PK and Safety of Twice Daily Dolutegravir in 3-20kg Children with HIV and TB on Rifampicin

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BACKGROUND

- Available data supporting global guidelines on the pharmacokinetics and safety of twice daily dolutegravir 10mg dispersible tablets (DT) in children 3-20kg with HIV and tuberculosis (TB) receiving rifampicin is scarce.
- We evaluated the pharmacokinetics and safety of twice-daily dolutegravir 10mg DT in children weighing 3-20kg on rifampicin.

METHODS

- We conducted an open-label, sequential non-randomised prospective study (**ORCHID**) in children initiated on a rifampicin-based TB regimen who concurrently received weight-based dosing of dolutegravir 10mg dispersible tablets twice daily (BD) during TB treatment and once daily (OD) after stopping rifampicin (NCT04746547).
- Serial plasma samples were collected at steady-state during and after TB treatment and assayed using a validated LC-MS/MS method.
- Non-compartmental pharmacokinetic (PK) analyses were conducted using the NCAPPC package in R. Participants underwent regular clinical, viral load and safety monitoring.

RESULTS

- We enrolled 21 children (3-20kg) between August 2023 and April 2025.
- Preliminary analysis of all data collected up to September 2025 showed a median (IQR) weight of 9.8 (7.5-11.3); age 2.0 (1.0-3.0); 48% males; 100% black race in this cohort.
- The median (IQR) viral load and CD4 at baseline were 3.2 (2.4-4.3) log10-copies/mL and 1161.0 (652.0-1495.0) cells/µl.
- Data from 19 children were included in the preliminary PK analysis, contributing 19 profiles for twice-daily dolutegravir plus rifampicin and 18 profiles for once-daily dolutegravir (total of 245 dolutegravir plasma concentration values)

Twice-daily DTG is safe for children (3-20kg) on rifampicin and provides drug levels comparable to standard once-daily dosing

Table 1: Dolutegravir pharmacokinetic parameters (geometric mean [%CV]) during and after TB treatment. Geometric mean ratio (GMR) for AUC0-24 and Ctau for 18 paired profiles

Parameter	DTG BID +RIF	DTG QD	GMR (90% CI)
$AUC_{0\text{-}24}$ (h*mg/L)	74.9 (96.1%)	81.0 (55.6%)	0.924 (0.688-1.24)
C_{tau} (mg/L)	1.31 (89.6%)	0.901 (91.3%)	1.41 (0.915-2.19)

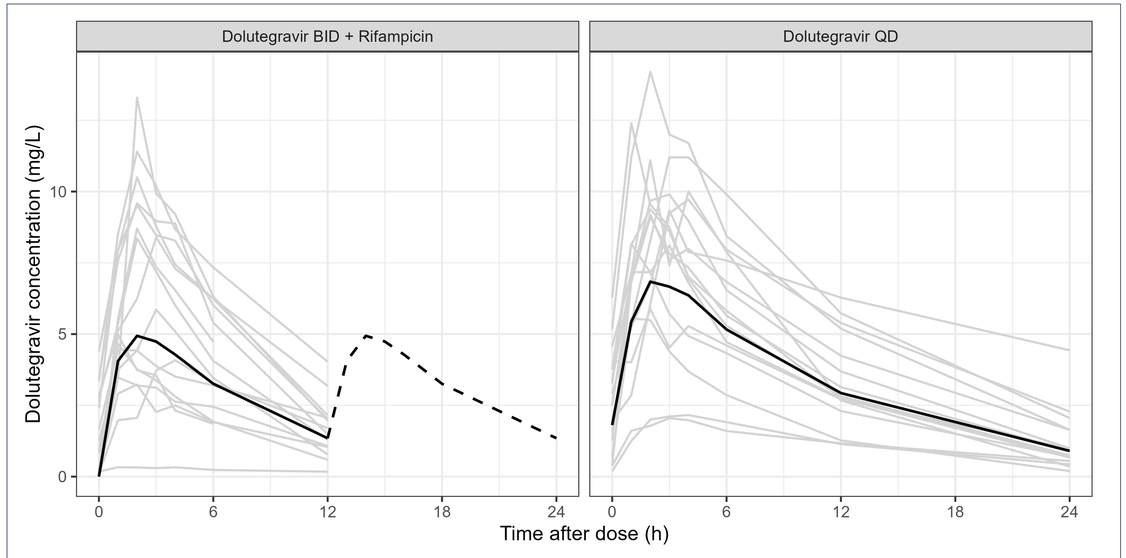


Figure 1: Dolutegravir 10mg DT plasma concentration-time profiles during and after TB treatment.

RESULTS continued

- Median trough concentration (CTau) was 1.31 and 0.901 mg/L, while AUC0-24 was 74.9 and 81.0 h*mg/L for participants on BID dolutegravir with rifampicin and OD dolutegravir, respectively, Table 1 & Figure 1.
- There were 14 grade 3 or higher adverse events and 9 SAEs, including one death, that were not related to study treatment.
- No treatment discontinuations due to AE's were observed. Viral load suppression (<50 copies/mL) was achieved in 73% of participants after six months of TB treatment.

CONCLUSIONS

Preliminary data from children weighing 3-20kg receiving twice-daily dolutegravir during TB treatment suggests that dosing strategy is safe and achieves PK values similar to those of daily dolutegravir without rifampicin. These findings support the WHO and global guideline recommendations for weight-based dolutegravir 10mg DT dosing in children 3-20kg.

Reference

[1]Acharya C, Hooker AC, Turkyilmaz GY, Jonsson S, Karlsson MO (2016). "A diagnostic tool for population models using non-compartmental analysis: The ncappc functionality for R." Computer Methods and Programs in Biomedicine, 127, 83-93.

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