# Dolutegravir Pharmacokinetics During Standard- and High-Dose Rifampicin Among Children With TB/HIV

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**Holly Rawizza**[1,2], Regina Oladokun[3], Agnes-Jane Dike[4], Babatunde Ogunbosi[3], Gbemisola Olugbade[3], Phil Inga[4], Medrine Kihanga[1], Prosper Okonkwo[5], Phyllis Kanki[2], Paolo Denti[6], Helen McIlleron[6]

[1]Brigham and Women's Hospital, Boston, Massachusetts, USA, [2]Harvard T.H. Chan School of Public Health, Boston, Massachusetts, USA, [3]University of Ibadan, University College Hospital, Ibadan, Nigeria, [4]Federal Medical Centre in Makurdi, Nigeria, [5]AIDS Prevention Initiative Nigeria (APIN), Ltd., Abuja, Nigeria, [6]University of Cape Town, South Africa

## BACKGROUND

- Current WHO-recommended rifampicin (RIF) dosage results in inadequate concentrations in most children, but high-dose RIF (RIF-HD) may improve outcomes and shorten treatment duration.[1,2]
- The impact of RIF-HD on dolutegravir (DTG) exposures among young children is unknown.

## METHODS

- We designed an open-label, phase I/II pharmacokinetic (PK) and safety trial (NCT05069688) to evaluate steady-state DTG and RIF exposures among Nigerian children living with TB/HIV coinfection (4 weeks – 5 years) during standard-RIF (10-20 mg/kg) and RIF-HD.
- RIF-HD consisted of weight-banded dosing that approximates exposures in adults receiving 35 mg/kg (based on Opti-Rif trial [3]; Table 1).

**Table 1. WHO-recommended RIF dosing (10-20 mg/kg) and high-dose RIF (RIF-HD) needed to approximate adult RIF dose of 35 mg/kg**

| | Standard-RIF | | RIF-HD | |
|---|---|---|---|---|
| Weight band (kg) | Current WHO RIF dose (10-20 mg/kg) (mg) | RIF dose range (mg/kg) | RIF-HD equivalent to adult 35 mg/kg (mg)^ | RIF-HD dose range (mg/kg) |
| 4-7.99 | 75 | 9.4-18.8 | 4-6.99 kg: 450<br>7-7.99 kg: 600 | 64.4-112.5<br>75.1-85.7 |
| 8-11.99 | 150 | 12.5-18.8 | 750 | 62.5-93.8 |
| 12-15.99 | 225 | 14.1-18.8 | 900 | 56.3-75 |
| 16-24.99 | 300 | 12-18.8 | 1200 | 48-75 |

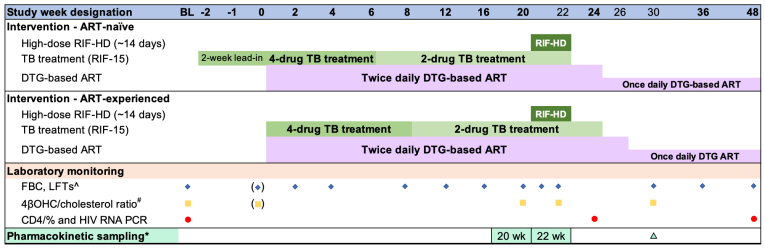
^Based on PK modeling from Opti-RIF.

- Children received weight-based DTG (twice daily) ART and standard TB therapy through week-20, after which additional RIF was given for two weeks to achieve steady-state RIF-HD (Figure 1).
- Intensive 24-hour PK sampling occurred at weeks 20 (standard-RIF) and 22 (RIF-HD).
- Primary PK targets include RIF peak serum concentration ($C_{max}$) >8 μg/mL and DTG trough concentration ($C_{trough}$) >0.32 μg/mL ($EC_{90}$).
- Safety monitoring occurred at 7 visits during standard-RIF and weekly visits during RIF-HD.

The current WHO-recommended dosage of rifampicin results in peak concentrations below optimal levels in most children. While high-dose rifampicin achieved target exposures in all participants, was not associated with liver toxicity or other serious adverse events, and did not reduce dolutegravir exposures.

## METHODS (cont.)

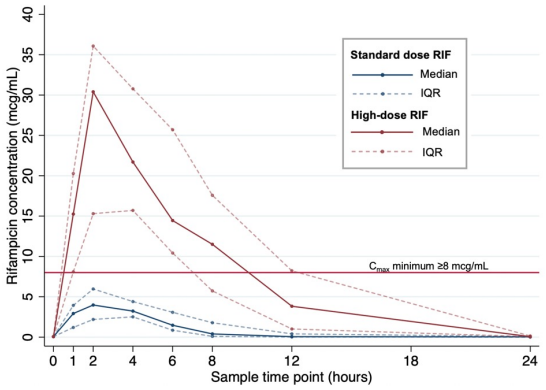
**Figure 1. Overview of treatment timing and PK sampling for DTG and RIF-HD study**




## RESULTS

- At interim analysis, 10 children (5 female) with median (range) age 3.5 (0.75-5) years and weight 10.8 (4.2-15.5) kg had complete PK visits at weeks 20 and 22.
- During standard-dose RIF (week 20), only one of 10 (10%) children had RIF $C_{max}$ above the therapeutic target.
- While during high-dose RIF (week 22), 100% achieved $C_{max}$ >8 μg/mL (Figure 2).
- Geometric mean (GM) RIF $C_{max}$ was 3.5 μg/mL and 30.4 μg/mL during standard and RIF-HD, respectively.

**Figure 2. Rifampicin concentration-time curves: Median (IQR) curves for standard versus high-dose RIF (n=10)**




## RESULTS (cont.)

- We observed no difference in DTG exposures during standard-RIF and RIF-HD, with GM DTG $C_{trough}$ of 1.7 and 2.1 μg/mL (all children had $C_{trough}$ >0.32 μg/mL), and $AUC_{0-12}$ of 46.6 and 46.7 μg·h/ml, respectively (Table 2).

**Table 2. DTG exposures during standard and RIF-HD**

| | PK week 20 (during RIF-15) | | PK week 22 (during RIF-HD) | |
|---|---|---|---|---|
| Patient ID | 12-hr AUC (mcg*h/mL) | $C_{12}$ (mcg/mL) | 12-hr AUC (mcg*h/mL) | $C_{12}$ (mcg/mL) |
| 1 | 56.3 | 2.57 | 59.3 | 2.36 |
| 2 | 48.9 | 2.4 | 55.4 | 3.87 |
| 3 | 49.1 | 1.3 | 12.5 | 6.54 |
| 4 | 44.3 | 1.02 | 65.7 | 1.79 |
| 5 | 70.9 | 2.72 | 103.4 | 6.08 |
| 6 | 36.6 | 1.56 | 38.3 | 0.678 |
| 7 | 43.8 | 2.34 | 48.4 | 1.39 |
| 8 | 39.7 | 1.21 | 47.3 | 1.5 |
| 9 | 42.7 | 2.71 | 46.6 | 1.16 |
| 10 | 42.1 | 0.873 | 43.7 | 1.07 |
| **Summary statistics** | | | | |
| GM | 46.6 | 1.7 | 46.7 | 2.0 |
| Median | 44.1 | 2.0 | 47.9 | 1.6 |

- Serious adverse events were uncommon; importantly, no elevations of alanine aminotransferase or aspartate aminotransferase were observed during 2-weeks of RIF-HD (no grade 1-4).

## CONCLUSIONS

- Most children did not achieve the minimum therapeutic $C_{max}$ target for rifampicin with standard weight-based dosing.
- High-dose RIF using weight-based dosing from the Opti-Rif trial achieved the target peak concentration in all children, without evidence of liver toxicity in this interim analysis.
- DTG exposures were unchanged during RIF-HD.

**References:** [1] Aruldhas BW *et al*. Br J Clin Pharmacol 2019; 85(3):644. [2] Boeree MJ *et al*. Lancet Infect Dis 2017; 17(1):39. [3] Garcia-Prats AJ *et al*. J Antimicrob Chemother 2021; 76(12):3237.

**Author Contact:** hrawizza@bwh.harvard.edu

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## PLAIN LANGUAGE SUMMARY

In this study, the current dosage of rifampicin used to treat TB in children fails to achieve optimal drug levels. A higher dose of rifampicin achieved the appropriate drug level in all children without any significant side effects.