

IMPAACT P1097

RALTEGRAVIR PHARMACOKINETICS AND SAFETY IN NEONATES

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

Sponsored by:

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and

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**Version 2.0
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SUMMARY OF CHANGES for P1097

Raltegravir Pharmacokinetic and Safety in Neonates, Version 2.0, dated 22 January 2014

All changes in this version appear in boldface type. Editorial changes, including corrections of typographical errors and other changes required to update information that does not affect regulatory issues or subject consent may also be included.

P1097, Version 1.0, dated 12/22/10 enrolled full term infants and closed to follow-up on 2/21/13. P1097 is being amended to enroll a new study population, low birth weight infants. All information pertaining to Version 1.0 is being retained in the amendment and the full term cohort that is closed to follow-up in Version 1.0 has been retroactively named Cohort 1. The new population being studied in the amendment, low birth weight infants, is named Cohort 2. Cohort 1 and Cohort 2 designations appear in all appropriate sections of the protocol.

- 1) The cover page has been updated to include Merck & Co., Inc. as providing Pharmaceutical Support and the DAIDS Document ID Number.**
- 2) The Team Roster has been updated.**
- 3) The Glossary has been updated.**
- 4) The Schema has been revised to describe the fully accrued and closed to follow-up of full term infants in Cohort 1, and the new study population of low birth weight infants in Cohort 2.**
- 5) Section 1.1, last sentence added: In addition, the use of raltegravir immediately prior to delivery in the HIV-infected mother in preterm labor may provide sufficient raltegravir drug levels in preterm infants at the time of birth to provide protection against peripartum HIV transmission.**
- 6) Section 1.11, Recent raltegravir data from Version 1.0 and *in vitro* analysis, has been added to describe washout elimination of raltegravir in full term infants studied in P1097, Version 1.0.**
- 7) Section 1.12, Background and rationale for opening Version 2.0, Cohort 2 (low birth weight infants), has been added to describe the rationale for studying raltegravir in low birth weight infants.**
- 8) Section 1.21, Raltegravir Pharmacokinetics in Adults, 3rd paragraph, 1st sentence has been added: Raltegravir is approved for use in both adults and children (age ≥ 2 years of age and weighing ≥ 10 kg). Raltegravir is commercially available as the 400 mg film-coated (poloxamer) tablet and the 100 mg and 25 mg chewable tablets.**

9) Section 1.24, Raltegravir in Children, 1st paragraph, 3rd sentence has been added: These data have supported the approval of the raltegravir film-coated tablet in children and adolescents \geq 12 years of age and the chewable tablet in children and adolescents 2 to $<$ 12 years of age.

10) Section 1.24, Raltegravir in Children, 2nd paragraph has been added: Raltegravir in the investigational oral granules for suspension formulation in children \geq 4 weeks to $<$ 2 years of age is currently being studied in IMPAACT P1066. PK and safety data in this age group are now available, including in children 6 months to $<$ 2 years of age (31) and an abstract by Frenkel, et al, in infants 4 weeks to $<$ 6 months of age (32). For infants \geq 6 months to $<$ 2 years of age, the GM t_{1/2} was 3.0 hours (range: 1.9-7.4 hours, n=8). For infants \geq 4 weeks to $<$ 6 months of age, the GM t_{1/2} was 8.2 hours (range: 2.5-111 hours, n=11). The younger children demonstrated a prolonged distribution phase that made direct estimation of raltegravir pharmacokinetic parameters difficult and a modeling approach was used to estimate these parameters, which may be responsible for some of the apparent increase in raltegravir elimination t_{1/2} in these subjects.

11) Section 1.25, Special Concerns for the Use of Raltegravir in the Neonate, has been revised to describe the effect of raltegravir on bilirubin-albumin binding and to provide mean standard deviation unbound bilirubin concentrations in Table 2.

12) Section 1.26, Results of Cohort 1 Full Term Neonates Enrolled in P1097, Version 1.0, has been added to describe study population accrual and demographics, and the safety and washout pharmacokinetics of raltegravir when given to the mother and passed transplacentally to full term infants enrolled in Cohort 1 in Version 1.0.

13) Section 3.0, Study Design, Cohort 1 and Cohort 2 designations have been added and the following sections have been added:

Version 1.0, Cohort 1

Version 1.0, Cohort 1 enrolled full term infants and is fully accrued and closed to follow-up. Cohort 1 women were followed until discharge from the labor/delivery units while their infants were followed for 20 weeks after birth.

Version 2.0, Cohort 2

Version 2.0, Cohort 2 will enroll up to 20 mother-infant pairs to achieve 15 evaluable low birth weight infants (\leq 2500 grams at birth).

Mother/infant pairs may be enrolled prior to delivery or within 48 hours after birth. In addition, infants may be enrolled up to 48 hours after birth if birth weight \leq 2500 grams and born to an HIV-infected pregnant woman who received at least one dose of raltegravir 400 mg within 2 to 24 hours prior to delivery. All infants will have a history, physical examination,

and hematology and chemistry laboratory evaluations performed around the time of birth and at a week 1-2 follow-up visit.

When possible, cord blood will be drawn immediately after cord is clamped and a single blood sample will be collected in women within one hour after delivery to determine maternal plasma raltegravir concentration.

Women will be followed until discharge from the labor/delivery unit. Infants will be followed for 6 weeks after birth. Since no toxicities attributed to raltegravir exposure were observed in Cohort 1 at the 6 or 20 week visits, and since raltegravir is not administered to infants in this study, infants in Cohort 2 will have their last study visit at 6 weeks of age.

Only infants who meet the following criteria are eligible for pharmacokinetic blood sampling in Cohort 2:

- Infant born to woman who received at least one dose of raltegravir within 2 to 24 hours prior to delivery. Dose administered to mother must have been at least 2 hours prior to delivery to allow time for adequate absorption and distribution.
- Infant birth weight \leq 2500 grams.
- Infant not receiving disallowed medications described in Section 4.8. If these medications are required for the infant's care, the infant will be ineligible for further PK (pharmacokinetic) sampling. Data will be obtained up to the time of the introduction of the disallowed medication, but such infant will not be considered one of the evaluable 15 infants.
- Infant \leq 48 hours of age.

Blood samples for raltegravir assay will be collected at 1-6, 12-24, 36-48, 72-84, and 108-132 hours after birth, and on day 7-14. Infants may enroll up to 48 hours of age, and any pharmacokinetic samples scheduled for collection prior to the time of enrollment will be skipped and not replaced. Safety/toxicity laboratory samples scheduled for collection prior to the time of enrollment must be collected after enrollment. Infants enrolling close to the 48-hour time point should have the first pharmacokinetic blood sample collected within 4 hours of enrollment (i.e., within 52 hours after birth) so that a minimum of three blood samples can be obtained for pharmacokinetic evaluation.

With regard to infant blood samples for safety/toxicity laboratory testing: In the event that the study-required study safety/lab samples have not been collected prior to enrollment, (e.g., due to infant enrolled after delivery), these must be collected as soon as possible after enrollment.

14) Section 3.0, Study Design, 9th paragraph, 2nd sentence changed to read: To meet the primary objectives of the study, only those infants who have at least 3 pharmacokinetic blood samples collected from the first 5 time points will be considered to be evaluable.

15) Section 3.0, Study Design, 10th paragraph, 1st and 2nd sentences changed to read:

Optional genotyping for polymorphisms of UGT1A1 **were performed on Cohort 1 infants and will be performed on Cohort 2** infants who undergo pharmacokinetic sampling. The goal of the **genotypic analysis** is to determine if certain polymorphisms, particularly those with the UGT1A1*28/*28 genotype have slower RAL elimination than those with the UGT1A1*1/*1 genotype.

16) Section 3.0, Study Design, 12th paragraph, 4th sentence changed to read: Refer to **Appendix II-A, Cohort 2 Maternal Schedule of Evaluations and Appendix II-B, Cohort 2 Infant Schedule of Evaluations**, for a complete description of the clinical and laboratory evaluations to be performed for **Cohort 2**.

17) Section 4.0, Selection and Enrollment of Subjects, has been revised to state that eligibility criteria for Cohort 1 can be found in Version 1.0 of the protocol and to add eligibility criteria for Cohort 2 mothers and infants.

18) Section 6.3, Premature Discontinuation/Early Withdrawal/ Safety Follow-up for PK Unevaluable Infants, 2nd paragraph has been added:

Cohort 2: If fewer than 3 pharmacokinetic samples from the first 5 time points are collected, the infant is not considered evaluable for pharmacokinetics but will continue with scheduled safety evaluations. If the parent withdraws consent at any time after enrollment, no further information will be collected and additional laboratory evaluations will not be performed.

19) Section 8.0, Statistical Considerations, has been revised to update information for Cohorts 1 and 2.

20) Section 9.3, Study Design, Modeling and Data Analysis, 4th, 5th, and 6th paragraphs, have been added:

Cohort 2

There will be no infant dosing for this study. Women must have received at least one dose of raltegravir within 2 to 24 hours prior to delivery. Dose must be administered at least 2 hours prior to delivery to allow adequate time for absorption and distribution.

Maternal and cord blood raltegravir concentrations: When possible one maternal blood sample will be obtained within one hour after delivery and a single cord blood specimen will be obtained at the time of birth. For infants enrolled after delivery up to 48 hours after birth, it will not be possible to obtain maternal or cord blood samples.

Neonatal raltegravir concentrations: Blood samples for raltegravir assay will be collected at 1-6, 12-24, 36-48, 72-84, and 108-132 hours after birth, and on day 7-14. Infants may enroll up to 48 hours of age, and any pharmacokinetic samples scheduled for collection prior to the time of enrollment will be skipped and not replaced. Infants enrolling close to the 48-hour time point should have the first pharmacokinetic blood sample collected within 4 hours of enrollment (i.e., within 52 hours after birth) so that a minimum three blood samples can be obtained for pharmacokinetic evaluation.

- 21) Section 10.1, Institutional Review Board and Informed Consent, 1st sentence has been revised: This protocol, the informed consent documents (Appendix IV-A and IV-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.**
- 22) Appendix I-B, Cohort 2 Maternal Schedule of Evaluations, has been added.**
- 23) Appendix II-B, Cohort 2 Infant Schedule of Evaluations, has been added.**
- 24) Appendix III, P1097 Testing Laboratories, has been added.**
- 25) Appendix IV-B, Sample Informed Consent for Cohort 2, has been added.**

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GLOSSARY

3TC	Lamivudine
ALT	Alanine aminotransferase
ARV	Antiretroviral
AST	Aspartate aminotransferase
AUC	Area under the curve
BID	Twice a day
CBC	Complete blood count
CI	Confidence interval
d4T	Stavudine
DAIDS PRO	Division of AIDS Protocol Registration Office
DMC	Data Management Center
EAE	Expedited adverse event
EC	Ethics Committee
FTC	Emtricitabine
HAART	Highly active antiretroviral therapy
HIV	Human immunodeficiency virus
IMPAACT	International Maternal Pediatric Adolescent AIDS Clinical Trials Group
IRB	Institutional Review Board
LAR	Legally authorized representative
LBW	Low birth weight
LDMS	Laboratory Data Management System
MD	Multiple dose
M-I	Mother-infant pairs
NFV	Nelfinavir
NVP	Nevirapine
OHRP	Office for Human Research Protections
PID	Patient Identification Number
PK	Pharmacokinetic
PMTCT	Prevention of Mother-to-Child Transmission
QD	Once a day
RAL	Raltegravir
RE	Regulatory entity
RSC	Regulatory Support Center
SD	Single dose
SES	Subject enrollment system
SID	Study Identification Number
UDP	Uridine diphosphate
UGT	Uridine diphosphate glucuronyl transferase
ZDV	Zidovudine

SCHEMA

RALTEGRAVIR PHARMACOKINETICS AND SAFETY IN NEONATES

<u>DESIGN:</u>	Phase 0, multicenter, washout pharmacokinetic trial
<u>SAMPLE SIZE:</u>	<p>Cohort 1 (Closed): 15 evaluable mother-infant pairs for the washout pharmacokinetic analysis (which is projected to require enrolling 25 mother-infant pairs)</p> <p>Cohort 1 was fully accrued and closed to follow-up under Version 1.0. The protocol is being amended to include low birth weight (LBW) infants in Version 2.0.</p> <p>Cohort 2: 15 evaluable low birth weight (LBW) infants (≤ 2500 grams at birth) for the washout pharmacokinetic analysis, and their mothers (projected to require enrolling 20 mother-infant pairs)</p>
<u>POPULATION:</u>	<p>Cohort 1 (Closed): HIV-infected pregnant women receiving raltegravir (RAL) 400mg twice daily for at least two weeks prior to delivery and continuing to receive ARVs during labor, and their infants.</p> <p>Cohort 2: HIV-infected pregnant women who received at least one dose of raltegravir (RAL) 400mg within 2 to 24 hours prior to delivery and their LBW infants ≤ 2500 grams at birth.</p>
<u>STRATIFICATION:</u>	None
<u>REGIMEN:</u>	No study-specific treatment will be given during this study.
<u>STUDY DURATION:</u>	<p>Women will be followed until discharge from the labor/delivery unit.</p> <p>Cohort 1 infants (Closed): Infants will be followed for 20 weeks after birth.</p> <p>Cohort 2 infants will be followed for 6 weeks after birth based on lack of toxicity observed in Cohort 1 (See Section 1.26).</p>

PRIMARY OBJECTIVES:

1. To evaluate the washout pharmacokinetics of raltegravir in infants born to HIV-infected pregnant women receiving raltegravir during pregnancy.
2. To evaluate bilirubin levels and the safety of *in utero*/intrapartum exposure to raltegravir in infants born to HIV-infected pregnant women receiving raltegravir during pregnancy.
3. To develop a neonatal raltegravir dosing regimen to be evaluated in a follow-up study of this protocol.

SECONDARY OBJECTIVE:

1. To investigate the relationship between neonatal raltegravir elimination and UGT1A1 genotype.

1.0 INTRODUCTION

1.1 Background and Rationale

Alternative antiretroviral (ARV) agents for use in neonates are urgently needed for both HIV prophylaxis and treatment. Postnatal prophylaxis with multiple antiretroviral agents is currently recommended for neonates at high risk for HIV infection. Turn-around time for diagnostic tests of HIV infection has improved in recent years, and HIV infected neonates are now routinely identified in the first weeks of life. These infants require immediate initiation of ARV treatment with potent three-drug combination ARV regimens. Strategies for early treatment of HIV-infected newborns with more intensive four drug regimens have been proposed, with a goal of either improving outcome or eradicating infection.

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, but its use is not approved in children less than 2 years old. The three-drug ARV regimen with the greatest experience in neonates 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 [1,2]. Lopinavir/ritonavir, another protease inhibitor, is available as a pediatric solution, but dosing is uncertain in the first weeks of life and its use has been discouraged in neonates after several cases of life-threatening bradyarrhythmias and cardiac dysfunction were reported in preterm infants [3,4].

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 extremely potent against HIV, 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 HIV-exposed neonates who are at high risk of becoming infected. The primary goal of this protocol is to describe raltegravir pharmacokinetics in infants < four weeks of age in order to develop an appropriate raltegravir dosing regimen for prophylaxis or treatment of HIV in neonates. This current study will determine washout pharmacokinetics of raltegravir in HIV-exposed neonates born to mothers receiving raltegravir during pregnancy. These data plus pharmacokinetic data from raltegravir pharmacokinetic studies in HIV-infected older infants will be used to develop a dosing regimen for raltegravir in infants at high risk of acquiring HIV-1 infection that will be

evaluated in a subsequent follow-up study. **In addition, the use of raltegravir immediately prior to delivery in the HIV-infected mother in preterm labor may provide sufficient raltegravir drug levels in preterm infants at the time of birth to provide protection against peripartum HIV transmission.**

1.11 Recent raltegravir data from Version 1.0 and *in vitro* analysis: Washout elimination of raltegravir in term infants studied in Version 1.0 of P1097 was prolonged but highly variable, with a median half-life of 26.6 hours and a range of 9.3 to 184 hours [5]. It is crucial to understand raltegravir pharmacokinetics in all newborn populations who may receive this drug in order to develop developmentally appropriate dosing regimens that will avoid accumulation of raltegravir to potentially toxic concentrations.

1.12 Background and rationale for opening Version 2.0, Cohort 2 (low birth weight infants): In mid and lower income settings, prematurity and/or low birth weight (LBW) occurs in 20% of pregnancies [6]. Maternal HIV infection is associated with an increased rate of preterm delivery and LBW, and HIV exposed infants who are premature or LBW are more likely to become HIV infected [7]. It is critically important to develop new and potentially more effective antiretroviral regimens for use in all neonates of all gestational ages, and especially for LBW infants for both postnatal prophylaxis to prevent mother-to-child transmission and for early treatment of HIV infection.

There are few antiretroviral agents with sufficient safety and pharmacokinetic data to allow their safe use in the term neonate, and only zidovudine (ZDV) can be used safely in LBW infants [8]. The physiologic immaturity of premature and LBW infants has a major impact on pharmacokinetics and any drug proposed for use in this population must be studied directly in such infants to obtain the necessary pharmacokinetic and safety data. The only ARV that has been well studied in LBW infants is ZDV [9]. These data demonstrated a reduction in ZDV elimination associated with prematurity/LBW and resulted in development of a gestational-age specific ZDV dosing regimen for premature/LBW infants. There is a critical need for analogous safety and pharmacokinetic data for additional antiretrovirals to be used in potent combination regimens in LBW infants, and raltegravir is high on the list of antiretrovirals that need to be studied. Raltegravir has the

potential to play an important role in both prophylaxis and treatment of infants at high risk of HIV-1 infection.

1.2 Raltegravir

Raltegravir (IsentressTM) 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 [10-16].

1.21 Raltegravir Pharmacokinetics in Adults

There is considerable variability in the pharmacokinetics of raltegravir. In adults raltegravir has an initial (α) $t \frac{1}{2}$ of approximately 1 hour and a terminal elimination (β) $t \frac{1}{2}$ of approximately 7 to 12 hours [17]. 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 [18].

Moderate hepatic insufficiency and severe renal insufficiency also had no clinically meaningful effect on raltegravir pharmacokinetics [19].

Raltegravir is approved for use in both adults and children (age ≥ 2 years of age and weighing ≥ 10 kg). Raltegravir is commercially available as the 400 mg film-coated (poloxamer) tablet and the 100 mg and 25 mg chewable tablets. Raltegravir poloxamer tablets are rapidly absorbed after oral administration, with T_{max} averaging 3-4 hours in the fasted or fed states [20]. Current dosing guidelines are to administer raltegravir without regard to food [21]. Raltegravir is approximately 83% bound to plasma protein.

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 subjects. Comparison of raltegravir pharmacokinetics in the absence and presence of ritonavir, efavirenz, or etravirine indicated no

clinically significant effect on raltegravir $C_{12\text{ hr}}$ to warrant dose adjustment. Co-dosing of raltegravir with atazanavir resulted in an increase in raltegravir pharmacokinetic parameters by ~50 to 100% (AUC, C_{\max} , and $C_{12\text{ hr}}$); however, the degree of increase does not warrant raltegravir dose adjustment when these drugs are co-administered. Plasma levels of raltegravir were modestly increased by co-dosing with atazanavir and ritonavir, although the effect was somewhat less than that observed for atazanavir alone [22]. Co-dosing of raltegravir with tenofovir disoproxil fumarate indicates that raltegravir $C_{12\text{ hr}}$ was similar in the presence and absence of tenofovir while raltegravir $AUC_{0-12\text{ hr}}$ and C_{\max} values were modestly increased. Additionally, co-administration of the 2 drugs did not substantially affect the overall plasma pharmacokinetic profile of tenofovir. Rifampin co-administered with raltegravir resulted in lower raltegravir plasma concentrations. The geometric mean raltegravir $C_{12\text{ hr}}$ is 60% lower in the presence versus absence of rifampin. Approximately 40% lower AUC and C_{\max} values were also observed for raltegravir following rifampin treatment [23]. When administration of raltegravir 800 mg q12h coadministered with rifampin was compared with administration of standard raltegravir doses of 400 mg q12h without rifampin, administration of the larger dose with rifampin resulted in a 27% increase in AUC, a 62% increase in C_{\max} but a 53% decrease in $C_{12\text{hr}}$ [24]. Doubling the dose of raltegravir in the presence of rifampin compensates for the effect of rifampin on raltegravir AUC and C_{\max} but does not overcome the effect of rifampin on raltegravir trough concentrations (C_{12}) and raltegravir trough concentrations in the presence of rifampin are likely to be at the lower limit of clinical experience. Midazolam is a known CYP 3A4 substrate sensitive to drug interactions. Co-administration of rifampin and midazolam is associated with a ~96% decrease in midazolam AUC. In contrast, co-administration of raltegravir and midazolam has no effect on plasma levels of midazolam, implying that raltegravir is not an inducer or inhibitor of CYP3A4 [25].

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

Antiretroviral	<u>C12h</u>	<u>AUC</u> †	<u>Cmax</u>
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-∞} 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.

In summary, drug interaction studies to date have investigated the effects of strong inducers and inhibitors on raltegravir metabolism, and it is anticipated that these data would bracket the effects of other more modest inhibitors or inducers. In particular, the impact on raltegravir of atazanavir (a UGT1A1 inhibitor) is modest and that of rifampin (a strong inducer) is clinically manageable. Additionally, 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.

1.23 Raltegravir in Pregnancy for Prevention of Mother to Child Transmission of HIV

There is limited data available describing raltegravir use during pregnancy. The potential for integrase inhibitors to prevent establishment of infection in viral reservoirs of exposed individuals or attenuating infection have not been studied. 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 [26].

Raltegravir is currently being prescribed most commonly in pregnant women who are highly treatment experienced and have drug resistant virus or in women intolerant of other antiretroviral agents [27,28]. Rosenvinge et al. described 3 cases of raltegravir use during the 3rd trimester of pregnancy, reporting rapid reduction in maternal viral load. Maternal raltegravir concentrations 3-9 hours after delivery ranged from 22-493 ng/mL while infant concentrations 3-13 hours after delivery ranged from 209 – 3634 ng/mL [29]. Pharmacokinetic data from 10 pregnant women during the 3rd trimester reported by Best et al., demonstrated raltegravir exposure equivalent to that seen in non-pregnant adults [30]. All subjects exceeded the target concentration of a raltegravir trough concentration of 33 ng/mL. Cord blood and maternal delivery raltegravir concentrations were available from 7 mother-infant pairs - median (range) cord blood raltegravir concentration was 125 (22-939) ng/mL, median (range) maternal plasma concentration was 145 (28-626) ng/mL and the ratio of cord blood/maternal plasma concentration was 1.20 (0.09-2.26).

1.24 Raltegravir in Children

IMPAACT P1066, a study of the International Maternal, Pediatric, Adolescent AIDS Clinical Trials (IMPAACT) Group, entitled, “A Phase I/II, Multicenter, Open-Label, Non-comparative Study to Evaluate the Safety, Tolerability, Pharmacokinetics, and Antiretroviral Activity of Raltegravir (Isentress™, MK-0518) in HIV-1 Infected Children and Adolescents,” is a study of 3 raltegravir formulations across the pediatric age range of 4 weeks to 18 years of age. Raltegravir therapy was well tolerated and associated with significant improvements in virologic and immunologic outcomes. **These data have supported the approval of the raltegravir film-coated tablet in children and adolescents ≥ 12 years of age and the chewable tablet in children and adolescents 2 to < 12 years of age.**

Raltegravir in the investigational oral granules for suspension formulation in children ≥ 4 weeks to < 2 years of age is currently being studied in IMPAACT P1066, and PK and safety data in this age group are now available, including in children 6 months to < 2 years of age [31] and in an abstract by Frenkel, et al, in infants 4 weeks to < 6 months of age [32]. For infants ≥ 6 months to < 2 years of age, the GM t_{1/2} was 3.0 hours (range: 1.9-7.4 hours, n=8). For infants ≥ 4 weeks to < 6 months of age, the GM t_{1/2} was 8.2 hours (range: 2.5-111 hours, n=11). The

younger children demonstrated a prolonged distribution phase that made direct estimation of raltegravir pharmacokinetic parameters difficult and a modeling approach was used to estimate these parameters, which may be responsible for some of the apparent increase in raltegravir elimination t_{1/2} in these subjects.

1.25 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 [33].

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 [34]. 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% [22]. 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 [35,36]. 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_{1/2} 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 [23].

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 [37]. 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 [38]. 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 [39,40]. The reduction in neonatal zidovudine glucuronidation was associated not only with reduced clearance but also with higher bioavailability, consistent with decreased first pass metabolism [41].

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 μ M and binds much less avidly to UGT than does bilirubin, which has a Km of 5 μ M for UGT1A1 [18]. 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 [42]. 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 [43]. 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 μ mol/L [44]. The 95% CI for raltegravir C_{max} following 400 mg doses in adults is 15.5 μ mol/L. 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. **In addition, raltegravir has a modest plasma binding activity which may indicate less affinity relative to bilirubin for the bilirubin binding site on albumin.** By comparison, kernicterus developed in premature infants when sulfisoxazole concentrations exceeded 205 μ mol/L [45].

Evaluation for the potential of raltegravir displacement of bilirubin from albumin **was performed in the laboratory of Dr. David Stevenson** at Stanford University [42,44,45].

The *in vitro* effect of raltegravir on bilirubin-albumin binding was measured in pooled neonatal serum using the peroxidase method. Raltegravir had minimal effect on bilirubin-albumin binding at concentrations of 5 and 10 μ M, caused a small but statistically significant increase in unbound bilirubin at 100 μ M, and caused potentially harmful increases at 500 and 1000 μ M [46]. These data suggest that the effect of raltegravir on neonatal bilirubin binding is unlikely to be clinically significant at typical peak concentrations reached with usual dosing. The median (range) adult peak concentration following twice daily dosing with 400 mg is 6.5 μ M (0.8-10.2 μ M) or 2889 ng/mL (356-4533 ng/mL) [14].

Table 2: 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≤0.05), n=6 for each concentration

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)	

1.26 Results of Cohort 1 Full Term Neonates Enrolled in P1097, Version 1.0

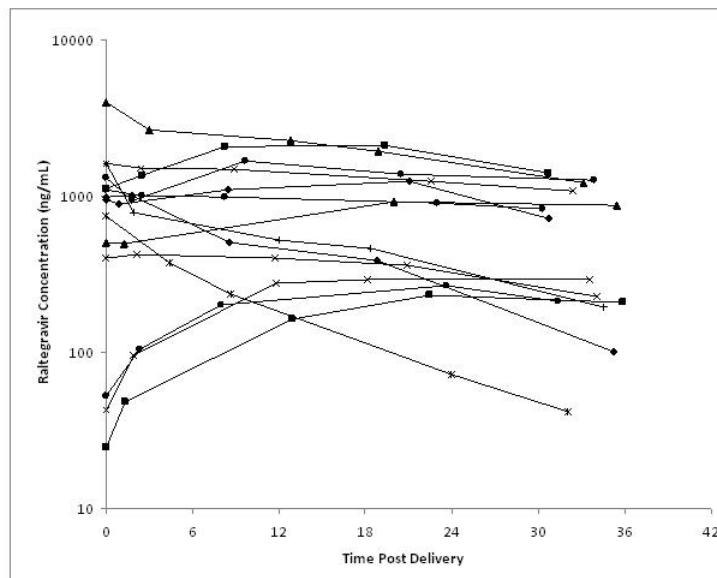
IMPAACT P1097, Version 1.0, *Raltegravir Pharmacokinetics and Safety in Neonates*, enrolled 22 mother-infant pairs: 59% of infants were African-American, 32% were white. Evaluable PK data were obtained from 19 mother-infant pairs. Median (range) PK parameters are listed below:

- Maternal delivery raltegravir concentration: 540 ng/mL (12-5809 ng/mL) or 1.22 µM (12-13.07 µM)
- Cord blood raltegravir concentration: 957 ng/mL (24-3974 ng/mL) or 2.15 µM (0.05-8.94 µM)
- Ratio of cord/maternal blood raltegravir concentration: 1.48 (0.32-4.33)
- Initial infant plasma raltegravir concentration: 671 ng/mL (13-2672 ng/mL) or 1.51 µM (0.03-6.01 µM)
- Infant plasma raltegravir concentration at 30-36 hours: 291 ng/mL (BLQ-1402 ng/mL) or 0.65 µM (BLQ-3.15 µM)
- Median infant apparent t ½ of raltegravir concentration: 26.6 (9.3-184) hours

Infant washout raltegravir concentrations initially increased before decreasing in 9 of 18 evaluable infants. All infants tolerated RAL exposure well with 20-week follow-up evaluations completed in all infants with no unexpected adverse events and no transmission of HIV infection.

From this study it was determined that raltegravir readily crosses the placenta. The plasma $t_{1/2}$ of raltegravir in neonates is highly variable suggesting potential roles for developmental aspects of neonatal UGT1A1 enzyme activity, redistribution and/or enterohepatic recirculation of raltegravir. Understanding the features of raltegravir PK in full-term and low birth weight neonates will be critical for development of a neonatal dosing regimen (see Figure 1).

Figure 1: Infant RAL Concentration-Time (hours) Plot (P1097, Version 1.0).



2.0 STUDY OBJECTIVES

2.1 Primary Objectives

- 2.11 To evaluate the washout pharmacokinetics of raltegravir in infants born to HIV-infected pregnant women receiving raltegravir during pregnancy.
- 2.12 To evaluate bilirubin levels and the safety of *in utero*/intrapartum exposure to raltegravir in infants born to HIV-infected pregnant women receiving raltegravir during pregnancy.

2.13 To develop a neonatal raltegravir dosing regimen to be evaluated in a follow-up study of this protocol.

2.2 Secondary Objective

2.21 To investigate the relationship between neonatal raltegravir elimination and UGT1A1 genotype.

3.0 STUDY DESIGN

This is a Phase 0 multi-center trial to determine the washout pharmacokinetics and safety of *in utero*/intrapartum exposure to raltegravir in infants born to HIV-infected pregnant women receiving raltegravir 400 mg twice daily.

Version 1.0, Cohort 1 (Closed)

Version 1.0, Cohort 1 enrolled full term infants and is fully accrued and closed to follow-up. Cohort 1 women were followed until discharge from the labor/delivery unit while their infants were followed for 20 weeks after birth.

Version 2.0, Cohort 2

Version 2.0 Cohort 2 will enroll up to 20 mother-infant pairs to achieve 15 evaluable low birth weight infants (≤ 2500 grams at birth).

Mother-infant (M-I) pairs may be enrolled prior to delivery or within 48 hours after birth. In addition, infants may be enrolled up to 48 hours after birth if birth weight ≤ 2500 grams and born to an HIV-infected pregnant woman who received at least one dose of raltegravir 400 mg within 2 to 24 hours prior to delivery. All infants will have a history, physical examination, and hematology and chemistry laboratory evaluations performed around the time of birth and at a week 1-2 follow-up visit.

When possible, cord blood will be drawn immediately after cord is clamped and a single blood sample will be collected from women within one hour after delivery to determine maternal plasma raltegravir concentration.

Women will be followed until discharge from the labor/delivery unit. Infants will be followed for 6 weeks after birth. Since no toxicities attributed to raltegravir exposure were observed in Cohort 1 at the 6 or 20 week visits, and since raltegravir is not administered to infants in this study, infants in Cohort 2 will have their last study visit at 6 weeks of age.

Only infants who meet the following criteria are eligible for pharmacokinetic blood sampling in Cohort 2:

- **Infant born to woman who received at least one dose of raltegravir within 2 to 24 hours prior to delivery. Dose administered to mother must have been at least 2 hours prior to delivery to allow time for adequate absorption and distribution.**
- **Infant birth weight \leq 2500 grams.**
- **Infant not receiving disallowed medications described in Section 4.8. If these medications are required for the infant's care, the infant will be ineligible for further PK (pharmacokinetic) sampling. Data will be obtained up to the time of the introduction of the disallowed medication, but such infant will not be considered one of the evaluable 15 infants.**
- **Infant \leq 48 hours of age.**

Blood samples for raltegravir assay will be collected at 1-6, 12-24, 36-48, 72-84, and 108-132 hours after birth, and on day 7-14. Infants may enroll up to 48 hours of age, and any pharmacokinetic samples scheduled for collection prior to the time of enrollment will be skipped and not replaced. Infants enrolling close to the 48-hour time point should have the first pharmacokinetic blood sample collected within 4 hours of enrollment (i.e., within 52 hours after birth) so that a minimum of three blood samples can be obtained for pharmacokinetic evaluation.

With regard to infant blood samples for safety/toxicity laboratory testing: In the event that the study-required study safety/lab samples have not been collected prior to enrollment, (e.g., due to infant enrolled after delivery), these must be collected as soon as possible after enrollment. To meet the primary objectives of the study, only those infants who have at least 3 pharmacokinetic blood samples collected from the first 5 time points will be considered to be evaluable.

Optional genotyping for polymorphisms of UGT1A1 **were performed on Cohort 1 infants and** will be performed **on Cohort 2** infants who undergo pharmacokinetic sampling. **The goal of the genotypic analysis** is to determine if certain polymorphisms, particularly those with the UGT1A1*28/*28 genotype have slower RAL elimination than those with the UGT1A1*1/*1 genotype. Because UGT1A1 activity is reduced in neonates, polymorphisms associated with reduced activity are likely to have a larger impact on the metabolism of raltegravir, especially those who are low birth weight.

No study-specific drugs will be given to women or infants during this study. Women will be receiving raltegravir for clinical indications outside of the study. Infants will receive standard of care antiretroviral therapy for prevention of mother-to-child transmission (PMTCT) as prescribed by their primary care physicians.

Refer to **Appendix II-A, Cohort 2 Maternal Schedule of Evaluations and Appendix II-B, Cohort 2 Infant Schedule of Evaluations**, for a complete description of the clinical and laboratory evaluations to be performed for **Cohort 2**.

4.0 SELECTION AND ENROLLMENT OF SUBJECTS

Mothers and infants will be enrolled as a pair but the accrual requirements will be based on the number of infants meeting the definition of evaluable for the washout PK analysis.

Cohort 1 (closed) eligibility criteria can be found in Version 1.0 of the protocol.

Cohort 2 will open to enrollment under Version 2.0 and will allow enrollment of mother-infant (M-I) pairs at two time points: prior to and within 48 hours after delivery.

- **For enrollment prior to delivery, the mother must meet all the eligibility criteria (i.e. there are no infant eligibility criteria for prenatal enrollment). However, only infants who meet all the eligibility criteria will have PK blood sampling performed. Infants must be PK eligible (see Section 4.3) and then meet the definition of evaluable to contribute to the sample size of 15 evaluable infants. PK ineligible infants will remain in the study and will be followed for safety (See Section 6.3).**
- **For enrollment within 48 hours after delivery, both mother and infant(s) must meet all the eligibility criteria. For multiple births, only infants who meet all the eligibility criteria will be enrolled.**

4.1 Maternal Inclusion Criteria, Cohort 2 - M-I pairs enrolled prior to delivery

4.11 Documentation of HIV-1 infection is defined as positive results from two samples collected at different time points. All samples tested must be whole blood, serum or plasma. For studies conducted under an IND, all test methods should be FDA-approved if available. If FDA-approved methods are not available, test methods should be verified according to GCLP and approved by the IMPAACT central laboratory.

Sample #1 may be tested by non-study public or PEPFAR programs. However, both the result and the assay date must be recorded in subject's charts. Source documentation {patient's medical record/chart, Ministry of Health (MOH) registers, laboratory results, etc.} must be available if requested.

Sample #2 must be performed in a CAP/CLIA-approved laboratory (for US sites) or in a laboratory that operates according to GCLP guidelines and participates in appropriate external quality assurance program (for international sites).

Acceptable Tests

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

- **Two rapid antibody tests from different manufacturers or based on different principles and epitopes.**
- **One EIA OR Western Blot OR immunofluorescence OR chemiluminescence**
- **One HIV DNA PCR**
- **One quantitative HIV RNA PCR (above the limit of detection)**
- **One qualitative HIV RNA PCR**
- **One HIV culture (prior to August 2009)**
- **One total HIV nucleic acid test**

If Sample #1 is positive, then collect and test Sample #2.

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

- **Rapid antibody test. If this option is used in combination with two rapid tests for Sample #1, at least one of the three rapid tests must be FDA-approved and the third rapid test must be from a third manufacturer or based on a third principle or epitope.**
- **One EIA OR Western Blot OR immunofluorescence OR chemiluminescence**
- **One HIV DNA PCR**
- **One quantitative HIV RNA PCR (above the limit of detection)**
- **One qualitative HIV RNA PCR**
- **One HIV culture (prior to August 2009)**
- **One total HIV nucleic acid test**

4.12 **Viable singleton or multiple birth pregnancy based on clinical or other obstetrical measurements with infant birth weight anticipated to be ≤ 2500 grams.**

4.13 **Raltegravir is currently used as part of maternal ARV regimen and planned to continue through labor and delivery.**

4.14 **Willing and intends to deliver at the study-affiliated clinic or hospital.**

4.15 **Willing and able to sign informed consent for participation of herself and her infant. Subject must be of an age to provide legal informed consent as defined by the country in which she resides. If not, informed consent must be signed by a legal guardian.**

4.2 **Maternal Exclusion Criteria, Cohort 2 M-I pairs enrolled prior to delivery**

4.21 **Receipt of disallowed medications within 4 weeks prior to enrollment (Section 4.8) or intent to be on any of the disallowed medications prior to delivery.**
Note: Infant(s) of a woman who received any of the disallowed medications will be ineligible for PK sampling.

4.3 **Infant PK blood sampling eligibility Criteria, for Cohort 2 M-I pairs enrolled prior to delivery**

Infants are enrolled prior to delivery so there are no infant inclusion criteria. Only infants who meet the following criteria will be eligible for pharmacokinetic blood sampling:

- **Infant born to woman who received at least one dose of RAL within 2 to 24 hours prior to delivery. Dose administered to mother must have been at least 2 hours prior to delivery to allow time for adequate absorption and distribution.**
- **Infant birth weight ≤ 2500 grams.**
- **Infant not receiving disallowed medications described in Section 4.8. If these medications are required for the infant's care, the infant will be ineligible for further PK sampling. Data will be obtained up to the time of the introduction of the disallowed medication, but such infant will not be considered one of the evaluable 15 infants if fewer than 3 PK samples from the first 5 time points are collected.**

- **Infant \leq 48 hours of age.**
- **Infant does not have any 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.**

4.4 Maternal Inclusion Criteria, Cohort 2 M-I pairs enrolled after delivery

4.41 Documentation of HIV-1 infection (See Section 4.11)

Enrollment is allowed if an initial HIV test is positive and a confirmatory test has been drawn and is pending.

4.42 Received at least one dose of RAL within 2 to 24 hours prior to delivery.

4.43 Willing and able to sign informed consent for participation of herself and her infant. Subject must be of an age to provide legal informed consent as defined by the country in which she resides. If not, informed consent must be signed by a legal guardian.

4.5 Maternal Exclusion Criteria, Cohort 2 M-I pairs enrolled after delivery

4.51 Receipt of disallowed medications within 4 weeks prior to delivery (See Section 4.8).

4.6 Infant Inclusion Criteria, Cohort 2 M-I pairs enrolled after delivery

4.61. Infant birth weight \leq 2500 grams.

4.62. Infant \leq 48 hours of age.

4.7 Infant Exclusion Criteria, Cohort 2 M-I pairs enrolled after delivery

4.71. Received disallowed medications described in Section 4.8.

Note: If any of the disallowed medications are required for the infant's care after enrollment, the infant will be ineligible for further PK sampling. Data will be obtained up to the time of the introduction of the disallowed medication, but such infant will not be considered one of the evaluable 15 infants if fewer than 3 PK samples from the first 5 time points are collected.

4.72 Infant has a 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.

4.8 Disallowed Medications

Raltegravir 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, raltegravir 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 $>50 \mu M$) and induction potential. Since raltegravir is neither an inducer nor inhibitor of cytochrome P-450 enzymes, raltegravir is not expected to result in metabolic drug interactions with substrates of cytochrome P-450.

The following medications/therapies are not permitted within 4 weeks prior to enrollment in women because these medications are potent broad inducers of drug metabolism and have been demonstrated to cross the human placenta. Their use with raltegravir may result in increased metabolism of raltegravir and lower raltegravir exposure in both mother and fetus: 1) phenobarbital; 2) phenytoin; 3) rifampin.

4.9 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.fstrf.org>) under the Systems heading.

If a potential P1097 woman who signs informed consent for herself and her infant does not meet the eligibility criteria as outlined in Section 4.0, or the woman withdraws consent prior to enrollment, the site **MUST** notify the protocol team. This communication should include the reason the woman or infant was ineligible or if the woman withdrew consent. Data on reasons why the woman or infant is ineligible will be collected in the DMC database. This information may be used by Merck & Co., Inc. when reporting to Regulatory Agencies.

4.10 Co-enrollment Procedures

Co-enrollment in the raltegravir arms of P1026S and P1081 will be allowed. Co-enrollment in other research protocols will require the consent of the protocol chair of P1097 and the other research protocol.

5.0 STUDY TREATMENT

No treatment or intervention will be provided as part of this study. Infants will receive standard of care antiretroviral therapy for PMTCT as prescribed by their primary care physicians. HIV-infected pregnant women will be receiving raltegravir as prescribed by their care provider as part of a regimen for treatment of maternal HIV disease and/or prevention of mother to child transmission of HIV.

6.0 SUBJECT MANAGEMENT

6.1 Toxicity Management

This study does not contain any study-specific treatment or intervention, thus there is no need for toxicity management through the DAERS system. However, safety data will be collected and reviewed by the study team on regular team conference calls.

6.2 Permanent Study Discontinuation

The woman and/or infant will be discontinued from the study for the following reasons:

- The woman and/or infant is lost to follow up.
- The woman and/or infant is not able to attend study visits as required by the study.
- The subject/parent/guardian withdraws consent.
- The investigator determines that further participation would be detrimental to the woman's or infant's health or well-being.

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 sponsor, or other governmental agencies.

6.3 Premature Discontinuation/Early Withdrawal/Safety Follow-up for PK Unevaluable Infants

Cohort 1 (Closed): If the infant is not eligible for pharmacokinetic sampling, study evaluations will be performed for safety monitoring between 8-14 hours after birth, 30-36 hours after birth, week 1-2 and week 20. If the parent withdraws consent at any time after enrollment, no further information will be collected and additional laboratory evaluations will not be performed.

Cohort 2: If fewer than 3 pharmacokinetic samples from the first 5 time points are collected, the infant is not considered evaluable for pharmacokinetics but will continue with scheduled safety evaluations. If the parent withdraws consent at any time after enrollment, no further information will be collected and additional laboratory evaluations will not be performed.

7.0 EXPEDITED ADVERSE EVENT REPORTING

This study does not contain any study-specific treatment or intervention, thus no expedited adverse event (EAE) reporting is required. Every effort will be made by study staff to provide appropriate care and counseling to the participant, and/or referral to appropriate resources for the safety of the participant as needed. Any unanticipated problems will be reported to the DAIDS Medical Officer at the

same time as the problems are reported to the responsible site IRB/Ethics Committees (ECs) overseeing the research according to pre-established procedures as required by 45 CFR 46.

8.0 STATISTICAL CONSIDERATIONS

8.1 General Design Issues

This is a multi-center pilot trial to estimate washout pharmacokinetics and safety of raltegravir in infants born to HIV-infected pregnant women receiving raltegravir prior to delivery and continuing during labor. Results of the washout pharmacokinetics will be used to develop an initial neonatal dosing regimen of raltegravir to be evaluated in a follow-up study.

There are two cohorts:

- **Cohort 1 (fully accrued and follow up complete): M-I pairs were enrolled prior to delivery (at \geq 35 weeks gestation); and**
- **Cohort 2: This cohort will enroll low birth weight infants (weight \leq 2500 grams at birth) prior to delivery or within 48 hours after delivery.**

The protocol was amended to Version 2.0 to enroll low birth weight (\leq 2500 grams) infants in Cohort 2. Cohort 2 will accrue mother-infant (M-I) pairs until 15 evaluable infants have been enrolled for the washout pharmacokinetic analysis.

No study-specific treatment will be given to mother or infant during this study. Washout pharmacokinetic data and analyses are described in detail in Section 9.0. Safety data will include adverse birth outcomes and infant adverse events observed during follow-up. **Cohort 1 safety data will be analyzed separately from Cohort 2 safety data.**

This is a pilot study and the sample size has been determined by the protocol pharmacologist to provide enough information needed to develop an initial LBW neonatal dosing regimen for a follow-up study (IMPAACT P1110). The safety analysis will include the data on all enrolled infants, including infants who were not evaluable for the washout pharmacokinetic analysis. The study is not powered for the analysis of the safety data. Descriptive statistics will be generated to summarize the safety data.

Unless otherwise indicated, the rest of the subsections below refer to both Cohorts 1 and 2.

8.2 Outcome Measures

8.21 Primary Outcome Measures:

Pharmacokinetic Outcome Measures:

- Neonatal raltegravir elimination ($t_{1/2}$). See Section 9.0.
- Raltegravir maternal-cord blood ratio. See Section 9.0 **for Cohort 1 only**

Note: Cord blood and maternal delivery plasma samples will not be collected from Cohort 2 M-I pairs who enroll after delivery.

Safety Outcome Measures:

- Infant adverse events of Grade 3 or 4 as defined in DAIDS Table for Grading the Severity of Adult and Pediatric Adverse Events (DAIDS AE Grading Table), Version 1.0, dated December 2004, Clarification August 2009, which is available on the RSC website at <http://rsc.tech-res.com/safetyandpharmacovigilance>
 - Adverse birth outcomes including stillbirth and low birth weight **(for Cohort 1 only)**
 - Infant death
 - Total bilirubin
 - Direct bilirubin

For Cohort 1, occurrence of infant adverse events of Grades 3 or 4 adverse birth outcomes, and infant death will constitute the infant meeting a toxicity endpoint. For Cohort 2, occurrence of infant adverse events of Grades 3 or 4 and infant death will constitute the infant meeting a toxicity endpoint. **As part of the secondary safety analysis for Cohorts 1 and 2, (i) information on number and proportion of infants requiring therapy (e.g. phototherapy, exchange transfusion) to reduce bilirubin and (ii) summary statistics for total and direct bilirubin will be provided.**

8.22 Secondary Outcome Measures:

Pharmacokinetic Outcome Measures:

- Optional genotyping for polymorphism of UGT1A1 from infants who are eligible for pharmacokinetic sampling as described in Section 9.0.

8.3 Randomization and Stratification

There will be no randomization and no stratification.

For Cohort 1, because of the potential for a drug interaction between atazanavir and raltegravir, the number of women enrolled receiving an atazanavir-containing regimen **was** limited to three. **This restriction has been removed for Cohort 2.**

8.4 Sample Size and Accrual

The target accrual for Cohort 1 was 15 evaluable infants which was projected to require enrolling up to 25 M-I pairs and approximately 12 months to fully accrue. Cohort 1 is fully accrued with 19 evaluable infants (22 M-I pairs).

Cohort 2 will enroll M-I pairs until a total of 15 evaluable infants are accrued which is projected to require enrolling up to 20 M-I pairs. The projected accrual period is 12 months. Evaluable infants will be those who have at least 3 PK blood samples collected following the PK schedule in Section 9.3.

This is a pilot study aimed at gathering information needed for the design of a follow-up study that will evaluate a neonatal raltegravir dosing regimen. The sample size of 15 evaluable infants reflects the judgment of the team pharmacologists with respect to the amount of washout pharmacokinetic data needed to design the later follow-up dosing study. It is based on practical considerations and experience with other antiretroviral drugs such as nevirapine and tenofovir in pregnant women and their neonates [47-50].

All infants enrolled to the study, including those not evaluable for the washout pharmacokinetic analysis, will be included in the safety analyses. The study is not powered for analysis of the safety data so that no hypothesis testing will be done but descriptive summary statistics will be calculated. Given the relatively small study sample, the precision of the estimates will be relatively low and the confidence interval (CI) estimates will be relatively wide. Table 2 shows the precision with which rates of serious adverse events can be estimated, given the sample size of 15, 20 or 25 infants.

Table 2. Point and 90% confidence interval estimates of proportion of infants meeting the toxicity endpoint^a

Number of infants	Proportion of infants meeting toxicity endpoint	90% CI of proportion of infants meeting the toxicity endpoint
15	0.00	(0.00, 0.22)
	0.20	(0.04, 0.48)
	0.40	(0.16, 0.68)
	0.60	(0.32, 0.84)
	0.80	(0.52, 0.96)
	1.00	(0.78, 1.00)
20	0.00	(0.00, 0.17)
	0.20	(0.06, 0.44)
	0.40	(0.19, 0.64)
	0.60	(0.36, 0.81)
	0.80	(0.56, 0.94)
	1.00	(0.83, 1.00)
25	0.00	(0.00, 0.14)
	0.20	(0.07, 0.41)
	0.40	(0.21, 0.61)
	0.60	(0.39, 0.79)
	0.80	(0.59, 0.93)
	1.00	(0.86, 1.00)

^a Clopper-Pearson exact confidence interval estimates using SAS Version 9.2.

8.5 Monitoring

Reports on accrual and toxicity, compiled by the Data Management Center (DMC), will be reviewed and discussed by the Protocol Team on conference calls held monthly. Conference calls will also be scheduled as needed in response to any adverse event that requires the immediate attention of the Protocol Team. Notification of team members will be by e-mail, phone or fax, depending on time differences.

The safety of maternal transfer of RAL to the neonate will be monitored by means of adverse events reports and toxicity reports presenting laboratory and clinical events. It is the responsibility of the protocol team to interpret the toxicity data, and make any decisions needed to protect subjects from undue risk.

The team will monitor feasibility quarterly, first based on site registration and then on accrual. Initially, the team will monitor site registration quarterly to ensure that an adequate number of sites have registered to complete the protocol. If less than one-third of eligible sites have registered after the protocol has been approved for 6 months, the team will re-assess the feasibility of the protocol and the reasons why sites have not registered, and will amend the protocol accordingly.

See P1097, Version 1.0, for the monitoring of Cohort 1 accrual.

Cohort 2 will be monitored for accrual by a Study Monitoring Committee (SMC) to be appointed per IMPAACT Standard Operating Procedures. The SMC will assess accrual 6 months after Cohort 2 opens to enrollment and protocol version 2.0 has been approved by IRB/ ECs at 50% of eligible sites, and perform an independent review of the data. If Cohort 2 has not met the accrual target subjects (7 eligible infants) by the 6-month timeframe, the protocol team will be required to provide a written plan to increase accrual prior to the SMC 6-month review at which time the SMC will consider whether to recommend closing the study to enrollment.

A full monitoring plan will be developed for each cohort before the cohort opens to accrual. The monitoring plan would include the study monitoring described above as well as the details for monitoring the specimens needed for the pharmacokinetic analyses.

8.6 Analyses

See Section 9.0 for a discussion of PK analyses.

The safety analysis will consist of descriptive statistics summarizing the safety data **through week 20 for Cohort 1 and through week 6 for Cohort 2**. 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 **composite** toxicity endpoint. Secondary safety analyses will include (1) point and 90% CI estimates of infants meeting each toxicity endpoint; (2) frequency tabulations of worst grade adverse events for each subject; **(3) summary statistics of total and direct bilirubin at each required sampling time and (4) point and 90% CI estimates of infants requiring therapy (e.g. phototherapy, exchange transfusion) to reduce bilirubin.**

A statistical analysis plan specifying details of administrative analyses and full details of primary and secondary analyses of the safety data will be

developed for each cohort. It is expected that analysis of Cohort 2 will combine data from M-I pairs enrolled pre- and post-delivery.

9.0 CLINICAL PHARMACOLOGY PLAN

9.1 Pharmacology Objective

The clinical pharmacology objective of this study is to estimate raltegravir elimination ($t_{1/2}$) in neonates born to women receiving raltegravir as part of HAART during pregnancy. When P1066 pharmacokinetic data are available for the 4 weeks to <2 year old cohort, there will be a much better understanding of infant dosing, and bioavailability of the new oral granules for suspension formulation will be known. Those data, coupled with data collected from this study examining the raltegravir washout pharmacokinetics in neonates born to women receiving raltegravir, will provide a more solid foundation upon which to base the design of the later follow-up study (active single dose and multiple dose raltegravir pharmacokinetic studies in infants).

9.2 Primary and Secondary Data

Demographic data and recent dosing history including food intake, delivery information and sample collection times will be collected. The goal is to estimate clearance in the infants and provide guidance on when to initiate dosing, dose and dosing regimen in the infants for the later (active single dose and multiple dose) follow-up study.

Information obtained about the effect of UGT1A1 polymorphisms on the pharmacokinetics of raltegravir will provide a better understanding of the effect of genetics on the metabolism of raltegravir in neonates.

Laboratory Analysis and Reporting

Blood samples will be collected in standard EDTA tubes. Frozen plasma will be batched and shipped to the University of Alabama Pharmacology Specialty Laboratory (UAB PSL). All PK samples and results will be registered in the Laboratory Data Management System (LDMS) database.

Raltegravir concentrations will be measured using a validated HPLC-MS-MS method [51].

9.3 Study Design, Modeling and Data Analysis

Cohort 1 (Closed)

There will be no infant dosing for this study. Women must have received at least two weeks of raltegravir prior to delivery and continue to receive raltegravir during labor prior to delivery as well as their other ARVs.

Maternal raltegravir concentration: One maternal blood sample will be obtained within one hour after delivery. In addition, a single cord blood specimen will be collected at the time of birth.

Neonatal: Blood samples for raltegravir concentration determinations will be collected between 1-5, 8-14, 18-24, and 30-36 hours post-delivery. Sample times chosen will allow for flexibility at the sites for the collection of raltegravir concentrations. The first pharmacokinetic sample will be close to the time of the peak raltegravir concentration while the next three samples will be collected during the elimination phase.

Cohort 2

There will be no infant dosing for this study. Women must have received at least one dose of raltegravir within 2 to 24 hours prior to delivery. Dose must be administered at least 2 hours prior to delivery to allow adequate time for absorption and distribution.

Maternal and cord blood raltegravir concentrations: When possible, for example, pre-delivery enrollment, one maternal blood sample will be obtained within one hour after delivery and a single cord blood specimen at the time of birth. For infants enrolled after delivery up to 48 hours after birth, it will not be possible to obtain maternal or cord blood samples.

Neonatal raltegravir concentrations: Blood samples for raltegravir assay will be collected at 1-6, 12-24, 36-48, 72-84, and 108-132 hours after birth, and on day 7-14. Infants may enroll up to 48 hours of age, and any pharmacokinetic samples scheduled for collection prior to the time of enrollment will be skipped and not replaced. Infants enrolling close to the 48-hour time point should have the first pharmacokinetic blood sample collected within 4 hours of enrollment (i.e., within 52 hours after birth) so that a minimum three blood samples can be obtained for pharmacokinetic evaluation.

Analysis for Cohort 1 and Cohort 2

Regression analysis will then be used to estimate the terminal phase of raltegravir elimination in the neonates. Since this study will not include a full intensive PK evaluation we will not have an estimate of distribution volume and thus clearance cannot be calculated directly. To resolve this, we will assume the same average distribution volume from subjects ≥ 4

weeks to <6 months of age in Cohort V in P1066 to calculate raltegravir clearance in the neonates. This will provide an initial estimate of the dose required in neonates to produce a similar AUC compared to the youngest P1066 cohort.

9.4 Anticipated Outcomes

The goal is to estimate raltegravir clearance in **both term and low birth weight** neonates following maternal dosing of raltegravir as part of HAART. These data, along with those collected from P1066 will assist in understanding how to dose this drug in the neonatal population.

10.0 HUMAN SUBJECTS

10.1 Institutional Review Board and Informed Consent

This protocol, the informed consent documents (Appendix IV-A and IV-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 subjects who cannot consent for themselves, such as those below the legal age. The informed consent will describe the purpose of the study, the procedures to be followed, and the risks and benefits of participation. A copy of the consent form will be given to the parent or legal guardian.

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

10.2 Subject Confidentiality

All laboratory specimens, evaluation forms, reports, and other records will be identified only by a coded number to maintain subject confidentiality. All records will be kept in a secured area. All computer entry and

networking programs will be done with coded numbers only. Clinical information will not be released without written permission of the subject, except as necessary for monitoring by the study staff, study monitors, drug company supporting the study, and 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 sponsor, or other governmental agencies as part of their duties to ensure that research subjects are protected.

11.0 PUBLICATION OF RESEARCH FINDINGS

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

12.0 BIOHAZARD CONTAINMENT

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

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

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APPENDIX I-A

COHORT 1 MATERNAL SCHEDULE OF EVALUATIONS (CLOSED)

	Screening	Labor/delivery
Informed Consent	X	
CLINICAL EVALUATIONS		
History	X ¹	X ²
PHARMACOKINETICS		
Maternal RAL concentration ³		1mL
OTHER		
Cord Blood ⁴		1mL
TOTAL BLOOD		2mL

1. Obtain complete history including documentation of HIV-1 infection, demographic data and antiretroviral medications.
2. Obtain complete history including maternal antiretroviral dosing history, labor and delivery record, and obstetrical gestational age.
3. Collect 1mL of blood within one hour after delivery.
4. Draw 1mL of cord blood immediately after cord is clamped.

APPENDIX I-B

COHORT 2 MATERNAL SCHEDULE OF EVALUATIONS

	Screening/entry	Labor/delivery ⁶	Post-Delivery (1-5 days after delivery)
Informed Consent	X		
CLINICAL EVALUATIONS			
History	X ¹	X ²	X ²
PHARMACOKINETICS⁷			
Maternal RAL concentration ³	1mL ⁴ If enrolled after delivery	1mL ⁴ If enrolled before delivery	
OTHER ⁷			
Cord Blood ^{3,5}		X	
TOTAL BLOOD	1mL	1mL	0mL

1. History data at Screening/entry includes documentation of HIV-1 infection, demographic data and antiretroviral dosing history 3 months prior to entry.
2. History data after Screening/entry includes antiretroviral dosing while on study, labor and delivery record, and obstetrical gestational age. It is strongly recommended that the site report, prospectively if possible, the mother to the Antiretroviral Pregnancy Registry (<http://www.apregistry.com/reg.htm>):
 US/Canada telephone: 800-258-4263, fax 800-800-1052
 Brazil: fax 888-259-5618
 International: phone: 910-679-1598, fax: 910-256-0637
 Email: pregnancyregistries@incresearch.com
3. Mother/infant pairs may be enrolled up to 48 hours after delivery. In these situations it may not be possible to collect the maternal and cord blood samples at labor and delivery.
4. For women enrolled prior to delivery, collect 1mL of maternal blood within one hour after delivery. For women enrolled after delivery, collect 1mL of maternal blood at the time of enrollment.
5. Draw cord blood immediately after cord is clamped.
6. Not applicable to women enrolled after delivery.
7. See the Laboratory Processing Chart (LPC) on the P1097 Protocol Specific Webpage on the IMPAACT website (<http://www.impaactgroup.org>) for collection, processing and shipping instructions.

APPENDIX II-A

COHORT 1 INFANT SCHEDULE OF EVALUATIONS
(CLOSED)

	Birth	1-5 hours after birth	8-14 hours after birth	18-24 hours after birth	30-36 hours after birth	Week 1-2	Week 20
CLINICAL EVALUATIONS							
History						X ²	X ²
Physical exam	X ¹					X ³	X ³
LABORATORY EVALUATIONS							
Hematology ^{4,6}			0.5 mL			0.5mL	
Chemistries ^{5,6}			1mL		1mL	1mL	
VIROLOGY							
Genotyping ⁷					Dried Blood Spot		
PHARMACOKINETICS*							
Washout ⁸		1mL	1mL	1mL	1mL		
TOTAL BLOOD	0mL	1mL	2.5mL	1mL	2 mL	1.5mL	0mL

*See section 3.0 and 4.3 for criteria for infants eligible for pharmacokinetic blood sampling.

1. Physical examination includes infant Apgar score, birth weight and length, gestational age, gender, sex, and ethnicity.
2. History includes all non-protocol laboratory tests, HIV test results, antiretroviral agents (for PMTCT), concomitant medications, and any intercurrent illnesses since the last visit.
3. Complete physical exam includes temperature, heart rate, respiratory rate, weight, length, and head circumference.
4. Hematology includes CBC (complete blood count) with differential and platelet count.
5. Chemistries include AST, ALT, creatinine and total and direct bilirubin.
6. Infants not eligible for pharmacokinetic sampling will have hematology and chemistries obtained at 8-14 hours after birth and at 1-2 weeks of age, with additional chemistries at 30-36 hours after birth.
7. Genotyping (optional) for UGT1A1 polymorphisms will be done using dried blood spot on filter paper. Only infants who have pharmacokinetic sampling will have genotyping done. (Option: Can collect at week 1-2 if unable to obtain immediately after birth).
8. Only infants eligible for pharmacokinetic blood sampling (See Section 3.0 and 4.3). Collect 1mL of blood for each sample

Priority of blood draw should be as follows: 1) Chemistries; 2) Hematology; 3) Pharmacokinetics; 4) Genotyping

APPENDIX II-B
COHORT 2 INFANT SCHEDULE OF EVALUATIONS

	Birth/Entry	1-6 hours after birth ¹¹	12-24 hours after birth ¹¹	36-48 hours after birth	72-84 hours after birth	108-132 hours after birth	Week 1-2 (7-14 days after birth)	Week 6 (35-49 days after birth)
CLINICAL EVALUATIONS								
History				X ²			X ²	X ²
Physical exam	X ¹						X ³	X ³
LABORATORY EVALUATIONS (if not obtained for standard of care)								
Hematology ^{4,6}				0.5mL ⁴			0.5mL	
Chemistries ^{5,6}					1mL ⁵		1mL	
Bilirubin ^{6,7}				1mL ⁷				
PHARMACOGENETICS¹⁰								
Genotyping ⁸					0.125mL			
PHARMACOKINETICS^{*10}								
Washout ⁹		0.25 mL	0.25 mL	0.25 mL	0.25mL	0.25mL	0.25mL	
TOTAL BLOOD	0mL	0.25mL	0.25mL	1.75mL	1.375mL	0.25mL	1.75mL	0mL

*See section 3.0 and 4.6 for criteria for infants eligible for pharmacokinetic (PK) blood sampling.

1. Physical examination includes infant Apgar score, birth weight and length, head circumference, gestational age, gender, sex, and ethnicity.
2. History includes all non-protocol laboratory tests, HIV test results, antiretroviral agents for PMTCT, concomitant medications, signs and symptoms, diagnoses, and any intercurrent illnesses since the last visit, including any treatment to reduce bilirubin.
3. Complete physical exam includes temperature, heart rate, respiratory rate, weight, length, and head circumference.
4. Hematology to include CBC with differential and platelet count: If hematology testing was done as part of clinical care within 48 hours, report values obtained for clinical care and do not obtain additional study sample.
5. Chemistries include AST, ALT, creatinine and total and direct bilirubin: If chemistry testing was done as part of clinical care within 24 hours, report values obtained for clinical care and do not obtain additional study sample.
6. Both PK eligible and ineligible infants will have laboratory evaluations collected unless obtained as part of clinical care (see Footnotes 4, 5, and 7). If infant enrolls after birth, hematology, chemistries, and bilirubin should be obtained with first PK blood draw for those infants eligible for PK.
7. Bilirubin includes total and direct: If bilirubin testing was done as part of clinical care within 24 hours, report values obtained for clinical care and do not obtain additional study sample.
8. Genotyping (optional) for UGT1A1 polymorphisms will be done using dried blood spot on filter paper. Only infants who have PK sampling will have genotyping.
9. Only infants eligible for PK blood sampling (See Section 3.0 and 4.3). Collect 0.25mL of blood for each sample. Infants enrolled after delivery up to 48 hours may not have the initial PK samples obtained but will start as soon as possible. (Note: Infants enrolled close to the 48-hour time point should have the first PK blood sample collected within 4 hours of enrollment (i.e., within 52 hours after birth).
10. See the Laboratory Processing Chart (LPC) on the P1097 Protocol Specific Webpage on the IMPAACT Website (<http://www.impaactgroup.org>) for collection, processing and shipping instructions.
11. Skip visit if enrolled after scheduled time of visit.

Priority of blood draws should be: chemistries, hematology, pharmacokinetics, genotyping.

APPENDIX III
P1097 TESTING LABORATORIES

PHARMACOKINETICS

University of Alabama at Birmingham
Attn: Kedria Walker
Division of Pharmacology
1670 University Blvd.
Volker Hall Room 270
Birmingham, AL 35294-0019
Phone: 205-975-2461
Fax: 205-934-6201
E-mail: kedria@uab.edu
LDMS Lab# 191

DBS FOR GENOTYPING

Stephen A Spector, M.D.
University of California, San Diego
Department of Pediatrics
Division of Infectious Diseases
Stein Clinical Research Bldg. Room 430
Attn: Rodney Trout
9500 Gilman Drive, Mail Code 0672
La Jolla, CA 92093-0672
Office Phone: 858-534-7055
Fax: 858-534-7411
E-mail: saspector@ucsd.edu
LDMS Lab# 173

APPENDIX IV-A

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

SAMPLE INFORMED CONSENT FOR COHORT 1 (CLOSED)

IMPAACT P1097: Raltegravir Pharmacokinetics and Safety in Neonates, Version 2.0,
dated 22 January 2014

INTRODUCTION

You and your baby are being asked to take part in this research study because you are infected with the Human Immunodeficiency Virus (HIV), the virus that causes AIDS. 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/allow your baby to take part in this study, you will be asked to sign this consent form. You will get a copy to keep.

WHY IS THIS STUDY BEING DONE?

The purpose of this study is to find out if raltegravir, one of the drugs you are taking while pregnant for treatment of your HIV infection and to prevent passing HIV to your unborn baby, is getting into your unborn baby. Another purpose of this study is to look for possible side effects of raltegravir in your baby, such as more jaundice (yellow color to skin). Another purpose of this study is to look at your baby's DNA and its effect on how raltegravir is broken down by the body. We know that some people break down medications differently based on their DNA and could have much higher blood levels than other people and have more side effects. Information from this study may be used to design a future study to find the right dose of raltegravir to give to infants who need additional anti-HIV medications to prevent them from getting HIV.

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

You will continue to take the anti-HIV medications prescribed by your doctor while you are in this study. After you deliver your baby, your baby's doctor may recommend that your baby take anti-HIV medication but neither you nor your baby will receive any medication as part of this study.

Screening visit to see if you can be in this study

If you agree to/ allow your baby to take part in this study, you will be asked to sign this consent form. If you decide you want you and your baby to be in this study, we will get your medical history and we will ask you questions about how you are feeling and what medications you are taking. This is the only test that will be done at screening.

Study visit at labor/delivery

You will have a medical history to find out how you are feeling and what medications you are taking. A blood sample will be collected from the placenta (afterbirth) after delivery. You will have one blood sample taken to measure the amount of medication in your blood. About 2mL (less than one-half of a teaspoon of blood) will be drawn at this visit. After these tests are taken, your participation in the study will end.

Study visits for your baby

- At birth and two other times while your baby is in this study, your baby will have a medical check-up and a physical examination that includes length, weight, head measurement and temperature, heart rate, and respiratory rate.
- All babies in this study will have blood taken 2 times within 36 hours after birth and once at 1-2 weeks of age for routine tests.
- If your baby is able to have repeat blood samples taken to find out how much raltegravir you took during pregnancy is getting into your baby, your baby will also have one blood sample taken at four time points immediately after birth to measure the amount of medication in the blood. About 1mL, or less than one-quarter of a teaspoon (*sites – add locally relevant description of blood volume*) of blood will be taken for each sample. These blood samples will be collected at the same time as the routine tests for this visit.
- If you agree and your baby had repeat blood samples taken to check the amount of raltegravir in your baby, your baby will have one drop of blood taken once during the study to check your baby's DNA (genes). 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 _____
- Each of your baby's study visits will last about (*sites – add local information about time for study visits*) and the total amount of blood to be drawn for these visits will be between 1-2.5 mL (less than one quarter to one-half of a teaspoon) [*sites - add locally relevant description of blood volume*] depending on the tests to be done.
- Your baby will be in this study until your baby is 5 months of age.

HOW MANY PEOPLE WILL TAKE PART IN THIS STUDY?

About 25 HIV-infected pregnant women and their infants 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 deliver your baby. Your baby will be in this study until your baby is 5 months of age.

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/your baby are/is not able to attend the study visits as required by the study.
- The investigator determines that further participation would be detrimental to your/your baby's health or well-being.

WHAT ARE THE RISKS OF THE STUDY?

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. Lightheadedness and fainting can also occur. The DNA blood test can also be done by heel stick. Heel stick test 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?

This study will be of no direct benefit to you or your baby. 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 in this study or allow your baby to take part in this study. You may leave the study at any time or take your baby out of this study at any time. Please talk to your doctor about other choices available to you.

WHAT HAPPENS IF I AM/MY BABY IS INJURED?

If you are/your baby is injured as a result of being in this study, you/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, 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, 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 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 company supporting the study, and 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 or your 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 company supporting this study and designees.

WHAT ARE THE COSTS TO ME?

There is no cost to you for your/your baby's study visits, examinations, or blood tests.
[Note to sites: This statement can be modified as needed for your site.]

Taking part in this study may lead to added costs to you and your insurance company. In some cases it is possible that your insurance company will not pay for these costs because you are/your baby is taking part in a research study. *[Note to sites: Language related to insurance can be deleted if it is not relevant to your site.]*

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

Taking part in this study is completely voluntary. You may choose not to take part/not to allow your baby to take part in this study or leave this study/take your baby out of the study at any time. Your decision will not have any impact on your or 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 or your baby are 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 take part in this study or to allow your baby to take part in this study, please sign your name below.

Participant's Name (print)

Participant's Signature and Date

Participant's Legal Guardian (print)

Legal Guardian's Signature and Date

(As appropriate)

Study Staff Conducting

Study Staff Signature and Date

APPENDIX IV-B

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

SAMPLE INFORMED CONSENT COHORT 2

IMPAACT P1097: Raltegravir Pharmacokinetics and Safety in Neonates, Version 2.0, dated 22 January 2014

INTRODUCTION

You and your baby are being asked to take part in this research study because you are infected with the Human Immunodeficiency Virus (HIV), the virus that causes AIDS. 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/allow your baby to take part in this study, you will be asked to sign this consent form. You will get a copy to keep.

WHY IS THIS STUDY BEING DONE?

The purpose of this study is to find out if raltegravir, one of the drugs you are taking while pregnant for treatment of your HIV infection and to prevent passing HIV to your unborn baby, is getting into your unborn baby. Another purpose of this study is to look for possible side effects of raltegravir in your baby, such as more jaundice (yellow color to skin). Another purpose of this study is to look at your baby's DNA and its effect on how raltegravir is broken down by the body. We know that some people break down medications differently based on their DNA and could have much higher blood levels than other people and have more side effects. Information from this study may be used to design a future study to find the right dose of raltegravir to give to infants who need additional anti-HIV medications to prevent them from getting HIV.

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

You will continue to take the anti-HIV medications prescribed by your doctor while you are in this study. After you deliver your baby, your baby's doctor may recommend that your baby take anti-HIV medication but neither you nor your baby will receive any medication as part of this study.

Screening visit to see if you can be in this study

If you agree to/ allow your baby to take part in this study, you will be asked to sign this consent form. If you decide you want you and your baby to be in this study, we will get your medical history and we will ask you questions about how you are feeling and what medications you are taking. Your doctor may ask your permission to report the medicine you take to a national registry, which collects information anonymously on the use of HIV medicine during pregnancy, and any effects these medicines may have on infants. This information is completely confidential and your name will not be used.

Study visit at labor/delivery

You will have a medical history to find out how you are feeling and what medications you are taking. A blood sample will be collected from the placenta (afterbirth) after delivery. You will have one blood sample taken to measure the amount of medication in your blood. About 1 mL (less than one-quarter of a teaspoon of blood) will be drawn at this visit. After these tests are taken, your participation in the study will end.

Study visits for your baby

- **Your baby will have a medical check-up and a physical examination 3 times during the study. The physical examination will include length, weight, head measurement and temperature, heart rate, and respiratory rate.**
- **Your baby will have blood taken 3 times during this study for routine tests if these tests were not done by your baby's doctor as part of your baby's routine care. Between 0.5 and 1.5mL (less than ¼ teaspoon of blood) will be taken for these tests if they are required.**
- **Your baby will have repeat blood samples taken to find out how much raltegravir you took during pregnancy is getting into your baby. About 0.25mL (about 1/20th of a teaspoon (*sites – add locally relevant description of blood volume*) of blood will be taken for each sample. These blood samples will be collected at 1-6 hours, 12-24 hours, 36-48 hours, 72-84 hours, 108-132 hours and day 7-14 after birth**

If you agree and your baby had repeat blood samples taken to check the amount of raltegravir in your baby, your baby will have about 0.125mL (about 1/20th of a teaspoon) of blood taken once during the study to check your baby's DNA (genes). 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 _____
- Each of your baby's study visits will last about (*sites – add local information about time for study visits*) and the total amount of blood to be drawn at each visit will be between 0.25 to 1.75mL (about 1/20th to 1/3rd of a teaspoon [*sites – add locally relevant description of blood volume*]) depending on the tests to be done. Your baby will be in this study until your baby is 6 weeks of age.

HOW MANY PEOPLE WILL TAKE PART IN THIS STUDY?

A total of 22 HIV-infected pregnant women and their infants have completed the first part of the study. An additional 20 HIV-infected pregnant women and their infants will be enrolled.

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

You will only be in this study until you are discharged from the labor/delivery unit. Your baby will be in this study until your baby is 6 weeks of age.

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 sponsor and other governmental agencies. An IRB/EC is a committee that watches over the safety and rights of research subjects.
- You/your baby are/is not able to attend the study visits as required by the study.
- The investigator determines that further participation would be detrimental to your/your baby's health or well-being.

WHAT ARE THE RISKS OF THE STUDY?

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. Lightheadedness and fainting can also occur. The DNA blood test can also be done by heel stick. The heel stick test 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?

This study will be of no direct benefit to you or your baby. 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 in this study or allow your baby to take part in this study. You may leave the study at any time or take your baby out of this study at any time. Please talk to your doctor about other choices available to you.

WHAT HAPPENS IF I AM/MY BABY IS INJURED?

If you are/your baby is injured as a result of being in this study, you/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, 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, 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 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 company supporting the study, and 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 or your 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 company supporting this study and designees.

WHAT ARE THE COSTS TO ME?

There is no cost to you for your/your baby's study visits, examinations, or blood tests. [Note to sites: This statement can be modified as needed for your site.]

Taking part in this study may lead to added costs to you and your insurance company. In some cases it is possible that your insurance company will not pay for these costs because you are/your baby is taking part in a research study. [Note to sites: Language related to insurance can be deleted if it is not relevant to your site.]

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

Taking part in this study is completely voluntary. You may choose not to take part/not to allow your baby to take part in this study or leave this study/take your baby out of the study at any time. Your decision will not have any impact on your or 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 or your baby are 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 take part in this study or to allow your baby to take part in this study, please sign your name below.

Participant's Name (print)

Participant's Signature and Date

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

(As appropriate)

Study Staff Conducting

Study Staff Signature and Date