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PHARMACOKINETICS OF RALTEGRAVIR IN HIV/TB CO-TREATED INFANTS AND YOUNG CHILDREN

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Abstract (as submitted)

Background: Current Antiretroviral (ARV) options for HIV/TB co-infected children are limited. Rifampin (RIF) induces UDP-glucuronosyltransferase activity, increasing the clearance of raltegravir (RAL). We sought to establish the optimal and safe dose of RAL when administered with RIF in HIV/TB co-infected infants and children

Methods: P1101 is a dose finding study of RAL in HIV-infected children at four South African sites receiving RIF-containing TB therapy for at least 1 wk, with three age cohorts spanning 4 wks to <12 yrs of age, aiming to enroll 12 evaluable participants for PK and safety in each. At entry, participants start RAL at 12 mg/kg/dose twice daily (twice the approved pediatric dose) and two nucleoside reverse transcriptase inhibitors. Intensive RAL PK sampling is done 5-8 days after ARV initiation and then a fourth ARV is added. RAL is stopped at the end of TB treatment with follow-up for another 3 mo. PK targets are a geometric mean (GM) AUC_{12h} of 14-45 µMxh and GM C_{12h} ≥75 nM.

Here we report the results from Cohort 3 (4 wks to <2 yrs) using RAL chewable tablets as a dispersible tablet; Cohorts 1 and 2 (ages 2 yrs to <12 yrs) were previously reported.

Results: Of 13 participants, 8 were male with median age 12.3 mo with baseline log_{10} HIV (RNA cpy/mL) of 5.13, CD4 count/µL of 1513, and CD4% of 16.8%. Wk 1 PK showed GM AUC_{12h} (%CV) of 32.7 µMxh (49%) and GM C_{12h} of 106 nM (57%). No adverse events were related to RAL.

12/13 had evaluable efficacy data at wk 8 (1/13 stopped RAL early due to use of a disallowed medication). By wk 8, 10/12 (83%) had HIV RNA <400 copies/mL; median changes from baseline were log_{10}RNA cpy/mL -3.05, CD4 count +105.5 cells/µL and CD4% +4.9%. RAL was permanently stopped in 6/13 participants, one each for Grade 4 neutropenia (likely related to TB medication), use of a disallowed medication, or AUC_{12h} exceeding the allowed AUC_{12h} maximum (asymptomatic). 3 stopped RAL for virologic failure (VF): 1 at wk 8 (above) who was very ill; 1 at wk 12 (non-adherence); 1 at wk 12 (VF unexplained).

Conclusions: A 12 mg/kg dose twice daily of RAL chewable tablets appears to safely achieve PK targets in HIV/TB co-infected children 4 wks to <2 yrs receiving rifampin, with high rates of virologic suppression by Week 8.

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 previously demonstrated that 12 mg/kg of RAL when administered twice daily with RIF-containing anti-TB therapy to children 2 years to <12 years of age children achieved protocol defined PK and safety targets.(2)
- Here we describe the results in Cohort 3: children 4 weeks to <2 years of age.

(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.

(2) Meyers T, P. S, Acosta E, Moye J, Townley E, Bradford S, et al. Pharmacokinetics and safety of a raltegravir containing regimen in HIV-infected children aged 2-12 years on rifampicin for tuberculosis *AIDS* 2019; 15;33(14):2197-2203

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

Methods

- IMPAACT P1101 was a Phase I/II dose finding study for RAL for HIV-infected children receiving RIF-containing TB therapy for at least one week. The data from Cohort 1 (2 to <6 years) and Cohort 2 (6 to <12 years of age) have been described[2]. Results from Cohort 3 (4 weeks to <2 years) are presented here.
- Each cohort required n=12 evaluable participants for pharmacokinetics and safety assessments.
- At enrollment, participants started 3 ARVs, including chewable RAL formulation at 12 mg/kg/dose twice daily (twice the recommended pediatric dose). To deliver this dose the RAL chewable tablets were crushed and dispersed in a small amount of water.
- Intensive RAL PK sampling was done 1 week after ARV therapy is initiated and a 4th ARV (LPV/r was added for all in Cohort 3).
- Clinical and laboratory assessments were performed at the time of screening and entry, then at 1,2,4 and 8 weeks after starting RAL, then monthly during RAL therapy
- RAL was stopped at TB treatment completion and participants followed for an additional 3 months.
- Clinical/lab assessments were done at the time of TB and/or RAL treatment discontinuation
- PK targets were geometric mean (GM) AUC_{12h} of 6-20 mgxh/L (14-45 µMxh) and GM C_{12h} ≥33 ng/mL (≥75 nM).
- Virologic Success was defined as achieving at least 1- log_{10} copies/mL drop from baseline, or HIV RNA ≤ 400 copies/mL at Week 8

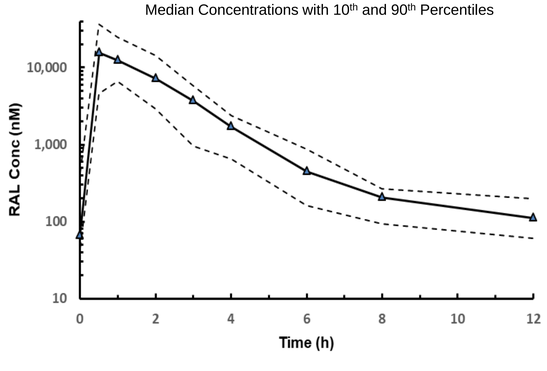
Baseline Characteristics

	Median	25th Percentile	75th Percentile
AGE (months)	12.3	10.9	18.0
CD4 (%)	16.8	15.4	19.1
CD4 (cells/µL)	1513	1337	2008
HIV RNA (log_{10}copies/ml)	5.13	5.01	5.60

- N= 13 (one set of twins)
- Male: 8 Female: 5
- Race: Black=13 (100%)
- Follow up (at time of data freeze) median = 24 weeks; IQR (19,32)
- 4th drug: All 13 received LPV/r

Intensive Pharmacokinetic Study Results (n=13)

Median Concentrations with 10th and 90th Percentiles



PK Targets	
GM AUC_{12h}	14-45 µMxh
GM C_{12h}	≥ 75 nM

Geometric Mean Values for Cohort		
GM AUC_{12h}	32.7 µMxh	CV=49%
GM C_{12h}	106 nM	CV=57%

CD4 Results

Week 8: Median CD4% and CD4 Change from Baseline

	Median	Q1, Q3
CD4 Count (µL^{-1})	105.5	-191, 755
CD4%	4.9	2.9, 6.05

HIV RNA Results

Week 8: HIV-1 Change from Baseline

At Week 8, 11/12 (92%, CI [62%, 100%]) of the participants met the primary virologic response criteria

- Median Change of -3.05 log_{10} IQR (-3.45,-2.63)
- 10/12 HIV RNA ≤400 copies/mL
- 2/12 (17%, CI [2%, 48%]) had a documented HIV viral load of < 50 copies/mL
- 3/12 children experienced virologic failure at or after 8 weeks
- 1/12 participant did not meet virological success criterion, despite acceptable RAL pharmacokinetic data.

Safety Results

- No participants had AE related to RAL, with no early treatment discontinuations due to RAL.
- Reasons for RAL Discontinuation included:
  - (1) Grade 3/4 Neutropenia, likely related to TB medications.
  - (1) Disallowed medication: Corticosteroids for > 7 days to treat possible nephritis
  - (1) AUC_{12hr} ≥ 63 µMxhr (discontinued at week 16)
  - (3) Virologic failure (discontinued at weeks 10, 12, 16)

Conclusions

- Doubling the dose of RAL for TB-HIV co-infected children 4 weeks to <2 years of age while taking rifampicin achieved adequate PK levels and was found to be safe.
- A dose of 12 mg/kg of the chewable formulation of RAL (crushed and dispersed in water) can be recommended for TB-HIV co-infected children taking rifampicin in this age group.
- Expanding options for infants and young children requiring simultaneous treatment for HIV treatment and tuberculosis is possible.

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