Raltegravir Pharmacokinetics and Safety in Neonates
Rationale

- Urgent need for alternative agents for infants at high risk of HIV-1 infection
- Limited safety and dosing information for ARVs in neonates, both for PMTCT and for early treatment
- Raltegravir (RAL) has potential to play an important role in both prophylaxis and treatment of infants at high risk of HIV-1 infection
  - RAL use associated with rapid decline in HVL
  - Integrase inhibitor - unique mechanism of action
  - Well tolerated in children and adults
  - Currently under study in infants in P1110
Background

- RAL metabolism likely to be much slower in neonates
  - RAL metabolized by UDP glucuronyl transferase (UGT) 1A1 – same metabolic pathway as bilirubin
  - UGT1A1 activity greatly reduced in neonates but increases over the first months of life

- Version 1.0, Cohort 1 enrolled full term infants
  - Fully accrued and closed (n=22, 19 PK evaluable)
  - Results published J Acquir Defic Syndr Nov 2014
Background

- Version 2.0, Cohort 2 is enrolling low birth weight (LBW) infants
  - Infant birth weight ≤ 2500 grams
  - Born to mothers who received RAL prior to delivery
  - Target accrual 15; enrolled n=2
Primary Objectives

➢ To determine the washout pharmacokinetics of RAL in infants born to HIV-infected pregnant women receiving RAL during pregnancy

➢ To evaluate the safety of in utero/intrapartum exposure to RAL in infants born to HIV-infected pregnant women receiving RAL during pregnancy

➢ To develop a neonatal RAL dosing regimen for LBW infants to be evaluated in cohort 3 of P1110
Schema

- Design - Multicenter, washout pharmacokinetic trial of RAL in low birth weight infants born to HIV-infected pregnant women who received at least one dose of RAL within 24 hours prior to delivery
- Sample size: 15 evaluable mother-infant pairs (projected to require enrolling 20 mother-infant pairs)
- Mother/infant pairs may be enrolled prior to delivery or up to 48 hours after delivery
IF ENROLLED PRIOR TO DELIVERY
Maternal Inclusion Criteria – if enrolled prior to delivery

- Documentation of HIV-1 infection
- Viable singleton or multiple birth pregnancy based on clinical or other obstetrical measurements with infant birth weight anticipated to be ≤ 2500 grams
- RAL currently being used as part of maternal ARV regimen and planned to continue through labor and delivery
- Willing and intends to deliver at the study-affiliated clinic or hospital.
- Able and willing to sign informed consent
Maternal Exclusion Criteria – if enrolled prior to delivery

- Receipt of disallowed medications within 4 weeks prior to enrollment or intent to be on any of the disallowed medications prior to delivery
  - Phenobarbital
  - Phenytoin
  - Rifampin

Note: Infants born to a mother who received any of the disallowed medications will be ineligible for PK sampling.
Infant Inclusion Criteria – if enrolled prior to delivery

- Infants may be enrolled prior to delivery so there are no infant inclusion criteria.
- Infants eligible for pharmacokinetic sampling if:
  - Born to mothers who received at least one dose of RAL within 2-24 hour prior to delivery.
  - Infant birth weight ≤ 2500 grams; ≤ 48 hours of age.
  - Infant not receiving disallowed medications: phenobarbital, phenytoin, rifampin.
  - 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.
IF ENROLLED AFTER DELIVERY
Maternal Inclusion Criteria – if enrolled after delivery

- Documentation of HIV-1 infection. Enrollment allowed if an initial HIV test is positive and confirmatory test has been drawn but pending results.
- Received at least one dose of RAL within 2-24 hours prior to delivery
- Able and willing to sign informed consent
Maternal Exclusion Criteria – if enrolled after delivery

- Receipt of disallowed medications within 4 weeks prior to delivery
  - Phenobarbital
  - Phenytoin
  - Rifampin
Infant Inclusion Criteria – if enrolled after delivery

- Infant birth weight $\leq 2500$ grams
- Infant less than 48 hours of age
Infant Exclusion Criteria

- Received disallowed medications
- 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
MATERNAL SCHEDULE OF EVALUATIONS
Maternal Schedule of Evaluations – Screening/Entry Visit

- Obtain Informed Consent.

- Obtain Maternal History - includes documentation of HIV-1 Infection, demographic data and antiretroviral dosing history 3 months prior to entry.

- If the Screening/Entry visit is after delivery, then collect 1mL EDTA maternal blood at time of enrollment. If Screening/Entry is prior to delivery, no blood is drawn at enrollment but rather at Labor/Delivery.
Maternal Schedule of Evaluations – Labor/ Delivery Visit

- Labor/ Delivery visit will likely only occur for mothers who enroll prior to delivery.

- Obtain Maternal History - includes antiretroviral dosing while on study, labor and delivery record and obstetrical gestational age.

- Maternal RAL concentration: Collect 1 mL EDTA maternal blood within 1 hour of delivery.

- Cord blood RAL concentration: Collect 1 mL EDTA cord blood, immediately after the cord is clamped.
Maternal Schedule of Evaluations – Post-Delivery Visit

- The Post-Delivery visit may be scheduled 1-5 days after delivery, but prior to the mother being discharged from the hospital.

- Obtain Maternal History - includes antiretroviral dosing while on study, labor and delivery record and obstetrical gestational age

- No Lab specimen collection
INFANT SCHEDULE OF EVALUATIONS (PK ELIGIBLE)
Infant Evaluations (PK eligible infants)

BIRTH
Physical exam – includes APGARS, birth weight, length, gestational age, sex, ethnicity. No blood collection

LABS:

1-6 hours post birth
0.25mL for pharmacokinetics

12-24 hours post birth
0.25mL for pharmacokinetics
Infant Evaluations (PK eligible infants – cont’d)

36-48 hours post birth

0.25mL for pharmacokinetics (Collect within 4 hours of enrollment if infant enrolled close to 48 hours after birth [i.e., within 52 hours from birth])

0.5mL for CBC/differential/platelets ONLY COLLECT IF NOT COLLECTED AS PART OF SOC WITHIN 48 hours. (Collect as soon as possible after enrollment if infant enrolled close to 48 hours after birth)

1mL for total and direct bilirubin ONLY COLLECT IF NOT COLLECTED AS PART OF SOC WITHIN 24 hours. (Collect as soon as possible after enrollment if infant enrolled close to 48 hours after birth)
Infant Evaluations (PK eligible infants – cont’d)

72-84 hours post birth
1mL for AST/ALT/creatinine/total and direct bilirubin ONLY
COLLECT IF NOT COLLECTED AS PART OF SOC WITHIN 24 hours.
0.25mL for pharmacokinetics
0.125ml Dried Blood Spot (Optional UGT1A1 genotyping for PK eligible only. CM#2: Genotyping can be obtained at any visit with another blood sample)

108-132 hours post birth
0.25mL for pharmacokinetics
Infant Evaluations (PK eligible infants – cont’d)

Week 1-2

History – includes all non-protocol lab tests, HIV test results, antiretroviral agents (for PMTCT), concomitant meds, inter-current illnesses (if any) including treatment to reduce bilirubin.

Physical exam – includes temperature, heart rate, respiratory rate, weight, length, head circumference

Labs:

0.5mL for CBC/differential/platelets ONLY COLLECT IF NOT COLLECTED AS PART OF SOC WITHIN 48 hours.

1mL for AST/ALT/creatinine/total and direct bilirubin ONLY COLLECT IF NOT COLLECTED AS PART OF SOC WITHIN 24 hours.

0.25mL for pharmacokinetics
Infant Evaluations (PK eligible infants – cont’d)

Week 6
History – includes all non-protocol lab tests, HIV test results, antiretroviral agents (for PMTCT), concomitant meds, intercurrent illnesses (if any) including treatment to reduce bilirubin

Physical exam – includes temperature, heart rate, respiratory rate, weight, length, head circumference

Labs: None
Infant Priority of blood draws

- Chemistries
- Hematology
- Pharmacokinetics
- Genotyping
INFANT SCHEDULE OF EVALUATIONS (PK INELIGIBLE)
Infant Evaluations (**PK Ineligible Infants**)

**BIRTH**

Physical exam – includes APGARS, birth weight, length, gestational age, sex, ethnicity. No blood

**Labs:**

36-48 hours post birth

- 0.5mL for CBC/diff/plts ONLY COLLECT IF NOT COLLECTED AS PART OF SOC WITHIN 48 hours.

- 1mL for total and direct bilirubin ONLY COLLECT IF NOT COLLECTED AS PART OF SOC WITHIN 24 hours.

72-84 hours post birth

- 1mL for AST/ALT/creatinine/total and direct bilirubin ONLY COLLECT IF NOT COLLECTED AS PART OF SOC WITHIN 24 hours.
Raltegravir Pharmacokinetics and Safety in Neonates

Infant Evaluations (**PK Ineligible Infants - cont’d**) (cont’d)

Week 1-2

History – includes all non-protocol lab tests, HIV test results, antiretroviral agents (for PMTCT), concomitant meds, inter-current illnesses (if any) including treatment to reduce bilirubin

Physical exam – includes temperature, heart rate, respiratory rate, weight, length, head circumference

Labs:

0.5mL for CBC/diff/plts ONLY COLLECT IF NOT COLLECTED AS PART OF SOC WITHIN 48 hours.

1mL for AST/ALT/creatinine/total and direct bilirubin ONLY COLLECT IF NOT COLLECTED AS PART OF SOC WITHIN 24 hours.
Infant Evaluations (**PK Ineligible Infants – cont’d**) 

Week 6

History – includes all non-protocol lab tests, HIV test results, antiretroviral agents (for PMTCT), concomitant meds, inter-current illnesses (if any).

Physical exam – includes temperature, heart rate, respiratory rate, weight, length, head circumference

Labs: None
IMPAAACT P1097 & NICHD P1081
CO-ENROLLMENT CONSIDERATIONS: BLOOD DRAW GUIDANCE
Co-enrollment Blood Draw Guidance

- The NIH recommends pediatric research studies **not to exceed 5mL/ kg of blood drawn in a single day (24-hour period)**, and **not to exceed 9mL/ kg in any 8-week period**.
  - Please also note that local regulatory and IRB/EC guidelines are also to be followed in the implementation of these studies.

- The P1097 protocol allows flexibility in utilizing clinical care laboratory results to reduce the number of blood draws needed:
  - Results from hematology done as part of clinical care within 48 hours may be reported and the hematology sample skipped.
  - Results from chemistries done as part of clinical care within 24 hours may be reported and the chemistries sample skipped.
Co-enrollment Blood Draw Guidance

- P1097 Clarification Memorandum (CM) #1 allows greater flexibility in obtaining the scheduled PK samples.

- PK samples at 1-6 hours after birth, and at 12-24 hours after birth have a collection window of up to 12 hours.

- If the PK collection falls close to the next scheduled sampling time, at least four hours should be allowed between collections of the samples, if possible.
For example, the 1-6 hour after birth PK collection has an allowable collection window until 18 hours after birth. If this PK sample is collected at 18 hours after birth, four hours should elapse before the scheduled 12-24 hour PK sample is collected.

<table>
<thead>
<tr>
<th>PK Sample Collection Schedule</th>
<th>Target Window</th>
<th>Allowable Window (Per CM #1)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1-6 hours after birth</td>
<td>1-6 hours after birth</td>
<td>1-18 hours after birth</td>
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<tr>
<td>12-24 hours after birth</td>
<td>12-24 hours after birth</td>
<td>12-36 hours after birth</td>
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</tbody>
</table>
Co-enrollment Blood Draw Guidance

- If sites project that the NIH recommended limit may be exceeded, prioritization between the two studies may be necessary and P1097 may take priority and the NICHD P1081 infant samples may be missed.

- Should further prioritization within P1097 samples be required, the order of blood draws per protocol are:
  - Chemistries, hematology, PK, and genotyping.
# Co-enrollment Blood Draw Guidance

<table>
<thead>
<tr>
<th>Birth/ Entry</th>
<th>1-6 hours after birth</th>
<th>Hour 12-24 after birth</th>
<th>Hour 36-48 after birth</th>
<th>72-84 Hours after birth</th>
<th>108-132 Hours after birth</th>
<th>Week 2</th>
<th>Week 6</th>
<th>Documentation/ confirmation of HIV Infection (P1081)</th>
</tr>
</thead>
<tbody>
<tr>
<td>-</td>
<td>0.25mL PK</td>
<td>0.25mL PK</td>
<td>0.25mL PK</td>
<td>0.25mL PK</td>
<td>0.25mL PK</td>
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<tr>
<td>-</td>
<td>0.5mL hematology</td>
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<td></td>
<td>0.5mL hematology</td>
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<td>-</td>
<td>1mL chemistries</td>
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<td>1mL chemistries</td>
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<tr>
<td>-</td>
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<td></td>
<td>0.125mL genotyping (P1097-can be obtained with any blood sample)</td>
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<td>2mL genotyping (P1081)</td>
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<tr>
<td>-</td>
<td>2mL HIV TNA/ HIV DNA/ HIV RNA</td>
<td></td>
<td></td>
<td>2mL HIV TNA/ HIV DNA/ HIV RNA</td>
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<td>-</td>
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<td></td>
<td>2mL HIV-1 RNA PCR</td>
</tr>
</tbody>
</table>
P1097, Version 2.0: Raltegravir Pharmacokinetics and Safety in Neonates

Bobbie Graham & Stephanie Popson
Data Managers, FSTRF/DMC
graham@fstrf.org, popson@fstrf.org
Pre-Screening
(for ALL mothers)

- Use the PS1097 Screening Log for IMPAACT P1097 to obtain a Screening Number.

- Available from drop-down list within the SES Subject Enrollment System on the DMC portal.
Enrollment

- **PS1097 Screening Number** needed to enroll and is entered into the Eligibility Checklist

- Mother is enrolled through the Subject Enrollment System

- Infant is enrolled based on mother’s checklist and they are enrolled as mother-infant pair.

- Infant(s) patid number(s) are entered at end of checklist after the demographics questions.
Enrollment

The following questions at the end of checklist are for the **MOTHER**, not the infant.

**Additional Information:**

- Network under which this enrollment should be counted:
  - ACTG
  - IMPAACT

- Birth Date (mm/dd/yyyy):

- Sex:
  - Male
  - Female

- IV Drug use?:
  - Never
  - Currently
  - Previously

**TIP:** You will get LCs if you incorrectly enter infant DOB or SEX as male.

Mom’s are females! 😊
Screening Failure

If mother-infant pair is ineligible, or chooses not to enroll for any reason, complete SCR0033 - IMPAAACT P1097 Cohort 2 Maternal-Infant Enrollment Failure form.

TIP: Enter mother’s PS1097 Screening number in form header.
Download CRF from the DMC portal, or available within CRF packet.
Screening Failure

There is embedded skip logic within form based on whether mother is enrolled before or after giving birth.

2. Was enrollment attempted before or after delivery? .......................... 1-Before delivery □
   If 2-After delivery, go to question 5.
   If 1-Before delivery, complete questions 3, 4 and then question 11.

FOR ENROLLMENTS ATTEMPTED BEFORE DELIVERY (MATERNAL):
  Question #3 collects MATERNAL INCLUSION REASONS
  Question #4 collects MATERNAL EXCLUSION REASONS

FOR ENROLLMENTS ATTEMPTED AFTER DELIVERY (MATERNAL):
  Question #5 collects MATERNAL INCLUSION REASONS
  Question #6 collects MATERNAL EXCLUSION REASONS

FOR ENROLLMENTS ATTEMPTED AFTER DELIVERY (INFANT):
7. Indicate the number of infants in this delivery .................................................................
8. Indicate the number of infants enrolled: ..............................................................................
   ▶ NOTE: Complete a separate form for each mother-infant pair that does not enroll.
   ▶ Use multiple sequence numbers for each additional mother-infant pair.
  Question #9 collects INFANT INCLUSION REASONS
  Question #10 collects INFANT EXCLUSION REASONS
**TRK0143 - IMPAAACT P1097 VISIT DETAILS**

**TIP:** Visit detail tracking CRF is keyed for mothers, but impacts BOTH mother and infant delinquency.

**IF** you have unexpected delinquencies, review this form for coding errors.

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### IMPAACT P1097 VISIT DETAILS

**NIAD AIDS CLINICAL TRIALS GROUP**

<table>
<thead>
<tr>
<th>Patient Number</th>
<th>Date of Patient Visit</th>
</tr>
</thead>
<tbody>
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</tbody>
</table>

<table>
<thead>
<tr>
<th>Protocol Number</th>
<th>Institution Code</th>
<th>Key Operator Code</th>
</tr>
</thead>
<tbody>
<tr>
<td>P1097</td>
<td></td>
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</tr>
</tbody>
</table>

**NOTE:**

- If an empty form is included, it indicates the earliest visit.
- Refer to the Data Collection Forms Schedule: Maternal - Cohort 2 for visit titles and form requirements.

1. **Which maternal visit does this represent?**
   - 1-Screening/Entry visit (for mothers who enroll before labor and delivery). [ ]
   - 2-Entry Visit (for mothers who enroll at or after labor and delivery). [ ]
   - 3-Labor/Delivery (for mothers who enroll before labor and delivery). [ ]
   - 4-Off Study/Discharge (for all mothers: Post-Delivery visits [1-5 days after delivery, or entry visit]). [ ]
   - 5-Premature Discontinuation (only required if mother enrolled, but did not complete requirements). [ ]

2. **Indicate time interval during which the mother-infant pair was enrolled.**
   - 1-Within 5 hours after birth ([ ])
   - 2-Within 24 hours after birth ([ ])
   - 3-Within 48 hours after birth ([ ])

### FOR MOTHER:

- 1-3, complete Entry visit evaluations. [ ]

### FOR INFANT:

- 1, complete all visits and evaluations. [ ]
- 2, complete Entry, 12-24 hours, 36-48 hours, 72-84 hours, Weeks 1-2 and Week 6 evaluations. [ ]
- 3, complete Entry, 36-48 hours, 72-84 hours, Weeks 1-2 and Week 6 evaluations. [ ]

3. **Indicate how the maternal visits are planned for the mothers who enrolled at, or after labor and delivery:**
   - 1-Single visit: Combined Entry and Off Study/Discharge visits. [ ]
   - 2-Separate visits: Separate Entry and Off Study/Discharge visits. [ ]

4. **Indicate how the maternal visits are planned for the mothers who enrolled before labor and delivery:**
   - 1-Three separate visits: Separate Screening/Entry, Labor/Delivery and Off Study/Discharge visits. [ ]
   - 2-Two separate visits: Separate Entry and Off Study/Discharge visits. [ ]

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EVW0251: IMPAACT P1097 Infant Eligibility for Study/Pharmacokinetic Sampling

For all infants who enroll, you will still need to verify that they are eligible for PKs.

Instructions are separated for enrollments made BEFORE vs AFTER birth.

<table>
<thead>
<tr>
<th>FOR ENROLLMENTS BEFORE BIRTH:</th>
</tr>
</thead>
<tbody>
<tr>
<td>2. Answer the following infant questions to establish eligibility for PK sampling:</td>
</tr>
<tr>
<td>NOTE: Answers of '2-No' or '1-Unknown' indicate that the infant was not eligible for PK sampling.</td>
</tr>
<tr>
<td>a. Was the infant born to a woman who received at least one dose of Raltegravir (RAL) within 2 to 24 hours prior to delivery? (The dose administered to the mother must have been at least 2 hours prior to delivery to allow time for adequate absorption and distribution)</td>
</tr>
<tr>
<td>b. Was the infant birth weight ≥2500 grams?</td>
</tr>
<tr>
<td>c. Can PK sampling begin before the infant is 48 hours of age?</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>FORM WEEK</th>
<th>*SEQ NO.</th>
<th>**STEP NO.</th>
<th>INSTITUTION CODE</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
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</tbody>
</table>

<table>
<thead>
<tr>
<th>FOR ENROLLMENTS AFTER BIRTH:</th>
</tr>
</thead>
<tbody>
<tr>
<td>4. Answer the following infant questions to establish eligibility for PK sampling:</td>
</tr>
<tr>
<td>NOTE: Answers of '2-No' or '1-Unknown' indicate that the infant was not eligible for PK sampling.</td>
</tr>
<tr>
<td>a. Did the infant receive any disallowed medications per protocol section 4.6? Of particular interest are: phenobarbital, phenytoin or tirapamil.</td>
</tr>
<tr>
<td>b. Can PK sampling begin before the infant is 48 hours of age?</td>
</tr>
<tr>
<td>NOTE: The infant was enrolled close to the 48 hour time point, collect first PK Sample within 4 hours of enrollment (i.e., within 52 hours after birth).</td>
</tr>
</tbody>
</table>
IMPORTANT NOTES
(Priority CRF Keying)

Key the following forms promptly after infant’s birth or infant’s enrollment to update the MASTER demographics tables.

These details also allow pharmacologist to calculate PK parameters.

- PE5802 - Newborn Demographics
- PE5896 - Newborn Exam – III
While the infant does not directly receive RAL treatment, the infant is exposed to RAL from mother’s usage.

Treatment is considered as being exposed to RAL. Assess relationship based on infant exposure to RAL.
NEW – JUST USE THE DAERS SYSTEM

Merck Research Laboratories – Clinical Study Adverse Event Report

- P1097 will not use the Expedited Adverse Event (EAE) reporting system
- Instead, we will use the “Merck Research Laboratories – Clinical Study Adverse Event Report” (also known as the “Merck AE / SAE Report”)
  - The CRFs will have a note indicating if the form may need to be completed
  - Once completed, the form is faxed to Merck - it does not go to the DMC!
- The form and its instructions are included in the books, and on the Portal site
If you have questions during the study...

- If you have questions about schedules or forms, e-mail the Protocol Data Managers:
  - Bobbie Graham: graham@fstrf.org
  - Stephanie Popson: popson@fstrf.org

- If you have questions about eData, Smart Update, or other technical issues, e-mail User Support: usersprt@fstrf.org

- If you have questions about patient management or the protocol itself, e-mail the P1106 Protocol Team:
  - impaact.teamp1097@fstrf.org

- impaact.protp1097@fstrf.org is used by protocol team to convey information to registered sites