SUMMARY OF CHANGES

INCLUDED IN THE FULL PROTOCOL AMENDMENT OF:

IMPAACT P1101
Phase I/II Dose-finding, Safety, Tolerance and Pharmacokinetics Study of a Raltegravir-Containing Antiretroviral Therapy (ART) Regimen in HIV-infected and TB Co-infected Infants and Children

IND# 77,787
DAIDS ES # 11831

THE AMENDED PROTOCOL IS IDENTIFIED AS:

FINAL Version 3.0, dated 24 April 2017

Information/Instructions to Study Sites from the Division of AIDS

The information contained in this protocol amendment impacts the IMPAACT P1101 study and must be submitted to site Institutional Review Boards and/or Ethics Committees (IRBs/ECs) as soon as possible for review and approval. This amendment impacts the study informed consent forms (ICFs); all study sites must prepare updated ICFs and obtain IRB/EC approval of the updated forms. Approval must also be obtained from other site regulatory entities if applicable per the policies and procedures of the regulatory entities. All IRB/EC and regulatory entity requirements must be followed.

Upon obtaining IRB/EC approval and any other applicable regulatory entity approvals, all sites should immediately begin implementing this amendment and using the updated ICFs. After all required approvals are obtained; updated ICFs should be used for all new participants. In addition, previously enrolled participants, at the next study visit, must be re-consented using the updated ICFs unless otherwise directed by the IRB/EC.

All study sites must submit an amendment registration packet to the DAIDS Protocol Registration Office (PRO); however, approval from the DAIDS PRO is not required prior to implementing this amendment.

This Summary of Changes, Version 3.0 of the protocol, corresponding site-specific ICFs, and all associated IRB/EC and regulatory entity correspondence should be retained in each site's essential document files for IMPAACT P1101.

Summary of Modifications and Rationale

The purpose of this amendment is to include an additional cohort of infants and children, ≥ 4 weeks to < 2 years of age, to evaluate the pharmacokinetics of raltegravir (RAL) chewable tablet formulation administered as a dispersible tablet in this population; clarify toxicity management requirements; incorporate prior protocol Clarification Memorandum; and include other updates and corrections to enhance the clarity and precision of protocol specifications. The changes and rationale are summarized below, generally in order of first appearance in the protocol.

- Throughout the protocol, the version number was updated to Version 3.0, the version date was updated to 24 April 2017, and the protocol title was modified (the age range ≥ 2 to < 12 years old was removed).
- A protocol signature page was added in accordance with DAIDS policies.
- The protocol team roster was updated to reflect current membership and contact information; the study management section and glossary were also updated.
- Throughout the protocol, Cohort III, ≥ 4 weeks to < 2 years of age, has been added to examine the pharmacokinetics and safety of RAL chewable tablet administered as a dispersible tablet in this age group, with the following associated modifications:
    - The study sample size has been modified to a minimum of 36 participants to a maximum of 108 participants (from 24 to 72 participants, respectively) to achieve a target of 12 evaluable in each cohort. This change applies to the Schema, Sections 3.0 and 8.4, and Appendix VI, Sample Informed Consent Form (ICF).
    - The study objectives have been updated in the Schema and Section 2.0 to reflect inclusion of infants. This change is also reflected in the pharmacology objectives in Section 9.1.
    - Additional information indicating the current FDA approval of RAL for children aged ≥ 4 weeks is added to Section 1.3 and Appendix VI, Sample ICF.
    - Section 1.4 is added to provide rationale for studying RAL chewable formulation administered as a dispersible tablet.
    - The minimum age for study entry is lowered to four weeks of age (from two years of age) in inclusion criterion 4.1.1.
    - The minimum weight at study entry is decreased to 3.5 kg (from 10 kg) in inclusion criterion 4.1.2.
    - The testing requirements for confirmation of HIV-1 infection prior to entry for participants < 2 years of age or have not ceased breastfeeding for 4 weeks have been added to inclusion criterion 4.1.3.
    - Sections 5.1.1 and 5.1.2 have been updated to reflect the study drug regimen and guidance for administration of chewable RAL as a dispersible tablet for participants enrolled in Cohort III.
    - The dosing tables in Appendix II have been modified to include weight bands for 3 – 5.9 kg and 6 – 9.9 kg for participants enrolled in Cohort III.
- The background, rationale, and attendant references were updated to reflect current World Health Organization (WHO) guidelines and additional relevant published data (Section 1.0 and throughout the protocol, where relevant).
- Inclusion criterion 4.1.7 has been updated for consistency with the WHO guidelines in the continuation phase of tuberculosis (TB) treatment.
- Exclusion criterion 4.2.2 has been modified to clarify potential participants with a Grade 4 or higher laboratory result at screening will be excluded from study participation.

- Exclusion criterion 4.2.13 has been added to ensure that potential participants that require disallowed medications per protocol Section 4.3.2 are not enrolled. The guidelines for precautionary medications are further clarified in Section 4.3.1.
- In Section 4.4, the fourth paragraph has been modified to clarify the date of participant enrollment is consistent with Day 0 on study for purposes of target dates for follow-up visits.
- Sections 3.0 and 5.0 have been updated to indicate that study drug should be initiated at Entry. This change is also reflected in footnote 4 of Appendix I, Schedule of Evaluations.
- Sections 5.1 and 9.2 have been modified to clarify the food/drink intake requirements for the intensive PK visit. This change is also reflected in footnote 12 of Appendix I, Schedule of Evaluations.
- Section 6.0, Participant Management, has been modified to provide additional operational guidance and gradation consistent with Version 2.0 of the DAIDS Toxicity Tables.
- Section 6.7, Criteria for Early Treatment Discontinuation, has been modified to clarify the visit schedule for participants that discontinue study drug early and continue on study. This change is also reflected in footnote 19 of Appendix I, Schedule of Evaluations.
- In Sections 6.2.1, 8.4, 9.2, and 9.3, C_{min} and C_{trough} have been replaced with C_{12h}. As C_{trough} and C_{min} may be influenced by the timing of the previous dose, C_{12h} will be used as the more appropriate parameter for cohort dosing management.
- Section 7.2, Reporting Requirements for this Study, has been updated to include Hy's Law liver toxicities as a requirement for EAE reporting, consistent with Section 6.1.2.
- Section 7.4, Expedited AE Reporting Period, has been updated to clarify that the EAE reporting period begins at the time of administration of the first dose of study drug.
- Section 8.2.1, Primary Endpoints, is modified to include Grade 4 non-life threatening adverse events deemed as probably or definitely related to RAL.
- Appendix I: Schedule of Evaluations
    - The blood volume required for HIV Confirmation/Documentation, HIV-1 RNA PCR, and Intensive PK sampling are modified for consistency with testing requirements and the corresponding total maximum blood volume is updated. The blood volume requirements for the intensive PK collection are also reflected in footnote 12 and Section 9.2.
    - Footnote 1 is modified to clarify the HIV-1 RNA PCR required at screening may serve as one of the tests required for confirmation of HIV-1 infection per inclusion criterion 4.1.3, if needed.
    - Footnote 2 is modified to reflect HIV clinical classification is required at Entry only.
    - Footnote 13 is modified to indicate that the frequency for viral sequencing sample shipping and testing will be provided in the study Laboratory Processing Chart (LPC).
    - Footnote 14 is updated to clarify participants that discontinue TB treatment and RAL due to completion of their prescribed TB treatment at the Week 4 or 8 visit should also have the evaluations specified in the column for TB and/or RAL Treatment Discontinuation if they are not already being done.
    - A note has been added to indicate the NIH recommendations for maximum pediatric blood draw volumes should be followed in P1101.

- Corrections made via Clarification Memorandum #1 have been included.
- References have been updated and other administrative updates and corrections have been incorporated throughout the protocol for accuracy, consistency, and clarity.

Modifications to Appendix VI: Sample Informed Consent Form for Study Participation

Modifications to the sample informed consent form are shown below, using ~~strikethrough~~ for deletions and **bold** type for additions.

WHY IS THIS STUDY BEING DONE?

This study is being done to measure the amount of raltegravir (RAL, Isentress™) in the blood when it is taken with the anti-TB medication Rifampicin. **Raltegravir is the study medication used in this study and it is a type of anti-HIV medicine called an integrase inhibitor. Integrase inhibitors work by blocking integrase, a protein that HIV needs to enter human cells and make more copies of itself. Raltegravir has been approved for the use in adults, adolescents and children ages 4 weeks to 18 years old by the United States Food and Drug Administration (FDA). The chewable tablet is approved for children ages 2 to less than 12 years old. For children under 2 years of age, this study will look at a new way to give this medicine to young children more easily. Infants and children 4 weeks to less than 2 years old will take the raltegravir chewable tablet mixed with water, juice, breast milk or formula. This study will provide the study medication raltegravir to your child.** ~~This study will compare the levels of raltegravir in the blood and the best dose of raltegravir in HIV-infected children who are taking rifampicin for the treatment of TB to those HIV-infected children who are only taking raltegravir and do not require treatment for TB with rifampicin. It will also evaluate the tolerance of anti-HIV treatment containing raltegravir when it is given with rifampicin. This study will also look at levels of raltegravir and antiretroviral drugs (ARVs) when taken together and help find out if taking raltegravir and ARVs with rifampicin is safe.~~

~~Raltegravir is the study medication used in this study and it is a type of HIV medicine called an integrase inhibitor. Integrase inhibitors work by blocking integrase, a protein that HIV needs to enter human cells and make more copies of itself. Raltegravir has been approved for the use in adults, adolescents and children ages 2 to 18 years old by the United States Food and Drug Administration (FDA). The chewable form is approved only for children ages 2 to < 12 years old. This study will provide the study medication raltegravir to your child.~~

The other medications used in this study are Rifampicin, other anti-TB medications, two anti-HIV medications that are **called** Nucleoside Reverse Transcriptase Inhibitor**s** (NRTIs) ~~as well as~~ **and** a fourth anti-HIV medication that will be chosen by your child's doctor. It is possible that the fourth ARV drug chosen by your doctor could be a combination drug of Lopinavir and ritonavir (LPV/r). This medication may need to be dose adjusted with additional ritonavir to obtain the correct dosing for your child. This would result in a fifth anti- HIV medication. Many people find the liquid form of this drug tastes bad. These medications will not be provided by the study. These medications will be provided at the ~~hospital~~ **clinic** where your child is receiving care ~~and will be provided free of charge~~. You will need to obtain them through a prescription from your child's doctor.

This study will look at the levels of raltegravir in the blood and the best dose of raltegravir in HIV-infected infants and children who are taking rifampicin for the treatment of TB compared to HIV-infected infants and children who are only taking raltegravir and do not require treatment for TB with rifampicin. This study will also look at how the anti-HIV treatment including raltegravir when it is given with rifampicin is tolerated, and the levels of raltegravir and antiretroviral drugs (ARVs)

when taken together in the blood to help find out if taking raltegravir and ARVs with rifampicin is safe.

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

Your child must be taking or starting to take anti-TB medications that include Rifampicin to be able to start in this study. Your child will be given raltegravir and will be asked to take it two times or three times a day in addition to your child's other ~~2~~ **two** new **anti-**HIV medicines. Raltegravir will be in a chewable tablet formulation **to be chewed or taken dissolved in a liquid**. **The study staff will explain to you how to give the medicine to your child.** Levels of raltegravir in the blood will be measured about one week after starting this medicine. Then your child will begin a fourth **anti-**HIV medicine along with his/her anti-TB medications including rifampicin, raltegravir and the other ~~2~~ **two anti-**HIV medicines. Your child will take raltegravir until he/she stops taking the anti-TB medications prescribed by his/her doctor. Your child will continue to take the third **anti-**HIV medicine and the other ~~2~~ **two anti-**HIV medicines for 3 months after the anti-TB medicines and raltegravir are stopped.

Deciding to allow your child to join this study is voluntary. You may choose to allow your child to join or not join. If you choose to allow your child to join, you can change your mind and take your child out of the study at any time. Your choices will have no effect on the medical care that your child receives at this clinic. Your child's access to services and the benefits and rights he or she normally has will not be affected.

Take your time and consider your decision carefully. If you wish, you can talk to other people about allowing your child to join the study. You can bring other people here to learn about the study with you.

If you decide to let your child join this study, we will first do some tests to see if your child qualifies.

Screening visit:

~~If you are interested in allowing your child to enroll in this study, we will see if your child is eligible for the study. The following will take place~~ **To find out if your child qualifies for this study, we will**:

- ~~A medical history and review of medications: We will a~~**A**sk **about** your child's medical history including questions about your child's health and what symptoms, medications, and illnesses your child has had.
- ~~A~~**Give your child a** physical exam**ination**: We will ~~do a physical exam including~~ **measure your child's** height, weight and vital signs (temperature, blood pressure, pulse and respiratory rate).
- **Draw your child's blood for the following** ~~Blood~~ tests: We will take a little more than 1~~–2~~ teaspoon (~~6–11~~ **4-6**mL) of blood for routine safety tests (a CBC, or complete blood count, which shows how many red and white blood cells there are; blood chemistries, which checks the blood sugar and how well the kidneys are working; a liver function test, which shows how well the liver is working) and to measure the amount of HIV in the blood (HIV viral load). We may draw up to an additional ~~5mL~~ **3 mL** to confirm your child's HIV infection if there is no **medical** record available.
- A pregnancy test: If your child is of child bearing age and pregnancy is suspected, your child may be asked to give an additional 1 mL of blood or a urine sample to test for pregnancy.
- You will be given the results of these tests.

If you agree to allow your child to enroll in this study, and your child does not qualify to **be** ~~participate~~ in ~~the~~ **this** study, **the reasons** your child~~'s~~ **cannot enroll in this study** ~~information~~ will be shared with the protocol team, including the pharmaceutical company supporting the study.

Enrollment visit (*Now titled "Entry visit")*:

If your child ~~is eligible~~ **qualifies** for this study and you allow your child to ~~enroll~~ **enter the study**, your child will come to the clinic for the first study visit (or the ~~enrollment~~ **Entry** visit) within 30 days after the screening visit. The following will take place **at the Entry visit**:

- Your child will have the examinations and tests shown in Table 1 under the column "Entry".
- ~~Adherence assessment~~ **Pill count at Entry**: If your child is already taking anti-TB medications, we will check how well your child is taking the medications (including missed doses).
- Blood tests: We will take a little more than **1.5 -** 2 teaspoons (**8.5 –** 10.5 mL) of blood.
  - About 1 ½ teaspoons (**5.5 –** 7.5 mL) will be for the tests in Table 1. The CD4/CD8 cell count is to check how well your child's immune system is working. The results of these tests will be provided to you/your child.
  - A little more than ½ teaspoon (3 mL) will be used for a test to check if your child's HIV is resistant to some anti-HIV medications (HIV resistance test). This test will be done after the study is over, and you will not be given the results.
- We will also ask your child to provide a urine sample for a routine test. The results of the test will be provided to you/your child.
- Your child will start taking raltegravir and 2 other **anti-**HIV medicines ~~(~~**called** NRTIs~~)~~.
- If your child **is a female and** started to have sex since the last visit (screening), or can become pregnant, your child will be asked to provide **a** urine **sample** or an additional 1 mL of blood at each visit for a pregnancy test. Your child will be asked to take birth control precautions (ways to prevent pregnancy) throughout the study period to remain in the study. If your child is pregnant, your child will not be allowed to continue on the study medicine, but will continue to come in for study visits.

Intensive PK visit (Day 5 to 8):

Approximately one week after starting raltegravir, your child will have ~~the~~ **an** intensive PK visit. The following will take place **at this visit**:

- You will be contacted by the study staff one day before the visit to confirm that your child took all of his/her medications during the 2 days before the visit.
- Your child will have the examinations and tests shown in Table 1 under the column "Day 5 to 8".
- In addition to the pill count that will be done by the study staff, you will need to write down the times your child took his/her medications during the 2 days before the visit and bring it with you to the clinic.
- ~~Your~~ **We will ask that you not give your** child ~~must bring the dose of~~ raltegravir, other anti-HIV medicines, and anti-TB medicines **at home on the day of this visit. Your child will need to bring these medicines** to the clinic. Your child will be given these medications while in the clinic~~,~~ after the first blood sample for the intensive PK test is taken.
- Blood tests: We will take ~~about 2~~ **a little more than 1** ½ teaspoon**s** (~~12~~ **7.5** mL) of blood.
  - A little more than ½ teaspoon (3 mL) will be for the tests in Table 1. The results of these tests will be provided to you/your child.
  - A little less than ~~2 teaspoons~~ **1 teaspoon** (~~9~~ **4.5** mL) of blood will be taken over 12 hours to measure the amount of raltegravir in your child's blood.

Your child must have taken all doses as prescribed and not missed any doses of raltegravir and his/her other **anti-**HIV and TB medicines ~~within~~ **the** 2 days before the PK test. If your child misses a dose within 2 days before the PK test, the ~~test~~ **visit** will be rescheduled. Your child ~~must~~ **should** not ~~take raltegravir on the morning of the PK visit. Your child cannot eat for 6 hours~~ **have breast milk, formula or any other high fat liquid for 2 hours** before the PK test **and 1 hour after taking the study medicines at the clinic**. Your child can have ~~milk and~~ **water or apple/orange** juice ~~4 to 6 hours before the PK test and water~~ at any time. We will take the first blood sample before your child takes raltegravir **at the clinic**.

Your child can have a small meal 2 hours after taking raltegravir. We will take blood samples 8 more times at ½ hour, 1 hour, 2 hours, 3 hours, 4 hours, 6 hours, 8 hours and 12 hours after your child takes raltegravir. **Your child should not be given a second dose of raltegravir until after the PK test.**
Fifth paragraph:
Your child will start taking a fourth ~~ARV~~ **anti-HIV** drug chosen by your doctor after the PK test is completed. Your child should take the fourth ~~ARV~~ **anti-HIV** drug at night, with the smallest amount of food or liquid (such as *formula, breast milk, mashed banana, yogurt, or maize-based porridge etc.*), and should not be mixed with water or juice.

Week 4 visit:
The following will ~~be done~~ **take place approximately** four weeks after **your child starts taking** ~~starting~~ raltegravir:

- Your child will have the examinations and tests shown in Table 1 under the column "Week 4".
- Blood tests: We will take a little more than **½ to** 1 teaspoon (**4-**6 mL) for the tests in Table 1. The results of these tests will be provided to you/your child.
- If your child ~~is~~ **will be** stopping the anti-TB medications ~~after~~ **at** the week 4 visit because your child has completed anti-TB treatment prescribed by your child's doctor, the following will also take place:
  - We will take less than ~~1~~ ½ teaspoon (~~4.5~~ **1.5** mL) of additional blood for a CD4/CD8 cell count test and an HIV resistance test. The results of the CD4/CD8 cell count test will be provided to you/your child. ~~Depending on the amount of HIV in your child's blood at this visit, the HIV resistance test may be done after the study is over and the results will not be provided to you/your child.~~
  - Your child will stop taking raltegravir at the same time the anti-TB medications are stopped. Your child will continue to take the **anti-**HIV medicines **as instructed by your child's doctor** ~~for 3 months~~.

Week 8 visit:
~~If your child will continue to take the anti-TB medications and raltegravir after the week 4 visit, your child will have a visit eight weeks after starting raltegravir.~~ The following will take place **approximately eight weeks after your child starts taking raltegravir**:

- Your child will have the examinations and tests shown in Table 1 under the column "Week 8".
- Blood tests: We will take about **1 –** 1 ½ teaspoons (**5.5 –** 7.5 mL) of blood for the tests in Table 1. The results of these tests will be provided to you/your child.
- If your child ~~is~~ **will be** stopping the anti-TB medications at this visit because your child has completed anti-TB treatment prescribed by your child's doctor, your child will stop taking raltegravir at the same time the anti-TB medications are stopped. **Your child will continue to take the anti-HIV medicines as instructed by your child's doctor.** ~~Your child will also have a little more than ½ teaspoon (3 mL) of additional blood taken for an HIV resistance test. Depending on the amount of HIV in your child's blood at this visit, this test may be done after the study is over, and the results will not be provided to you/your child.~~

Visits every 4 weeks:
If your child will continue to take the anti-TB medications and raltegravir **after the Week 8 visit**, your child will have visits every 4 weeks until the anti-TB medications and raltegravir are stopped. The following will take place at these visits:

- Your child will have the examinations and tests shown in Table 1 under the column "Every 4 weeks".
- Blood tests: We will take about **1 –** 1 ½ teaspoons (**5.5 –** 7.5 mL) of blood ~~at most visits~~ for the tests in Table 1. The results of the tests will be provided to you/your child.
- Depending on the amount of HIV in your child's blood ~~at the Week 8 visit or at a visit after Week 8~~, we may also ~~do an HIV resistance test at your child's next visit. A~~ **take a** little more than ½ teaspoon

(3 mL) of additional blood ~~will be taken for this test~~ **for an HIV resistance test**. This test ~~will~~ **may** be done after the study is over, and you/your child will not be given the results.

- If your child is stopping the anti-TB medications at any of these visits because your child has completed anti-TB treatment prescribed by your child's doctor, your child will stop taking raltegravir at the same time the anti-TB medications are stopped.

Early TB and/or RAL treatment discontinuation visit:
If your child ~~must~~ **needs to** stop taking **the anti-**TB medications and/or raltegravir ~~before completing the study~~ **early**, your child will have ~~an early~~ **a** treatment discontinuation visit. The following will take place **at this visit**:

- Your child will have the examinations and tests shown in Table 1 under the column "~~Early~~ **TB and/or RAL** treatment discontinuation".
- Blood tests: We will take about **1** – 1 ½ (**5.5** – 7.5 mL) ~~a little over 2 teaspoons (10.5 mL)~~ of blood~~. About 1 ½ teaspoons (7.5 mL) will be~~ for the tests in Table 1. The results of these tests will be provided to you/your child.
- **Depending on** ~~If your child is stopping raltegravir because~~ the amount of HIV in your child's blood**,** ~~did not go down enough to continue taking raltegravir,~~ **we may also take** a little more than ½ teaspoon (3 mL) of **additional** blood ~~will be used~~ for an HIV resistance test. This test ~~will~~ **may** be done after the study is over, and you/**your child** will not be given the results.

~~Your~~ **Even if your** child ~~will~~ **stops taking the study medicines, your child will stay in the study and** return for the visits at 4 weeks and 12 weeks after stopping raltegravir described below.

Four weeks after stopping RAL visit:
Four weeks after your child stops taking raltegravir, ~~your child will have a visit and~~ the following will take place:

- Your child will have the examinations and tests shown in Table 1 under the column "4 weeks ~~after stopping RAL~~ **off RAL treatment/on study**".
- Blood test: We will take a little more than ½ **-** 1 teaspoon (**4** – 6 mL) of blood for the tests shown in Table 1. The results of the tests will be provided to you/your child.

Final visit:
Twelve weeks after your child stops taking raltegravir your child will have the last study visit. Or, if your child stops participating in the study before completing the study, your child will have a study discontinuation visit. At the last study visit or study discontinuation visit, the following will take place:

- Your child will have the examinations and tests shown in Table 1 under the column "Final visit". ~~The adherence assessment~~ **A pill count** will only be done if your child ~~will have a study discontinuation visit~~ **is discontinuing raltegravir early at this visit**.
- Blood tests: We will take a little over **½ -** 1 teaspoon (**3.5** – 5.5 mL) of blood for the tests shown in Table 1. The results of the tests will be provided to you/your child.

Second, third, and fourth paragraphs:
The study will first enroll a small group of 6 participants into ~~2~~ **three** age groups and **participants in** each group will take the same dose of raltegravir. If the results of the intensive PK test in a specific age group show that the level of raltegravir is too low or too high or is found not to be safe, a new group of 6 participants will be enrolled into that age group and will take a new dose of raltegravir. The enrollment of a new group of 6 participants in each age group will be done until the best dose of raltegravir is found.

When the best dose of raltegravir is found for that age group, an additional 6 participants will be enrolled in each age group and will take the best dose so **that** there will be a total of 12 participants that will be

studied on the best dose. If the results of the intensive PK test ~~in the 6 additional participants~~ for a specific group show that the level of raltegravir is too low or too high or is found not to be safe, a new group of 6 participants will be enrolled into that age group and will take a new dose of raltegravir. This process will repeat until the best and safe level of raltegravir is found in a group of 12 participants for a specific age group. If the best dose is not found when raltegravir is taken two times a day, it may have to be taken three times a day.

If the group that your child belongs to (whether a group of 6 or 12 participants) has raltegravir PK test levels that are either too low, too high or is found not to be safe, the entire group (including your child) will take the new dose of raltegravir that will be tested in the new group of participants, if **it is considered safe to do so and** your child's group is still taking TB treatment and raltegravir**.** Changes in the dose of raltegravir will be done for the entire group that a participant belongs to and not on an individual basis. If the PK tests suggest that the new dose should be given three times a day, this will not apply to your child who will continue to take raltegravir twice a day. The dose of raltegravir will only be changed once for your child and the intensive PK will not be repeated after the dose is changed. Your child will continue in the study and have the rest of the visits. This will be discussed with you by the study doctor and will depend on what is safest for your child.

HOW MANY **INFANTS AND** CHILDREN WILL TAKE PART IN THIS STUDY?

About ~~24~~ **36** to ~~72~~ **108 infants and** children will take part in this study.

WHY WOULD THE DOCTOR HAVE MY CHILD STOP TAKING RALTEGRAVIR EARLY?, *the following bullet has been added*:

- **Your child becomes pregnant or is a female that is sexually active and does not agree to take birth control precautions.**

Integrase Inhibitor

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

The following side effects have been associated with the use of raltegravir:

- Rash, which can become severe or life-threatening. Contact your ~~Healthcare Provider~~ **child's doctor** right away if your child develops a rash.
- Nausea
- Headache
- Tiredness
- Weakness
- Trouble sleeping
- Stomach pain
- Dizziness
- Depression
- Suicidal thoughts and actions
- Feeling anxious, Paranoia
- ~~D~~ **Easy bleeding (d**ecreased blood clotting cell**,** ~~(L~~ **l**ow platelet count)
- Diarrhea
- Liver failure
- Clumsiness and lack of coordination

- **Changes in behavior, like low or high activity in children**
- Muscle tenderness, weakness or injury which can be serious and lead to kidney damage

Serious skin and allergic reactions including a rash which can become severe or life-threatening and can be fatal. If ~~you~~ **your child** develop**s** a rash with any of the following symptoms stop using raltegravir and contact your ~~Healthcare Provider~~ **child's doctor** right away:

- Fever
- Generally ill feeling
- Extreme tiredness
- Muscle or joint aches
- Blisters or sores in mouth
- Blisters or peeling of the skin
- Redness or swelling of the eyes
- Swelling of the mouth or face
- Problems breathing

Sometimes allergic reactions can affect the body, like the liver and cause liver problems which can lead to liver failure. Contact your ~~Healthcare Provider~~ **child's doctor** right away if ~~you~~ ~~have~~ **your child has** any of the following signs or symptoms of **a** liver problem:

- Yellowing of the skin or whites of the eyes
- Dark or tea colored urine
- Pale colored stools/bowel movements
- Nausea/vomiting
- Loss of appetite
- Pain, aching or tenderness on the right side below the ribs

In some patients receiving raltegravir blood tests showed abnormally high levels of a muscle enzyme—creatine kinase which may cause muscle pain, tenderness or weakness this type of muscle break down can be serious and lead to kidney damage including kidney failure. Contact your child's doctor right away if your child has any unexplained muscle pain, tenderness, or weakness.

~~Additional Side Effects Include:~~

~~• Changes in behavior, like low or high activity in children~~

Note: Raltegravir chewable tablets contain phenylalanine, a component of the sugar substitute aspartame. Phenylalanine can be harmful to children and adults with phenylketonuria, a birth defect that can lead to a variety of health problems.

ARE THERE RISKS RELATED TO PREGNANCY?, *second paragraph*:

Your child will have a medical history and physical exam and we will ask you or your child questions to check if your child is having sex that could lead to pregnancy. If your child is pregnant or breastfeeding, ~~your child~~ **she** cannot be in the study. If your child is **a female and is** sexually active**,** she must agree to use two methods of birth control to take the study medicine. Approved methods of birth control for this study include hormonal birth control, such as slow release inserts placed under or on the skin, and a medically accepted barrier method including condoms, an intrauterine device (IUD), a diaphragm or cervical cap with a cream or gel that kills sperm. If your child is **a female and is** sexually active while in the study and does not agree to use two of these methods of birth control**,** she can remain in the study, but cannot take the study medicine. If your child is having sex while in the study, your child will be referred to ~~his/her~~ **their** primary provider for prevention of pregnancy. Your child may also be asked to provide

urine or 1 mL of blood for a pregnancy test at each visit to check if she is pregnant. If the pregnancy test is positive, the study staff will refer your child to her primary provider for counseling about pregnancy and pregnancy care and she should stop taking raltegravir. **Your child will continue to come in for study visits and will be followed until the outcome of your child's pregnancy.** If you think your child has started having sex or you/your child thinks she may be pregnant at any time during the study, tell ~~your~~ **the** study staff right away. The study staff will talk to you/your child about your/~~his/her~~ **your child's** choices. If your child becomes pregnant, she will be entered in the Antiretroviral Pregnancy Registry.

ARE THERE BENEFITS TO TAKING PART IN THIS STUDY?

If your child takes part in this study, there may be a direct benefit to your child, ~~but no guarantee can be made~~ **however we do not know if being in the study will benefit your child in any way**. It is also possible that your child may receive no benefit from being in this study. **Your child will have regular visits and frequent checks on his or her health, including tests for the amount of HIV in your child's blood, called viral load, and for the amount of cells that fight HIV, called CD4.** Information learned from this study may help others who have HIV and TB.

WHAT ABOUT CONFIDENTIALITY?

Efforts will be made to keep your child's personal information confidential. **Study records and specimens will be kept in secure locations.** We cannot guarantee absolute confidentiality. **Despite our best efforts to keep your child's information private, it is possible that the information could be obtained by someone who should not have it. If this were to happen, your child could be treated unfairly. You could feel stress or embarrassment.** Your child's personal information may be disclosed if required by law. Any publication of this study will not use your child's name or identify your child personally.

WHAT HAPPENS IF MY CHILD IS INJURED?

Your child's health is important to us. We will make every effort to protect your child's well-being and minimized risk to him or her. If your child is injured as a result of being in this study, the study doctor will give or refer your child for immediate treatment for your child's injuries. The cost for this treatment ~~will~~ **may** be charged to you or your insurance company. There is no program for compensation either through this institution or the National Institutes of Health (NIH). You will not be giving up any of your legal rights by signing this consent form.