Adequate dolutegravir exposure in infants on rifampicin treatment receiving twice-daily dolutegravir

#831

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BACKGROUND

- Dolutegravir (DTG) is recommended by WHO as first-line treatment option for children living with HIV.[1]
- Adapting the DTG dosing interval from once-daily (OD) to twice-daily (BID) during rifampicin-based TB treatment has been found to be safe and effective for both adults and older children.[2,3]
- No pharmacokinetic (PK) data is yet available for children weighing <14kg while the outcome of the rifampicin-DTG interaction may be different in infants as maturation of metabolic enzyme activity may not have been completed.

We evaluated plasma DTG pharmacokinetics in infants living with HIV receiving DTG BID with rifampicin-based TB-treatment.

METHODS

- This is a 2-arm pharmacokinetic sub-study of the EMPIRICAL randomized controlled trial (#NCT03915366) to evaluate whether empirical treatment against cytomegalovirus and tuberculosis improves survival of infants living with HIV and presenting with severe pneumonia.
- Eligible infants aged 1-12 months, weighing ≥3kg, receiving DTG OD (control) or DTG BID with rifampicin-based TB-treatment, were recruited in Mozambique, Uganda, Zambia, and Zimbabwe.
- Infants received DTG dispersible tablets following WHO weight-band dosing (3-6kg: 5mg; 6-10kg: 15mg).
- Six blood samples were taken over 12 (BID) or 24 (OD) hours, 30-90 days after start of rifampicin and at least 14 days after initiation of DTG.
- Relevant PK parameters were compared between study arms, and the proportion of infants with DTG C_{trough} below the clinical PK target (EC_{90}; 0.32 mg/L) and below the protein-adjusted 90% inhibitory concentration (IC_{90}: 0.064 mg/L) was reported.

- **Twice-daily dosing of dolutegravir in infants receiving rifampicin, following WHO weight-band dosing, resulted in adequate exposure to dolutegravir.**
- **These PK data support the use of twice daily dolutegravir for infants living with HIV receiving rifampicin-based TB treatment.**

RESULTS

- 27/30 included infants had evaluable PK curves; participant's demographics and combined PK parameters are shown in **Table 1**. Mean plasma concentration versus time profiles for both arms are shown in **Fig 1**.
- Only 1/21 infants in the RIF arm had DTG C_{trough} below the EC_{90} vs 0/6 in the control arm; none of the infants had DTG C_{trough} below the IC_{90}. Individual C_{trough} are shown in **Fig 2**.
- Apparent oral DTG clearance was 2-fold higher for infants receiving rifampicin. Geometric mean ratio (GMR) RIF arm versus control arm were 1.05 (90% CI 0.69 - 1.60) and 1.09 (90% CI 0.76 - 1.57) for C_{trough} and $AUC_{0\text{-}24h}$, respectively.

Fig 1. Geometric mean dolutegravir concentration-time profiles for infants receiving rifampicin *(the same curve included twice)* and the control arm.

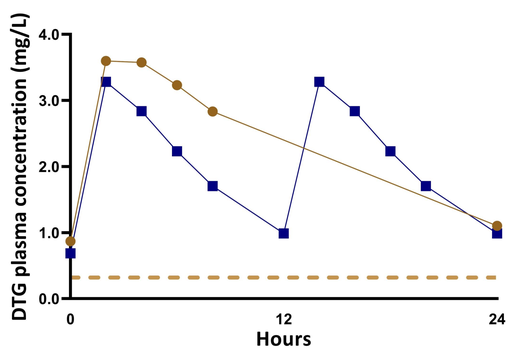

Fig 2. DTG trough concentrations in infants using DTG without RIF (control arm) or with rifampicin. Dots and squares in blue represent infants receiving 5mg (3-6kg WB) and those in red 15mg (6-10kg WB) DTG

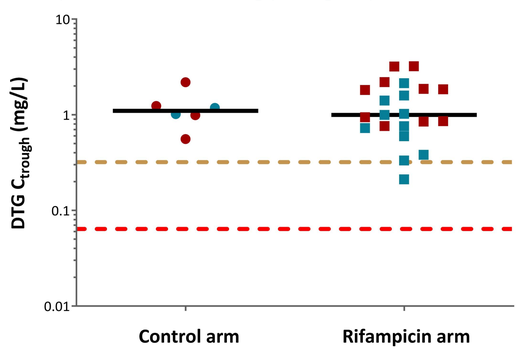

Table 2. Participant demographics and PK parameters per study arm.

Parameter		Control arm (n=6)	Rifampicin arm (n=21)
Male/Female		3/3	13/8
Weight (kg)		5.9 (5.8-8.0)	6.4 (4.9-7.1)
Weight-band	3-6kg	2	11
	6-10kg	4	10
Age (months)		7.4 (6.4-8.8)	6.6 (5.6-10.5)
DTG dose (mg/kg)		1.86 (1.09-2.36)	1.33 (1.00-2.08)
C_{trough} (mg/L)		1.11 (46)	1.05 (82)
$AUC_{0\text{-}24h}$ (h*mg/L)		54.4 (39)	49.7 (70)
C_{max} (mg/L)		3.86 (38)	3.36 (65)

Reported for demographics: median (IQR)
Reported for PK parameters: geometric mean (CV%)

CONCLUSIONS

- Consistent with data from older children and adults, twice-daily dosing of dolutegravir in infants receiving rifampicin, following WHO weight-band dosing, resulted in adequate exposure to dolutegravir.
- These PK data support the use of this dosing regimen in infants living with HIV and receiving rifampicin therapy.

REFERENCES

[1] WHO HIV treatment guidelines https://www.who.int/publications/i/item/9789240031593
[2] Dooley KE, et al. CID 2020
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ADDITIONAL KEY INFORMATION

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EDCTP
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