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# P1101: PHASEI/II STUDY OF RALTEGRAVIR CONTAINING REGIMEN IN HIV-TB COTREATED CHILDREN

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## Abstract (as submitted)

**Background:** Current antiretroviral (ARV) treatment options for children co-infected with TB and HIV-infection are limited. RIF induces UDP-glucuronosyltransferase activity accelerating the clearance of raltegravir (RAL). In adults, doubling the RAL dose partially overcame this PK interaction with no safety concerns. We sought to determine the optimal and safe dose of RAL when administered with RIF-containing anti-TB therapy in HIV-infected children.

**Methods:** P1101 is a dose finding study for RAL for HIV-infected children receiving RIF-containing TB therapy for at least one week, with three age cohorts: Cohort 1: 2 to <6 years (closed), Cohort 2: 6 to <12 years of age and Cohort 3: 4 weeks to <2 years, aiming to enroll 12 evaluable children for PK and safety in each cohort.

At enrollment children start 3 ARVs, including chewable RAL formulation at 12 mg/kg/dose twice daily (twice the recommended pediatric dose). Intensive RAL PK sampling is done 1 week after ARV therapy is initiated and then a 4th ARV is added. Clinical and lab assessments are routinely completed. RAL is stopped at TB treatment completion and children are followed for additional 3 mos. PK targets are a geometric mean (GM) $AUC_{12h}$ of 14-45 (μM-h) and GM $C_{12h}$ ≥75 nM. Here we report the results from Cohort 1.

**Results**: Among 12 children, 7 (58%) were male, median age 3 years (IQR 2-5), baseline $log_{10}$ RNA median 4.91 (IQR 4.42-5.42), median CD4 count 559 cells/μL (IQR 390-1185), median CD4 percent 15% (IQR 9-24). PK at Week 1 showed GM $AUC_{12h}$ (%CV) of 28.8 μM-h (50%); the GM $C_{12h}$ was 229 nM (76%). 1/12 (8% with 95% CI [0%,34%]) had a grade 3 elevation of ALT at Week 4 deemed possibly related to RAL. RAL/ART were temporarily withheld for 21 days and then restarted, with no subsequent recurrence. While RAL was held temporarily, this child did not achieve virologic success (>1 $log_{10}$ drop from baseline at Week 8 or HIV RNA ≤400 copies/mL). 11/12 (92%), were virologically suppressed by Week 8, with 95% CI (62%, 100%). For n=12 at Week 8, median $log_{10}$RNA change from baseline was -3.16 (IQR -3.79, -2.55), median CD4 change from baseline was 101 cells/μL (IQR -70 to 230], median CD4 percent change from baseline was 6.1% (IQR 1.9-9.7).

**Conclusions:** A 12 mg/kg dose twice daily of the oral chewable formulation of RAL safely achieved PK targets in HIV-infected children 2 to <6 years with TB.

## Background

- The burden of tuberculosis (TB) among HIV-infected adults and children is high in many resource-limited settings (RLS).
- Antiviral options for children co-infected with TB are limited because of drug interactions, especially with rifampicin-containing (RIF) TB regimens.
- Pediatric clinical trials for new drugs usually exclude TB co-infected children making it difficult to determine drug efficacy and safety in these co-infected children.
- RIF induces UDP-glucuronosyl transferase activity accelerating the clearance of raltegravir (RAL).
- In adults, doubling the RAL dose partially overcame this PK interaction with no safety concerns.(1)
- We sought to determine the optimal and safe dose of RAL when administered with RIF-containing anti-TB therapy in HIV-infected children.

**(1)** Wenning LA, Hanley WD, Brainard DM, Petry AS, Ghosh K, Jin B, et al. Effect of rifampin, a potent inducer of drug-metabolizing enzymes, on the pharmacokinetics of raltegravir. Antimicrobial agents and chemotherapy. 2009;53(7):2852-6.

## Methods

- IMPAACT P1101 is a Phase I/II dose finding study for RAL for HIV-infected children receiving RIF-containing TB therapy for at least one week.
- The 3 age cohorts include: Cohort 1: 2 to <6 years (closed), Cohort 2: 6 to <12 years of age (closed) and Cohort 3: 4 weeks to <2 years (enrolling). Results from Cohort 1 are presented here.
- Each cohort requires n=12 evaluable participants for pharmacokinetics and safety assessments.
- At enrollment, participants start 3 ARVs, including chewable RAL formulation at 12 mg/kg/dose twice daily (twice the recommended pediatric dose).
- Intensive RAL PK sampling is done 1 week after ARV therapy is initiated and then a 4th ARV (standard of care with TB treatment) is added, usually efavirenz (EFV) or lopinavir/ritonavir (LPV/r)
- Clinical and laboratory assessments are routinely completed.
- RAL is stopped at TB treatment completion and participants are followed for an additional 3 months.
- PK targets are geometric mean (GM) $AUC_{12h}$ of 6-20 mgxh/L (14-45 μMxh) and GM $C_{12h}$ ≥33 ng/mL (≥75 nM).
- 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

## Objectives

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

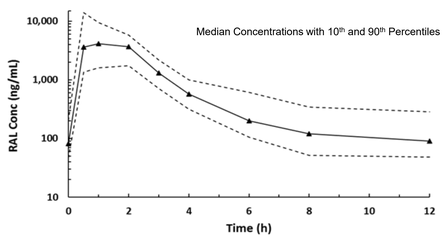
## Baseline Characteristics

| | Median | 25th Percentile | 75th Percentile |
|---|---|---|---|
| **AGE (years)** | 3 | 2 | 5 |
| **CD4 (%)** | 15 | 9 | 24 |
| **CD4 (cells/μL)** | 559 | 390 | 1185 |
| **HIV RNA ($log_{10}$copies/ml)** | 4.91 | 4.42 | 5.42 |

- N=12
- Male: 7 (58%)
- Race: Black=12 (100%)
- Study Follow-up: 33 weeks (IQR: 28, 37)
- 4th drug: 11/12 EFV and 1/12 LPV/r

## Intensive Pharmacokinetic Study Results

**Figure 1: PK Profile of Intensive PK Studies n=12**




PK Targets
- GM $AUC_{12h}$ of 6-20 mgxh/L (14-45 μM-h)
- GM $C_{12h}$ ≥ 33 ng/mL (≥ 75 nM)

PK Results
- GM $AUC_{12h}$ was 12.8 mgxh/L (28.8 μMxh; CV=50%)
- GM $C_{12h}$ was 102 ng/mL (230 nM; CV=76%)

## CD4 Results

Week 8: Median CD4% and CD4 Change from Baseline

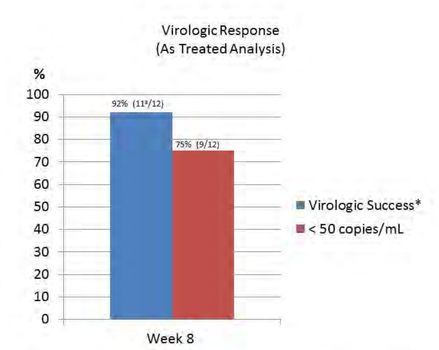
| | Median | Q1, Q3 |
|---|---|---|
| **CD4 Count (μL$^{-1}$)** | 101 | -70, 230 |
| **CD4%** | 6.1 | 1.9, 9.7 |

## Safety Results

- Only one out of n=12 had an adverse event (AE) deemed at least possibly related to RAL.
  - Participant: 3 year old male.
  - At Week 4: Grade 3 AST and Grade 3 ALT elevations, assessed by the site and Protocol Team as possibly related to RAL.
  - RAL and other ARVs were temporarily held for 3 weeks, then resumed RAL+ARVs, until the end of the study.

## HIV-1 RNA Results

**Figure 2: Virologic Profile**




Note: Week 8 $Log_{10}$HIV-RNA Change from Baseline: Median: -3.16, IQR (-3.79,-2.55).

**All (11) participants with Virologic Success also had HIV RNA < 400 copies/mL.**
- **(10/11) participants remained < 400 copies/mL through week 24 or last day of treatment.**
- **(1/11) participant after week 8 had RNAs > 400 copies/mL at weeks 16 and 20, but still had approximately 4-log decreases from baseline.**

***[a]The participant who did not meet the virologic success criterion is the same participant who had RAL held temporarily for 3 weeks due to an AE. Samples were collected for resistance testing at RAL discontinuation, and results will be analyzed in batch at the end of the study per protocol.***

## Conclusions

- Doubling the dose of RAL for TB-HIV co-infected children ≥ 2 to < 6 years of age while taking rifampicin achieved adequate PK levels and was found to be safe.
- A dose of 12 mg/kg of RAL can be recommended for TB-HIV co-infected children taking rifampicin in this age group.
- Expanding options for treating co-infected children is possible
- Further data from Cohort 2 (≥6 to <12 years) and Cohort 3 (≥4 weeks to < 2 years) are required prior to recommending the doubled dose for all TB-HIV co-infected infants and children who are treated with rifampicin.

***The study team would like to thank the P1101 participants and families for their participation.***

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