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

DAIDS Document ID #11831
IND # 77,787

This file contains the current IMPAACT P1101 protocol, which is comprised of the following documents, presented in reverse chronological order:

- Letter of Amendment #2, dated 21 June 2018
- Letter of Amendment #1, dated 15 March 2018
- Protocol Version 3.0, dated 24 April 2017

Letter of Amendment #2 for:

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

Version 3.0, dated 24 April 2017

DAIDS Document ID #11831
IND #77,787 Held By DAIDS

Letter of Amendment Date: 21 June 2018

Information/Instructions to Study Sites from the Division of AIDS

The information contained in this Letter of Amendment (LoA) 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 their review and approval. Approval must also be obtained from site regulatory entities if applicable per the policies and procedures of the regulatory entities. All IRB/EC and regulatory entity requirements must be followed.

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

Please file this LoA, all associated IRB/EC and regulatory entity correspondence, and all correspondence with the DAIDS PRO in your essential documents files for P1101. If the P1101 protocol is amended in the future, the contents of this LoA will be incorporated into the next version of the protocol.

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

Version 3.0, dated 24 April 2017
DAIDS Document ID #11831

Version 3.0, Letter of Amendment #2
Dated 21 June 2018

Letter of Amendment Signature Page

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

Signature of Investigator of Record	Date
Name of Investigator of Record (printed)	

Summary of Modifications and Rationale

The following modifications are included in this LoA:

1. Sections 6.5, 6.7, and 9.2 are modified to clarify the pharmacokinetic (PK) criteria for early study drug discontinuation for participants with $AUC_{0\text{-}12hr} \geq 63$ µMxhr.
2. Section 7.2 is updated to clarify that confirmed Grade 3 and 4 adverse events are required to be reported as expedited adverse events.

Implementation

Detailed modifications of the protocol text included in this LoA are listed below. Additions to the text are indicated in **bold**; deletions are indicated by ~~strikethrough~~.

1. Pharmacokinetic criteria for early study drug discontinuation

   a. Section 6.5, Pharmacokinetic Endpoint, second paragraph:

   ~~RAL will be stopped in any individual that has an $AUC_{0\text{-}12hr} \geq 63$ µMxhr, per Section 9.0.~~ **Per Section 9.0, if any individual has an $AUC_{0\text{-}12hr} \geq 63$ µMxhr, the Protocol Team will review all available clinical, safety, PK, immunologic, and virologic data for the participant and determine if discontinuation of RAL is indicated. For participants that permanently discontinue RAL, evaluable PK and safety data will be used in the assessment of the dose for that cohort.**

   b. Section 6.7, Criteria for Early Treatment Discontinuation, fifth bullet:

   - Participant has an $AUC_{0\text{-}12hr} \geq 63$ µMxhr, **and the protocol team determines that RAL should be permanently discontinued,** per Section 9.0.

   c. Section 9.2, Study Design, Modeling and Data Analysis, Pharmacokinetic Guidelines, sixth paragraph:

   If any individual has an $AUC_{0\text{-}12hr} \geq 63$ µMxhr **, the **Protocol Team will review all available clinical, safety, PK, immunologic, and virologic data for the participant and determine if discontinuation of RAL is indicated** ~~participant will stop taking RAL~~. ~~However, their~~ **For participants that permanently discontinue RAL, evaluable** PK and safety data will be used in the assessment of the dose for that cohort.

2. Expedited Adverse Event Reporting Requirements

   Section 7.2, Reporting Requirements for this Study, second bullet:

   - Other medically significant events for which expedited reporting is required include all cancers and pregnancies, fetal losses, IRIS events that qualify as serious adverse events, Hy's Law liver toxicities, and all **confirmed** Grade 3 and 4 toxicities.

Letter of Amendment #1 for:

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

Version 3.0, dated 24 April 2017

DAIDS Document ID # 11831
IND # 77,787 Held By NIAID

Letter of Amendment Date: 15 March 2018

Information/Instructions to Study Sites from the Division of AIDS

The information contained in this Letter of Amendment (LoA) impacts the IMPAACT P1101 study, including the sample informed consent form (ICF), and must be submitted to site Institutional Review Boards and/or Ethics Committees (IRBs/ECs) as soon as possible for their review and approval. Approval must also be obtained from site regulatory entities if applicable per the policies and procedures of the regulatory entities. All IRB/EC and regulatory entity requirements must be followed.

Upon receiving IRB/EC approval and any other applicable regulatory entity approvals, all sites should immediately begin implementing this LoA and using the updated ICFs. After all required approvals are obtained, the updated ICFs should be used for all new participants. In addition, all previously enrolled participants must reconsent to ongoing study participation using the updated site-specific ICF. Re-consenting should take place at each enrolled participant's next study visit after all required approvals are obtained.

Sites are required to submit a LoA registration packet to the DAIDS Protocol Registration Office (DAIDS PRO) at the Regulatory Support Center (RSC). Sites will receive a registration notification for the LoA after the DAIDS PRO verifies that all required registration documents have been received and are complete. Sites should not await this notification before implementing this LoA.

Please file this LoA, all associated IRB/EC and regulatory entity correspondence, and all correspondence with the DAIDS PRO in your essential documents files for P1101. If the P1101 protocol is amended in the future, the contents of this LoA will be incorporated into the next version of the protocol.

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

Version 3.0, dated 24 April 2017
(DAIDS Document ID 11831)

Version 3.0, Letter of Amendment #1
Dated 15 March 2018

Letter of Amendment Signature Page

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

Signature of Investigator of Record	Date
Name of Investigator of Record (printed)	

Summary of Modifications and Rationale

This LoA updates language regarding regulatory entities that may review study records. Per ICH GCP E6 4.8.10(n) and DAIDS requirements, it is mandatory that all DAIDS-sponsored and/or supported trials include language that informs participants that other US, local, and international regulatory entities may also review study records. Protocol Section 10.2 and the sample ICF have been updated accordingly.

Implementation

The modifications included in this LoA are listed below in order of appearance in the protocol. Additions to the text are indicated in **bold**; deletions are indicated by ~~strikethrough~~.

In Section 10.2, Participant Confidentiality:

All laboratory specimens, evaluation forms, reports, and other records will be identified only by a coded number to maintain participant confidentiality. All records will be kept in a secured area. All computer entry and networking programs will be done with coded numbers only. Clinical information will not be released without written permission of the participant, except as necessary for monitoring by the study staff, study monitors, FDA, the OHRP, NIH, the local IRB/EC, ~~or~~ Merck & Co., Inc, **and other US, local, and international regulatory entities**.

In Appendix VI, Sample Informed Consent Form for Study Participation, WHAT ABOUT CONFIDENTIALITY?, second paragraph:

Your child's records may be reviewed by the U.S. Food and Drug Administration (FDA), the Office of Human Research Protections (OHRP), (insert name of site) IRB/EC, National Institutes of Health (NIH), study staff, study monitors, ~~and~~ Merck & Co., Inc. (the drug company supporting this study)**, and other US, local, and international regulatory entities**.

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

(DAIDS Document ID 11831)

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

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

Pharmaceutical Support Provided by:
Merck & Co., Inc.

IND# 77,787 held by NIAID

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VERSION 3.0
FINAL
24 April 2017

PROTOCOL SIGNATURE PAGE

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

DAIDS Document ID 11831

Version 3.0, dated 24 April 2017

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

_____ _____

Signature of Investigator of Record Date

_____

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STUDY MANAGEMENT

- All questions concerning this protocol, including questions regarding clinical management of study participants, should be sent via email to the IMPAACT P1101 Protocol Team (impaact.teamp1101@fstrf.org). Remember to include the participant's PID when applicable. The appropriate team member will respond to questions via e-mail. A response should generally be received within 24 hours (Monday - Friday).

- For protocol registration questions email protocol@tech-res.com or call (301) 897-1707. Protocol registration material can be sent electronically to epr@tech-res.com or via fax at 1-800-418-3544 or (301) 897-1701.

- For data management computer and screen problems email user.support@fstrf.org or call the DMC at (716) 834-0900 x7302.

- For questions or problems regarding study drug supplies, records, and returns, contact the DAIDS Protocol Pharmacist at thucuma.sise@nih.gov or call (301) 451-2775.

- For Expedited Adverse Event (EAE) reporting questions contact the DAIDS RSC Safety Office via email (DAIDSRSCSafetyOffice@tech-res.com) or phone (1-800-537-9979 or +1-301-897-7448) or fax (1-800-275-7619 or +1-301-897-1710). For questions about the DAIDS Adverse Experience Reporting System (DAERS), please contact NIAID CRMS Support at CRMSSupport@niaid.nih.gov. Questions may also be sent within the DAERS application.

- Email the Computer Support Group at the Data Management Center (DMC) (user.support@fstrf.org) to have relevant site personnel added to the protocol email group (impaact.protp1101@fstrf.org). Inclusion in the protocol email group will ensure that sites receive important information about the study during its implementation and conduct.

TABLE OF CONTENTS

GLOSSARY

ABC	Abacavir
ACTG	AIDS Clinical Trials Group
AE/EAE	Adverse Event
AFB	Acid Fast Bacilli
AIDS	Acquired Immunodeficiency Syndrome
ALT	Amino Alaninetransferase
ART/ARV	Antiretroviral Therapy / Antiretroviral
AST	Aspartate Aminotransferase
AUC/AUC_{12}/AUC_{24}	Area Under the Curve
BCG	Bacille Calmette-Guerin
C_{12h}	Plasma concentration at the end of the 12 hour dosing interval
C_{max}	Maximum Plasma Concentration
C_{min}	Minimum Plasma Concentration
C_{trough}	Trough Plasma Concentration
CRF	Case Report Form
CRPMC	Clinical Research Products Management Center
CXR	Chest X-ray
DAERS	DAIDS Adverse Experience Reporting System
DAIDS	Division of AIDS, NIAID
DILI	Drug-Induced Liver Injury
DMC	Data Management Center
DSMB	Data and Safety Monitoring Board
EAE	Expedited Adverse Event
EC	Ethics Committee
EFV	Efavirenz
FDA	Food and Drug Administration
FDC	Fixed Dose Combination
GM	Geometric Mean
HAART	Highly Active Antiretroviral Therapy
HIV	Human Immunodeficiency Virus
HSR	Hypersensitivity Reaction
ICF	Informed Consent Form
IC_{50}/IC_{90}	Inhibitory Concentration – 50% / Inhibitory Concentration 90%
IMPAACT	International Maternal Pediatric Adolescent AIDS Clinical Trials Network
INH	Isoniazid
IRB	Institutional Review Board
IRIS	Immune Reconstitution Inflammatory Syndrome
IUATLD	International Union against Tuberculosis and Lung Disease
IUD	Intrauterine Device
LDMS	Laboratory Data Management System
LFT	Liver Function Test
LPC	Laboratory Processing Chart
LPV/r	Lopinavir/Ritonavir
M.tb./MTB	*Mycobacterium tuberculosis*
MDR TB	Multi-Drug-Resistant Tuberculosis
NEC	Network Executive Committee
NEVEREST	Nevirapine Resistance Study
NIAID	National Institute of Allergy and Infectious Diseases
NICHD	The Eunice Kennedy Shriver National Institute of Child Health and Human Development
NIH	National Institutes of Health

NNRTI	Non-Nucleoside Reverse Transcriptase Inhibitor
NRTI	Nucleoside Reverse Transcriptase Inhibitor
NVP	Nevirapine
OHRP	Office for Human Research Protections
PCP	*Pneumocystis jirovecii* (previously *Pneumocystis carinii)* Pneumonia
PCR	Polymerase Chain Reaction
PDMC	Protocol Development and Monitoring Committee
PI	Protease Inhibitor
PK	Pharmacokinetics
PMTCT	Prevention of Mother To Child Transmission
PRO	Protocol Registration Office
PSWP	Protocol-Specific Web Page
PZA	Pyrazinamide
RAL	Raltegravir
RE	Regulatory Entity
RIF	Rifampicin
RLS	Resource-Limited Settings
RSC	Regulatory Support Center
RTV	Ritonavir
SAE	Serious Adverse Event
SJS	Stevens-Johnson Syndrome
SES	Subject Enrollment System
SMC	Study Monitoring Committee
SUSAR	Suspected Unexpected Serious Adverse Reaction
TB / PTB	Tuberculosis / Pulmonary TB
TEN	Toxic Epidermal Necrolysis
T_{max}	Time to C_{max}
TST	Tuberculin Skin Test
UGT	Uridine Diphosphate Glucuronosyltransferase
ULN	Upper Limit of Normal
US	United States
WHO	World Health Organization
XDR TB	Extensively Drug-Resistant Tuberculosis
ZDV	Zidovudine

SCHEMA

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

DESIGN:	Phase I/II, dose-finding, safety, tolerability and pharmacokinetics study of raltegravir (RAL) in infants and children who have received ≥ 1 week and ≤ 20 weeks of Rifampicin (RIF)-based TB therapy prior to initiation of antiretroviral therapy.
SAMPLE SIZE:	Approximately 36 to 108 to achieve a target of 12 evaluable infants and children for each cohort at the final recommended dose.
POPULATION:	HIV-infected and TB co-infected infants and children ≥ 4 weeks to < 12 years of age taking RIF-based TB therapy and who are eligible for antiretroviral (ARV) treatment as defined by local or WHO guidelines.
STRATIFICATION:	Participants will be enrolled into the study into the following cohorts: Cohort I: ≥ 2 to < 6 years of age on TB treatment (n = 12 minimum) Cohort II: ≥ 6 to < 12 years of age on TB treatment (n = 12 minimum) Cohort III: ≥ 4 weeks to < 2 years of age on TB treatment (n = 12 minimum) Cohorts I, II, III will enroll simultaneously. Each age cohort will start with a mini-cohort of six participants, followed by six additional participants to make up a full cohort.
REGIMEN:	Chewable RAL tablet, starting dose of 12 mg/kg (up to a maximum dose of 800 mg) orally twice daily in addition to, as part of standard of care, two NRTIs plus RIF-containing regimen for treatment of TB. Following an intensive PK visit, a fourth ARV drug will be added to the RIF-containing regimen. <u>TREATMENT DURATION:</u> The four drug ARV regimen (including RAL, 2 NRTIs plus an additional ARV drug per local standard of care) will be continued until TB treatment is completed and then RAL will be discontinued. The three drug ARV regimen will be continued per local standard of care after RAL is discontinued.
STUDY DURATION:	Participants will be followed for up to three months post discontinuation of RAL.

PRIMARY OBJECTIVES:

1. To determine the pharmacokinetics and appropriate dose of RAL when administered with a RIF-containing anti-TB therapy in HIV/TB co-infected infants and children that generates PK parameters generally comparable to those seen in HIV-infected infants and children in the absence of RIF.

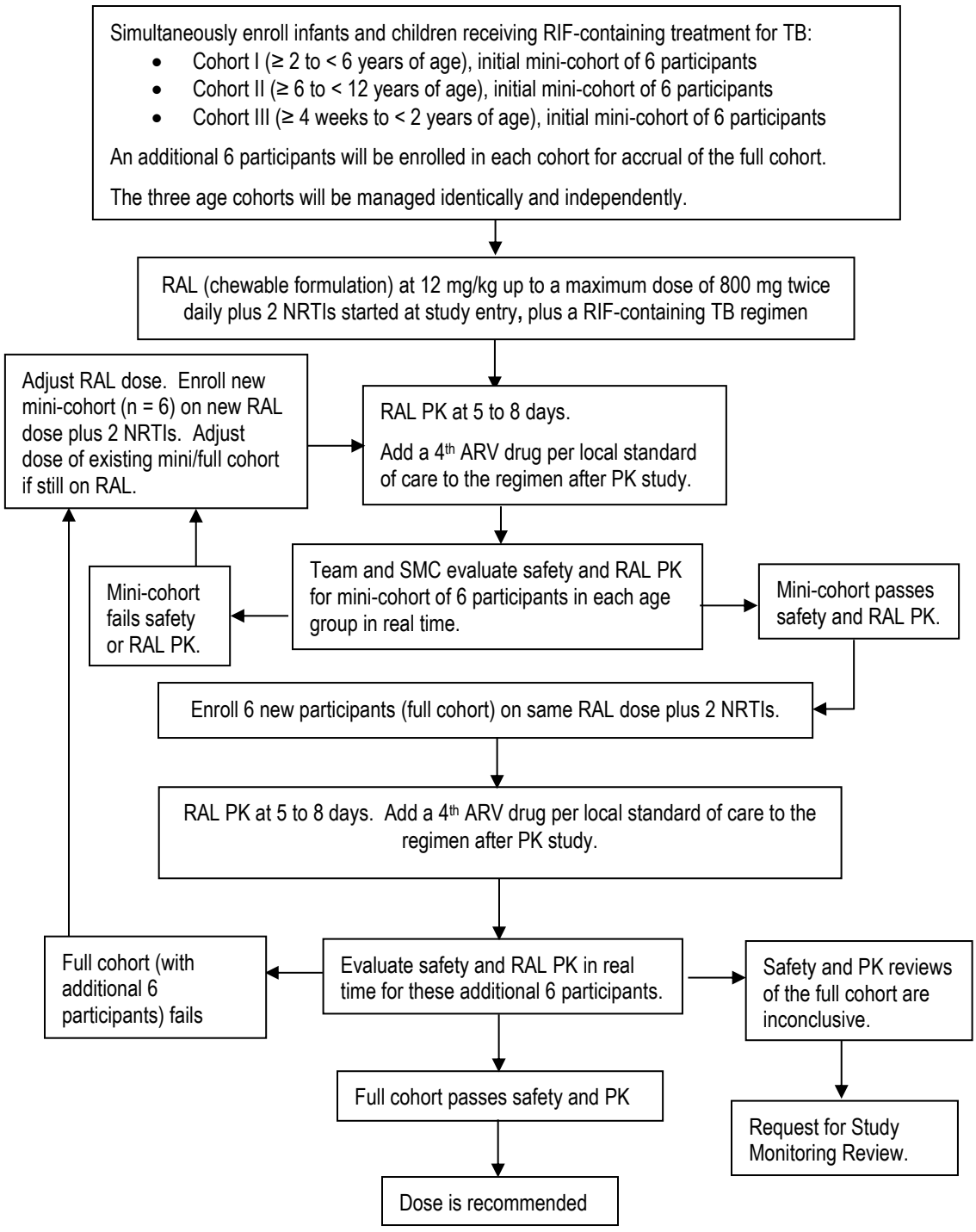
2. To determine safety and tolerance of RAL-containing ART when administered with a RIF-containing anti-TB therapy in HIV/TB co-infected infants and children.

SECONDARY OBJECTIVES:

1. To describe the short-term treatment outcomes of infants and children using a RAL-containing ART regimen co-treated with a RIF-containing TB treatment (see Sections 8.2.3 and 8.2.4).

2. To explore whether infants and children receiving a RAL-containing ART regimen, co-treated with a RIF-containing TB treatment, develop ARV drug associated resistance mutations (see Section 6.2.3).

SCHEMA



Notes:

- For each mini-cohort, a routine Study Monitoring Committee (SMC) review of the safety and PK data will be done prior to accrual of the full-cohort.
- All participants will stop RAL after TB treatment is completed. The ARV regimen will continue per local standard of care. All participants will be followed for 3 months after RAL is discontinued.
- RAL dose adjustment will only be done once in a mini/full cohort that fails safety and RAL PK.
- RAL PK will not be repeated in mini/full cohort that has adjustment in RAL dose.

1.0 INTRODUCTION

1.1 Background

The burden of tuberculosis (TB) among HIV-infected adults and children is very high in many resource-limited settings (RLS). This is of particular concern in Sub-Saharan Africa where up to 75% of HIV-infected people may have infection with agents of TB (1). In Cape Town, South Africa, 70% of adult patients initiated on antiretroviral therapy (ART) either had a previous episode of active TB or had been treated for TB within the first year of initiating ART (2). It is estimated that children account for about 15 to 20% of the annually reported TB cases (3). Up to a quarter of children starting ART have been reported to be receiving TB treatment in South Africa (4, 5).

Bacille Calmette-Guerin vaccine (BCG) disease has also been shown to be prevalent among HIV-infected children, particularly as immune reconstitution inflammatory syndrome (IRIS) in the first weeks of administration of ART. In the Nevirapine Resistance Study (NEVEREST), BCG disease was the most common form (71%) of IRIS, exceeding TB (6). Although usually localized, BCG disease is often treated with a Rifampicin (RIF)-containing regimen because of fear of dissemination of BCG in the immunocompromised child. In addition, incident TB has been described to occur after the start of ART (5, 6). The implications of this are that a high proportion of children on ART in TB prevalent areas will require TB treatment during the course of ART. Regimens that minimize interactions between the two therapies are being investigated.

The current World Health Organization (WHO) guidelines for ART in infants and children provide recommendations based on the patient age, drug availability, and history of exposure to nevirapine as part of efforts to prevent infection. Nevirapine (NVP)-based therapy has been the first-line regimen for infants and children in most resource limited settings as NVP is relatively inexpensive, can be used in infants and children under 2 years of age, and is frequently a component of fixed dose combination (FDC) therapy. The consolidated guidelines for HIV management, which were released in 2013, recommend the boosted protease inhibitor lopinavir/ritonavir (LPV/r) for use in first line therapy for infants and children who are younger than three years of age. These changes were based on evidence from the P1060 study which demonstrated that LPV/r containing regimens were superior to NVP-containing treatment in terms of virologic outcomes. Efavirenz (EFV)-based treatment regimens are still recommended for first-line therapy in children older than 3 years (7). Second-line therapy for children who fail the initial non-nucleoside reverse transcriptase inhibitor (NNRTI)-containing regimen should contain protease inhibitor (PI)-based therapy usually LPV/r.

Drug interactions between TB treatment and ART are well described. RIF, as a component of first-line antibacterial regimen for TB, is usually used in combination with isoniazid (INH) and pyrazinamide (PZA). RIF is a strong inducer of the cytochrome P450 enzymes including the CYP 3A4 isoenzymes, uridine diphosphate-glucuronosyltransferases, and P-glycoprotein.

1.2 Recommended ARV Regimen in the Presence of Rifampicin-Containing TB Treatment

There are limited data to guide treatment options for HIV/TB coinfection in infants and children. WHO recommendations include; triple NRTI regimens, NVP-containing regimens with NVP dosed at 200 mg/m^2, EFV for children who are older than 3 years, and LPV/r with extra ritonavir known as "super-boosted" LPV/r. (8)

Evidence from the ARROW study, which showed that three-NRTI long-term maintenance was immunologically and clinically similar to NNRTI-based ART, was used to support this strategy for use with TB coinfected children. However, data were limited in the context of TB co-treatment. (9)

Lower NVP levels during co-administration with RIF have been documented in adults (10). In children, there are limited and conflicting data (See Table 1).

Table 1: Impact of Rifampicin on Nevirapine Pharmacokinetics

	Thailand (11)	Uganda (12)	Zambia (13)	
N	8 with TB	7 with TB	21 with TB	16 controls - NO TB
Median Age (years) (range)	9.7 (4.4-11.8)		1.55 (0.66 – 3.18)	1.33 (0.56 – 2.51)
Daily dose (mg/m^2)	342 (median) (range: 300-526)		353 (mean) (IQR: 326 – 375)	362 (mean) (IQR: 318 – 405)
Median C_{min} (mg/L) (range)	6.48 (3.03-13.66) *0% < 3 mg/L*	2.92 (1.67-9.98)	2.93 (1.06–11.4) *52% < 3 mg/L*	5.93 (3.28–18.1) *0% < 3 mg/L*

NVP at a dose of 200 mg/m^2 is recommended for use in conjunction with RIF-containing TB treatment because of the aforementioned PK problems where enhanced metabolism of NVP occurs when co-administered with RIF.

EFV is a commonly used NNRTI in combination therapy in RLS for older children who are starting ART. In a small study of EFV pharmacokinetics (PK) with RIF-containing TB regimens, no significant difference was documented in the levels of EFV between those with and without concomitant TB treatment (14). Based on these limited findings, EFV-containing therapy without dose-adjustment is recommended for use with TB treatment. This finding is the participant of further evaluations in younger children (IMPAACT P1070, Dose-Finding and Pharmacogenetic Study of Efavirenz in HIV-Infected and HIV/TB Co-infected Infants and Children ≥ 3 Months to < 36 Months of Age) and may require further investigations in older children.

A study in healthy adult volunteers treated with RIF showed that the C_{min} of LPV was best preserved by taking additional ritonavir to the fixed LPV/r preparation yielding a LPV: Ritonavir (RTV) ratio of 1:1 which is referred to as "super boosted" LPV/r (15). This was investigated in a study involving an HIV-infected pediatric cohort. The combination of additional RTV with RIF was well tolerated in a small cohort of children and therapeutic LPV levels were maintained (16).

While LPV/r is a potent agent, the liquid formulation of the drug has an unpleasant flavor, requires refrigeration for storage, and has long term lipid safety concerns. Although it has been demonstrated that adequate drug exposure can be maintained by 'super-boosting', this method of treatment is complex and may be poorly tolerated outside of a clinical trial. Care providers will be challenged in insuring adherence with high dose RTV due to poor palatability, toxicity and extra dosing volume. RTV has a very short shelf life causing challenges with ensuring that pharmacies have adequate stock on hand, and families can store drug as required.

There is an urgent need for better tolerated, potent, simple agents (i.e. simple dosing, administration and storage) to be included in first line ART regimens to widen the treatment options for infants and children co-infected with TB and HIV.

1.3 Rationale for Using Raltegravir with TB Treatment

There is a clear requirement for newer ART agents which are well tolerated, potent and which have minimal interactions with rifampicin-containing TB therapy. One potential class of drugs to consider is the group of HIV-1 integrase inhibitors. The HIV-1 integrase catalyzes the stepwise process that results in the integration of the HIV-1 DNA into the genome of the host cell. This ordered series of reactions includes the assembly of integrase in a stable complex with the viral DNA, the endonucleolytic processing of the viral DNA ends, and strand transfer or joining of the viral and cellular DNAs. Integration is required for stable maintenance of the viral genome as well as efficient viral gene expression.

Raltegravir (Isentress™, RAL) is a potent and selective inhibitor of HIV-1 integrase catalyzed strand transfer (IC_{50}=10 nM). Raltegravir exhibits >1,000-fold selectivity over other phosphotransferases, including the structurally related enzyme HIV-1 RNase H and the human DNA polymerases, α, β, and γ (IC_{50} values > 50 μM). The antiretroviral potency of raltegravir (initially estimated as having an IC_{95} of 31 ± 20 nM; 50% human serum) measured in vitro is comparable to many clinically efficacious antiretroviral therapeutics.

RAL is not a CYP3A4 inducer or inhibitor and therefore could potentially be used with drugs metabolized by CYP3A4. However, as noted above, RIF induces phase II enzymes such as UDP-glucoronosyl transferase and since RAL undergoes glucuronidation in the liver a precaution has been placed on the co-administration of the two drugs without drug dose modification of RAL. In adults, doubling the dose of RAL when given in conjunction with RIF partially overcame this PK interaction, resulting in adequate RAL plasma C_{max} and AUC, but did not overcome the RIF effect on C_{trough} concentrations (C_{12h}) (17). RAL was granted traditional approval by the U. S. Food and Drug Administration (FDA) in January 2009. This approval was updated in February 2009 to include the recommendation to increase RAL dose to 800 mg twice daily during co-administration with RIF. Additionally, caution is recommended when co-administering RAL with other strong UGT1A1 inducers due to reduced RAL plasma concentrations. This experience suggests a doubling of formulation in children would also be warranted.

However, recent data from a study showing inferior efficacy with 800 mg once daily raltegravir compared to 400 mg twice daily (HIV RNA < 50 copies/mL at Week 48: QD 83.2%, BID 88.9%) have indicated that the shape of the raltegravir concentration-time curve is also important for long-term efficacy, as both regimens had the same daily exposure ($AUC_{0\text{-}24hr}$), but the BID treatment arm exhibited mean trough concentrations 5-6 fold higher than those observed for the QD treatment arm. More specifically, trough (C_{12h}) concentrations were correlated with antiviral effect, with patients in the lowest quartile for C_{12h} showing the highest rate of virologic failure (18, 19). Based on these data, a minimum target for GM C_{12h} of approximately 75 nM is now considered to be more appropriate than the previous target of 33 nM.

Raltegravir is currently being investigated in pediatric populations in IMPAACT P1066 [A Phase I/II, Multicenter, Open-Label, Noncomparative Study of the International Maternal, Pediatric, Adolescent AIDS Clinical Trials (IMPAACT) Group to Evaluate the Safety, Tolerability, Pharmacokinetics, and Antiretroviral Activity of Raltegravir (Isentress™, MK-0518) in HIV-1 Infected Children and Adolescents] including a novel chewable ethylcellulose preparation for children 2 to < 12 years of age and granules for suspension for infants and children ≥ 4 weeks to < 2 years of age.

Based on the results from P1066, final dosing recommendations for evaluation in Stage II of the study were made for Cohorts I and IIA receiving the adult tablet and Cohorts IIB and III receiving the chewable tablet.

Cohort I (12 through < 19 years) and Cohort IIA (6 through < 12 years and ≥ 25 kg): 400 mg adult tablet twice daily (20-23).

Cohort IIB (6 through < 12 years) and Cohort III (2 through < 6 years): Weight based dosing of chewable tablet to approximate 6 mg/kg twice daily up to a maximum of 300 mg twice daily (Doses: 50 mg, 75 mg, 100 mg, 150 mg, 200 mg and 300 mg) (24, 25).

Cohort IV (6 months through < 2 years) and Cohort V (4 weeks through < 6 months): Weight based dosing of oral granules for suspension (20 mg/mL) to approximate 6 mg/kg twice daily. (26)

The mean raltegravir pharmacokinetic parameters associated with the final recommended doses for each age group are listed in Table 2. As shown, the oral bioavailability of RAL chewable tablets is substantially greater than the adult tablets, with a final mean dose of approximately 6 mg/kg.

Table 2: Summary of Raltegravir Pharmacokinetic Parameters Following Administration of Final Recommended Doses in P1066 (26, 27)

Age	Cohort	Formulation	Final Recommended Dose	N†	Mean Weight (kg)	Mean Dose mg (mg/kg)	Geometric Mean (%CV) $AUC_{0\text{-}12hr}$ (μMxhr)	Geometric Mean (%CV) C_{12hr} (nM)
12 through < 19 y (20)	I	Adult tablet	400 mg BID, regardless of weight‡	11	43.55	390.91 (9.28)	15.71 (98)	332.63 (78)
6 through < 12 y (23)	IIA	Adult tablet	400 mg BID, for patients ≥25 kg	11	31.54	400.00 (13.45)	15.84 (120)	246.09 (221)
6 through < 12 y (25)	IIB	Chewable tablet	6 mg/kg BID, maximum of 300 mg BID	10	36.36	230.00 (6.47)	22.58 (34)	129.60 (88)
2 through < 6 y (24)	III	Chewable tablet	6 mg/kg BID, maximum of 300 mg BID	12	14.24	89.58 (6.24)	17.95 (59)	71.16 (55)
6 mo through < 2 y (15)	IV	Granules for suspension	6 mg/kg BID	8	8.49	47.89 (5.93)	19.8 (34)	108.2 (52)
4 wk through < 6 mo (12)	V	Granules for suspension	6 mg/kg BID	11	5.50	30.76 (5.70)	22.3 (40)	116.6 (68)

† Number of participants with intensive PK results at the final recommended dose.

‡ Cohort I participants received approximately 8 mg/kg dose at time of intensive PK which met PK and safety targets. Based on review of the individual profiles and receipt of a mean dose of 390 mg the team selected 400 mg BID as the recommended dose for this age group. Participants receiving a dose other than 400 mg BID were switched; no repeat PK was performed.

The U.S. FDA granted approval on December 21, 2011 for use of RAL chewable tablets in combination with other antiretroviral agents for the treatment of HIV-1 infection in pediatric patients ≥ 2 to < 12 years of age and weighing at least 10 kg. The FDA approved RAL granules for oral suspension on December 20, 2013, in combination with other antiretroviral agents for the treatment of HIV-1 infection in pediatric patients four weeks of age and older, weighing ≥ 3 kg to < 20 kg.

Based on data from prior studies of drug interactions of RIF and RAL in adults, doubling the dose of RAL to 12 mg/kg/dose (maximum 800 mg/dose) is an appropriate starting point for this study (17). The UGT1A1 metabolic pathway is fully mature after the first 3 months of life (28); therefore, co-administration of RAL and RIF is expected to lead to significant reductions in RAL concentrations in children. As pediatric RAL dosing regimens have been shown to achieve PK parameters comparable to those in adults, doubling the RAL dose for children when given with RIF will likely yield similar improvements in PK parameters.

Of note, doubling the RAL dose given with RIF in adults did increase AUC (GMR 1.27) and C_{max} (GMR 1.62) when compared with standard RAL dosing. However, the increased exposures lay well within a well-studied range that has been safe and well-tolerated. Data from the Merck sponsored QTc study (PN024) provides guidance as to the safety of higher doses of RAL. In this study, single doses of 1600 mg of the lactose formulation were given to adults resulting in the following pharmacokinetic parameters: C_{max} = 19.63 μM and $AUC_{0\text{-}12hr}$ = 63.05 μMxhr. To date in the development program for RAL, there have been no acute safety findings that were temporally associated with peak concentrations, and RAL has been found to be generally well tolerated with no dose-related toxicities.

In addition, after approval of the initial protocol version of P1066, data became available from a Phase I relative bioavailability/biocomparison study in adults (Protocol 068). Protocol 068 compared the PK of raltegravir poloxamer (adult tablet) and ethylcellulose chewable tablet formulations and the granules for oral suspension. This was a 4-period, crossover study in healthy, adults in which 12 participants each received 4 treatments (Treatments A, B, C, and D) randomized in a balanced, crossover design in Periods 1 through 4. Treatment A consisted of a single oral dose of 400 mg raltegravir adult formulation tablet. Treatment B consisted of a single oral dose of 400 mg raltegravir ethylcellulose pediatric chewable tablet formulation (administered as 4 x 100 mg tablets). Treatment C consisted of a single oral dose of 400 mg raltegravir oral granules in a liquid suspension. Treatment D consisted of a single oral dose of 400 mg raltegravir ethylcellulose pediatric chewable tablet formulation (as 4 x 100 mg tablets) administered following a high fat meal. Treatments A-C were administered in the fasted state. There was a minimum of 4 days of washout between the single doses in each treatment period.

The geometric mean pharmacokinetic parameter values for the raltegravir pediatric chewable tablet and oral granules for suspension formulations were estimated and compared to the corresponding values for the adult tablet, all following single dose administration of 400 mg in the fasted state, with results shown in Table 3. The geometric mean C_{12hr} values were similar for all formulations, while $AUC_{0\text{-}\infty}$ and C_{max} values were higher for both the pediatric chewable tablet and the oral granules formulation compared to the adult tablet. For the oral granules formulation, $AUC_{0\text{-}\infty}$ and C_{max} were moderately higher (2.6- and 4.6-fold) than those obtained with the adult tablet and slightly higher (1.5- and 1.4-fold) than those obtained with the pediatric chewable tablet. Both the pediatric chewable tablet and oral granules formulations had earlier median T_{max} values compared with the adult tablet (0.5 and 1.0 hours for the chewable tablet and oral granules, respectively, compared to 4.0 hours for the adult tablet). Half-life values for both the initial (α) and terminal (β) phases were similar for all formulations. The results were consistent with there being some difference between formulations in the absorption phase of the pharmacokinetic profile, but little difference in the distribution and elimination phases of the profile.

Table 3: Comparison of Raltegravir Plasma Pharmacokinetics Following Single-Dose Administration of the Raltegravir Adult Tablet, Pediatric Chewable Tablet (Fasted or Fed), and Raltegravir Oral Granules in a Liquid Suspension to Healthy, Adult, Male and Female Participants (Protocol 068)

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

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

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

· Median values presented for T_{max}.

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

The higher $AUC_{0-\infty}$ and C_{max} values for the oral granules formulation are not expected to have any meaningful clinical consequences. The pharmacokinetic properties of the two pediatric formulations (chewable tablet and oral granules) are similar to the raltegravir Phase I lactose formulation which was well tolerated in adults (P007). Additional data using the lactose formulation was generated in the QTc study (P024) and Protocol 001 (P001), a single and multiple dose PK and safety study, both performed in adult healthy volunteers. In P024, a single 1600 mg raltegravir fasted dose produced a geometric mean AUC_{0-12hr} of 63.05 µMxhr and C_{max} of 19.63 µM. Raltegravir was generally well tolerated with no serious clinical or serious laboratory adverse experiences reported and no participants discontinued because of an adverse experience. All adverse experiences reported were transient and, with the exception of a report of severe toothache, judged to be mild or moderate in intensity.

In P001, the 1600 mg single dose fasted arm produced a geometric mean $AUC_{0-\infty}$ of 95.60 µMxhr and C_{max} of 36.06 µM and the 800 mg multiple dose fasted arm produced a geometric mean AUC_{0-12hr} of 45.27 µMxhr and C_{max} of 19.73 µM. In both arms of P001, raltegravir was generally well tolerated with no serious clinical or serious laboratory adverse experiences reported and no participants discontinued because of an adverse experience. There were no consistent treatment-related changes in laboratory, vital signs, or ECG safety parameters.

Based on the lack of a statistically significant difference in trough values, and the otherwise moderate dissimilarities in the other pharmacokinetic parameters, these results supported continued clinical development of both the chewable tablet and oral granules for suspension pediatric formulations in P1066. The hypothesis is that doubling the dose of RAL given with RIF-containing TB treatment in HIV/TB co-infected infants and children will result in RAL PK levels similar to those achieved in HIV-infected infants and children in the absence of RIF.

1.4 Rationale for Studying Raltegravir Chewable Formulation as a Dispersible Tablet

Administration of RAL granules for oral suspension formulation requires a complex constitution procedure, including use of single–dose 100 mg packets, mixing cups and syringes, and potable water required for each dose. This may not be feasible for caregivers, particularly as multiple sachets of RAL granules for oral suspension for doses > 100 mg will be needed if the dose needs to be increased for use with RAL-containing TB treatment. Merck has generated both biocomparison and modeling data indicating that the Isentress chewable tablet used in 25 mg dose increments should provide appropriate PK to achieve both efficacy and safety PK targets across the 3 to 25 kg weight range, and in particular in children < 10 kg, in whom the chewable tablet was not directly studied in the pediatric development studies. Data indicate that the 25 mg chewable tablet can be used as a dispersible tablet, meeting WHO dispersibility criteria after simple crushing or pre-wetting (followed by stirring and crushing as needed to remove any chunks) of the chewable tablet in a variety of vehicles. Thus, this alternative proposed dosing scheme, using chewable tablets as dispersible for infants and children at least four weeks of age and from 3 to 10 kg can be expected to achieve appropriate PK for both good efficacy and acceptable safety." [*Raltegravir: Merck's perspective on chewable as dispersible for WHO*. Unpublished data.] The pharmacokinetics of the raltegravir chewable tablet formulation have been compared to the granules for suspension formulation in a single-dose study in adults (P068) (29). A summary of the study results is show below in Table 4.

Table 4: Raltegravir Plasma Pharmacokinetics After Single-dose Administration of the Ethylcellulose (EC) Chewable Tablet and Oral Granules for Suspension (GFS) Formulations in Healthy Adults (29)

Pharmacokinetic Parameter	*n*	GMR (90% CI) (400 mg chewable/ 400 mg granules)	GM Chewable	GM Granules
C_{12h} geometric mean, nM	12	0.83 (0.64, 1.09)	134	162
$AUC_{0-\infty}$ geometric mean, µM•h	12	0.68 (0.56, 0.82)	34.2	50.4
C_{max} geometric mean, µM	12	0.69 (0.51, 0.94)	16.1	6.14

A uniform pediatric formulation of raltegravir which is chewable or dispersible will also assist with the harmonization process for antiretroviral formulations which are recommended by the WHO.

1.5 Rationale for Adding a Fourth ARV Drug with RAL during TB Treatment

Inadequate dosing of one or more drugs in an antiretroviral regimen can lead to virologic failure, progression of disease, and selection of HIV resistance mutations that may compromise future treatment regimens. This is of particular concern in the setting of co-infection with tuberculosis and HIV infection, in which virologic failure is more common than in the absence of HIV infection alone in children. In view of the uncertain nature of interactions between RAL and RIF in children, we plan to add a fourth antiretroviral agent after completion of the intensive pharmacokinetic study of RAL given with two NRTIs receiving therapy. The fourth drug will be added in line with local treatment recommendations for treatment of HIV/TB coinfection and in discussion with the Protocol Team. All ARVs, other than EFV or LPV/r, must be approved by the Protocol Team prior to inclusion in the study drug regimen.

2.0 STUDY OBJECTIVES

2.1 Primary Objectives

1. To determine the pharmacokinetics and appropriate dose of RAL when administered with a RIF-containing anti-TB therapy in HIV/TB co-infected infants and children that generates PK parameters generally comparable to those seen in HIV-infected infants and children in the absence of RIF.

2. To determine safety and tolerance of RAL-containing ART when administered with a RIF-containing anti-TB therapy in HIV/TB co-infected infants and children.

2.2 Secondary Objectives

1. To describe the short-term treatment outcomes of infants and children using a RAL-containing ART regimen co-treated with a RIF-containing TB treatment (see Sections 8.2.3 and 8.2.4).

2. To explore whether infants and children receiving a RAL-containing ART regimen, co-treated with a RIF-containing TB treatment, develop ARV drug associated resistance mutations (see Section 6.2.3).

3.0 STUDY DESIGN

P1101 is a Phase I/II, dose-finding, safety, tolerability and pharmacokinetics study of RAL chewable tablet in HIV-infected infants and children ≥ 4 weeks to < 12 years of age who are TB co-infected and on ≥ 1 week and ≤ 20 weeks of RIF-based TB therapy who are eligible for ARV treatment by current local or WHO guidelines. The study's objective is to determine the appropriate and safe dose of RAL to be used with a RIF-based TB treatment regimen to provide additional ART options in co-infected infants and children.

- At least 12 participants will be enrolled in each of the three age cohorts: Cohort I: ≥ 2 to < 6 years of age, Cohort II: ≥ 6 to < 12 years of age, and Cohort III: ≥ 4 weeks to < 2 years of age. Enrollment into each age cohort will be simultaneous, with RAL treatment initiated at Entry. Each age cohort will start with a mini-cohort of six participants to assure that preliminary PK and safety criteria are met at that dose. See Section 9.2 for details on the intensive PK procedure.
- For each mini-cohort, a routine Study Monitoring Committee (SMC) review of the safety and PK data will occur prior to accrual of the full-cohort.

- Data from each age cohort will be reviewed independently and, if the mini-cohort data meets established metrics (see Section 8.1), an additional 6 participants per age cohort will be enrolled (full cohort), and evaluated for safety and PK.
- If upon review of all PK and safety data from the mini-cohort the dose is not acceptable, the existing mini-cohort dose will be adjusted and a new mini-cohort group of six participants will be enrolled (see Section 6.2). The new mini-cohort, treated at the adjusted dose, will undergo safety and PK evaluations and, if PK and safety guidelines are satisfied, the full cohort will be enrolled.
- This process will be repeated until the PK and safety evaluations result in an acceptable dose for that cohort. See Section 8.1 for details on the dosing algorithm.
- It is anticipated that at least 36 to 108 participants will be enrolled to achieve 12 evaluable participants in each cohort at the recommended dose. Participants enrolled to mini-/full cohorts with failing doses (if not already completed TB treatment) may continue their RAL and have a dose adjustment as described in Section 6.2.1, Cohort Dosing Management. The participants will continue on study following the visits in the Schedule of Evaluations (see Appendix I).
- If the PK data for twice daily dosing of RAL is not acceptable, the team may decide to adjust the dose to three times daily. The RAL three times daily dosing will be incorporated into a future amendment of the protocol.
- If the results of the intensive PK are in question, unexpectedly low or high and may put the participant at risk for toxicity, the Protocol Team may request a repeat of the intensive PK. The site will be notified by the team and the time period for obtaining the repeat PK will be given.

These HIV-infected participants, diagnosed with pulmonary TB or TB adenitis according to the criteria in Section 4.1.6, will be treated with a RIF-containing TB regimen for approximately six months, dosed according to the most current WHO TB dosing guidelines and Guidelines for Prevention and Treatment of Opportunistic Infections among HIV-Exposed and HIV-Infected Children (30, 31). RAL will initially be dosed at 12 mg/kg twice daily up to a maximum of 800 mg BID and administered with two new NRTIs. Intensive PK for RAL will then be conducted after 5 to 8 days. After the intensive PK study, a fourth ARV drug per local standard of care for treatment in HIV/TB co-infected infants and children requiring RIF therapy, will be added to the regimen to provide additional ARV activity. Safety data for RAL and TB drugs will also be evaluated at each study visit. The four-drug ARV regimen will be continued until TB treatment is completed, typically after six months of therapy. RAL will be discontinued when TB therapy is completed, and the ARV regimen will continue per local standard of care. See Section 5.0 for additional information regarding the drug regimen.

If an appropriate dose has not yet been established when accrual reaches 60 to 66 participants, the team will evaluate if the maximum sample size should be increased. An increase in the maximum sample size will require approval by the IMPAACT network. Notice of an increase in the sample size will be sent to sites via a Letter of Amendment which will need to be submitted to each Institutional Review Board (IRB) or Ethics Committee (EC) per each site's normal procedures. Any additional guidance issued by a site's IRB or EC will need to be followed by that site.

4.0 SELECTION AND ENROLLMENT OF PARTICIPANTS

4.1 Inclusion Criteria

4.1.1 Age ≥ 4 weeks to < 12 years at entry.

4.1.2 Weight ≥ 3.5 kg at entry.

4.1.3 Confirmation 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 Laboratory Center.

For participants less than 2 years of age or have not ceased breastfeeding for at least 4 weeks, Sample #1 and Sample #2 may be tested using any of the following:

- One HIV DNA PCR
- One quantitative HIV RNA PCR (above the limit of detection)
- One qualitative HIV RNA PCR
- One total HIV nucleic acid test

For these participants, at least one of the two samples must be tested in the study site's designated VQA-certified laboratory. For tests performed in other (non-VQA-certified) settings, adequate source documentation, including the date of specimen collection, date of testing, test performed, and test result, must be available.

For participants 2 years of age and older who have ceased breastfeeding for at least 4 weeks, 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 total HIV nucleic acid test

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

For participants 2 years of age and older who have ceased breastfeeding for at least 4 weeks, 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 total HIV nucleic acid test

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 an appropriate external quality assurance program (for international sites).

Note: HIV RNA PCR is a required screening evaluation that must be performed in a VQA-certified laboratory (refer to Appendix I). Assuming the result of this test is above the limit of detection of the assay, this test may serve as one of the two tests required for documentation of HIV infection.

4.1.4 ARV treatment naïve or has not received ARVs for at least 30 days prior to entry.

Note: Participants with prior exposure to ARVs for PMTCT or treatment - regardless of duration - are eligible provided the participant has not received ARVs for at least 30 days prior to entry. The reasons for interruption could include drug toxicity, poor adherence, or treatment failure that preceded enrollment and has not been imposed by study staff. ARVs should not be withheld for the purposes of enrollment into the study and against the participant's best interest.

4.1.5 ARV treatment eligible as defined by:

- Country-specific guidelines
  OR
- WHO pediatric treatment algorithm (http://apps.who.int/iris/bitstream/10665/208825/1/9789241549684_eng.pdf?ua=1)

4.1.6 Diagnosis of pulmonary TB or TB adenitis.

- Diagnosis of pulmonary TB with either:
  - A positive smear or GeneXpert test
    OR
  - If smear negative, having either a positive household contact, suggestive chest x ray (CXR), or positive tuberculin skin test (TST). In addition to having at least one of these findings, the child must also have at least one of the following symptoms for more than 2 weeks: weight loss, chronic cough and/or night sweats.

- Diagnosis of TB adenitis is made by at least one of the following criteria:
  - Smear or culture of aspirated, biopsied, or draining material positive for acid fast organisms (smear) or MTB
    OR
  - Presence of painless, asymmetric lymph node(s) in cervical, supraclavicular or axillary region AND 2 or more of the following: positive TB household contact, weight loss, night sweats, suggestive CXR, or a positive TST reaction.

Note: Participants with BCG disease treated with rifampicin-containing TB treatment can be included.

4.1.7 Participant has initiated at least a two drug TB regimen containing rifampicin, and has tolerated at least 1 week of the TB drug regimen prior to initiation of raltegravir.

Note: TB treatment may be started after being diagnosed by the site investigator. Treatment regimens may include isoniazid, pyrazinamide, ethambutol and streptomycin in addition to rifampicin.

ART should ideally be started within 2 weeks of starting TB treatment. A patient who has started therapy for TB elsewhere but has not yet been started on ART is eligible for enrollment provided they have not had >20 weeks of TB therapy. Delay between starting TB treatment and ART is not encouraged, and local or international guidelines should be followed for managing TB and HIV coinfection in infants and children.

4.1.8 Female participant who is of child bearing potential and sexually active has agreed to use two reliable methods of contraception, including a medically accepted barrier method of contraception (e.g., female/male condoms, diaphragm or cervical cap with a cream or gel that kills sperm (excluding nonoxydyl-9), intrauterine device [IUD], others*)* together with another reliable form of contraception while on study and for 4 weeks after stopping RAL.

4.1.9 Parent, legal guardian, or designated guardian according to country-specific guidelines, able and willing to provide signed informed consent and to have the participant followed at the clinical site.

4.2 Exclusion Criteria

4.2.1 Grade ≥ 2 AST (aspartate aminotransferase) or ALT (alanine aminotransferase) at screening, which must be within 30 days of entry.

Note: Participants can be re-screened provided that they will have at least 4 weeks of TB treatment remaining at the time of entry.

4.2.2 Any Grade ≥ 4 clinical toxicity or laboratory result at screening except fever, chills, fatigue or malaise, unintentional weight loss, and dyspnea or respiratory distress which could be associated with TB.

4.2.3 Acute, serious infections other than TB requiring active treatment (e.g. Pneumocystis jirovecii [previously Pneumocystis carinii] pneumonia [PCP], cryptococcal meningitis, etc.). Infants and children diagnosed with acute bacterial pneumonia at time of diagnosis of TB may be included. Prophylaxis against opportunistic infections will be allowed.

4.2.4 Diagnosis of Kwashiorkor (< 80% expected weight-for-age with the presence of edema and hypoalbuminemia).

4.2.5 Current chemotherapy for active malignancy or history of chemotherapy discontinued within one year of entry.

4.2.6 Rifampicin therapy of > 20 weeks duration immediately prior to enrollment.

4.2.7 Known or suspected MDR or XDR TB, including contact with a documented MDR or XDR TB source case, as these may require longer duration of therapy or non-rifampicin containing regimen.

Note: Participants found to have MDR or XDR TB before or during the study will be informed of their illness and referred for appropriate care as determined by local guidelines.

4.2.8 Current TB regimen containing rifabutin, macrolides and any other anti-mycobacterial agents with known interactions with RAL.

4.2.9 Any clinically significant diseases (other than HIV and TB infection) or clinically significant findings during the screening medical history or physical examination that, in the investigator's opinion, would compromise the outcome of this study.

4.2.10 Participant is pregnant or breastfeeding.

4.2.11 Participant is unlikely to adhere to the study procedures or keep appointments.

4.2.12 Participant is planning to relocate during the study to a non-IMPAACT study site.

4.2.13 Participant is taking any disallowed medications (see Section 4.3.2).

4.3 Concomitant Medication Guidelines

Whenever a concomitant medication or study agent is initiated or a dose changed, investigators must review the concomitant medications' and study agents' most recent package inserts, Investigator's Brochures, or updated information from Division of AIDS, NIAID (DAIDS) to obtain the most current information on drug interactions, contraindications, and precautions.

Additional drug information may be found in the AIDS Clinical Trials Group (ACTG) Drug Interactions Database located at: https://actgnetwork.org/ACTG-Drug-Interactions-Database.

4.3.1 Precautionary Medications

The following medications should be avoided, if possible, and alternative treatments sought. Please contact the Protocol Team if treatment with any of these medications is necessary for clinical care.

- Medications which cause myopathy or rhabdomyolysis in patients at risk.
- Strong inducers of uridine diphosphate glucuronosyltransferase (UGT) 1A1 other than RIF.
- Short courses of systemic corticosteroids (≤ 7 days) are permitted. Topical corticosteroids are permitted. Longer courses need to be discussed with the Protocol Team.

4.3.2 Disallowed Medications

The following medications/therapies are not allowed in this study:

- Dolutegravir
- Elvitegravir
- Astemizole
- Cisapride
- Ergot alkaloids and derivatives
- Benzodiazepines
- Zolpidem
- Antiepileptic drugs
- St. John's wort
- Cytokines
- Growth hormone
- Rifabutin

- Omeprazole
- Praziquantel
- Nifedipine
- Voriconazole
- Sirolimus
- Quinine
- Imatinib
- Itraconazole
- Cyclosporine
- Tacrolimus
- Atovaquone
- Mycophenolate
- Sunitinib
- Quetiapine
- Tolvaptan
- Immunosuppressive therapy other than intralesional or localized electron beam therapy for cutaneous Kaposi's sarcoma.
- Other: warfarin, oral and injectable contraceptives, ketoconazole, doxycycline, digoxin, verapamil, simvastatin, everolimus, atorvastatin, rosiglitazone/pioglitazone, celecoxib, clarithromycin, caspofungin, fluconazole, and diltiazem.

Investigational agents are not permitted, unless first approved for use by the Protocol Team.

4.4 Protocol Registration and Enrollment Procedures

Prior to implementation of this protocol, and any subsequent full version amendments, each site must have the protocol document and the consent form(s) approved, as appropriate, by their local Institutional Review Board (IRB)/Ethics Committee (EC), and any other applicable regulatory entity (RE). A Site Implementation Plan (SIP) will be required from each site participating in the study. The SIP will be reviewed and approved by members of the Protocol Team and sites will be notified that authorization to participate has been granted.

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 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.

DAIDS notification of approval to begin enrollment is required before participants can be enrolled in this study. Participants meeting the study eligibility criteria will be enrolled through the Data Management Center (DMC) Subject Enrollment System (SES) eligibility checklist screens. Written informed consent for study participation must be obtained before any study related procedures are performed. Eligible participants will be considered enrolled in the study upon successful entry into the DMC's SES (date of participant enrollment = Day 0 for determining the target dates of all follow-up visits).

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 SES on the DMC website (https://www.frontierscience.org). For all participants from whom informed consent is obtained, but who are deemed ineligible or who do not enroll into the protocol for any reason, a Screening Failure Results form must be completed and keyed into the database.

4.5 Co-enrollment Procedures

Co-enrollment in other research protocols will require the consent of the P1101 Protocol Team and the other research Protocol Team. Please contact the P1101 Protocol Team for co-enrollment questions.

5.0 STUDY TREATMENT

Study treatment is defined as chewable RAL tablet(s), which will be provided by the study and initiated at Entry.

The TB drugs (including RIF) and ARV drugs (excluding RAL) will not be provided by the study and must be obtained locally by the site.

5.1 Drug Regimen, Administration and Duration

5.1.1 Drug Regimen

Cohort I: Participants ≥ 2 to < 6 years of age.

- Chewable RAL tablet, starting dose of 12 mg/kg (up to a maximum dose of 800 mg) orally twice daily (refer to Table C in Appendix II), with two NRTIs plus RIF-containing regimen for treatment of TB. After the intensive PK samples are taken, a fourth ARV drug per local standard of care for treatment in HIV/TB co-infected children, will be added to the regimen. ARVs, other than EFV or LPV/r, must be approved by the Protocol Team prior to inclusion in the study drug regimen.

Cohort II: Participants ≥ 6 to < 12 years of age.

- Chewable RAL tablet, starting dose of 12 mg/kg (up to a maximum dose of 800 mg) orally twice daily (refer to Table C in Appendix II), with two NRTIs plus RIF-containing regimen for treatment of TB. After the intensive PK samples are taken, a fourth ARV drug per local standard of care for treatment in HIV/TB co-infected children, will be added to the regimen. ARVs, other than EFV or LPV/r, must be approved by the Protocol Team prior to inclusion in the study drug regimen.

Cohort III: Participants ≥ 4 weeks to < 2 years of age.

- Chewable RAL tablet as a dispersible tablet, starting dose of 12 mg/kg (up to a maximum dose of 800 mg) orally twice daily (refer to Table C in Appendix II), with two NRTIs plus RIF-containing regimen for treatment of TB. After the intensive PK samples are taken, a fourth ARV drug per local standard of care for treatment in HIV/TB co-infected infants and children, will be added to the regimen. ARVs, other than EFV or LPV/r, must be approved by the Protocol Team prior to inclusion in the study drug regimen.

Note: If dose adjustment is required based on review of all available data, this will be communicated by the Protocol Team to Sites. Refer to Appendix II for raltegravir dosing tables based on 6, 9, 15 and 18 mg/kg. A new prescription will be required for the site pharmacist.

Intensive PK should be scheduled so that witnessed dosing of the ARVs is as close as possible to 12 hours after the previous dosing. PK dosing should be given within a range of 11 to 13 hours after the previous dose. Parents/Guardians must report that the participants have not missed any doses of the ARVs, including RAL, in the 48 hours prior to the intensive PK visit. If a missed dose is reported, the intensive PK visit must be re-scheduled. Participants should not ingest breast milk, formula, or any other high fat food/liquid for 2 hours prior to and 1 hour after dosing on the intensive PK day. The participant must bring to the clinic the doses of RAL, other ARVs and TB medications so they can be taken after the pre-dose (0) blood is drawn. Doses vomited within 15 minutes may be re-dosed once, and time restarted to be the time of the repeat dosing. If dose is vomited > 15 minutes after dosing, PK must be cancelled and may be re-scheduled. See Section 9.2 for details on the intensive PK procedure.

5.1.2 Administration and Dispensing

5.1.2.1 RAL will be administered orally twice daily.

Cohort I and Cohort II:
RAL chewable tablets dosing instructions: RAL chewable tablets are to be chewed before swallowing. If they prefer, participants may swallow the chewable tablets whole. The method by which the participant takes the chewable tablet (either chewing or swallowing whole) must be documented.

Cohort III:
RAL chewable tablets to be dispersed dosing instructions: RAL chewable tablets should be crushed and dispersed in water, liquid-apple juice, breast milk or formula. Dissolve the required dose as per Table C in Appendix II.

Up to three of the 25 mg chewable tablets (a total of 75mg) may be dissolved in approximately 5 mL of water, juice, breast milk of formula; 100 mg tablets should be dissolved in 10 mL of water, juice, breast milk or formula.
Once the tablet is wetted, crush the tablet while in the liquid with a spoon and stir until dispersed. The full amount of liquid must be administered orally within 30 minutes post-dissolution.

RAL may be taken without regard to food, except on pharmacokinetic evaluation days (see Section 9.0).

5.1.2.2 The three-drug ARV regimen in addition to RAL will be dosed according to local standard of care.

5.1.3 Duration

Participants will be followed from the time of entry until three months after discontinuation of RAL. On completion of therapy for tuberculosis, RAL will be discontinued while treatment for HIV will continue per local standard of care.

5.2 Drug Formulation

5.2.1 Description of Formulation of Raltegravir

Chewable ethylcellulose tablets in 25 mg and scored 100 mg dose.

The ethylcellulose tablet formulation is an orange-banana flavor, and contains the following: raltegravir, hydroxypropylcellulose, ethylcellulose 20 cP, saccharin sodium, sucralose, monoammonium glycyrrhizinate, sorbitol, fructose, natural and artificial flavors (orange, banana, and masking), sodium citrate, crospovidone, mannitol, red ferric oxide, yellow ferric oxide, magnesium stearate, sodium stearyl fumarate, ammonium hydroxide, medium chain triglycerides, oleic acid, hypromellose 2910/6cP, and macrogol/PEG 400.

5.2.2 Storage Instructions

Stability studies for the ethylcellulose tablet formulation of raltegravir are ongoing. Store at or below 30°C (86°F) and protect from moisture. The bottles of the ethylcellulose tablets contain desiccant and may contain rayon coil. The desiccant should remain in the bottle. Ethylcellulose tablets are to be dispensed and stored in the original manufacturer's container.

5.3 Drug Supply, Distribution and Pharmacy

5.3.1 Study Product Acquisition/Distribution

RAL chewable tablets will be manufactured and supplied by Merck Research Laboratories and available through the NIAID Clinical Research Products Management Center (CRPMC). The site pharmacist can obtain the study product for this protocol by following the instructions in the manual Pharmacy Guidelines and Instructions for DAIDS Clinical Trials Networks in the section: Study Product Management Responsibilities.

The background ARV drugs and TB drugs (including RIF) will not be provided through this study and must be obtained locally by the site. They will be prescribed by the health care provider according to local national and/or international guides for treatment of HIV/TB co-infected infants and children and supplied via non-study prescription.

5.3.2 Study Product Accountability

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

5.3.3 Instructions for breaking the raltegravir scored 100 mg chewable tablet

Note: Merck has developed the scored 100 mg tablet to be broken into two halves by hand using the following method:

i. Pick up the tablet, then using two hands, hold the tablet between the thumb and forefinger of each hand by placing the thumb on top of the tablet and the forefinger on the bottom of the tablet.

ii. Break the tablet by either bending the outer portions of the tablet either upwards or downwards.

iii. When the second half of the scored tablet is not administered with this dose, ensure that it is returned to the manufacturer's bottle immediately after breaking the tablet.

6.0 PARTICIPANT MANAGEMENT

6.1 Toxicity Management

Except for rash toxicity grading, which is provided in Appendix III and discussed in Section 6.1.3, toxicities will be graded according to the DAIDS Table for Grading the Severity of Adult and Pediatric Adverse Events, (DAIDS AE Grading Table), Version 2.0, November 2014, available on the RSC website at http://rsc.tech-res.com/safetyandpharmacovigilance/gradingtables.aspx.

Management of adverse experiences will be according to the best clinical practice and the judgment of the site investigator, except when noted below. For any other scenarios not described below, consult the Protocol Team on study drug management and frequency of repeat assessments.

Consultation on all aspects of clinical management is available from the Protocol Team at any time. Alternate explanations for clinical and laboratory abnormalities must be sought. Laboratory normals will be the institutional values. However, if a site does not have an age-specific normal range/value for a particular lab, the site should use the latest edition of the Harriet Lane Handbook for normal ranges/values and document this for monitoring purposes. The site investigator should attempt to confirm any abnormal laboratory test results as soon as possible and within 3 days of site awareness. All Grade ≥ 3 abnormal clinical and laboratory findings should be followed until resolution to ≤ Grade 2.

Toxicity and adverse events in laboratory and clinical evaluations must be entered into the database within 48 hours of the time at which the results become available for the evaluation of safety and tolerability of RAL.

Gradation of relationship will use the following terminology:

- Definitely Related: The adverse event and administration of the medication are related in time, and a direct association can be demonstrated.
- Probably Related: The adverse event and administration of the medication are reasonably related in time, and the adverse event is more likely explained by the medication than other causes.
- Possibly Related: The adverse event and administration of the medication are reasonably related in time, and the adverse event can be explained equally well by causes other than the medication.
- Probably Not Related: A potential relationship between the medication and the adverse event could exist (i.e., the possibility cannot be excluded), but the adverse event is most likely explained by causes other than the medication.
- Not Related: The adverse event is clearly explained by another cause not related to the medication.

NOTE: The above classification applies for AE documentation (source documentation and CRF completion) and management but does not apply for expedited adverse event (EAE) reporting. EAEs will be reported, per the DAIDS EAE Manual, as related or not related. Please see Section 7.0 below for more information on EAE reporting.

6.1.1 General Toxicity Management

The toxicity management guidelines are for events for which a relationship to RAL (defined as the study drug) cannot be excluded. Clinical or laboratory adverse events (AEs) that are definitely unrelated to RAL may not result in RAL interruption. TB medication will normally be continued unless, in the judgment of site investigators, the toxicity is deemed related to TB medication.

General guidelines (see separate stopping rules for Liver, Rash and Abacavir toxicities below in Sections 6.1.2 – 6.1.4):

- Grade 1 – Continue RAL; routine monitoring.
- Grade 2 – Continue RAL; monitor closely with more frequent visits as per site investigator, work-up to exclude other causes.

- Grade 3 – Repeat test within 3 days to confirm. Continue RAL while awaiting confirmatory results as determined by the site investigator.

  If repeat assessment is ≤ Grade 2, manage as per grade of repeat result. For confirmed Grade 3 toxicities assessed as possibly, probably, or definitely related to RAL, RAL and concomitant ARVs should be withheld as follows:

  Participants not receiving EFV

  Hold RAL and NRTIs until the abnormalities resolve to ≤ Grade 2 unless the site investigator, with the approval of the Protocol Team, determines that withholding ART (including RAL) would be harmful to the participant.

  - Follow abnormal laboratory values weekly until toxicity resolves to ≤ Grade 2.
  - If toxicity resolves to ≤ Grade 2 in ≤ 21 days, all held ARVs, including RAL, may be restarted with approval from the Protocol Team.
  - If Grade 3 toxicity persists for > 21 days or recurs to ≥ Grade 3 after reintroduction of ARVs, RAL should be permanently discontinued.

  Participants receiving EFV

  Hold RAL and EFV, but NRTIs can be continued for up to two weeks at the discretion of the site investigator in consultation with the Protocol Team.

  - Follow abnormal laboratory values weekly until toxicity resolves to ≤ Grade 2.
  - If toxicity resolves to ≤ Grade 2 in ≤ 21 days, all held ARVs, including RAL, may be restarted with approval from the Protocol Team.
  - If Grade 3 toxicity persists for > 21 days, or recurs to ≥ Grade 3 after reintroduction of ARVs, EFV and RAL should be permanently discontinued.

- Grade 4 – Hold RAL and concomitant ARVs and notify the Protocol Team. Repeat test within 3 days to confirm.

  - If the site investigator determines that withholding ART (including RAL) would be harmful to the participant and that continuing ARVs would pose little additional risk, the site investigator must contact the Protocol Team for approval before continuing RAL and the concomitant ARVs.
  - If repeat assessment is ≤ Grade 3, manage as per grade of repeat result.
  - Confirmed Grade 4 toxicities that are assessed as possibly, probably, or definitely related to RAL, RAL should be permanently discontinued.
  - Confirmed Grade 4 toxicities assessed as not related or probably not related to RAL that resolve to ≤ Grade 2 in ≤ 21 days, all held ARVs, including RAL, may be restarted following approval from the Protocol Team.
  - Continue to monitor weekly until the toxicity resolves to ≤ Grade 2.

  Confirmed Grade 4 AEs that are determined to be not related or probably not related to RAL and do not resolve to ≤ Grade 2 in ≤ 21 days, the site investigator should contact the Protocol Team to determine when RAL may be safely resumed.

For Grade 4 toxicities, all ARVs including RAL should be started or stopped together whenever possible, except when one nucleoside analogue can be substituted for another when the etiology of the toxicity can be reasonably determined, e.g. neutropenia associated with zidovudine (ZDV) use.

6.1.2 Liver Toxicity

RAL has seldom been associated with clinically significant liver toxicity. However, since liver toxicity can occur with other antiretroviral agents and TB medications, liver chemistry threshold holding criteria for interruption of therapy have been designed to assure participant safety and to evaluate liver event etiology during administration of RAL, TB treatment as well as the fourth antiretroviral agent and the follow-up period. RAL and concomitant ARVs should be stopped at the same time if any of the following liver chemistry stopping criteria is met. Stopping TB medication will occur at the discretion of the site staff in consultation with the Protocol Team. All AEs related to liver toxicity should be recorded on the CRF at each visit.

The following guidance should be followed if any of the liver chemistry stopping criteria listed below are met:

- Hold RAL and other ARVs and notify the Protocol Team within 24 hours. The site investigator should assign attribution of adverse event to RAL after discussion with Protocol Team.
- TB medications can be continued at the discretion of the site clinician. Consultation with the Protocol Team is recommended but not required prior to stopping/continuing TB medications.
- Report Hy's Law liver toxicities (as described below) to the RSC as an EAE.
- Complete and submit the liver toxicity CRF within one week to the DMC.

Liver Stopping Criteria:

- Hy's Law: ALT > 3 times the upper limit of normal (ULN) and bilirubin > 2 x ULN; Direct Bilirubin > 35% of Total Bilirubin.
  Note: Hy's Law is a set of laboratory criteria used to identify potential drug-induced liver injury (DILI). Such liver injury, leading to jaundice, without a hepatic transplant, has a case fatality rate of 10-50%. Increased ALT or total bilirubin are relatively common (particularly in HIV/AIDS) but the combination of ALT > 3 x ULN and total bilirubin > 2 x ULN is rare in drug development and is of clinical concern. This judgment follows exclusion of viral Hepatitis (hepatitis A, B, or C virus) or other known liver disease.
- ALT ≥ Grade 4: If another cause of ALT elevation is identified, the participant may be re-challenged after receiving the approval of the Protocol Team.
- ALT ≥ Grade 3 for more than two weeks: If another cause of ALT elevation is identified, the participant may be re-challenged after receiving the approval of the Protocol Team.
- ALT ≥ Grade 2 with symptoms of hepatitis or hypersensitivity (e.g., fatigue, nausea, vomiting, right upper quadrant pain, fever, rash or eosinophilia): If another cause of ALT elevation is identified, the participant may be re-challenged after receiving the approval of the Protocol Team.

NOTE: Participants who develop ALT ≥ Grade 3 should be followed weekly until resolution to ALT ≤ Grade 2.

6.1.3 Rash Toxicity

The Supplemental Toxicity Table for Grading Severity of Cutaneous/Skin Rash/Dermatitis Adverse Events (Appendix III) must be used for grading rash toxicities. (If a participant is taking abacavir [ABC] and an ABC hypersensitivity reaction is suspected, see Appendix IV).

- Grade 1 or Grade 2A – All ARVs and TB medications should be continued. If rash does not resolve ≤ 14 days of onset, contact the Protocol Team.

- Grade 2B – If the fourth ARV drug is EFV, hold EFV and RAL, obtain liver function tests (LFTs), continue NRTIs unless participant is on ABC in which case all medications, including RAL, should be stopped.
  - If a definitive, alternative explanation for the rash/skin reaction cannot be determined, EFV should be permanently discontinued. RAL should also be discontinued when EFV discontinued. Continuing the NRTIs and TB medications is at the discretion of the site investigator. The site investigator must notify the Protocol Team of the decision.
  - If the rash/skin reaction is definitely due to an alternative diagnosis EFV and RAL may be reintroduced after consultation with and permission from the Protocol Team AND after the rash has resolved.

- Grade 3 – If the fourth ARV drug is EFV, EFV and RAL should be permanently discontinued. Continuing the NRTIs and TB medications is at the discretion of the site investigator. LFTs should be obtained.

- Grade 4 – If the fourth ARV drug is EFV, EFV and RAL should be permanently discontinued. Continuing the NRTIs and TB medications is at the discretion of the site investigator. LFTs should be obtained.

6.1.4 Abacavir (ABC) Toxicity

ABC may be used as a background NRTI treatment. Since ABC will be started prior to introduction of the fourth ARV drug and any hypersensitivity reaction occurring in the absence of the fourth ARV drug if ABC toxicity is suspected should be managed per Appendix IV.

ABC and the fourth ARV drug may subsequently be used together and therefore management of rash will occur as above for management of rash toxicity. However, if a participant on EFV, RAL and ABC develops ≥ 2B rash, all ARV medications, including RAL, should be stopped immediately unless the site investigator with approval from the Protocol Team, deems that the rash is not drug related. Continuing the TB medications is at the discretion of the site investigator.

6.2 Participant Management Plan

The DMC will maintain accrual reports on the DMC web portal informing sites of the number of slots available.

The Protocol Team will respond to sites who contact the team with questions regarding toxicity management, dose modifications, or other issues within one business day.

All dose modifications of RAL will be recommended by the Protocol Team. See Section 6.2.1 for information on dose modifications for a mini-cohort or full cohort. The Protocol Team will review data from the initial mini-cohort of six participants enrolled into Cohort I (≥ 2 to < 6 years of age), Cohort II (≥ 6 to < 12 years of age) and Cohort III (≥ 4 weeks to < 2 years of age) to determine whether a cohort dose adjustment is required, before opening enrollment to the remainder of the cohort. The dose recommendation must be approved by the Protocol Team. In addition, for each mini-cohort, a routine SMC review of the safety and PK data will be done prior to accrual of the full-cohort. If the dose fails to achieve PK targets or there are safety concerns, the dose (and/or frequency) is adjusted at the discretion of the Protocol Team. A new mini-cohort group of six participants will be enrolled to evaluate the adjusted dose. If the dose passes safety and PK considerations, an additional six participants will be enrolled to complete that cohort. The additional six participants in each age cohort will be evaluated for safety and PK. If the dose passes, then a dose is recommended for that cohort. If a dose cannot be selected by the Protocol Team, a SMC review will be convened to review the data, understanding that no dose will be used to complete enrollment of one of the cohorts without the approval of the Lead Merck Representative in the Protocol Team.

The Protocol Team will notify sites of the change in dose (and/or frequency) for any participant and request that the site investigator provide acknowledgement of receipt and action taken (changed dose or did not change dose). This management plan does not apply to dose changes due to weight gain (See Appendix II).

6.2.1 Cohort Dosing Management

Enrollment will begin simultaneously into the three age stratified cohorts with a mini-cohort of six participants. Enrollment to the cohort will pause upon entry of the six participants to allow for evaluation of PK and safety results. These six participants will have RAL combined with two NRTIs as their ARV regimen (see Section 5.0). Steady state RAL levels will likely be achieved within 3 days of drug initiation; an intensive PK evaluation will be performed between days 5 and 8. RAL levels will be assayed in real time (ideally within two weeks) and the Protocol Team will evaluate the results.

Immediately after completion of the intensive PK sampling, participants will continue taking the assigned RAL therapy and a fourth ARV drug will be added to the ARV (see Section 5.1.1).

In addition, for each mini-cohort, a routine SMC review of the safety and PK data will be done prior to accrual of the full-cohort.

If mini-cohort PK data for RAL are acceptable (see Section 9.3) and 4 week safety data are acceptable (see Section 8.5.1), enrollment will open to complete the full cohort (six additional participants).

If on review of all PK data the dose does not yield an acceptable $AUC_{0\text{-}12h}$, the mini-cohort dose may be adjusted, at the discretion of the team, assuming linear dose-proportionality and taking all data available into consideration.

If the dose for the initial mini-cohort yields acceptable $AUC_{0\text{-}12h}$ values but does not yield acceptable C_{12h} values, the team will consider increasing the dose if able to project that the adjusted dose would still maintain acceptable $AUC_{0\text{-}12h}$ values while satisfactorily increasing the C_{12h}. If dose adjustment would not be predicted to achieve acceptable $AUC_{0\text{-}12h}$ and C_{12h} values, then the Protocol Team will also consider dosing RAL three times daily.

An additional six participant mini-cohort will be recruited at this new dose. If the PK guidelines are satisfied at the new mini-cohort dose and the safety data are acceptable, enrollment to complete the full cohort of 12 participants on the same dose will open, pending an SMC review. This dose adjustment is likely to enhance the $AUC_{0\text{-}12h}$, but may not yield a trough (C_{12h}) in the range desired. If this dose does not result in acceptable PK parameters, the process will be repeated with a third mini-cohort and RAL may continue in the previous failed mini-cohort. If dose adjustment fails to yield acceptable values for C_{12h}, despite acceptable $AUC_{0\text{-}12h}$ values, or acceptable C_{12h} is associated with unacceptably high values for C_{max} or $AUC_{0\text{-}12h}$, the Protocol Team will consider enrolling a mini-cohort with RAL given three times daily.

If the mini-cohort (or full cohort) fails the safety and PK evaluations, and dose adjustment is warranted, then participants in the failing mini-cohort (or full cohort) will have their dose adjusted to the new dose being tested. This dose change will be implemented for any participants still receiving RAL at the previous dose (see Section 9.2), and without impeding treatment-related toxicities. However, if the Protocol Team decides to adjust the dose to three times daily, it will not apply to the previous failed mini or full cohort who may remain in the initial twice daily dosing. There will be no individualized PK-driven dose adjustments.

Adjustment of RAL dose will only be done once for a mini cohort (or full cohort) that fails safety and PK evaluations. Intensive PK for RAL will not be repeated in a mini cohort (or full cohort) that has a RAL dose adjustment.

Participants who are replaced for PK purposes because they have discontinued due to toxicity will not be replaced with respect to applying safety guidelines to their cohorts; rather, they will continue to be counted as failures. However, the safety data from the participants who replace them for PK purposes will also be used when applying the safety guidelines (see Section 6.7). Participants opting to discontinue in the mini or full cohort prior to completion of the intensive PK will be replaced for PK and safety purposes, provided there are no toxicities. A patient that discontinues prior to the completion of his/her week 4 safety visit, provided there are no toxicities, should be replaced for the purposes of applying the safety guidelines.

If the results of the intensive PK are in question, unexpectedly low or high and may put the participant at risk for toxicity, the Protocol Team may request a repeat of the intensive PK.

On completion of therapy for tuberculosis, RAL will be discontinued and antiretroviral therapy will continue with the fourth ARV drug and two NRTI drugs per local standard of care. Participants will continue to be followed for an additional three months after discontinuation of RAL.

6.2.2 Virologic Failure Management

For the purposes of participant management, virologic failure in this study is defined as:

- Non-response defined as the participant never achieved ≥ 1 log drop from baseline in plasma HIV RNA or HIV RNA ≤ 400 copies/mL while on RAL.
- Virologic Rebounder while on RAL is defined as:
  - HIV RNA > 400 copies/mL after initial response with HIV RNA ≤ 400 copies/mL;
    OR
  - > 1.0 $\log_{10}$ increase in HIV RNA above nadir level after initial response. For the purposes of this study, nadir is defined as the lowest HIV RNA while on study drug.

If − at Week 8 − a participant meets the definition for virologic failure AND is clearly not clinically responding, the participant may be taken off RAL after consultation with the Protocol Team and following the local standard of care for HIV, and followed off treatment/on study as per Appendix I for 3 months, with visits at 4 and 12 weeks off treatment (see Section 6.7).

If − at Week 8 − a participant meets the definition for virologic failure, but the site clinician, in consultation with the Protocol Team believes that there has been a good clinical response to therapy and that the viral load is likely to continue to decrease and suppress, the participant may remain on RAL. If − at Week 12 − the definition of virologic failure is still met, RAL will be discontinued within one week of receiving the Week 12 viral load result. The treatment regimen will then be changed according to local treatment standards.

Participants who are virologic failures at Week 12 as defined above will, after consultation with the Protocol Team, be taken off study drug and follow local standard of care for HIV treatment. These participants will be followed off treatment/on study as per Appendix I for 3 months with visits at 4 and 12 weeks off treatment (see Section 6.7).

6.2.3 Viral Resistance Samples/Testing

For all participants after enrollment but prior to initiation of RAL, blood samples for viral genotyping will be collected at entry. In addition, to evaluate development of resistance to RAL and to other antiretroviral agents used in the treatment regimen, blood samples will be collected (if there is evidence of virologic failure per Section 6.2.2) while the participant is on RAL and at any early treatment discontinuation visit (see Appendix I).

6.2.4 Algorithm for Resistance Testing

- All participants will have genotyping of entry specimens; these will be analyzed at the end of the study.
- While on RAL, if a participant is a virologic failure (see Section 6.2.2) with HIV RNA > 1,000 copies/mL, the collected specimen should be sent for resistance testing, as outlined in the Laboratory Processing Chart (LPC), which can be found on the IMPAACT website at http://impaactnetwork.org/
- If a participant discontinues from the study treatment early for any reason at any time point, the collected specimen will be sent for resistance testing if the participant's HIV RNA level is > 1,000 copies/mL at the time of discontinuation.
- Genotyping will not be conducted in real time.

6.2.5 Immune Reconstitution Inflammatory Syndrome (IRIS)

IRIS will be diagnosed and managed according to Appendix V. After a diagnosis of IRIS is made, the site investigator should consult with the Protocol Team in deciding whether or not continuation of study treatment is in the participant's best interests. However, clinical management of IRIS will be at the discretion of the site investigator. Other clinical scenarios suggestive of IRIS should be discussed with the Protocol Team.

6.3 Toxicity Endpoints

- Permanent discontinuation of RAL due to an adverse event of ≥ Grade 3 severity, deemed to be possibly, probably, or definitely related to RAL.
- Death, Grade 4 life-threatening adverse events deemed to be possibly, probably or definitely related to RAL.
- Grade 2B rash

6.4 Virologic Endpoints

Virologic Success is defined as: achieving at least 1- $\log_{10}$ copies/mL drop from baseline OR HIV RNA ≤ 400 copies/mL at Week 8.

Failure to respond is defined as:

- HIV RNA (copies/mL) > 400 copies/mL;
  AND
- Less than 1-$\log_{10}$ copies/mL drop from baseline.

6.5 Pharmacokinetic Endpoint

The principal goal of this study is to determine the PK and appropriate dose of RAL when administered with a RIF-containing anti-TB therapy in HIV/TB co-infected infants and children that generates PK parameters generally comparable to those seen in HIV-infected infants and children from P1066 in the absence of RIF. Key PK parameters that will be assessed include C_{max}, $AUC_{0\text{-}12h}$, and C_{12h}.

RAL will be stopped in any individual that has an $AUC_{0\text{-}12hr} \geq 63$ μMxhr, per Section 9.0.

6.6 Permitted Changes to ARV Background Regimen

Any changes in background ARV therapy after initial selection must be discussed with the Protocol Team. Permitted changes include:

- Substitution within class or rarely, across class, for documented toxicity or tolerance.
- Formula substitutions (substituting single agents for fixed dose combinations and vice versa of the same ARV).

The Protocol Team should be notified before changes occur.

6.7 Criteria for Early Treatment Discontinuation

- The participant experiences drug toxicity as defined in Section 6.1 and continuing RAL would be detrimental to the participant's health.
- The participant requires treatment with medications that are disallowed while on this study.
- Drug resistant TB (MDR or XDR) is discovered after the participant is already on study.
- New data become available that indicate treatment should be discontinued.
- Participant has an $AUC_{0\text{-}12hr} \geq 63$ µMxhr, per Section 9.0.
- PK results indicative of consistent non-adherence with the ARV regimen, or anomalously low absorption of RAL.
- The participant becomes pregnant, see Section 6.9.2.
- A female participant becomes sexually active and does not agree to use contraception as specified in Section 6.9.1
- Virologic failure and participant does not meet criterion for continuation of RAL (see Section 6.2.2).

Note that in the event of early treatment discontinuation, participants will still be asked to continue on study/off study drug for 3 months, and complete the TB and/or RAL treatment discontinuation, 4 weeks off RAL treatment/on study, and end of study evaluations listed in Appendix I.

6.8 Criteria for Early Study Discontinuation

- The participant or legal guardian refuses further treatment and/or follow-up evaluations.
- The site investigator determines that further participation would be detrimental to the participant's health or well-being.
- The participant fails to comply with the study requirements to cause harm to him/herself or seriously interfere with the validity of the study results.
- The study is discontinued by the IMPAACT network, the Office for Human Research Protections (OHRP), the National Institutes of Health (NIH), the local IRB or EC, US FDA, other governmental agencies, or Merck & Co, Inc.
- An IMPAACT SMC recommends that the study be stopped early.
- The study is discontinued for other administrative reasons.

6.9 Contraception Counselling, Pregnancy Testing and Pregnancy

6.9.1 Contraception and Pregnancy Testing

All female study participants of child bearing potential should be counseled about NOT becoming pregnant while in the study. Female study participants of reproductive potential

are defined as girls who have reached menarche and have not undergone a sterilization procedure (bilateral tubal ligation, hysterectomy or bilateral oophorectomy).

If participating in sexual activity that could lead to pregnancy, female participants of childbearing potential must agree to use two reliable methods of contraception simultaneously while receiving RAL and for four weeks after stopping RAL. Hormonal birth control alone would not be considered adequate (e.g. slow release inserts placed under/on the skin). Oral and injectable contraceptives are not permitted per Section 4.3.2. An effective, medically accepted barrier method of contraception (e.g. female/male condoms, diaphragm or cervical cap with a cream or gel that kills sperm (excluding nonoxydyl-9), intrauterine device [IUD], others) also must be used during the study. Condoms are recommended because their appropriate use is the only contraception method effective for preventing HIV-1 transmission. Use of an IUD may increase the risk of pelvic inflammatory disease.

All female participants who are sexually active must have a negative pregnancy test at screening to be eligible for enrollment. During follow-up, pregnancy testing, if indicated, will be conducted at all visits and at any time during the trial when pregnancy is suspected. Pregnancy tests may be performed on either blood or urine.

At every visit for youth that are at risk of becoming pregnant, pregnancy prevention will be discussed with these participants, including specific counseling, provision of information and advice as needed. Verbal confirmation of the use of two methods of contraception should also be obtained. This discussion should be documented in the participant's study record.

6.9.2 Pregnancy

Any participant who becomes pregnant (intrauterine) while receiving RAL will have study drug discontinued. However, these participants should remain on study but off study drug.

The pregnancy must also be followed to determine the outcome (including premature termination) and status of mother and child(ren), which will be recorded and submitted to the Statistical and Data Management Center (SDMC) using the Pregnancy Outcome form within one week of the site becoming aware of the outcome.

HIV-1 infected women who are pregnant should be treated according to the most recent Public Health Service Task Force Recommendations for Use of Antiretroviral Drugs in Pregnant HIV-Infected Women for Maternal Health and Interventions to Reduce Perinatal HIV Transmission in the United States: Tables (http://www.aidsinfo.nih.gov/Guidelines/) or WHO Antiretroviral drugs for treating pregnant women and preventing HIV-infection in infants (2010) and locally applicable guidelines.

NOTE: The Protocol Team encourages the clinical sites to prospectively register the participant's pregnancy in the Antiretroviral Pregnancy Registry. http://www.apregistry.com/.

7.0 EXPEDITED ADVERSE EVENT (EAE) REPORTING

7.1 Adverse Event Reporting to DAIDS

Requirements, definitions and methods for expedited reporting of Adverse Events (AEs) are outlined in Version 2.0 of the DAIDS EAE Manual, which is available on the RSC website at http://rsc.tech-res.com/clinical-research-sites/safety-reporting.

The DAIDS Adverse Experience Reporting System (DAERS), an internet-based reporting system, must be used for EAE reporting to DAIDS. In the event of system outages or technical difficulties, EAEs may be submitted via the DAIDS EAE Form. This form is available on the DAIDS RSC website at http://rsc.tech-res.com/clinical-research-sites/safety-reporting/daids/paper-eae-reporting**.**

For questions about DAERS, please contact NIAID CRMS Support at CRMSSupport@niaid.nih.gov. Please note that site queries may also be sent from within the DAERS application itself.

For questions about expedited reporting, please contact the DAIDS RSC Safety Office at DAIDSRSCSafetyOffice@tech-res.com.

7.2 Reporting Requirements for this Study

- The SAE (Serious Adverse Event) Reporting Category, as defined in Version 2.0 of the DAIDS EAE Manual, will be used for this study for the period of time defined in Section 7.4.

- Other medically significant events for which expedited reporting is required include all cancers and pregnancies, fetal losses, IRIS events that qualify as serious adverse events, Hy's Law liver toxicities, and all Grade 3 and 4 toxicities.

- Overdoses, (defined as two times the prescribed dose within a 24-hour period) of RAL, do not require expedited reporting, but will be reported to Merck quarterly by the SDMC. Overdoses of RAL should be recorded on the CRF and keyed in the database in a timely manner.

- The drug for which expedited reporting is required is raltegravir (RAL).

7.3 Grading Severity of Events

The Division of AIDS Table for Grading the Severity of Adult and Pediatric Adverse Events (DAIDS AE Grading Table), Version 2.0, November 2014, must be used and is available on the DAIDS RSC website at http://rsc.tech-res.com/safetyandpharmacovigilance/.

The Supplemental Toxicity Table for Grading Severity of Cutaneous/Skin Rash/Dermatitis Adverse Events (Appendix III) will also be used. The parameters specified in this table supersede the DAIDS Toxicity Table when grading these events.

For reporting of all adverse experiences, the investigator will determine the causality and relationship to study drug. However, in regards to patient safety and PK evaluations which will support the selection of a dose for a given cohort, the Protocol Team will also have input as to the causality and drug relation of specific adverse experiences.

7.4 Expedited AE Reporting Period

- The expedited AE reporting period for this study is up to the end of TB treatment for an individual participant (from study enrollment until end of TB treatment or discontinuation of the participant from study participation for any reason), beginning at the time of administration of the first dose of study drug.

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

8.0 STATISTICAL CONSIDERATIONS

8.1 General Design Issues

P1101 is a Phase I/II, dose-finding, safety, tolerability and pharmacokinetics study of RAL chewable tablets in HIV-infected infants and children ≥ 4 weeks to < 12 years of age who are TB co-infected and on a stable RIF-based TB therapy who are eligible for ARV treatment by current local or WHO guidelines. The study's objective is to determine the proper and safe dose of RAL to be used with a RIF-based TB treatment regimen to provide additional ART options in co-infected infants and children.

An initial dose of RAL chewable tablets will be given at 12 mg/kg twice daily (up to a maximum of 800 mg twice daily), with two NRTIs. Following intensive PK sampling for RAL (5 to 8 days after the start of RAL therapy), a fourth ARV drug per local standard of care will be added to the regimen (see Section 5.1.1). The four drug ARV regimen will be continued until TB treatment is completed. Each child will be followed up to assess safety, clinical, immunological and virological parameters, from the time that RAL is started until 3 months after stopping RAL while standard of care treatment continues. See Section 3.0 for details. Participants aged ≥ 4 weeks to < 12 years of age who have had at least one week and not more than 20 weeks of RIF-containing TB therapy will be enrolled. The sample will be stratified, by age into the following groups: Cohort I: ≥ 2 to < 6 years; Cohort II: ≥ 6 to < 12 years; Cohort III: ≥ 4 weeks to < 2 years of age, and these three cohorts will accrue simultaneously. At least 12 participants in each age cohort will be enrolled.

For each age cohort, initial tests of safety and PK will examine data from the first mini-cohort of n = 6. These tests will proceed as follows: The starting dose administered to the first six participants will be evaluated on the basis of RAL PK data, based on blood samples taken 5 to 8 days after the start of therapy on that dose. For all participants, safety will be evaluated on the basis of all available data collected through the fourth week on a given dose within each cohort.

The overall safety and PK data of the first six participants on a given cohort will be evaluated with respect to the safety guidelines specified in Section 8.5.1 and the PK guidelines specified in Section 9.0. In addition to the P1101 team's assessment, a routine SMC review of the safety and PK data will be performed for each mini-cohort prior to accrual of the full-cohort. If the initial mini-cohort of n = 6 fails either the safety (see Section 8.5.1) or the PK (see Section 9.2) guidelines in this initial test, then the dose will be adjusted in the appropriate direction, unless dose reduction is likely to result in inadequate PK values. An initial evaluation of the new dose level will be made on the basis of data from the first six new participants treated at this dose. If the first six participants of a cohort meet both sets of guidelines, then six additional participants will be accrued to this cohort. The additional six participants will be evaluated on both safety and PK; if the full cohort of n = 12 passes both safety and PK criteria, then this dose will become the selected dose. Otherwise, a new starting dose may be tested on a new cohort of participants.

If a mini-cohort of n=6 (or a full cohort) fails the safety guidelines per Section 8.5.1, then the dose may be reduced and the new dose evaluated on a new cohort. If a mini-cohort (or a full cohort) fails, due to inadequate PK, then the dose may be increased, provided that safety criteria have been met. Whenever a new dose is to be tested, safety criteria will be evaluated on a new cohort of participants whose exposure has been to the dose to be tested. PK and safety results from failed doses will not be included in the evaluation of new doses, since this would introduce bias.

If the mini-cohort (or full cohort) fails the safety and/or PK evaluations, and dose adjustment is warranted, then participants in the failing mini-cohort (or even full cohort) will have their dose adjusted to the new dose being tested. This dose change will be implemented for any participants still receiving RAL at the previous dose (see Section 9.2), and without impeding treatment-related toxicities. However, if the Protocol Team decides to adjust the dose to three times daily, it will not apply to the previous failed mini or full cohort. There will be no individualized PK-driven dose adjustments.

For these safety algorithm guidelines, "evaluable" will be defined as "having been treated exclusively on the dose being evaluated for a given age cohort and having either four (4) weeks of exposure to the study drug or having been classified as a safety failure, due to a study drug related adverse event occurring during the first four weeks of treatment".

If the Protocol Team judges a given participant's PK data to be unevaluable (e.g., because of non-adherence), that participant will be replaced for dose finding purposes. Note that the participant would be replaced for evaluating safety, as well as PK, criteria, if unevaluable PK data reflect uncertainty about appropriate exposure to the study medication.

8.2 Outcome Measures

8.2.1 Primary Endpoints

- Toxicity Endpoint for Analytic Purposes:
  - Termination from treatment due to adverse events of ≥ Grade 3 deemed at least possibly related to RAL.
  - Death, Grade 4 life-threatening adverse events deemed at least possibly related to RAL.
  - Grade 4 non-life threatening adverse events deemed as probably or definitely related to RAL.
  - Adverse events of ≥ Grade 3 deemed at least possibly related to RAL.

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

- Early termination of TB therapy if there is MDR/XDR detected subsequent to starting ARV treatment or if due to toxicity attributable to TB medication.

8.2.2 Primary Response Variables

- Pharmacokinetic parameters (See Section 9.0)

8.2.3 Secondary Endpoints

- Virologic Endpoint: Failure to respond at Week 8
  - HIV RNA (copies/mL) > 400 copies/mL;
    AND
  - Less than 1-log10 drop from baseline.

Therefore, virologic success is defined as achieving at least 1- $\log_{10}$ drop from baseline OR HIV RNA ≤ 400 copies/mL.

A secondary, more stringent definition of virologic response is to achieve HIV RNA ≤ 50 copies/mL.

- Development of new OIs

8.2.4 Secondary Response Variables

- Changes in log-RNA from baseline to Week 8
- Changes in CD4 percent/count from baseline to Week 8
- Clinical response (weight, height, BMI gains)
- Genotypic resistance measures

8.3 Randomization and Stratification

There will be no randomization. Participants will be stratified by age:
Cohort I: ≥ 2 to < 6 years; Cohort II: ≥ 6 to < 12 years; Cohort III: ≥ 4 weeks to < 2 years of age.

8.4 Sample Size and Accrual

Each successful age cohort will include at least 12 participants almost all of whom will have been treated continuously on the recommended dose. To achieve 12 evaluable participants in each cohort at the recommended dose, 36 – 108 participants are anticipated to be enrolled.

The following tables show the width of estimated 95% confidence intervals for the geometric mean for $AUC_{0\text{-}12hr}$ (μMxhr) and C_{12h} (nM) with sample sizes of 6, 12 and 18 and standard deviations equal to that seen in P1066 (for AUC 0.52 and for C_{12h} 0.85 on natural logarithm scale) and for standard deviations either 30% smaller or larger than in P1066. The confidence intervals are centered around the estimated geometric means for P1066.

- As the sample size increases, the width of the estimated confidence interval decreases.
- As the standard deviation increases, the width of the estimated confidence interval increases.
- Note that the estimated confidence intervals are not symmetric as they are calculated on the natural logarithm scale and then anti-logged, and the width would be different if centered at a different value.
- The choice of sample size of 12 per cohort reflects the Protocol Team's assumption that the standard deviation of the RAL on the current study will not exceed 130% of that observed in the absence of TB drugs on IMPAACT P1066. Given this assumption, the team's judgment is that samples of 12 participants would estimate AUC and C_{12h} parameters with adequate precision.

Table 4: $AUC_{0\text{-}12hr}$ (µMxhr) - geometric mean - centered at 19.93

N	SD	95%-	-CI	Width of 95% CI
6	70% of P1066 SD	14.89	26.68	11.79
	P1066 SD	13.14	30.23	17.09
	130% of P1066 SD	11.60	34.25	22.65
12	70% of P1066 SD	16.22	24.50	8.28
	P1066 SD	14.85	26.76	11.91
	130% of P1066 SD	13.59	29.23	15.64
18	70% of P1066 SD	16.85	23.59	6.74
	P1066 SD	15.67	25.35	9.68
	130% of P1066 SD	14.58	27.25	12.67

Table 5: C_{12h} (nM) - geometric mean - centered at 92.85

N	SD	95%-	CI	Width of 95% CI
6	70% of P1066 SD	57.67	149.52	91.85
	P1066 SD	47.02	183.38	136.36
	130% of P1066 SD	38.34	224.91	186.57
12	70% of P1066 SD	66.30	130.05	63.74
	P1066 SD	57.39	150.24	92.85
	130% of P1066 SD	49.68	173.57	123.90
18	70% of P1066 SD	70.53	122.25	51.72
	P1066 SD	62.69	137.55	74.85
	130% of P1066 SD	55.72	154.75	99.03

8.5 Monitoring

The study will be monitored monthly by the Protocol Team which will review safety and pharmacokinetic data as required during the dose-finding stage with the aim of determining the optimal dose for each cohort while protecting patient safety. In addition, the IMPAACT Network will appoint a Study Monitoring Committee (SMC) prior to study commencement to provide independent reviews to ensure participant safety. In accordance with IMPAACT and DAIDS procedures, this committee will be composed of two individuals from the Primary Scientific Committee, one Protocol Development and Monitoring Committee (PDMC) member and a statistician, independent of the Protocol Team and drug manufacturer (Merck). Members of said SMC will have:

1) No financial interest in the study;
2) No planned authorship in publication of study results; and
3) No involvement in the conduct of the study.

8.5.1 Safety Guidelines

8.5.1.1 Evaluation of the Starting Doses During the Dose-Finding Stage

The attribution of relationship of serious adverse events, including all ≥ Grade 3, to study drug for the purposes of employing the start, stop and pause rules specified below will be by consensus among the site investigator, the Protocol Team (which includes representatives from Merck) and the DAIDS medical officers. If unanimous agreement between them cannot be established, the relevant data will be reviewed by the independent SMC, which will make the final judgment concerning the relationship between study drug and the adverse event. Within this committee the decision will be determined by the majority opinion of this study's independent SMC clinicians.

Gradation of relationship will use the following terminology:

- Not related
- Probably not related
- Possibly related
- Probably related
- Definitely related

8.5.1.2 Initial Safety Guidelines for the Evaluation of Starting Doses For the first n = 6 of each age mini-cohort (See Section 9.0 for Pharmacokinetic Guidelines)

For each age cohort, the frequency of adverse events to the starting dose of the study medication will be evaluated on the first six participants. The data will extend to the Week 4 visit for these six participants. Further accrual into this cohort will be contingent upon meeting PK targets as well as the following safety guidelines. In addition to the team's assessment, a routine SMC review of the safety and PK data from each mini-cohort will be performed prior to accrual of the full-cohort.

If any of the first six participants experiences death, has a life threatening Grade 4 adverse event deemed at least possibly related to the study medication, or any Grade 4 event that is at least possibly attributable to the study medication, stop accrual into this dose group until a safety review by an independent Study Monitoring Committee composed according to DAIDS/IMPAACT policies has occurred. (Note: A possibly related Grade 4 non-life threatening event would trigger an accrual stop and SMC review, but if confirmed by SMC as possibly related, and if only such event, then accrual could restart). Only proceed if this review has led to a recommendation that it is safe to do so and the Protocol Team agrees. The safety review may lead to a recommendation that the dose be de-escalated. Before implementing such a recommendation, the study team will review the PK and safety data to determine whether a lower dose is likely to achieve adequate drug exposure.

If none of the first six participants has experienced death, a life-threatening Grade 4 adverse event deemed at least possibly related to the study medication, or any Grade 4 event that is probably or definitely attributable to the study medication and no more than 2 of these 6 participants have permanently

discontinued study drug due to a Grade 3 or Grade 4 adverse event that is at least possibly treatment related, then this cohort has passed the initial safety guidelines, pending a SMC review. If these six participants also meet the PK guidelines, accrue additional six participants into this cohort and re-evaluate both safety and PK. Note that a routine SMC review of both safety and PK data is required for each mini-cohort before enrolling the full cohort of 12 participants.

Given the small sample sizes within each cohort, the information available for preliminary safety decisions will be imperfect. Two types of sampling errors are possible: 1) in a cohort where the true rate of toxicity is too high to warrant increased exposure to the current starting dose of the medication, the sample data may pass the safety guidelines; 2) in a cohort where the true rate of toxicity is low enough that further exposure to the current starting dose is warranted, the sample data may fail the guidelines.

The extent to which the safety guidelines protect against the errors described above can be assessed by examining various hypothetical rates of "true toxicity" which could occur, if the study medication were used extensively among the patient population at the dose level under question. The hypothetical situations presented below range from conditions under which a given dose level would cause a high incidence of severe and life threatening adverse events deemed to be at least possibly related to study drug to conditions under which severe adverse events would be relatively rare and would not be life threatening. For each of these hypothetical situations, we assume that a sample of 6 participants is drawn from the patient population and that the safety guidelines, summarized above, are followed.

Table 6: Probability of Failing Safety Guidelines Under Potential Rates of True Toxicity

True Toxicity Rates		Probability of Failing Safety Guidelines
Non-Life Threatening Grade 3 or Grade 4 deemed at least possibly related to study medication that would result in Tx discontinuation, excluding Grade 4 events probably or definitely attributable to study medication	Life Threatening serious adverse events (including death) deemed to be at least possibly related to study medication or Grade 4 events probably or definitely attributable to study medication	
.50	.00	.66
.50	.05	.78
.50	.25	.98
.25	.00	.17
.25	.05	.41
.25	.25	.88
.10	.00	.02
.10	.05	.28
.10	.25	.83
.05	.00	.00
.05	.05	.27
.05	.25	.82
.00	.05	.26
.00	.25	.82

Table 6 shows (e.g.) that there is a 78% chance of failing the safety guidelines under conditions in which the true rate of life-threatening toxicity is 5% and the rate of non-life threatening Grade 3 or Grade 4 events is 50%. Assuming that it would be undesirable to open a new cohort at a dose that had these true rates of adverse events, the 22% chance of NOT failing the safety guidelines would represent the probability of error. The table also shows that there is a 2% chance of failing, when the true rate of non-life threatening Grade 3 or Grade 4 events is only 10% and the true rate of life threatening toxicity is zero. Assuming that the potential benefits associated with exposing a new cohort to this dose of the drug would outweigh the risks associated with this relatively low rate of toxicity, failing the safety guidelines under these conditions would be an error.

8.5.1.3 Final Evaluations of Starting Doses For the Full Cohort of Each Age Group Based on Safety Guidelines (Section 8.5.1.2) and PK guidelines (Section 9.2).

The final safety guidelines applied to a given starting dose of the study medication within a cohort will make use of data from all participants (n = 12) in that cohort who have taken the dose under evaluation. For all participants, safety will be evaluated on the basis of all available data collected through the fourth week since initiation of RAL on a given dose as described in Section 8.1 above.

If any of these participants experiences death, a life threatening Grade 4 adverse event deemed at least possibly related to the study medication, or any Grade 4 event that is probably or definitely attributable to the study medication, this starting dose will fail the safety guidelines for the cohort under investigation.

If none of these participants has experienced death, a life-threatening Grade 4 adverse event deemed at least possibly related to the study medication, or any Grade 4 event that is probably or definitely attributable to the study medication, and no more than 33% of these participants have permanently discontinued from the study drug due to a Grade 3 or Grade 4 adverse event that is deemed at least possibly treatment related, then this starting dose will pass the safety guidelines for the cohort under investigation.

8.5.2 Study Safety Monitoring

The safety and tolerability of the study agent will be monitored by means of adverse events reports and toxicity reports presenting laboratory and clinical events. It is required that these data be entered into the database within 48 hours of the time at which the results of the laboratory tests or clinical examinations become available.

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

Since Phase I studies are not routinely reviewed by a Data and Safety Monitoring Board (DSMB), it is the responsibility of the Protocol Team to interpret the toxicity data, and make any decisions regarding adverse events that are needed to protect participants from undue risk. The SMC appointed by the IMPAACT Network will review the data if a situation arises which requires independent review.

Adverse events will be monitored by the Protocol Team throughout the follow-up period. If the Protocol Team identifies any potentially treatment-related toxicities, which may compromise participant safety, it will determine whether the study needs to be suspended or modified.

8.5.2.1 Rules for Suspending Accrual to Assess Safety Following an Adverse Event

Accrual will be temporarily suspended if any participant experiences death, has a life threatening Grade 4 adverse event deemed at least possibly related to the study medication or any Grade 4 event that may not be judged to be life-threatening but is judged to be possibly, probably or definitely attributable to the study medication. (Note: A possibly related Grade 4 non-life threatening event would trigger an accrual stop and SMC review, but if confirmed by SMC as possibly related, and if only such event, then accrual could restart).

Following temporary suspension of accrual, the SMC will be convened and will further review the safety data within 48 hours of notification of the event to

determine if continuation of accrual is appropriate. If the SMC agrees that the study drug is likely to be safe for additional participants, they may allow accrual to resume. Regulatory agencies will be notified of the event and the team's decision after this review of the safety data has taken place.

8.5.2.2 Accrual Rate Evaluation

Accrual into this study will be monitored by the by the team and IMPAACT leadership. Monthly conference calls will be held by the study team to review accrual reports prepared by the Data Management Center. Rate of enrollment will be closely monitored with input provided from team members and participating sites. If any of the dosing cohorts has not accrued half of its evaluable participants within six months after opening the current version of the protocol, the team will communicate with all sites to identify potential barriers to accrual and take corrective actions to improve enrollment. In the event that barriers identified by the team involve current protocol specifications, consideration may be given to amending the protocol to address the identified barriers.

8.6 Analyses

8.6.1 Summary of Dose Finding Data

The analysis of dose finding data will consist of descriptive statistics summarizing the safety and PK data from the dose finding phase of the study (See Section 9.0 for PK analysis). The safety data will be broken down by cohort and will present the results of the safety evaluations applied to each starting dose tested within each cohort, including information indicating which starting doses have passed or failed the safety guidelines. For each starting dose within each cohort, every adverse event of ≥ Grade 3 will be listed, along with patient demographics, the dose prescribed to the patient at the time of the event and the Protocol Team's assessment of the probability that this event was due to the study treatment.

8.6.2 Analysis of Data Representing Exposure to the Doses Selected for Each Cohort

The following analyses will be applied to each age cohort.

The primary analyses will be conducted on patients who were only exposed to the final selected dose. Secondary analyses will be done to include all patients.

8.6.2.1 Primary Analyses

The following analyses will be performed through the final study visit.

Safety

Each participant's safety data will be summarized as: the worst grade of adverse event experienced while on the selected dose of the study treatment and the worst grade of adverse event judged to be at least possibly due to study treatment during this time period. Frequency distributions of these safety outcomes will be presented. Listings of all ≥ Grade 3 events, including deaths, will be provided, broken down by type of toxicity (hepatic, hematologic, etc.).

The proportions of participants experiencing grade 3+ adverse events, bounded by exact 95% confidence intervals. Similar analyses will present the proportions of participants exhibiting ≥ Grade 3 events (including deaths) which have been judged to be at least possibly related to study medication, again bounded by exact 95% confidence intervals.

8.6.2.2 Key Secondary Analyses

Viral Load

A descriptive assessment of virologic response will be assessed on the basis of HIV viral load HIV-1 RNA (copies/mL), after 8 weeks of RAL-containing ARV therapy when most participants will still be on RAL, thus having relatively complete data. This will be an as-treated analysis. Note that participants who discontinue RAL due to TB-drug cessation will be excluded from the analysis. Virologic response will also be summarized at other time points (see Appendix I).

The primary definition of virologic response is defined as achieving: (1) at least a 1 log10 reduction in HIV-1 RNA (copies/mL) from baseline OR (2) HIV-1 RNA ≤ 400 copies/mL. A secondary, more stringent definition of virologic response is to achieve HIV RNA ≤ 50 copies/mL.

The proportions of participants meeting the criteria for virologic response at each of these time points will be bounded by exact 95% confidence intervals, and will be presented in aggregate and by age cohort.

CD4

As Treated Analysis:
For participants who have remained on the study treatment and have data for both baseline and Week 8: Change in CD4 count and percent from baseline at Week 8 will be bounded by 95% confidence intervals and presented in aggregate and by age cohort. Immunologic response will also be summarized at other time points (see Appendix I).

9.0 CLINICAL PHARMACOLOGY PLAN

9.1 Pharmacology Objectives

9.1.1 Primary Objective

To determine the pharmacokinetics and appropriate dose of RAL when administered with a RIF-containing anti-TB therapy in HIV/TB co-infected infants and children that generates PK parameters generally comparable to those seen in HIV-infected infants and children in the absence of RIF.

9.1.2 Secondary Objective

To evaluate the pharmacokinetics of RAL in HIV/TB co-infected infants and children ages ≥ 4 weeks to < 2 years, ≥ 2 to < 6 years and ≥ 6 to < 12 years also receiving concomitant ARVs in the presence of rifampicin to determine the influence of the other ARVs on RAL pharmacokinetics.

9.2 Study Design, Modeling and Data Analysis

P1101 is a Phase I/II, dose-finding, safety, tolerability and pharmacokinetics study of RAL chewable tablet in HIV-infected infants and children ≥ 4 weeks to < 12 years of age who are TB co-infected and on a stable RIF-based TB regimen who are eligible for ARV treatment by current local or WHO guidelines. The study's objective is to determine the proper and safe dose of RAL to be used with a RIF-based TB treatment regimen to provide additional ART options in co-infected infants and children.

An initial dose of RAL will be given at 12 mg/kg (up to a maximum of 800 mg) twice daily for chewable formulation, with two NRTIs. Following the intensive PK study for RAL (5 to 8 days after the start of RAL therapy), a fourth ARV drug will be added to the regimen (see Section 5.1.1). The four-drug ARV regimen will be continued until TB treatment is completed. Each child will be followed up to assess safety, clinical, immunological and virological parameters, from the time that RAL is started on a TB containing regimen until 3 months after stopping RAL while standard of care treatment continues. See Section 3.0 for details.

Participants aged ≥ 4 weeks to < 12 years of age who have had ≥ 1 week and ≤ 20 weeks of RIF-containing TB therapy will be enrolled. The sample will be stratified, by age into the following groups: Cohort I: ≥ 2 to < 6 years; Cohort II: ≥ 6 to < 12 years; Cohort III: ≥ 4 weeks to < 2 years of age, and these three cohorts will accrue simultaneously. At least 12 participants in each age cohort will be enrolled.

For each age cohort, initial tests of safety and PK will examine data from the first mini-cohort of n = 6. These tests will proceed as follows: The starting dose administered to the first six participants will be evaluated on the basis of RAL PK data, based on blood samples taken 5 to 8 days after the start of therapy on that dose. For all participants, safety will be evaluated on the basis of all available data collected through the fourth week on a given dose within each cohort as described in Section 8.5.1.2.

The overall safety and PK data of the first six participants on a given cohort will be evaluated with respect to the safety guidelines specified in Section 8.5.1 and the PK guidelines specified below. In addition to the team's assessment, a routine SMC review of the safety and PK data for each mini-cohort will be performed prior to accrual of the full-cohort accrual. If the initial mini-cohort of n = 6 fails either the

safety (see Section 8.5.1) or the PK guidelines in this initial test, then the dose will be adjusted in the appropriate direction, unless dose reduction is likely to result in inadequate PK values. An initial evaluation of the new dose level will be made on the basis of data from the first six new participants treated at this dose. If the first six participants of a cohort meet both sets of guidelines, then six additional participants will be accrued to this cohort. The additional six participants will be evaluated on both safety and PK; if the full cohort of n = 12 passes both safety and PK criteria, then the dose on which they have been treated will become the selected dose. Otherwise, a new starting dose may be tested (see Section 8.1).

If the mini-cohort (or full cohort) fails the safety and/or PK evaluations, and dose adjustment is warranted, then participants in the failing mini-cohort (or even full cohort) will have their dose adjusted to the new dose being tested. This dose change will be implemented for any participants still receiving RAL at the previous dose, and without impeding treatment-related toxicities. However, if the Protocol Team decides to adjust the dose to three times daily, it will not apply to the previous failed mini or full cohort. There will be no individualized PK-driven dose adjustments.

The regimen of medications for TB and their dosages will be reviewed at the screening visit to ensure that entry criteria are met. The importance of adherence and of reporting deviations in adherence will be emphasized. The PK evaluation of RAL will be performed between days 5 and 8 after treatment initiation. Parents/Guardians must report that the participants have not missed any doses of the ARVs, including RAL, in the 48 hours prior to the intensive PK visit. If a missed dose is reported, the intensive PK visit must be rescheduled. Participants should not ingest breast milk, formula, or any other high fat food/liquid for 2 hours prior to and 1 hour after dosing on the intensive PK day. Water and other fluids (i.e. apple/orange juice and oral rehydration solution) may be consumed as desired. Participants may consume a light meal of their choice two hours after RAL dosing on the intensive PK day. Parents/Guardians should be instructed not to administer the second dose of RAL to participants until the intensive PK sampling is completed. Once the intensive PK visit is scheduled, a reminder call to the parent/guardian regarding the PK visit, the required fasting and reinforcing adherence will be made 3 to 4 days prior to the PK visit. A follow-up call to the parent/guardian should be made 1 day prior to the PK visit to confirm adherence. If a missed dose is reported the scheduled PK visit should be cancelled and rescheduled.

The participant must bring to the clinic the doses of RAL, other ARVs and TB medications so they can be taken after the pre-dose (0) blood is drawn. Doses vomited within 15 minutes may be re-dosed once, with t = 0 to then be time of repeat dosing. If vomited > 15 minutes after dosing, PK must be cancelled and may be rescheduled. A (0.5) mL of blood sample will be drawn at pre-dose (0), 0.5, 1, 2, 3, 4, 6, 8, and 12 hours post dosing.

All PK samples will be registered in the Lab Data Management System (LDMS) database. The Laboratory Processing Chart (LPC) provides instructions regarding processing and shipping of intensive PK samples. The study database will be kept up to date by close tracking of samples. Sample assays and PK calculations for RAL will be performed in real time and the reported to the Protocol Team and sites.

Pharmacokinetic Guidelines

Pharmacokinetic parameters will be determined from plasma concentration-time profiles using noncompartmental methods (32). Calculated pharmacokinetic parameters will be: area-under-the-curve ($AUC\tau$), maximum plasma concentration (C_{max}), time to C_{max} (T_{max}), and plasma concentration at the end of the 12 hour dosing interval (C_{12h}). $AUC\tau$ will be determined using the linear-log trapezoidal rule. C_{max} and T_{max} will be taken directly from the observed concentration-time data.

This is a RAL $AUC_{0\text{-}12hr}$ and C_{12h}-targeted study where participants between the ages of ≥ 4 weeks and < 12 years of age will be enrolled simultaneously into three cohorts (≥ 4 weeks to < 2 years, ≥ 2 to < 6 years and ≥ 6 to < 12 years). Each cohort will start with enrollment of a mini-cohort of n = 6 participants.

If the mini-cohort (n = 6) at a RAL dose of 12 mg/kg achieves 1) a geometric mean RAL $AUC_{0\text{-}12hr}$ of approximately 14 to 45* μMxhr and 2) an approximate GM C_{12h} ≥ 75nM, and meets safety criteria, then 6 additional participants will be enrolled at this dose. The data from these participants will be combined with the previous 6 for evaluation of this dose using the same criteria.

Note: * The cohort upper bound is based on mean exposures observed in the 800 mg multiple dose arm of P001 in adults, the highest raltegravir multiple dose exposure data available.

If the minimum targets above are not achieved, the dose will be increased in linear fashion, up to a maximum of 18 mg/kg not exceeding 800 mg/dose. If the GM RAL $AUC_{0\text{-}12hr}$ falls above a maximal acceptable target of 45 μMxhr, the dose will be similarly reduced. Use of a three times daily regimen may also be considered by the Protocol Team in order to provide adequate cohort GM C_{12h} values (≥ 75nM) without exceeding exposures observed in the 800 mg multiple dose arm of P001 (GM $AUC_{0\text{-}12hr}$ ≤ 45 μMxhr).

If any individual has an $AUC_{0\text{-}12hr}$ ≥ 63 μMxhr **, the participant will stop taking RAL. However, their PK and safety data will be used in the assessment of the dose for that cohort.

Note: ** Individual limit is based on mean exposure observed in the raltegravir QTc study (P024), since this study was closely monitored for safety.

Dosing decisions will be made by the Protocol Team after careful deliberation of all available data pertaining to the study drug.

If the results of the intensive PK are in question, unexpectedly low or high and may put the participant at risk for toxicity, the Protocol Team may request a repeat of the intensive PK.

9.3 Anticipated Outcomes

We anticipate that doubling the RAL dose in the presence of RIF will produce RAL $AUC_{0\text{-}12h}$ and C_{12h} within the acceptable range (33). If acceptable $AUC_{0\text{-}12h}$ and C_{12h} are not achieved up to 800mg per dose, the use of RAL with RIF-containing TB treatment in infants and children may not be advisable.

10.0 HUMAN PARTICIPANTS

10.1 Institutional Review Board and Informed Consent

This protocol, the informed consent document (Appendix VI), and any subsequent modifications must be reviewed and approved by the IRB or EC responsible for oversight of the study. Written informed consent must be obtained from the participant (or parents or legal guardians of participants who cannot consent for themselves, such as those below the legal age). The participant's assent must also be obtained if he or she is able to understand the nature, significance, and risks of the study. 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 participant (or 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 Participants (also known as the Common Rule)

should have on record at the site a plan that detects and addresses any change in guardianship occurring in pediatric participants and determines when a study participant must have a consent process which involves a legally authorized representative (LAR) other than a family member with guardianship. The plan will include how the site determines when a LAR is initially or no longer needed and how frequently the LAR re-signs the consent. The plan should follow all IRB/EC, local, state, national and/or host country guidelines. Confirmation of such a plan at a site should be submitted with protocol registration materials.

10.2 Participant Confidentiality

All laboratory specimens, evaluation forms, reports, and other records will be identified only by a coded number to maintain participant confidentiality. All records will be kept in a secured area. All computer entry and networking programs will be done with coded numbers only. Clinical information will not be released without written permission of the participant, except as necessary for monitoring by the study staff, study monitors, FDA, the OHRP, NIH, the local IRB/EC, or Merck & Co., Inc.

10.3 Study Discontinuation

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

11.0 PUBLICATION OF RESEARCH FINDINGS

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

12.0 BIOHAZARD CONTAINMENT

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

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

SCHEDULE OF EVALUATIONS

	Screening[1]	On treatment study weeks						TB and/or RAL Treatment Discontinuation[17, 19]	4 Wks Off RAL treatment / On study (± 2 wks)[19]	Early Study Discontinuation or End of Study (at 12 wks off RAL treatment ± 2 wks)[19]
		Entry	Day 5 - 8	Day 14 (± 3 days)	Wk 4[14] (± 1 wk)	Wk 8[14] (± 2 wks)	Every 4 wks[15] (± 2 wks)			
CLINICAL EVALUATIONS										
Informed Consent	x									
History[2]	x	x	x	x	x	x	x	x	x	x
Physical exam[3]	x	x	x	x	x	x	x	x	x	x
Pill count[4]		x	x	x	x	x	x	x		x
LABORATORY EVALUATIONS										
Hematology[5]	1 mL	1 mL	1 mL		1 mL	1 mL	1 mL	1 mL	1 mL	1 mL
LFT[6]	1 mL	1 mL	1 mL	1 mL	1 mL	1 mL	1 mL	1 mL	1 mL	
Chemistries[7]	1 mL	1 mL	1 mL	1 mL	1 mL	1 mL	1 mL	1 mL	1 mL	
Urinalysis[8]		x								
Pregnancy test[9]	1 mL [x]	1 mL [x]	1 mL [x]	1 mL [x]	1 mL [x]	1 mL [x]	1 mL [x]	1 mL [x]	1 mL [x]	1 mL [x]
Confirmation/Documentation of HIV Infection	[0-3 mL]									
Virology										
HIV-1 RNA PCR[10]	1-3 mL	1-3 mL			1-3 mL	1-3 mL	1-3 mL	1-3 mL	1-3 mL	1-3 mL
Sequencing[13]		3 mL					3 mL[16]	3 mL[18]		
Immunology										
Lymphocyte subsets[11]		1.5 mL				1.5 mL	1.5 mL	1.5 mL		1.5 mL
Pharmacology										
Intensive PK[12]			4.5 mL							
Total Maximum Blood Volume	4 – 10 mL	8.5 – 11.5 mL	7.5 – 8.5 mL	2 – 3 mL	4 – 7 mL	5.5 – 8.5 mL	5.5 – 11.5 mL	5.5 – 11.5 mL	4 – 7 mL	3.5 – 6.5 mL

APPENDIX I FOOTNOTES

1. Screening evaluations must be performed within 30 days of Entry. Participants must be enrolled ≥ 1 week to ≤ 20 weeks after starting TB treatment. If sufficient documentation of HIV status as specified in Section 4.1.3 is not available, HIV diagnostic testing is to be done according to the definition. If testing is required to fulfill the requirements of inclusion criterion 4.1.3, the HIV-1 RNA PCR required at Screening may serve as one of the two required tests, and additional blood (1-3 mL) may be collected as Sample #1 and/or Sample #2.
2. A complete history is required at Screening; a targeted history is sufficient at subsequent visits. Targeted history should include symptoms of toxicity (such as skin rash, liver dysfunction) and diagnosis. HIV clinical classification is required at Entry only. ARV and concomitant medications will be recorded at each visit. For participants of reproductive potential, onset of sexual activity will be assessed by history. A female participant who becomes sexually active while on study will be referred for contraception as specified in Section 6.9.1; additionally, female participants will have a pregnancy test (see footnote 9 below).
3. Physical exam should include height, weight, and vital signs (temperature, blood pressure, pulse and respiratory rate). Evaluation for lymphadenopathy should be done at baseline. Evaluations for presence of jaundice, hepatosplenomegaly, skin rash, chest signs, musculoskeletal abnormalities, and joint abnormalities for TB should be performed at all study visits.
4. Adherence will be measured using the standardized IMPAACT pill count. Adherence to TB medications will be assessed at the time that study drug is initiated at Entry. Adherence to HIV and TB medications will be assessed at all on-treatment visits and at early discontinuation of study drug. The participant should be reminded of the importance of adherence and of reporting deviations in adherence at all on-treatment visits.
5. Hematology should include complete blood count (CBC) with cell differential and platelet count.
6. ALT, AST, Alkaline phosphatase, Total Bilirubin, Indirect Bilirubin and Direct Bilirubin.
7. Chemistries should include BUN, electrolytes (bicarbonate, sodium, potassium, calcium, and magnesium), glucose, creatinine, and total amylase. If total amylase is elevated, serum fractionated pancreatic amylase should be performed and recorded on the CRF. If amylase fractionation is not available, lipase may be used instead of pancreatic amylase for clinical assessment of pancreatitis.
8. Dipstick urinalysis is sufficient. The following dipstick results should be reported: specific gravity, pH, blood, ketones, glucose, protein and nitrite. Abnormal findings should be followed with complete urinalysis and microscopic examination. The following microscopic results should be reported: RBC, WBC, squamous epithelial cells, hyaline casts and granular casts.
9. Pregnancy test will be done at screening if participant is sexually active. During follow-up, sexually active females will have pregnancy testing done if clinically indicated by the study site clinician. A urine or blood pregnancy test will be done. See Section 6.9.
10. Must be performed at a DAIDS VQA-certified laboratory. Blood volume may vary from 1 – 3 mL depending on the FDA-approved method that the laboratory is VQA-certified to perform. Screening viral load must be performed within 30 days of Entry.
11. Lymphocyte subsets include CD4/CD8 counts and percentages. Must be performed at DAIDS IQA-certified laboratory.
12. Intensive PK should be scheduled so that witnessed dosing of the ARVs is as close as possible to 12 hours after the previous dosing. PK dosing within a range of 11-13 hours after the previous dose is acceptable. Participants should not ingest breast milk, formula, or any other high fat food/liquid for 2 hours prior to and 1 hour after dosing on the intensive PK day. Water and other fluids (i.e. apple/orange juice and oral rehydration solution) can be taken at any time. Participants may consume a light meal of their choice 2 hours after RAL dosing on the intensive PK day. Parents/Guardians must report that the participants have not missed any doses of the ARVs, including RAL, in the 48

hours prior to the intensive PK visit. If a missed dose is reported, the intensive PK visit must be rescheduled. Parents/Guardians should be instructed not to administer the second dose of RAL to participants until the intensive PK sampling is completed.

- Once the intensive PK visit is scheduled, a reminder call regarding the PK visit, the required food/liquid limitations and reinforcing adherence should be made about 3 to 4 days prior to the PK visit. A follow-up call to the parent/guardian should be made 1 day prior to the PK visit to confirm adherence. If a missed dose is reported, the scheduled PK visit should be cancelled and rescheduled.
- Sampling time points: 0.5 mL is to be collected at pre-dose (0) and 0.5, 1, 2, 3, 4, 6, 8 and 12 hours post-dose.
- Doses vomited within 15 minutes may be re-dosed once, with t = 0 to then be time of repeat dosing. If dose is vomited > 15 minutes after dosing, PK must be cancelled and may be rescheduled.
- If the results of the RAL intensive PK are in question, unexpectedly low or high and may put the participant at risk for toxicity, the Protocol Team may request a repeat of the intensive PK. The site will be notified by the team and the time period for obtaining the repeat PK will be given.
- ARVs must be taken at night the day before the RAL PK. The RAL PK samples will be taken in the morning and timed to the RAL dose.

13. Refer to the LPC for shipping instructions for viral sequencing.
14. If a participant will discontinue TB treatment and RAL at the Week 4 or 8 visit due to completion of their prescribed TB treatment, the evaluations at the TB and/or RAL Treatment Discontinuation visit should also be completed. Only the evaluations that are not already being done for the Week 4 or 8 visit need to be completed.
15. These visits will only be done if a participant will continue TB treatment and RAL after the Week 8 visit.
16. If a participant is not virally suppressed by the Week 8 visit, or has viral rebound subsequently, blood will be collected for sequencing at the next visit.
17. Evaluations for TB and/or RAL Treatment Discontinuation will be performed at any of the on-treatment visits that coincide with the discontinuation of TB treatment and/or RAL or when a participant has met the criteria for virologic failure and early treatment discontinuation as defined in Sections 6.2.2 and 6.7, respectively. Only the evaluations that are not already being done for the on-treatment visit need to be completed. Discontinuation of TB treatment and RAL due to completion of prescribed TB treatment can occur anytime beginning at Week 4 depending on the duration that the participant has been on TB treatment at the time of entry.
18. If a participant discontinues RAL early due to virologic failure per Section 6.2.2, blood will be collected for sequencing at the treatment discontinuation visit.
19. Participants that discontinue treatment early for any reason will continue on study/off study drug for 3 months, and complete the TB and/or RAL treatment discontinuation, 4 weeks off RAL treatment/on study, and end of study evaluations.

Note: NIH recommendations for maximum pediatric blood draw volumes will be followed in this study. The volume of blood drawn at any study visit should not exceed 5 mL/kg in a single day and 9.5 mL/kg over any eight-week period. Priority of draw should be as follows: (1) Safety (hematology, chemistries, LFT) (2) Pharmacokinetics, (3) Virology, (4) Immunology.

APPENDIX II

RALTEGRAVIR WEIGHT BAND DOSING TABLES FOR CHEWABLE TABLET

Note: The tables below should be followed for chewable RAL tablet administered as a chewable and as a dispersible tablet. If the Protocol Team determines that a cohort dose adjustment is required and the appropriate dose is not included in the tables below, an updated dosing table will be provided via a Clarification Memorandum.

Table A – Dose of ~6 mg/kg

Weight Band (kg)	6 mg/kg	# of Tablets
	Dose	Administer
3 – 5.9	25	1 x 25 mg
6 – 9.9	50	2 x 25 mg
10 – 13.9	75	3 x 25 mg
14 – 19.9	100	1 x 100 mg
20 – 27.9	150	1.5 x 100 mg
28 – 39.9	200	2 x 100 mg
> 40	300	3 x 100 mg

Table B – Dose of ~9 mg/kg

Weight Band (kg)	9 mg/kg	# of Tablets
	Dose	Administer
3 – 5.9	50	2 x 25 mg
6 – 9.9	75	3 x 25 mg
10 – 13.9	100	1 x 100 mg
14 – 19.9	150	1.5 x 100 mg
20 – 27.9	200	2 x 100 mg
28 – 39.9	300	3 x 100 mg
> 40	400	4 x 100 mg

Table C – Dose of ~12 mg/kg

Weight Band (kg)	12 mg/kg	# of Tablets
	Dose	Administer
3 – 5.9	50	2 x 25 mg
6 – 9.9	100	1 x 100 mg
10 – 13.9	150	1.5 x 100 mg
14 – 19.9	200	2 x 100 mg
20 – 27.9	300	3 x 100 mg
28 – 39.9	400	4 x 100 mg
> 40	500	5 x 100 mg

Table D – Dose of ~15 mg/kg

Weight Band (kg)	15 mg/kg	# of Tablets
	Dose	Administer
3 – 5.9	75	3 x 25 mg
6 – 9.9	125	1 x 100 mg and 1 x 25 mg
10 – 13.9	200	2 x 100 mg
14 – 19.9	250	2.5 x 100 mg
20 – 27.9	350	3.5 x 100 mg
28 – 39.9	500	5 x 100 mg
> 40	600	6 x 100 mg

Table E – Dose of ~18 mg/kg

Weight Band (kg)	18 mg/kg	# of Tablets
	Dose	Administer
3 – 5.9	75	3 x 25 mg
6 – 9.9	150	1.5 x 100 mg
10 – 13.9	225	2 x 100 mg and 1 x 25 mg
14 – 19.9	300	3 x 100 mg
20 – 27.9	450	4.5 x 100 mg
28 – 39.9	600	6 x 100 mg
> 40	800*	8 x 100 mg

*maximum dose = 800 mg twice daily

APPENDIX III

SUPPLEMENTAL TOXICITY TABLE FOR GRADING SEVERITY OF CUTANEOUS/SKIN RASH/DERMATITIS ADVERSE EVENTS

GRADE 1	GRADE 2	GRADE 3	GRADE 4
CUTANEOUS/SKIN RASH/DERMATITIS			
Erythema, with or without pruritis	A. Diffuse erythematous macular or maculopapular cutaneous eruption or dry desquamation with or without pruritis (without the presence of any additional constitutional findings as described in Grade 3 of DAIDS Toxicity tables); OR typical target lesions without blistering, vesicles, or ulcerations in the lesions. B. Urticaria	A. Diffuse erythematous macular or maculopapular cutaneous eruption or moist desquamation with or without pruritis together with any of the following constitutional findings considered related to study drug: 1. 5 x ULN AST, ALT or 2 x baseline if baseline > ULN. 2. fever, >39ºC 3. blistering and/or vesiculation of cutaneous eruptions 4. any site of mucosal lesions; OR B. angioedema; OR C. exfoliative dermatitis defined as severe widespread erythema and dry scaling of the skin, with generalized superficial lymphadenopathy, and with other constitutional findings such as fever, weight loss, hypoproteinemia possibly related to study drug; OR D. diffuse rash and serum sickness-like reactions defined as a clinical symptom complex manifested as fever, lymphadenopathy, edema, myalgia, and/or arthralgia; OR E. diffuse cutaneous eruptions, usually starting on the face, trunk or back, often with prodromal symptoms plus one of the following: 1. cutaneous bullae, sometimes confluent with widespread sheet-like detachment of skin (<10% body surface area), (Nikolski's sign) (Stevens Johnson Syndrome, SJS) 2. two or more anatomically distinct sites of mucosal erosion or ulceration not due to another cause.	Diffuse cutaneous eruptions, usually starting on the face, trunk or back, often with prodromal symptoms plus cutaneous bullae with widespread sheet-like detachment of skin (>10% of body surface area), (Nikolski's sign), (SJS/Toxic Epidermal Necrolysis (TEN) overlap syndrome; TEN)
For all Grade 3 and 4 cutaneous/skin rash/dermatitis adverse experiences, photo documentation of the rash is strongly recommended.			

APPENDIX IV

MANAGEMENT GUIDE FOR SUSPECTED ABACAVIR (ABC) HYPERSENSITIVITY REACTIONS

I. Hypersensitivity Reaction to ABC

a. Prior to initiating therapy with abacavir, screening for the HLA-B*5701 allele is recommended; this approach has been found to decrease the risk of hypersensitivity reaction (HSR).

b. For HLA-B*5701-positive patients, treatment with an abacavir-containing regimen is not recommended and should be considered only with close medical supervision and under exceptional circumstances when the potential benefit outweighs the risk.

c. The diagnosis of hypersensitivity to ABC remains a clinical diagnosis. There is no pathognomonic clinical sign or laboratory finding that renders the diagnosis. The key feature is that HSR is a multi-organ system reaction.

d. Hypersensitivity Reaction

The following is a brief description of the signs, symptoms and laboratory abnormalities that have been associated with ABC HSR.

In clinical studies, approximately 3%-5% of patients receiving ABC develop a HSR that in rare cases has proved fatal. HSR is characterized by the appearance of symptoms indicating multiorgan/body system involvement. Symptoms usually appear within the first six weeks of starting treatment with ABC (median time to onset is 11 days), but may occur at any time while on therapy, and most often include fever, rash, gastrointestinal symptoms (nausea, vomiting, diarrhea, or abdominal pain), respiratory symptoms (dyspnea, sore throat, cough), and lethargy or malaise. Other signs and symptoms may include musculoskeletal symptoms (myalgia, rarely myolysis, arthralgia), headache, paresthesia, and edema. Respiratory tract symptoms (dyspnea, sore throat, and cough) have been observed in approximately 20% of participants who experience HSR. Some patients with HSRs were initially thought to have respiratory tract disease (pneumonia, bronchitis, pharyngitis) or a flu-like illness. The multisystem nature of the HSR has led to misdiagnosis of the HSR as an intercurrent medical illness or as being related to another medication. HSR also has been unrecognized when it presents with less common symptoms or as a single symptom.

This misattribution of the symptoms of HSR to another medical condition or delay in diagnosis of hypersensitivity has resulted in ABC being continued or reintroduced, leading to more severe or rapid (within hours) onset of HSR or death. Therefore, the diagnosis of HSR should be carefully considered for patients presenting with symptoms of these diseases, even if another medical diagnosis seems likely. Renal failure and anaphylaxis have also been reported in association with HSRs. Reintroduction of ABC in participants after treatment interruption, with no preceding symptoms of HSR, has, rarely, resulted in HSR.

Physical findings may include lymphadenopathy and, occasionally, mucous membrane lesions (conjunctivitis and/or mouth ulceration) and hypotension. The rash is variable and

may be absent, but often appears maculopapular or urticarial. Laboratory abnormalities that may accompany ABC hypersensitivity include elevated liver function tests (LFTs), creatine kinase, or creatinine or lymphopenia.

II. Severity of HSR:

Fatal HSRs have been associated with ABC therapy. ABC therapy SHOULD NOT be restarted following a HSR, because more severe symptoms will occur within hours and may include life-threatening hypotension and death. Participants who develop signs or symptoms of hypersensitivity should discontinue treatment as soon as a HSR is first suspected and should seek medical evaluation immediately, preferably on the same day that symptoms are reported.

III. Management of HSR:

If a participant reports symptoms suggestive of hypersensitivity, the participant should be instructed not to take any additional doses and should be evaluated at the clinic. The evaluation should consist of a careful history and physical examination. Laboratory studies should be obtained as clinically indicated. There is no diagnostic test available to confirm the clinical diagnosis. If, upon evaluation, the participant does have a presentation consistent with hypersensitivity, therapy with ABC must be immediately and permanently discontinued and the Protocol Team should be notified.

The hematology, chemistry, signs and symptoms, diagnoses, and event evaluation forms in the CRF should also be completed as indicated.

Symptoms usually start to resolve soon (within 24 hours) after stopping therapy. Symptomatic support, such as intravenous fluids for those who develop hypotension, is advised. There are no clinical data demonstrating the benefit of antihistamines or corticosteroids in the management of hypersensitivity. Nevertheless, symptomatic and/or supportive treatment may be reasonable.

IV. Discontinuation and Re-initiation of ABC Therapy:

Participants who discontinue ABC for any reason should be queried regarding signs and symptoms of HSR. Unrecognized HSR at the time of discontinuation can lead to serious, rapid, and fatal HSR if the drug is reinitiated. Rarely, ABC HSR has occurred when ABC was stopped and restarted for reasons other than medical illness, such as an interruption of drug supply. In those rare cases, no preceding signs and symptoms of ABC HSR could be identified.

If any participant has discontinued ABC due to symptoms that are judged by the site PI to be suspicious for HSR, the team should be notified and reintroduction of ABC is prohibited.

Participants who have had a HSR must be advised that they should never take ABC or an ABC-containing drug combination again, since a life-threatening second HSR can occur. Patients should be advised to return all unused ABC at the time of discontinuation to reduce the risk of inadvertent rechallenge.

a. Rash in Participants Receiving ABC

Participants receiving ABC who develop rash of any grade should be evaluated as soon as possible for the possibility of hypersensitivity. Notify the Protocol Team within 3 days. If

there is no indication of any other organ system involvement and the participant has no systemic symptoms (fever, malaise, fatigue, headache), ABC may be continued for rash ≤ Grade 2 with the warning to discontinue immediately and permanently if other signs and/or symptoms consistent with hypersensitivity appear.

b. Fever in Participants Receiving ABC

The onset of fever may also herald hypersensitivity in persons treated with ABC. Participants reporting fever should be evaluated as soon as possible for the possibility of hypersensitivity. Notify the Protocol Team within 3 days. In the event of a clinical presentation consistent with hypersensitivity, ABC should be discontinued immediately and permanently.

APPENDIX V

TERMINOLOGY, DEFINITIONS AND MANAGEMENT GUIDE FOR IMMUNE RECONSTITUTION INFLAMMATORY SYNDROME (IRIS)

I. BCG IRIS

BCG IRIS usually occurs at a median of 7 to 8 months of age, and is unlikely to affect the study population to be enrolled in P1101. Criteria have been developed for diagnosis of BCG IRIS by the BCG Safety Working Group of the International Union against Tuberculosis and Lung Disease (IUATLD). Criteria for this study are as follows:

a. Acute onset enlargement of ≥ 2 cm in the vertical and horizontal diameter of a single or multiple regional lymph-node/s draining the arm on which BCG vaccine was administered, occurring between 1 week to 6 months after the initiation of highly active antiretroviral therapy. The horizontal and/or the vertical diameter of the affected lymph node should have increased by at least 2 cm if the lymph-node was documented to have been previously enlarged.

b. The lymph-node should show one or more of the following features:

- granulomatous infiltrate with or without necrosis
- presence of acid fast bacilli
- culture of mycobacterium tuberculosis complex, which should include attempt at specification between MTB and M. bovis

II. TB IRIS

Since all infants and children will be on TB treatment, the definition of TB IRIS for this study will be paradoxical flare up of TB symptoms in a patient who is on treatment for TB. Pulmonary/extra-pulmonary TB may occur.

a. In participants already receiving TB treatment, initial improvement of symptoms of TB is required, such as:

- Defervescence
- Improvement of respiratory symptoms
- Decrease in size of lymph nodes

b. Clinical symptoms/manifestations suggestive of TB-IRIS may include one or more of the following:

- General: persistent fever, weakness
- Pulmonary: cough, new/worsening dyspnea, stridor as minor criteria
- CNS: headache, fever, meningismus, neck pain, photophobia
- Abdominal pain, diarrhea
- Localized symptoms (e.g., lymphadenitis, subcutaneous nodules and abnormal skin lesions)

c. Based on the presentation, the TB IRIS events can be classified as:

- Pulmonary TB

  Presence of a new pulmonary infiltrate that is associated with intra-thoracic lymphadenopathy, which may or may not cause compression of large airways, or an increase of an existing pulmonary infiltrate, occurring 1 week to 6 months after the initiation of ARV regimen.

- TB Pleuritis

  New pleural effusions or deterioration of existing pleural effusions, occurring 1 week to 6 months after the initiation of ARV regimen.

- TB Brain

  Demonstration of a ring-enhancing lesion on CT scan of the brain which is demonstrated 1 week to 6 months after the initiation of ARV regimen in an individual that did not have any previous documented intracerebral lesion, or no clinical abnormalities suggesting central nervous abnormality, or deterioration or enlargement of preexisting CNS lesions.

- TB Meningitis

  New-onset signs and symptoms of meningitis or deteriorating symptoms of meningitis, all 1 week to 6 months after the initiation of ARV regimen.

- TB Peritonitis

  Abdominal pain plus ultrasound evidence of peritonitis/abdominal lymphadenopathy with/without ascites occurring 1 week to 6 months after the initiation of ARV regimen.

d. Other factors that can aid the diagnosis of TB-IRIS:

- Alternative explanations for deterioration or appearance of new clinical presentation have been excluded
- The diagnosis of pulmonary TB or of "tuberculoma" is substantiated by a reactive TST ($\geq$ 10 mm) using the Mantoux method.
- HIV viral load decline (> 1 $\log_{10}$ decline of HIV RNA) or substantial increase in CD4 (> 5 percentage points) favor the diagnosis of IRIS but are not essential or sufficient.
- Growth of *M. tuberculosis* upon culture of clinical specimens: Positive AFB smear or positive histopathology consistent with TB are suggestive of TB-IRIS; clinical criteria only can confirm suggested TB IRIS. Where facilities are available, PCR/other assays will be used to perform species identification of Mycobacterium spp.

In the case of TB IRIS, continued treatment with anti-tuberculosis therapy is warranted and this should be continued. If the participant is taking a 3-drug TB regimen and addition of a fourth drug is indicated, this may be allowed in consultation with the Protocol Team.

Since there are many different organisms which may cause IRIS, if other medication is indicated and provided the medication is not on the disallowed list (see Section 4.3.2), this may be added with approval from the Protocol Team.

APPENDIX VI

SAMPLE INFORMED CONSENT FORM FOR STUDY PARTICIPATION

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

SHORT TITLE FOR THE STUDY: P1101

Version 3.0, dated 24 April 2017

INTRODUCTION

Your child is being asked to take part in this research study because your child has the Human Immunodeficiency Virus (HIV), which is the virus that causes AIDS, and has not taken any medications for the treatment of HIV in the past 30 days. Your child also has Tuberculosis (TB) and is taking or will be starting anti-TB medications that include Rifampicin, a medication commonly used to treat TB. This study is sponsored by the National Institutes of Health (NIH). The doctor in charge of this study at this site is: (insert name of Principal Investigator). Before you decide if you want your child to be a part of this study, we want you to know about the study.

This is a consent form. It gives you information about this study. The study staff will talk with you about this information. You are free to ask questions about this study at any time. If you agree to allow your child to take part in this study, you will be asked to sign this consent form. You will get a copy to keep.

WHY IS THIS STUDY BEING DONE?

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.

The other medications used in this study are Rifampicin, other anti-TB medications, two anti-HIV medications that are called Nucleoside Reverse Transcriptase Inhibitors (NRTIs) 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 clinic where your child is receiving care. 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 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 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 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 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:

To find out if your child qualifies for this study, we will:

- Ask about your child's medical history including questions about your child's health and what symptoms, medications, and illnesses your child has had.
- Give your child a physical examination: We will measure your child's height, weight and vital signs (temperature, blood pressure, pulse and respiratory rate).
- Draw your child's blood for the following tests: We will take a little more than 1 teaspoon (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 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 in this study, the reasons your child cannot enroll in this study will be shared with the protocol team, including the pharmaceutical company supporting the study.

Table 1

	Entry	Day 5 to 8	Day 14	Week 4	Week 8	Every 4 weeks	TB and/or RAL treatment discontinuation	4 weeks off RAL treatment/on study	Final visit
Medical history and review of medications	X	X	X	X	X	X	X	X	X
Physical exam	X	X	X	X	X	X	X	X	X
Pill Count	X	X	X	X	X	X	X		X
CBC	X	X		X	X	X	X	X	X
Liver enzymes	X	X	X	X	X	X	X	X	
Blood chemistries	X	X	X	X	X	X	X	X	
HIV viral load	X			X	X	X	X	X	X
CD4/CD8 cell count	X				X	X	X		X

Entry visit:
[*Sites: add local information regarding how long the entry visit will take*].

If your child qualifies for this study and you allow your child to enter the study, your child will come to the clinic for the first study visit (or the 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".
- 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.

Your child will be asked to return to the clinic about 4 to 10 times in about 16 to 36 weeks (or 4 to 9 months) until your child stops taking the anti-TB medications. One visit will last a little over 12 hours where the amount of raltegravir and ARVs in the blood will be measured over 12 hours (intensive pharmacokinetics or intensive PK visit). [*Sites: add local information regarding how long the visits will take*].

Intensive PK visit (Day 5 to 8):
Approximately one week after starting raltegravir, your child will have 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.
- We will ask that you not give your child raltegravir, other anti-HIV, and anti-TB medicines at home the day of this visit. Your child will need to bring these medicines to the clinic. Your child will be given these medications in the clinic after the first blood sample for the intensive PK test is taken.
- Blood tests: We will take a little more than 1 ½ teaspoons (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 1 teaspoon (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 the 2 days before the PK test. If your child misses a dose within 2 days before the PK test, the visit will be rescheduled. Your child should not 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 water or apple/orange juice 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.

Your child may be stuck by a needle 9 times or a special needle may be inserted into your child's arm so that he/she may not have to be stuck by a needle multiple times. If possible an intravenous line will be placed in your child's vein for the whole day from which blood may be drawn to avoid as much discomfort as possible.
[Sites: modify or add language as appropriate regarding your site-specific arrangements for the PK visit]

If your child vomits within 15 minutes after taking raltegravir, your child will be given another dose of raltegravir. If your child vomits more than 15 minutes after taking raltegravir, the intensive PK test will be cancelled. The test may be re-scheduled.

Your child will start taking a fourth anti-HIV drug chosen by your doctor after the PK test is completed. Your child should take the fourth 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.

<u>Day 14 visit</u>
Your child will have a visit approximately two weeks after starting raltegravir. The following will take place at this visit:
- Your child will have the examinations and tests shown in Table 1 under the column "Day 14".
- Blood tests: We will take a little less than ½ teaspoon (2 mL) of blood at this visit for the tests in Table 1. The results of the tests will be provided to you/your child.

<u>Week 4 visit:</u>
The following will take place approximately four weeks after your child starts taking 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 will be stopping the anti-TB medications 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 ½ teaspoon (1.5 mL) of additional blood for a CD4/CD8 cell count test. The results of the CD4/CD8 cell count test will 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.

Week 8 visit:

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 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.

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 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, we may also take a little more than ½ teaspoon (3 mL) of additional blood for an HIV resistance test. This test 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 needs to stop taking the anti-TB medications and/or raltegravir early, your child will have 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 "TB and/or RAL treatment discontinuation."
- Blood tests: We will take about 1 – 1 ½ (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.
- Depending on the amount of HIV in your child's blood, we may also take a little more than ½ teaspoon (3 mL) of additional blood for an HIV resistance test. This test may be done after the study is over, and you/your child will not be given the results.

Even if your child 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, the following will take place:

- Your child will have the examinations and tests shown in Table 1 under the column "4 weeks 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". A pill count will only be done if your child 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.

The study will first enroll a small group of 6 participants into 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 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 there is a question about the results of the intensive PK test of your child, or the results are lower than what is expected or too high and may be a risk to your child, the study doctor may ask your child to have another intensive PK test. Your child's study doctor will let you know when the intensive PK test will be repeated.

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.

If your child is still taking raltegravir and the anti-TB medications when the best dose of raltegravir is found, and your child is still in the study, the study doctor will change your child's dose of raltegravir to the best dose. Your child will continue taking the new dose of raltegravir until your child stops taking the anti-TB medications.

OTHER INFORMATION

Your child's blood samples for the intensive PK tests will be shipped to a laboratory in the United States where the tests will be performed.

Any leftover blood samples after testing is completed for this study will be destroyed.

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

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

About 36 to 108 infants and children will take part in this study.

HOW LONG WILL MY CHILD BE IN THIS STUDY?

Your child will be in this study for about 4 to 9 months.

WHY WOULD THE DOCTOR HAVE MY CHILD STOP TAKING RALTEGRAVIR EARLY?

The study doctor may need to take your child off raltegravir early without your permission if:

- Your child develops a side effect and continuing the study drug(s) may be harmful to your child.
- Your child needs a treatment that your child may not take while on the study.
- Your child is found to have multi-drug resistant (MDR) or extensively drug-resistant (XDR) TB. MDR-TB and XDR-TB happens when the bacteria that cause TB infection changes and cannot be treated by the medicines that are usually effective in treating TB. If your child is found to have MDR or XDR TB, your child will be referred to the proper doctor or clinic for care.
- Your child is not able to take the study drug(s) as required by the study.
- New information that becomes available shows that your child should stop taking the study drug(s).
- The result of the intensive PK test shows that your child has not been taking the study drugs or the level of raltegravir that your child's body is taking is abnormally high or low.
- The amount of HIV in your child's blood does not go down to the levels low enough to continue the study drug(s).
- Your child becomes pregnant or is a female that is sexually active and does not agree to take birth control precautions.

If your child must permanently stop taking the study drug(s) before your child's study participation is completed or before the study is over, the study staff will discuss other options that may be of benefit to your child. In addition, your child will have the early treatment discontinuation visit and the visits four weeks and twelve weeks after stopping the study drug(s) as described above.

After the study:

After your child has completed study participation, the study will not be able to continue to provide your child with the raltegravir that he/she received on the study. If continuing to take these or similar drugs would be of benefit to your child, the study staff will discuss how you may be able to obtain them.

WHY WOULD THE DOCTOR TAKE MY CHILD OFF THE STUDY EARLY?

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

- You do not want your child to continue or your child does not want to continue taking raltegravir or completing the required visits.

- The study doctor determines that continuing participation could be harmful to your child's health or well-being.
- Your child is not able to attend the study visits or meet the requirements of the study, which may cause harm to him/her and affect the results of the study.
- The study is cancelled by the IMPAACT Network, Office for Human Research Protections (OHRP), National Institutes of Health (NIH), the site's Institutional Review Board (IRB) or Ethics Committee (EC), the U.S. Food and Drug Administration (FDA), other government agencies, or Merck & Co., Inc. (the drug company supporting this study). An IRB or EC is a committee that watches over the safety and rights of research participants.
- An IMPAACT Study Monitoring Committee (SMC) recommends that the study be stopped early. The SMC is a group of experts who monitor the study.
- The study has to be stopped for other administrative reasons.

WHAT ARE THE RISKS OF THE STUDY?

The drugs used in this study may have side effects, some of which are listed below. Please note that these lists do not include all the side effects seen with these drugs. These lists include the more serious or common side effects with a known or possible relationship. If you have questions concerning additional study drug side effects, please ask the medical staff at your site.

For your child's safety, it is important that you tell the study doctor or nurse about all medications that your child is taking before your child starts the study, and also before your child starts taking any new medications while on the study, including medicines bought from the store or pharmacy and herbal or natural medicines. In addition, it is important that you tell the study doctor or nurse before your child enrolls in any other clinical trials while on this study.

Your child's HIV may develop resistance to raltegravir and anti-HIV drugs that are being used in this study. Drug resistance develops when the HIV changes so the anti-HIV drugs become less effective. It is possible that your child may not receive the correct dose of raltegravir, which can also lead to drug resistance. If drug resistance develops in your child, the HIV virus may not be controlled. However, the reason for adding a fourth ARV drug early in the study is to try to avoid the development of resistance to raltegravir.

Use of Combination Antiretroviral Drugs

Immune Reconstitution Syndrome: When your child is treated with a combination of at least 3 anti-HIV drugs (which is called highly active antiretroviral therapy or HAART), the way your child's body is able to fight infection may change. The immune system is the body's defense against infection. Your child's immune system may respond in a stronger way to some types of infections that your child may already have. This immune response may cause your child to become sick and the condition is then called "immune reconstitution inflammatory syndrome" or IRIS.

We do not understand who will get IRIS and who will not. IRIS can be serious or mild. It can begin soon after a person starts HIV medication for the first time. It can also begin in people who restart their HIV medications after being off (or not taking) them for some time. IRIS happens when your child's immune system recovers too quickly. It can start to "overact" and respond to other infections that may or may not have been known before starting therapy, even ones that may have already been under control.

When your child's immune system over acts this way it can cause inflammation (redness and tenderness), which is sometimes very serious. For some people, these symptoms can be life-threatening. Even though most cases of IRIS get better after a few weeks, the symptoms may be mistaken by you, and your child's

doctor as the HIV disease getting worse or another condition. IRIS can be very confusing because, as your child's immune system fights an infection, the inflammation that takes place actually makes your child's symptoms worse.

When IRIS does happen, it happens more often after the BCG injection. BCG stands for Bacille Calmette-Guerin vaccine, a vaccine that is used to prevent tuberculosis (TB) in infants. The injection site can get bigger and the glands in the right armpit may become painful. IRIS also happens more often with TB in 1 out of 10 infants. Many other bacteria and viruses can lead to IRIS. Usually, IRIS causes a return or worsening of at least some of the symptoms from an infection your child may have had before starting HAART. While some of these reactions can be serious, they usually last for a short time and can be treated without stopping the anti-HIV drugs or HAART.

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

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

Integrase Inhibitor

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

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

- Rash, which can become severe or life-threatening. Contact your 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
- Easy bleeding (decreased blood clotting, low 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 your child develops a rash with any of the following symptoms stop using raltegravir and contact your 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 child's doctor right away if 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.

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.

Risks of Blood Draws

There is risk of some discomfort, bruising, or bleeding at the site where the blood is drawn. Occasionally, there is swelling in the area where the needle enters the body and a small risk of fainting and/or infection.

Other Risks

Your child may feel uncomfortable or embarrassed by some parts of your child's physical exam and with some of the questions related to sexual development and activity.

ARE THERE RISKS RELATED TO PREGNANCY?

It is not known if the study drug raltegravir harms fetuses. Tests in pregnant animals do show some risk.

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, 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 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 the study staff right away. The study staff will talk to you/your child about your/your child's choices. If your child becomes pregnant, she will be entered in the Antiretroviral Pregnancy Registry.

Pregnancy test results will be shared confidentially with participants, even if a parent or other adult is consenting for the child's participation in the study. *[Sites should modify preceding language about confidentiality of pregnancy test results to conform to their local practice, regulations and IRB requirements.]*

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, 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 OTHER CHOICES DOES MY CHILD HAVE BESIDES THIS STUDY?

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

- treatment with prescription drugs available to your child
- treatment with experimental drugs, if your child qualifies
- no treatment

Please talk to your doctor about these and other choices available to your child. Your doctor will explain the risks and benefits of these choices.

WHAT ABOUT CONFIDENTIALITY?

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.

Your child's records may be reviewed by the U.S. Food and Drug Administration (FDA), the Office of Human Research Protections (OHRP), (insert name of site) IRB/EC, National Institutes of Health (NIH), study staff, study monitors, and Merck & Co., Inc. (the drug company supporting this study).

WHAT ARE THE COSTS TO ME?

Taking part in this study may lead to added costs to you and your insurance company. In some cases it is possible that your insurance company will not pay for these costs because your child is taking part in a research study. *[Sites: Delete or modify as appropriate with any site-specific information regarding insurance and local costs.]*

WILL I RECEIVE ANY PAYMENT?

You and your child may receive reimbursement for some expenses for this study. You and your child may receive payment for transportation and meals.
[Sites: Delete or modify as appropriate with any site-specific information about payment.]

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 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.
[Sites: Delete or modify as appropriate with any site-specific information regarding insurance and local costs.]

WHAT ARE MY CHILD'S RIGHTS AS A RESEARCH PARTICIPANT?

Taking part in this study is completely voluntary. You may choose not to allow your child to take part in this study or take your child out of the study at any time. Your child will be treated the same no matter what you decide.

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

WHAT DO I DO IF I HAVE QUESTIONS OR PROBLEMS?

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

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

For questions about your/your child's/baby's rights as a research participant, contact:

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

SIGNATURE PAGE

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

_____ Participant's Name (print)	_____ Participant's Signature and Date
_____ Participant's Parent or Legal Guardian (print)	_____ Parent or Legal Guardian's Signature and Date
_____ Study Staff Conducting Consent Discussion (print)	_____ Study Staff Signature and Date
_____ Witness' Name (print) (As appropriate)	_____ Witness's Signature and Date
_____ Father's Name (If father's consent is required)	_____ Father's Signature and Date (If father's consent is required)