

A pooled population PK analysis investigating once-daily standard dosing of DTG in HIV/TB co-infected children weighing 3 kg or more.

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Introduction

- Dolutegravir (DTG) is a widely used integrase inhibitor (INSTI) for HIV treatment in adults and children
- Rifampicin, used for tuberculosis (TB) and other infections, induces UGT1A1 and CYP3A4, increasing DTG clearance and lowering plasma levels
- To overcome this, twice-daily (BID) dosing is recommended, but this may reduce adherence, especially in children
- In adults, once-daily (OD) DTG has shown non-inferior virological suppression compared to BID despite rifampicin co-treatment (Griesel et al., 2021)

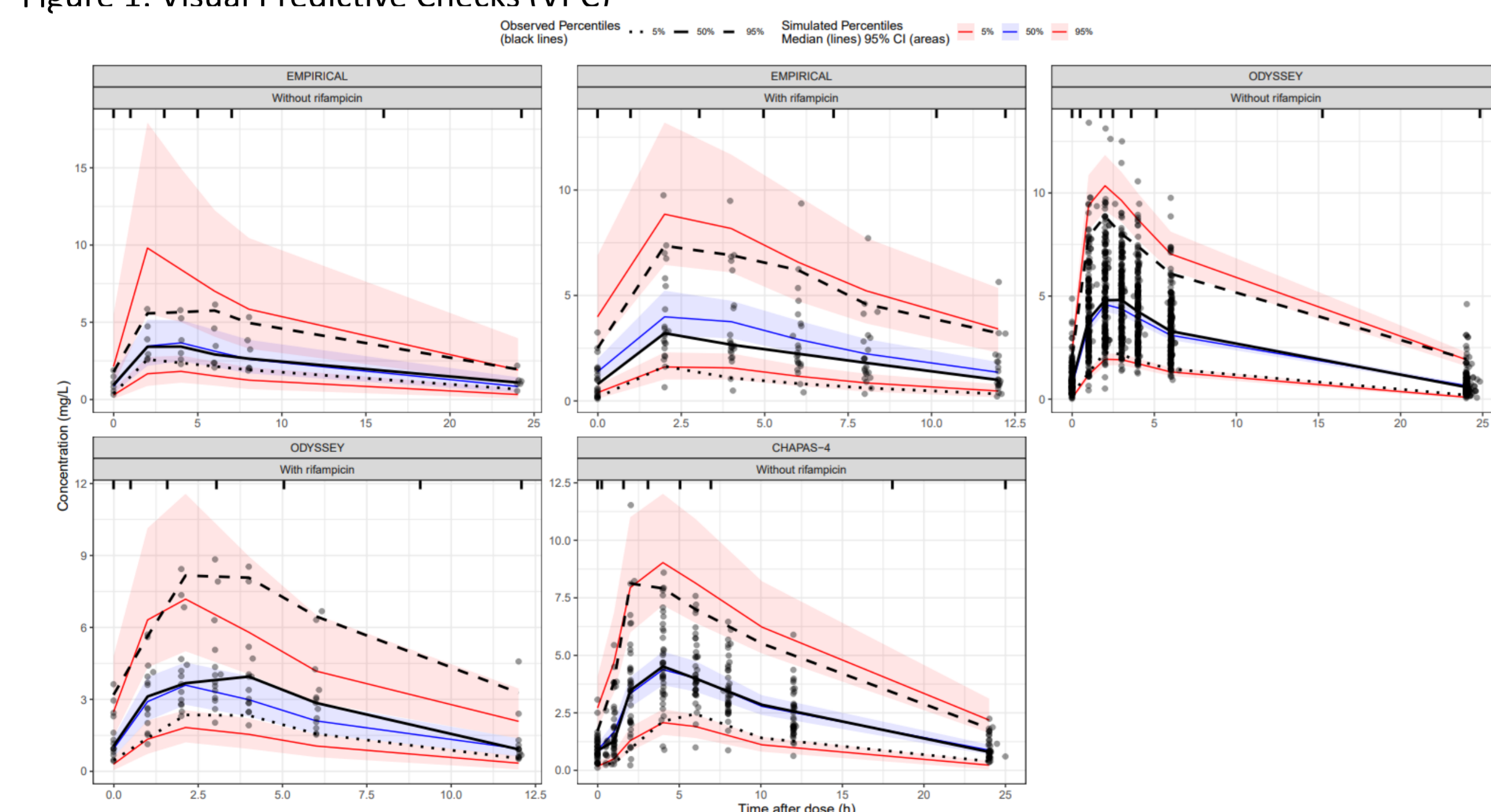
We pooled data from three paediatric trials to assess if OD DTG with rifampicin provides adequate exposure in children, and to identify key PK covariates

Methods

Population model developed using intensive PK data from ODYSSEY, CHAPAS4, and EMPIRICAL trials

- Parameters scaled **allometrically** to median weight (19.8 kg) with exponents of 0.75 for clearance, 1 for volume, and -0.25 for absorption rate constants.
- **Covariates assessed:** age, weight, food, formulation, NRTI backbone, and rifampicin coadministration
- Covariate confidence intervals estimated **via Sampling Importance Resampling (SIR)**
- Simulations in a virtual cohort of 7000 children (3-<40 kg; 1000 per weight band)
- **Primary endpoint:** % of children with DTG trough concentration \geq PA-IC90 (0.064 mg/L)

Figure 1: Visual Predictive Checks (VPC)



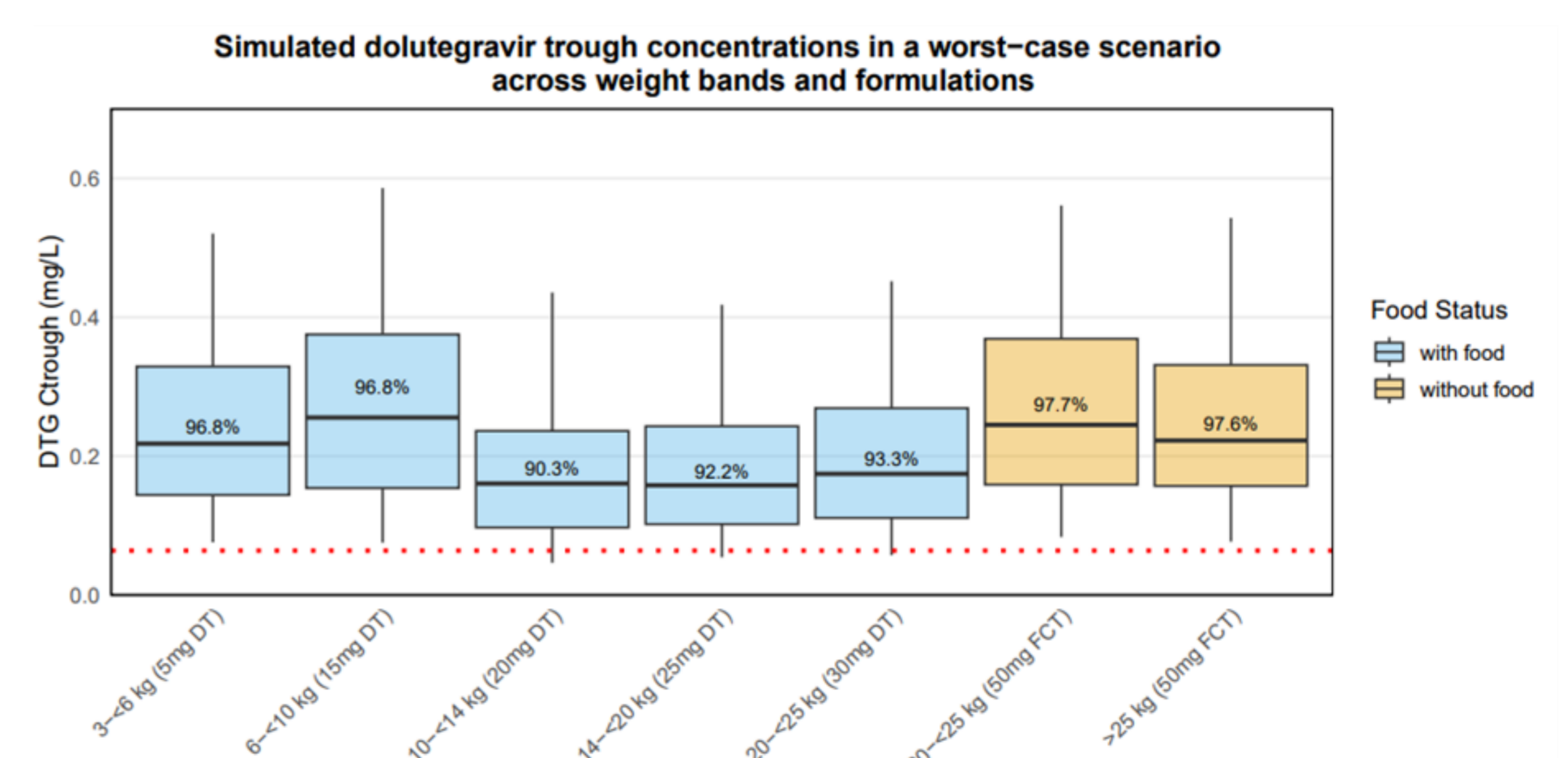
Results & Conclusion

- **Data:** 1942 DTG plasma concentrations from 235 children (3 months – 18 years), including 36 with rifampicin co-treatment.
- **Model:** Two-compartment model with first-order elimination and Erlang-type absorption
- **Clearance maturation:** Broken-stick model; full maturation is reached by 2.67 years.

Table 1: Parameter estimates of the final model and corresponding 95% CI

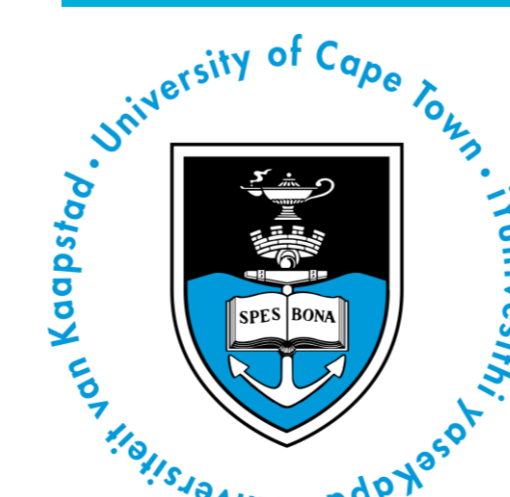
Component	Parameter	Parameter estimate (95% CI)
Fixed Effects	Clearance (CL, L/h)	0.705 (0.66-0.75)
	Rifampicin on CL	1.6 (1.4 – 1.8)
	Central volume of distribution (V1, L)	6.21 (5.81-6.67)
	Peripheral volume of distribution (V2, L)	1.67 (1.23-2.21)
	Intercompartmental clearance (Q, L/h)	0.265 (0.18-0.38)
	Absorption rate constant (KTR, 1/h)	3.12 (2.92-3.31)
	Number of transit compartments (NN)	2 FIX
	Food on KTR (vs. fasted)	0.466 (0.41-0.52)
	Bioavailability (BIO), relative to FCT fasted	1 FIX
	Food on BIO (FCT with food)	1.22 (1.05-1.37)
	Form on BIO (DT fasted)	1.47 (1.32-1.61)
	Food and form on BIO (DT with food)	1 FIX
	Maturation of CL	Fraction of adult CL at birth
Age at full maturation (y)		2.67 (2.66-2.68)
Inter-individual Variability (IIV)	CL (%)	21.1 (18.4-24.2)
	BIO (%)	25.2 (19.0-30.8)
	Extra IIV on unobserved concentrations (pre-dose)	1.57 (1.36-1.75)
	KTR (%)	26.2 (14.5-34.3)
Inter-occasion Variability (IOV)	BIO (CV%)	24.5 (19.6-29.6)
	KTR (CV%)	29.5 (22.2-36.7)
Residual Variability	Proportional error (%)	29.6 (27.4-31.6)
	Additive error (mg/L)	0.194 (0.162-0.229)

Figure 3: Boxplots of DTG C_{trough} following OD WHO-recommended dosing with rifampicin. Whiskers represent the 5th and 95th percentiles. The red dotted line indicates the PK target (0.064 mg/L). Percentages show the proportion of individuals in each weight band exceeding 0.064 mg/L. The worst-case scenario includes DT with food and FCT fasted, resulting in the lowest bioavailability.



- This pooled population pharmacokinetic analysis provided key insights into DTG metabolism in children, including effects of age related maturation, formulation, food, and rifampicin co-administration.
- Simulations showed OD standard dosing of DTG with rifampicin can achieve adequate exposure in children, supporting simplified, child-friendly HIV/TB treatment regimens

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