculated summarizing the proportion of infants who had an adverse event of Grade 3 or 4 severity or death based on safety data from study entry through 24 weeks of age on all safety evaluable infants in each of the four study groups. A similar analysis will be done to summarize proportion of infants who had an SADR of Grade 3 or 4 severity or death.

To investigate the relationship between neonatal raltegravir elimination and UGT1A-1 genotype, participants will be divided into subgroups, based on whether or not they exhibit polymorphisms on UGT1A-1. Descriptive analyses will be performed to compare these subgroups with respect to measures of central tendency and dispersion for raltegravir AUC.

Similar descriptive analyses will also be performed to investigate the association of UGT1A1 (*28/*28) and SLCO1B3 (rs2117032-C/T) with hyperbilirubinemia. If the sample size and the data distributions make this possible, a logistic regression model predicting for probability of neonatal hyperbilirubinemia with UGT1A1 (*28/*28) genotype, SLCO1B3 (rs2117032-C/T) genotype, gestational age and gender as predictors will be fitted on the pooled data across the two cohorts. Note that the sample size may be too small and/or there may be insufficient cases of hyperbilirubinemia to make this possible. If this analysis can be done, it will have minimal power, but the size and directionality of effects will be compared with those predicted on the basis of previous findings.

9.0 CLINICAL PHARMACOLOGY PLAN

Protocol exposure limits from non-compartmental analysis for each participant were Cmax ≤ 8723.6 ng/mL and AUC12 ≤ 28 mg*h/L. A population PK model was developed incorporating cohort 1 PK data with RAL concentration data from 24 infants and children ages 4 weeks to < 2 years enrolled in IMPAACT P1066, a phase I/II, multicenter, open-label non-comparative intensive PK treatment study of RAL in infants and children [20]. Population modeling using PsN/3.7.6, NONMEM/7.3.0 and R/3.1.0 was performed to estimate RAL PK parameters, which were then used in simulations of potential dosing regimens. The regimen that best met PK exposure targets (Ctrough, Cmax, AUC) defined for safety and efficacy from studies in older infants, *children*, and adults was selected for evaluation Cohort 2 infants (RAL-exposed and RAL- naïve).

9.1 Pharmacology Objective

This study is designed to assess the pharmacokinetics of raltegravir in newborn infants. Based on pharmacokinetic data from IMPAACT P1097 and P1066, a starting dose of 3 mg/kg has been chosen, which is 25% of the total daily dose (6 mg/kg BID) currently under study in infants 4 weeks to <6 months of age in IMPAACT P1066. In Cohort 1 of the study, raltegravir will be administered as a single dose using 3 mg/kg of the oral granules for suspension within 48 hours of birth, and a second dose will be administered at 7 to 10 days of life.

PK evaluable infants are those whose PK results provide data on the primary pharmacokinetic parameters of interest.

The PK targets for Cohort 1 are:

- RAL concentrations in each individual that do not exceed a C_{max} of 19.63 μM and do not exceed an AUC12 of 63.05 μM-hr

Prior to the start of Cohort 2, the initially proposed dosing regimen was modified based on observed pharmacokinetic data, including data from the Cohort 1 RAL-naïve and RAL-exposed groups, coupled with modeling and simulation to determine the optimal multiple dosing regimen capable of meeting the selected PK targets, as well as the optimal PK sampling scheme for that dosing regimen.

Based on these data, in addition to standard of care ARV for PMTCT prophylaxis, Cohort 2 will receive the following dosing regimen (refer to tables in Appendix III):

- 1.5 mg/kg once daily during Days 1-7 of life (week 1)
- 3.0 mg/kg twice daily during Days 8-28 of life (weeks 2-4)
- 6.0 mg/kg twice daily during Days 29-42 of life (weeks 5-6)

The PK target AUC will depend on whether the drug is dosed once or twice daily. The PK target GM trough is the same for both once daily and twice daily dosing.

The PK targets for Cohort 2 are target exposures for:

- once-daily dosing of AUC24 of 28-90 μMxhr (12-40 mgxh/L) and an approximate GM trough (C24hr) > 75nM (33ng/mL)
- twice-daily dosing of AUC12 of 14-45 μMxhr (6-20 mgxh/L) and an approximate GM trough (C12hr) > 75nM (33ng/mL)

9.2 Primary and Secondary Data

The primary data to be collected are plasma raltegravir concentrations for pharmacokinetic parameter estimation. All PK samples will be registered in the Lab Data Management System (LDMS) database, and will be sent to the University of Alabama (UAB) Laboratory. The study database will be kept up to date by close tracking of samples. Intensive PK sample

assays and pharmacokinetic calculations will be performed on a regular basis in the UAB Laboratory so that ongoing interim analysis can be done by the protocol team.

9.3 Study Design, Modeling and Data Analysis

First dose and multiple dose raltegravir concentration-time data will be analyzed using standard non-compartmental methods. Whole blood for determination of raltegravir in plasma will be collected according to cohort. These sample collection times may change depending upon the ongoing analyses of the pharmacokinetic results.

Cohort 1
Pharmacokinetic sampling for infants in Cohort 1 included the following:

Dose 1 (within 48 hours of birth): Pre-dose, and 1-2 hours post-dose, 4-8 hours post-dose, 12 (±1) hours post-dose, and 24 (±1) hours post-dose.

Day 3-4 of life: One random PK sample will be obtained with laboratory evaluations.

Dose 2 (7-10 days of life): Pre-dose, and 1-2 hours post-dose and 24 (±1) hours post-dose.

*Note: For the 12 and 24 hour PK sampling time points, it is necessary to collect blood samples within the window of ±1 hour for the accurate calculations of PK parameters of raltegravir. However, in the event that a sample collection in this window is not possible, the sample should be obtained within ±2 hours and this deviation from the sampling instructions should be recorded.

Modeling and simulation will be utilized after the completion of each RAL-exposed or RAL-naïve group in Cohort 1 to generate a multiple dosing scheme for the respective group in Cohort 2. Specifically, data may be integrated from P1110 Cohort 1, P1097, P1066 (Cohorts IV and V), P1026s, and adult oral granule data to construct a population PK model capable of describing the raltegravir pharmacokinetics of oral granules for suspension. A two-compartment model will be fit using NONMEM version VII software, where various population attributes including, but not limited to, age, weight, sex and creatinine clearance will be examined to determine their influence on the pharmacokinetics of raltegravir, including the absorption, bioavailability and clearance. Both intensive and sparse PK data from the above mentioned studies in both adults and children will be utilized to maximize the available information on the oral granules formulation and provide a rich and diverse dataset with regards to patient population, which should enable characterization of the population PK and associated variability for the oral granules for suspension formulation. By incorporating all available information regarding the evolution of raltegravir clearance and UGT1A1 ontogeny with age, the model can be used to simulate an optimal dosing scheme (with dose and/or frequency adjustments at appropriate times, such as at Day 14 and Day 28) to meet the PK targets throughout the course of dosing [76].

Cohort 2

Pharmacokinetic sampling for infants in Cohort 2 will occur at the Entry with first dose, after second dose, Day 6-9, Day 15-18, Day 28-32 visits, and Week 5-6 (33-42 Days of life) visit and include the following:

Note: PK sampling will ideally be scheduled after RAL has reached steady state (approximately 7-10 days after the dose increase). For example, the Day 15-18 PK sampling collection visit should ideally be scheduled 7-10 days after the infant received his/her RAL dose regimen increased from 1.5 mg/kg once daily to 3 mg/kg twice daily.

Entry with first dose: within 1 hour pre-dose, and 1-2 hours, 6-10 hours, 20-24 hours post-dose.

After second dose: PK sample obtained 3-6 hours post-dose with laboratory evaluations.

Day 6-9 of life: within 1 hour pre-dose of initiating 3mg/kg twice daily. A physical exam will also be conducted at this visit.

Day 15-18 of life: within 1 hour pre-dose, and 1-2 hours post-dose, 4-6 hours post-dose, and 8-12 hours post-dose.

Day 28-32 of life: within 1 hour pre-dose of initiating 6 mg/kg twice daily.

Week 5-6 of life (33-42 Days of life): within 1 hour pre-dose, and 3-6 hours post-dose.

For sparse PK samples, the time of the previously administered dose (unobserved dose) should be recorded.

9.4 Anticipated Outcomes

At the end of this trial we hope to have a much better understanding of raltegravir pharmacokinetics in neonates, the ontogeny of raltegravir metabolism, and to have defined the dose(s) and dosing interval that achieves the desired systemic exposure in this population.

10.0 HUMAN SUBJECTS

10.1 Institutional Review Board and Informed Consent

This protocol, the informed consent document (Appendix V-A and V-B), and any subsequent modifications must be reviewed and approved by the Institutional Review Board (IRB) or Ethics Committee (EC) responsible for oversight of the study. Written informed consent must be obtained from the parents or legal guardians of participants who cannot consent for themselves, such as those below the legal age. The informed consent will describe the purpose of the study, the procedures to be followed, and the risks and benefits of participation. A copy of the consent form will be given to the parent or legal guardian.

Each site which receives US HHS funding and follows the United States Code of Federal Regulations Title 45-Public Welfare, Part 46-Protection of Human Subjects (also known as the Common Rule) should have on record at the site a plan that detects and addresses any change in guardianship occurring in pediatric participants and determines when a study participant must have a consent process which involves a legally authorized representative (LAR) other than a family member with guardianship. The plan will include how the site determines when a LAR is initially or no longer needed and how frequently the LAR re-signs the consent. The plan should follow all IRB/EC, local, state, national and/or host country guidelines. Confirmation of such a plan at a site should be submitted with protocol registration materials.

10.2 Participant Confidentiality

All laboratory specimens, evaluation forms, reports, and other records will be identified only by a coded number to maintain participant 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 participant, except as necessary for monitoring by the study staff, study monitors, drug companies supporting the study, and their designees, the OHRP, NIH, FDA, or the local IRB/EC.

10.3 Study Discontinuation

The study may be discontinued at any time by the IMPAACT network, the OHRP, NIH, FDA, or local IRB/EC, the pharmaceutical sponsors, or other governmental agencies as part of their duties to ensure that research participants are protected.

11.0 PUBLICATION OF RESEARCH FINDINGS

Publication of the results of this trial will be governed by IMPAACT policies. Any presentation, abstract, or manuscript will be made available for review by the pharmaceutical sponsors prior to submission.

12.0 BIOHAZARD CONTAINMENT

As the transmission of HIV and other blood borne pathogens can occur through contact with contaminated needles, blood, and blood products, appropriate blood and secretion precautions will be employed by all personnel in the drawing of blood and shipping and handling of all specimens for this study, as currently recommended by the Centers for Disease Control and Prevention. All infectious specimens will be sent using the ISS-1 SAF-T-PAK mandated by the International Air Transport Association Dangerous Goods Regulations-Packing Instruction 602. Refer to individual carrier guidelines (e.g., Federal Express or Airborne) for specific instructions.

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APPENDIX I

MATERNAL SCHEDULE OF EVALUATIONS

	Screening[1]	Entry (V1.0 within 48 hours of delivery and V 2.0 within 60 hours of delivery) [1]	Labor and delivery[4]
Informed Consent	X	(or) X	
CLINICAL EVALUATIONS			
History[2]	X	(or) X	
HIV Test[3]		6mL	
TOTAL BLOOD		6mL	

1. May be done at screening or at entry.
2. Obtain complete history including documentation of HIV-1 infection, demographic data, maternal antiretroviral dosing history, mode of delivery and obstetrical gestational age.
3. If maternal HIV status is unknown at the time of delivery, HIV testing is required as described in Section 4.11
4. The mother's participation in the study ends when she is discharged from the labor and delivery unit.

APPENDIX II-A

INFANT SCHEDULE OF EVALUATIONS FOR COHORT 1*

* Pharmacokinetic sampling collection times may be changed based on initial results from Cohort 1.

	Entry (within 48 hours of birth)	Dose 1 (within 48 hours of birth) Pre-dose	Dose 1 1-2 hours post-dose	Dose 1 4-8 hours post- dose	Dose 1 12 hours (±1hours) post- dose	Dose 1 24 hours (±1hours) post- dose	Day 3-4 of life	Dose 2 7- 10 days of life pre-dose	Dose 2 7-10 days of life 1-2 hours post-dose	Dose 2 7-10 days of life 24 hours (±1hours) post-dose	2 weeks of life (± 2 days)	6 weeks of life (±1 week)	24 weeks of life (±4 weeks)	Event Driven	Early Discontinuation
CLINICAL EVALUATIONS															
Informed consent	X														
History[1]	X						X	X			X	X	X		X
Physical exam	X[2]						X[3]	X[3]			X[3]	X[3]	X[3]		X[3]
Pre-dose Monitoring[4]							X	X							
Post-dose Monitoring[4]										X			X		
LABORATORY EVALUATIONS[12]															
Hematology[5]	0.5mL							0.5mL			0.5mL	0.5mL	0.5mL		
Chemistries[6]	1mL						1mL[7]	1mL			1mL	1mL	1mL		
VIROLOGY															
HIV nucleic acid test (HIV NAT)[8]	3mL[9]											3mL	3mL		
Resistance testing[10]														2mL	
PHARMACOGENETICS[16]															
Genotyping[11]	250-400 µl														
PHARMACOKINETICS[12,13,16]															
PK sampling		0.25mL	0.25mL	0.25mL	0.25mL[14]	0.25mL[14]	0.25mL[15]	0.25mL	0.25mL	0.25mL[14]					
TOTAL BLOOD	1.5-4.9mL	0.25mL	0.25mL	0.25mL	0.25mL	0.25mL	1.25mL	1.75mL	0.25mL	0.25mL	1.5mL	4.5mL	4.5mL	2mL	

APPENDIX II-A - FOOTNOTES FOR INFANT SCHEDULE OF EVALUATIONS FOR COHORT 1

1. History includes all non-protocol laboratory tests, HIV test results, antiretroviral agents (for PMTCT), concomitant medications, and any intercurrent illnesses since last visit.
2. Physical examination includes infant Apgar score, birth weight and length, gestational age, gender, and ethnicity.
3. Complete physical examination includes temperature, blood pressure, heart rate, respiratory rate, weight, length, and head circumference.
4. Pre and post-dose monitoring includes a telephone call by study staff to review medication instructions and check any side effects before and after PK sampling visits.
5. Hematology includes CBC with differential and platelet count which may be obtained any time on the first day of life.
6. Chemistries include AST, ALT, creatinine, and total and direct bilirubin which may be obtained any time on first day of life but must be obtained prior to enrollment of the infant.
7. Only total and direct bilirubin required.
8. HIV NAT may be either HIV RNA or HIV DNA. Collect 1-3mL depending on the type of platform performed at the site.
9. Obtain HIV NAT at entry if NOT done as part of standard of care.
10. Participants with confirmed vertical transmission should have 2mL of blood drawn for viral resistance testing to raltegravir and other ARVs as soon as possible after confirmation of HIV infection and should have safety assessments as described in Appendix II-C.
11. Genotyping (optional) for UGT1A1 and SLCO1B1 polymorphisms will be done using dried blood spot on filter paper. May be obtained with any blood sample.
12. Acceptable methods of blood collection for PK samples and laboratory evaluations are by venipuncture, heel stick or indwelling line.
13. When possible, an assessment of infant feeding (type and time of last infant feeding prior to RAL dose) should be recorded.
14. For 12 hour and 24 hour PK samples, window of ±1 hour is necessary for the accurate calculations of the PK parameters of raltegravir. In the event that it is not possible to obtain sample within the ±1 hour window, obtain within ±2 hours.
15. Random PK sample.
16. See the Laboratory Processing Chart (LPC) on the P1110 Protocol Specific Webpage on the IMPAACT Website (http://www.impaactgroup.org) for collection, processing and shipping instructions.

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

APPENDIX II-B

INFANT SCHEDULE OF EVALUATIONS FOR COHORT 2*

	Entry (within 48 hours of birth v1.0 and within 60 hours of birth v2.0)	After second dose	Day 6-9 of life	Day 15-18 of life	Day 28-32 of life	5-6 weeks of life	8-10 weeks of life (±1 week)	24 weeks of life (±4 weeks)	Event Driven	Early Discontinuation
CLINICAL EVALUATIONS										
Informed Consent	X									
History	X	X	X	X	X	X	X	X		X
Physical exam	X[2]	X[3]	X[3]	X[3]	X[3]	X[3]	X[3]	X[3]		X[3]
Pre-dose monitoring[4]		X	X	X	X	X				X
Post-dose monitoring[4]		X	X	X	X	X				X
LABORATORY EVALUATIONS[13]										
Hematology[5]	0.5mL		0.5mL	0.5mL	0.5mL	0.5mL	0.5mL	0.5mL		
Chemistries[6]	1mL	1mL[7]	1mL	1mL	1mL	1mL	1mL	1mL		
VIROLOGY										
HIV nucleic acid test (HIV NAT)[8]	1mL - 3mL[9]					1mL - 3mL		1mL - 3mL		
Resistance testing[10]									2mL	
PHARMACOGENETICS[15]										
Genotyping[11]	250-400 uL									
PHARMACOKINETICS [13,14,15]										
PK sampling[12]	0.8mL	0.2mL	0.2mL	0.8mL	0.2mL	0.4mL				
TOTAL BLOOD	2.3-5.7mL	1.2mL	1.7mL	2.3mL	1.7mL	2.9-4.9mL	1.5mL	2.5-4.5mL	2mL	

APPENDIX II-B - FOOTNOTES FOR INFANT SCHEDULE OF EVALUATIONS
FOR COHORT 2

1. History includes all non-protocol laboratory tests, HIV test results, antiretroviral agents (for PMTCT), concomitant medications, and any intercurrent illnesses since last visit.
2. Physical examination includes infant Apgar score, birth weight and length, gestational age, gender, and ethnicity.
3. Complete physical examination includes temperature, blood pressure**,** heart rate, respiratory rate, weight, length, and head circumference.
4. Pre and post-dose monitoring includes a telephone call by study staff to review medication instructions and check any side effects. Clinic staff will call the participant's home prior to PK sampling days to confirm adherence, understanding of dosing, and no intercurrent illnesses that might preclude PK sampling. If correct doing for 48 hours prior to PK sampling is not confirmed, PK sampling will be rescheduled. Post PK sampling visit days, study staff will review for adverse events and answer any questions for participants' parents by phone. If adverse events are noted, early return visits to clinic may be arranged.
5. Hematology includes CBC (complete blood count) with differential and platelet count which may be obtained any time on the first day of life.
6. Chemistries include AST, ALT, creatinine, and total and direct bilirubin which must be obtained prior to enrollment of the infant.
7. Only total and direct bilirubin required.
8. HIV NAT may be either HIV RNA or HIV DNA. Collect 1-3mL depending on the type of platform performed at the site.
9. Obtain HIV NAT at entry if NOT done as part of standard of care.
10. Participants with confirmed vertical transmission should have 2mL of blood drawn for viral resistance testing to raltegravir and other ARVs as soon as possible after confirmation of HIV infection and should have safety assessments as described in Appendix II-C.
11. Genotyping (optional) for UGT1A1 and SLCO1B1polymorphisms will be done using dried blood spot on filter paper which may be obtained with any blood sample.
12. Collect PK samples at time points as specified in Section 3.0.
13. Acceptable methods of blood collection for PK samples and laboratory evaluations are by venipuncture, heel stick or indwelling line.
14. When possible, an assessment of infant feeding (type and time of last infant feeding prior to RAL dose) should be recorded.
15. See the Laboratory Processing Chart (LPC) on the P1110 Protocol Specific Webpage on the IMPAACT Website (http://www.impaactnetwork.org) for collection, processing and shipping instructions.
    Priority of blood draw should be as follows:
    1) Chemistries
    2) Hematology
    3) Pharmacokinetics

APPENDIX II-C

SCHEDULE OF EVALUATIONS
FOR INFANTS WHO BECOME HIV-INFECTED

EVALUATION		
LABORATORY		
Hematology[1]	0.5 mL	Every 3 months up to 24 weeks of life
Chemistries[2]	1mL	Every 3 months up to 24 weeks of life
Lymphocyte subsets	1mL	Every 3 months up to 24 weeks of life
VIROLOGY		
HIV viral load	2mL	Every 3 months up to 24 weeks of life
TOTAL BLOOD	4.5 mL	

1. Hematology includes CBC with differential and platelet count.
2. Chemistries include AST, ALT, creatinine and total and direct bilirubin.

APPENDIX III

RALTEGRAVIR WEIGHT BAND DOSING TABLES FOR ORAL GRANULES FOR SUSPENSION

Note: Dosing Tables A through F will not be used in protocol Version 2.0 and therefore have been removed.

Dosing Tables G-I reflect reconstitution for suspension 10 mg/mL. Refer to section 5.11 for the dosing regimen (i.e. once or twice daily).

Table G. Dose of 1.5 mg/kg using RAL Oral Granules for Suspension 10 mg/mL

Weight Band (kg)	1.5 mg/kg	Volume (mL)
	Dose in (mg)	Volume to Administer
2 to <3	4 mg	0.4 mL
3 to <4	5 mg	0.5 mL
4 to <5	7mg	0.7 mL

Table H. Dose of 3 mg/kg using RAL Oral Granules for Suspension 10 mg/mL

Weight Band (kg)	3 mg/kg	Volume (mL)
	Dose in (mg)	Volume to Administer
2 to <3	8 mg	0.8 mL
3 to <4	10 mg	1mL
4 to <5	15 mg	1.5 mL

Table I. Dose of 6 mg/kg using RAL Oral Granules for Suspension 10 mg/mL

Weight Band (kg)	6 mg/kg	Volume (mL)
	Dose in (mg)	Volume to Administer
2 to <3	20 mg	2 mL
3 to <4	25 mg	2.5 mL
4 to <5	30 mg	3 mL

Note: The Tables J-M are included for potential future dose adjustments. Refer to section 5.11 on dosing schedule (i.e., once or twice daily).

Table J. Dose of 2 mg/kg using RAL Oral Granules for Suspension 10 mg/mL

Weight Band (kg)	2 mg/kg	Volume (mL)
	Dose in (mg)	Volume to Administer
2 to <3	5 mg	0.5 mL
3 to <4	7 mg	0.7 mL
4 to <5	9 mg	0.9 mL

Table K. Dose of 4 mg/kg using RAL Oral Granules for Suspension 10 mg/mL

Weight Band (kg)	4 mg/kg	Volume (mL)
	Dose in (mg)	Volume to Administer
2 to <3	10 mg	1 mL
3 to <4	15 mg	1.5 mL
4 to <5	20 mg	2 mL

Table L. Dose of 5 mg/kg using RAL Oral Granules for Suspension 10 mg/mL

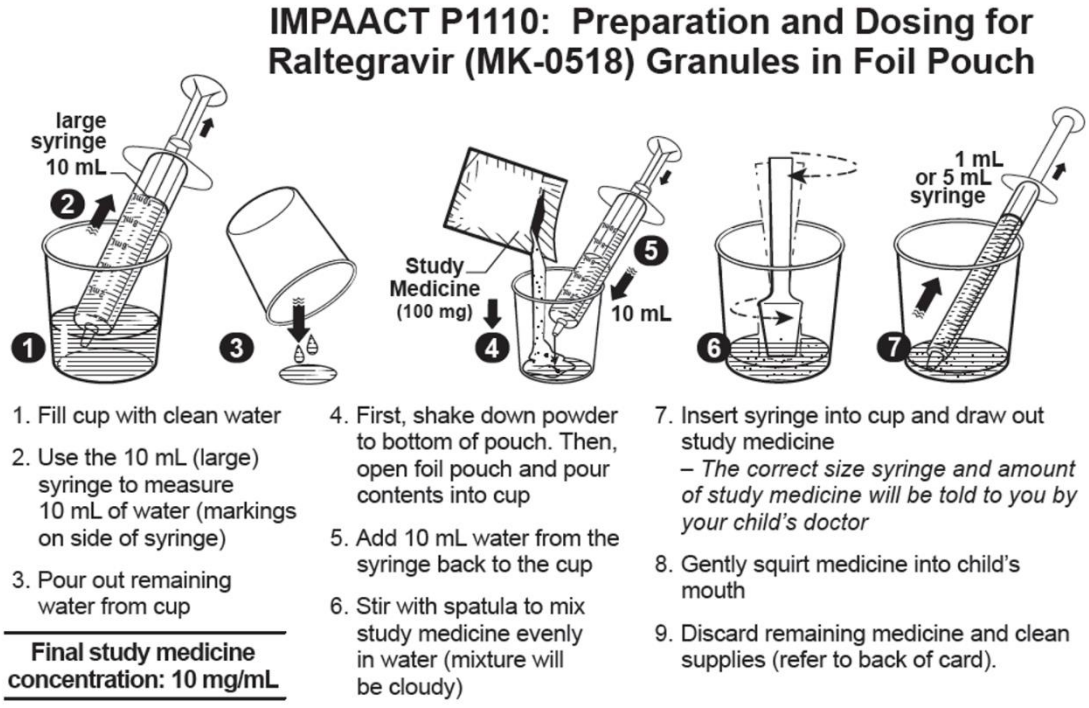
Weight Band (kg)	5 mg/kg	Volume (mL)
	Dose in (mg)	Volume to Administer
2 to <3	15 mg	1.5 mL
3 to <4	20 mg	2 mL
4 to <5	25 mg	2.5 mL

Table M. Dose of 1 mg/kg using RAL Oral Granules for Suspension 10 mg/mL

Weight Band (kg)	1 mg/kg	Volume (mL)
	Dose in (mg)	Volume to Administer
2 to <3	3 mg	0.3 mL
3 to <4	4 mg	0.4 mL
4 to <5	5 mg	0.5 mL

APPENDIX IV

DIAGRAM AND CAREGIVER INSTRUCTIONS FOR PREPARING AND ADMINISTERING RALTEGRAVIR ORAL GRANULES FOR SUSPENSION
10 mg/mL



Caregiver Instructions for Preparing and Administering RAL oral granules for suspension 10 mg/mL

Prepare raltegravir oral granules as follows:

1. Get one foil pouch containing the study medicine.

2. Using the mixing cup, fill approximately two-thirds full with room temperature (maximum 30° C), clean water (as defined by local standards).

3. Using the 10 mL large syringe and the markings on the side of the syringe as a guide, withdraw 10 mL of water from cup into syringe. Discard any remaining water from cup.

4. Shake down powder. Open the foil pouch of study medicine and pour the entire contents of pouch into mixing cup.

5. Add 10 mL of water from the large syringe back into the cup.

6. Stir with spatula until the study medicine and water are evenly mixed.

7. Using the dosing syringe withdraw the study medicine from the mixing cup; use the size syringe and amount of study medicine that the doctor has prescribed. Administer the study medicine into the baby's mouth. Use the markings on the side of syringe as a guide.

*Note: Once the study medicine is mixed with water, it should be given to the baby as soon as possible (ideally within 10 to 15 minutes) and no later than 1 hour after mixing with water. If the baby spits up most or all the dose in the first 30 minutes after administration, the dose should be repeated.

8. Throw away any remaining study medicine from the mixing cup in one of the following ways:

a. Pour excess medicine in the household trash bag containing an absorbent material such as paper tissue, coffee grounds, compost items, or dirt. Then, the trash bag may be thrown away in the communal trash area.
b. If wastewater runs to a wastewater collection system, rinse the cup with water into the wastewater drain.

Cleaning Supplies: After each use do the following: Hand wash syringe, mixing cup, and spatula in warm water with a mild soap. Rinse with water and air dry.

APPENDIX V-A

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

Sample Informed Consent Form for Cohort 1 [CLOSED]

IMPAACT P1110
A Phase I Trial to Evaluate the Safety and Pharmacokinetics of Raltegravir in HIV-1-Exposed Neonates at Risk of Acquiring HIV-1 Infection
VERSION 2.0, DATED 18 January 2017

INTRODUCTION

You and your baby are being asked to take part in this research study because you are or may be infected with the Human Immunodeficiency Virus (HIV), the virus that causes AIDS and your baby is or may be at increased risk of getting the infection. This study is sponsored by the National Institutes of Health. The doctor in charge of this study at this site is: (insert name of Principal Investigator). Before you decide if you want to be/want your baby 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 be/allow your baby to be 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 purpose of this study is to find out if Raltegravir, an anti-HIV medicine, when given with other anti-HIV medicines, can help prevent infants from getting HIV. Raltegravir is a drug that has been used to treat infants and children with HIV. Raltegravir is not yet approved by the Food and Drug Administration (FDA) in children less than two year of age and its use in this study is experimental. We are trying to find out the best dose (amount) of Raltegravir to use to prevent babies from getting HIV infection. Another purpose of this study is to look for possible bad effects of Raltegravir in babies such as more jaundice (yellow color to skin). Another purpose of this study is to look at your baby's DNA (genes) and to see how it breaks down the raltegravir. Some people break down medicines differently based on their DNA and this can change the levels of the medicines in their bodies. Information from this study will help us to find the right dose (amount) of Raltegravir to give to infants to prevent them from getting HIV infection.

WHAT DO I/DOES MY BABY HAVE TO DO AS PART OF THIS STUDY?

Your participation in this study is minimal. Only your medical record will be reviewed unless you need to have blood drawn to check for HIV. Your baby will be given two doses of Raltegravir in water by mouth within 48 hours of birth and another when he/she is 7 to 10 days old. The study staff will call you several times during the study to see how your baby is doing and to check for any bad effects. After your baby takes the Raltegravir, blood samples will be taken at different times to measure the amount of medicine in your baby's body at these different times. These blood samples will be sent to the U.S. University of Alabama for testing. Your baby will also be taking other anti-HIV medicine(s) that are prescribed by your baby's doctor that will start shortly after your baby is born. The study will supply the Raltegravir for your baby as long as your baby is in this study, but not any of the other anti-HIV medicines.

Screening visit to see if you can be in this study

- If you agree to be in this study, we need to make sure you are eligible to enroll in this study. We will collect information like your age and race. We will look at your medical record and ask you questions about your pregnancy, the birth of your baby and what medications you are taking. This review of your medical record may be done while you are pregnant or within 48 hours after you deliver your baby. If your HIV status is unknown at the time you deliver your baby, blood will be drawn to test you for HIV. The amount of blood needed for the HIV test is 6mL (slightly more than 1 teaspoon). You will be in this study until you are discharged from the labor and delivery unit, but no other tests will be done.

Study visits for your baby

- If you agree to allow your baby to be in this study, we will do some tests to make sure your baby should be in this study. Some of the study visits will occur while your baby is still in the hospital. Within 48 hours of birth, we will ask how your baby has been doing, if he/she has been sick, and any medicines he/she has been taking. We will check your baby's blood pressure, vital signs, length, weight, gender and race. Routine blood tests will be done to tell us about your baby's blood cells and how well your baby's liver and kidneys are working. We will draw blood to test your baby for HIV if this has not already been done as part of your baby's routine care. The total amount of blood drawn at this visit will be between 1.5-4.9mL (less than ½ to 1 teaspoon) depending on the tests taken.

- If your baby is found to have HIV, every three months until your baby is 24 weeks old, your baby will have 3.5mL (a little more than ½ teaspoon) of blood drawn for routine tests, and to check how well your baby's immune system is working and the amount of HIV in your baby's blood. Blood will also be drawn once during the study to see if the medicines your baby is taking are working against your baby's type of HIV. The total amount of blood for this test will be 2mL (½ teaspoon).

HOW MANY PEOPLE WILL TAKE PART IN THIS STUDY?

About 50 HIV-infected women and their babies will take part in this study.

HOW LONG WILL I/MY BABY BE IN THIS STUDY?

You will only be in this study until you are discharged from labor and delivery unit. Your baby will be in this study until he/she is 6 months old (24 weeks).

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

The study doctor may need to take you/your baby off the study early without your permission for the following reasons. If this happens, no further information will be collected and no further study visits or laboratory tests will be done.

- The study is cancelled by the IMPAACT network, the National Institutes of Health, the Office for Human Research Protections, the U.S. Food and Drug Administration, the site's Institutional Review Board (IRB) or Ethics Committee (EC), the pharmaceutical sponsors and other governmental agencies. An IRB/EC is a committee that watches over the safety and rights of research participants.
- You are/your baby is not able to attend the study visits as required by the study.
- The investigator determines that further participation would be harmful to your/your baby's health or well-being.
- Your baby requires treatment with medications that are disallowed while on this study.

IF MY BABY HAS TO PERMANENTLY STOP TAKING STUDY-PROVIDED MEDICINE, OR ONCE MY BABY LEAVES THE STUDY, HOW WOULD THE STUDY MEDICINE BE PROVIDED?

During the study:
If your baby has to stop taking his/her study medicine before the study ends, you will be asked to allow your baby to continue in the study and have regular study visits until your baby is 24 weeks of age, to make sure your baby is continuing to do well. If you decide you do not want your baby to continue to have the regular study visits, you will be asked to allow your baby to have a final visit. At this final visit, a review of your baby's medical records and a physical examination will be done, but no blood will be drawn.

After the study:
Once your baby finishes the study, if your baby's doctor decides your baby should continue taking the study medicine, it will be provided to your baby. The study staff will talk to you about how to continue to get the study medicine for your baby.

WHAT ARE THE RISKS OF THE STUDY?

General Disclaimer

The drugs used in this study may have side effects, some of which are listed below. Please note that these lists do not include all the side effects seen with these drugs. These lists include the more serious or common side effects with a known or possible relationship. If you have questions concerning additional study drug side effects please ask the medical staff at your site. If your baby becomes infected with HIV, there is a risk that your baby may develop resistance to the study drug. This means that the virus may grow and multiply even if your baby is taking the study drug.

Use of Combination Antiretroviral Drugs

Immune Reconstitution Syndrome: In some people with advanced HIV infection, symptoms from other infections or certain diseases may occur soon after starting combination anti-HIV treatment but can also occur later. Some of these symptoms may be life threatening. If your baby starts having new symptoms, or you notice that existing symptoms are getting worse after starting antiretroviral therapy, tell your healthcare provider right away**.**

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

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

Integrase Inhibitor

Raltegravir, (RAL, Isentress™)
Merck & Co., Inc.

The following side effects have been associated with the use of raltegravir. There may be unforeseen risks as this is the first time Raltegravir will be given to babies.

- Rash which can become severe or life-threatening. Contact your Healthcare Provider right away if your baby develops a rash.
- Nausea
- Headache
- Tiredness
- Weakness
- Trouble sleeping
- Stomach pain
- Dizziness
- Depression
- Suicidal thoughts and actions, change in behavior
- Feeling anxious, paranoia
- Decreased blood clotting cell (Low platelet count)
- Diarrhea

- Liver failure
- Clumsiness and lack of coordination
- Muscle tenderness, weakness or injury which can be serious and lead to kidney damage

Because raltegravir has been studied mostly in adults, we do not know as much about how it will affect babies. Newborn jaundice (yellow skin and eyes) has not been seen so far but it may be possible and is being carefully looked for in this study

Blood drawing risks

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

ARE THERE BENEFITS TO TAKING PART IN THIS STUDY?

You may benefit from this study by knowing the HIV status of your baby through study-provided HIV testing. Your baby may receive benefit from taking the Raltegravir along with other anti-HIV medicines but no guarantee can be made. Your baby 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/DOES MY BABY HAVE BESIDES THIS STUDY?

You may choose not to be/allow your baby to be in this study. You may withdraw/take your baby out of this study at any time. Please talk to your doctor about other choices available to you/your baby.

WHAT HAPPENS IF MY BABY IS INJURED?

If your baby is injured as a result of being in this study, your baby will be given immediate treatment for your 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. You will not be giving up any of your legal rights by signing this consent form.

WHAT ABOUT CONFIDENTIALITY?

U.S. sites:

To help us protect your 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 you/your baby, 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 you/your baby, 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 U.S. Food and Drug Administration.

People who may review your/your baby's records include the U.S. Food and Drug Administration, the Office for Human Research Protections, the site IRB/EC (insert name of site IRB/EC), the National Institutes of Health, study staff, study monitors, the IMPAACT network representatives, drug companies supporting the study, 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 you/your baby or your/your baby'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.

Sites outside the U.S.:

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

Your/your baby's records may be reviewed by the U.S. Food and Drug Administration, the Office for Human Research Protections, the site IRB/EC (insert name of site IRB/EC), National Institutes of Health, study staff, study monitors, and drug companies supporting this study and their designees.

WHAT ARE THE COSTS TO ME?

There is no cost to you for your study visits or your baby's study visits, examinations, blood tests, or the study medication, Raltegravir. However, the study will not pay for the cost to deliver your baby. 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 you are/your baby is taking part in a research study. [Note to sites: Modify or delete language regarding insurance as appropriate for your site and insert appropriate language for added local costs if relevant].

WHAT ARE MY/MY BABY'S RIGHTS AS A RESEARCH SUBJECT?

Taking part in this study is completely voluntary. You may choose not to be/allow your baby to be in this study or withdraw yourself or your baby from the study at any time. Your decision will not have any impact on your/your baby's participation in

other studies conducted by the National Institutes of Health and will not result in any penalty or loss of benefits to which you are/your baby is otherwise entitled.

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

WHAT SHOULD 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 baby's rights as a research subject, contact:

- name or title of person on the Institutional Review Board (IRB) or other organization appropriate for the site
- telephone number of above

SIGNATURE PAGE

If you have read this consent form (or had it explained to you), all your questions have been answered and you agree to be/allow your baby to be in this study, please sign your name below.

Participant's Legal Guardian (print)	Legal Guardian's Signature and Date

(As appropriate)

Father (print) As appropriate)	Father's Signature and Date (As appropriate)
Study Staff Conducting Study	Study Staff Signature and Date

APPENDIX V-B

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

Sample Informed Consent Form for Cohort 2

IMPAACT P1110
A Phase I Trial to Evaluate the Safety and Pharmacokinetics of Raltegravir in HIV-1-Exposed Neonates at Risk of Acquiring HIV-1 Infection
VERSION 2.0, DATED 18 January 2017

INTRODUCTION

You and your baby are being asked to take part in this research study because you are or may be infected with the Human Immunodeficiency Virus (HIV), the virus that causes AIDS and your baby is or may be at risk of getting the infection. This study is sponsored by the National Institutes of Health. The doctor in charge of this study at this site is: (insert name of Principal Investigator). Before you decide if you want to be/want your baby 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 be/allow your baby to be 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 purpose of this study is to find out if Raltegravir, an anti-HIV medicine, when given with other anti-HIV medicines, can help prevent infants from getting HIV. Raltegravir is a drug that has been used to treat infants and children with HIV. Raltegravir is not yet approved by the Food and Drug Administration (FDA) in children less than 4 weeks of age and its use in this study is experimental. We are trying to find out the best dose (amount) of Raltegravir to use to prevent babies from getting HIV infection. Another purpose of this study is to look for possible bad effects of Raltegravir in babies such as more jaundice (yellow color to skin). Another purpose of this study is to look at your baby's DNA (genes) and to see how it breaks down the raltegravir. Some people break down medicines differently based on their DNA and this can change the levels of the medicines in their bodies. Information from this study will help us to find the right dose (amount) of Raltegravir to give to infants to prevent them from getting HIV infection.

WHAT DO I/DOES MY BABY HAVE TO DO AS PART OF THIS STUDY?

Your participation in this study is minimal. Only your medical record will be reviewed unless you need to have blood drawn to check for HIV. Your baby will be started on Raltegravir in water by mouth beginning within 12 to 60 hours of birth and your baby will continue to take this medicine every day for 6 weeks. The study staff will give you instructions on how to give the medicine to your baby. The study staff will call you before your baby takes his/her dose of raltegravir to make sure you understand how to give the medicine and several times during the study to check for any bad effects. After your baby takes the Raltegravir, blood samples will be taken at different times to measure the amount of medicine in your baby's body at these different times. These blood samples will be sent to the U.S. University of Alabama for testing. Your baby will also be taking other anti-HIV medicine(s) that are prescribed by your baby's doctor that will start shortly after your baby is born. The study will supply the Raltegravir for your baby but not any of the other anti-HIV medicines.

Screening visit to see if you can be in this study

- If you agree to be in this study, we need to make sure you are eligible to enroll in this study. We will collect information like your age and race. We will look at your medical record and ask you questions about your pregnancy, the birth of your baby and what medications you are taking. This review of your medical record may be done while you are pregnant or within 60 hours after you deliver your baby. If your HIV status is unknown at the time you deliver your baby, blood will be drawn to test you for HIV. The amount of blood needed for the HIV test is 6mL (slightly more than 1 teaspoon). You will be in this study until you are discharged from the labor and delivery unit, but no other tests will be done.

Study visits for your baby

- During the first 6 weeks of your baby's life, 6 study visits will be scheduled for observed raltegravir dosing and blood will be drawn to measure the amount of raltegravir in your baby's body.
- At the first study visit we will also draw blood to test your baby for HIV if this has not already been done as part of your baby's routine care. If your baby is found to have HIV, every three months until your baby is 24 weeks old, your baby will have blood drawn for routine tests, and to check how well your baby's immune system is working and the amount of HIV in your baby's blood. Blood will also be drawn once during the study to see if the medicines your baby is taking are working against your baby's type of HIV.
- The first study visits and blood draws may be done while you and your baby are still in the hospital, and later study visits will require a return to the clinic.
- It is important that you can tell study staff the exact time of the last dose given to your baby at home before returning to the clinic. For some visits, study staff will

ask that the dose not be given at home so that Raltegravir can be given to your baby during the study visit in the clinic.

- At each study visit, we will ask how your baby has been doing, if he/she has been sick, and any medicines he/she has been taking, and a physical examination of your baby will be done. At each study visit, routine blood tests will be done to tell us about your baby's blood cells, and/ or how well your baby's liver and kidneys are working.
- The blood draws will be obtained from your baby's vein or heel. The total amount of blood drawn from your baby at any single visit will range from 1.2–5.7 mL (less than 1/3 of a teaspoon to less than 1 ¼ teaspoons).
- The study staff will review the visit schedule with you.
- Your baby will have one drop of blood taken once during the study to check your baby's DNA (genes) to see how it breaks down the Raltegravir. Some people break down medicines differently based on their DNA and this can change the levels of the medicines in their bodies. You may decide that you do not want your baby's DNA to be tested. Your baby can still participate in this study even if you make this decision. Please read the following statement carefully and then mark your initials in the appropriate space provided:

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

Yes_____ No_____ Initials _____ Date _____

Study Visit	Entry (within 60 hours of birth)	After second dose of RAL	Day 6-9 of life	Day 15-18 of life	Day 28-32 of life	5-6 weeks of life	8-10 weeks of life	24 weeks of life
Physical exam	X	X	X	X	X	X	X	X
Routine blood test	X	X	X	X	X	X	X	X
HIV test	X					X		X
DNA test	X							
RAL blood test	X	X	X	X	X	X		

- Your baby will stop taking Raltegravir when he/she is 6 weeks old, and your baby's participation in this study will end when he/she is 6 months old (24 weeks).

HOW MANY PEOPLE WILL TAKE PART IN THIS STUDY?

About 50 HIV- infected women and their babies will be enrolled in this study.

HOW LONG WILL I/MY BABY BE IN THIS STUDY?

You will only be in this study until you are discharged from the labor and delivery unit. Your baby will be in this study until he/she is 6 months old (24 weeks).

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

The study doctor may need to take you/your baby off the study early without your permission for the following reasons. If this happens, no further information will be collected and no further study visits or laboratory tests will be done.

- The study is cancelled by the IMPAACT network, the National Institutes of Health, the Office for Human Research Protections, the U.S. Food and Drug Administration, the site's Institutional Review Board (IRB) or Ethics Committee (EC), the pharmaceutical sponsors and other governmental agencies. An IRB/EC is a committee that watches over the safety and rights of research subjects.
- You are/your baby is not able to attend the study visits as required by the study.
- The investigator determines that further participation would be harmful to your/your baby's health or well-being.
- Your baby requires treatment with medications that are disallowed while on this study**.**

IF MY BABY HAS TO PERMANENTLY STOP TAKING STUDY-PROVIDED MEDICINE, OR ONCE MY BABY LEAVES THE STUDY, HOW WOULD THE STUDY MEDICINE BE PROVIDED?

During the study:
If your baby has to stop taking his/her study medicine before the study ends, you will be asked to allow your baby to continue in the study and have regular study visits until your baby is 24 weeks of age, to make sure your baby is continuing to do well. If you decide you do not want your baby to continue to have the regular study visits, you will be asked to allow your baby to have a final visit. At this final visit, a review of your baby's medical records and a physical examination will be done, but no blood will be drawn.

After the study:
Once your baby finishes the study, if your baby's doctor decides your baby should continue taking the study medicine, it will be provided to your baby. The study staff will talk to you about how to continue to get the study medicine for your baby.

WHAT ARE THE RISKS OF THE STUDY?

General Disclaimer
The drugs used in this study may have side effects, some of which are listed below. Please note that these lists do not include all the side effects seen with these drugs.

These lists include the more serious or common side effects with a known or possible relationship. If you have questions concerning additional study drug side effects please ask the medical staff at your site. There is a risk that your baby may develop resistance to the study drug. This means that the virus may grow and multiply even if your baby is taking the study drug.

Use of Combination Antiretroviral Drugs
Immune Reconstitution Syndrome: In some people with advanced HIV infection, symptoms from other infections or certain diseases may occur soon after starting combination anti-HIV treatment but can also occur later. Some of these symptoms may be life threatening. If your baby starts having new symptoms, or you notice that existing symptoms are getting worse after starting antiretroviral therapy, tell your healthcare provider right away.

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

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

Integrase Inhibitor

Raltegravir, (RAL, Isentress™)
Merck & Co., Inc.

The following side effects have been associated with the use of raltegravir. There may be unforeseen risks as this is the first time Raltegravir will be given to babies.

- Rash which can become severe or life-threatening. Contact your Healthcare Provider right away if your baby develops a rash.
- Nausea
- Headache
- Tiredness
- Weakness
- Trouble sleeping
- Stomach pain
- Dizziness
- Depression
- Suicidal thoughts and actions, changes in behavior
- Feeling anxious, paranoia
- Decreased blood clotting cell (Low platelet count)
- Diarrhea
- Liver failure
- Clumsiness and lack of coordination
- Muscle tenderness, weakness or injury which can be serious and lead to kidney damage

Because raltegravir has been studied mostly in adults, we do not know as much about how it will affect babies. Newborn jaundice (yellow skin and eyes) has not been seen so far but it may be possible and is being carefully looked for in this study.

Blood drawing risks

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

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WHAT ABOUT CONFIDENTIALITY?

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projects or for information that must be disclosed in order to meet the requirements of the U.S. Food and Drug Administration.

People who may review your/your baby's records include the U.S. Food and Drug Administration, the Office for Human Research Protections, the site IRB/EC (insert name of site IRB/EC), the National Institutes of Health, study staff, study monitors, drug companies supporting the study, and their designees.

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Sites outside the U.S.:
Efforts will be made to keep your/your baby's personal information confidential. We cannot guarantee absolute confidentiality. Your/your baby's personal information may be disclosed if required by law. Any publication of this study will not use your/your baby's name or identify you/your baby personally.

Your/your baby's records may be reviewed by the U.S. Food and Drug Administration, the Office for Human Research Protections, the site IRB/EC *(insert name of site IRB/EC)*, National Institutes of Health, study staff, study monitors, IMPAACT network representatives, and drug companies supporting this study and their designees.

WHAT ARE THE COSTS TO ME?

There is no cost to you for your study visits or your baby's study visits, examinations, blood tests, or the study medication, Raltegravir. However, the study will not pay for the cost to deliver your baby. 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 you are/your baby is taking part in a research study. *[Note to sites: Modify or delete language regarding insurance as appropriate for your site and insert appropriate language for added local costs if relevant]*.

WHAT ARE MY/MY BABY'S RIGHTS AS A RESEARCH SUBJECT?

Taking part in this study is completely voluntary. You may choose not to be/allow your baby to be in this study or withdraw yourself or your baby from the study at any time. Your decision will not have any impact on your/your baby's participation in other studies conducted by the National Institutes of Health and will not result in any penalty or loss of benefits to which you are/your baby is otherwise entitled.

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

WHAT SHOULD 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 baby's rights as a research subject, contact:

- name or title of person on the Institutional Review Board (IRB) or other organization appropriate for the site
- telephone number of above

SIGNATURE PAGE

If you have read this consent form (or had it explained to you), all your questions have been answered and you agree to be/allow your baby to be in this study, please sign your name below.

_____	_____
Participant's Legal Guardian (print) (As appropriate)	Legal Guardian's Signature and Date
_____	_____
Father (print) As appropriate)	Father's Signature and Date (As appropriate)
_____	_____
Study Staff Conducting Study	Study Staff Signature and Date