Pharmacokinetics of a Novel Dose Ratio of DTG/FTC/TAF for African Children with HIV (UNIVERSAL1)

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BACKGROUND

- A dispersible fixed dose combination (FDC) with dolutegravir (DTG), emtricitabine (FTC) and tenofovir alafenamide fumarate (TAF) for treatment of ART naïve and experienced children living with HIV was marked as a priority for development by the WHO-led Paediatric Antiretroviral Drug Optimization group.
- A novel dose ratio was identified for development of a pediatric DTG/FTC/TAF FDC tablet that can be used in children across WHO-weight bands (WB). The proposed FTC/TAF dose ratio differed from approved doses.
- The aim of the UNIVERSAL1 (#NCT05993767) was to confirm if the proposed doses achieved safe and effective exposures within each of the WHO WBs.

PARTICIPANTS AND METHODS

Inclusion

- Participants 3-<25 kg and 4 weeks-<10 years were enrolled.
- Children were dosed DTG and FTC/TAF as separate formulations, but in the same doses as proposed for the dispersible FDC, by weight band (WB) (Table 1).

Pharmacokinetics

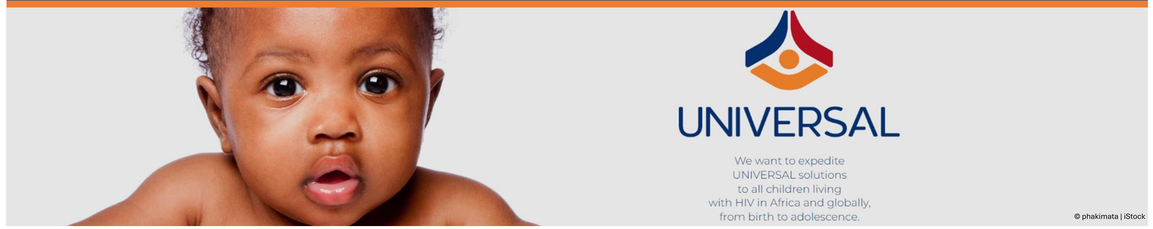
- Seven blood samples were taken at steady-state after a standardized breakfast or breastfeeding at t=0 (pre-dose), 0.5, 1, 2, 4, 6, and 24 hours post-dose.
- Pharmacokinetic (PK) parameters for DTG, FTC, TAF, and TFV (non-compartmental analysis) were compared with values from the pediatric CHAPAS-4[1] trial and adult[2,3] trials.
- The number of children with DTG C_{trough} below 0.32 mg/L (EC_{90}), with TAF AUC_{last} below 55 h*ng/mL (value found to have near-maximal TAF antiviral activity and similar antiviral activity to tenofovir disoproxil (TDF) 300 mg), and with TFV $AUC_{0\text{-}24h}$ above 2586 h*ng/mL (mean value observed in children taking 8 mg/kg TDF) were reported.

Table 1. DTG and FTC/TAF dosing recommendations per WB

WB (kg)	DTG dose	FTC/TAF dose	Proposed dose DT DTG/FTC/TAF FDC
3-<6 kg	5 mg DT QD	15/1.88 mg TOS QD	**5/15/1.88 mg QD** (1 tablet)
6-<10 kg	15 mg DT QD +10 mg	30/3.75 mg TOS QD X 2	**15/45/5.64 mg QD** (3 tablets)
10-<14 kg	20 mg DT QD +5 mg	60/7.5 mg TOS QD X 2	**20/60/7.52 mg QD** (4 tablets)
14-<20 kg	25 mg DT QD +5 mg	120/15 mg TOS QD X 2 120/15 mg FCT QD	**25/75/9.4 mg QD** (5 tablets)
	DTG dose	**FTC/TAF dose**	**Proposed dose FCT DTG/FTC/TAF FDC**
20-<25 kg	50 mg FCT QD or 30 mg DT QD	120/15 mg FCT QD	**50/200/25 mg QD** (1 tablet)

Dosing recommendations of DTG and FTC/TAF from the WHO and US FDA are shown in black, and recommendations from the innovator are shown in grey. FCT = film-coated tablet

Pharmacokinetics and safety of DTG, FTC, TAF and TFV in children with HIV treated with a novel dose ratio were adequate across WHO weight bands, supporting the dispersible pediatric FDC (DTG/FTC/TAF 5/15/1.88 mg) under development for children weighing 3-<20 kg, and the extension of the adult DTG/FTC/TAF (50/200/25 mg) tablet down to 20 kg.



RESULTS

- DTG PK parameters ($AUC_{0\text{-}24h}$, C_{trough}, C_{max}) were overall higher than observed in CHAPAS-4[1] (Table 2), however $AUC_{0\text{-}24h}$ values were comparable to PK data of DTG once and twice daily in adults[2] (Figure 1). No child had DTG C_{trough} below the EC_{90} of 0.32 mg/L. FTC PK parameters were overall comparable to adult data[3]. As expected, FTC $AUC_{0\text{-}24h}$ was higher in children weighing 20-<25 kg (Table 2, Figure 1).
- PK parameters of TAF and TFV varied across WBs (Figure 1), three children had a TAF AUC_{last} below 55 ng*h/mL and no TFV $AUC_{0\text{-}24h}$ were above 2590 ng*h/mL (Figure 1)

[1]Bevers et al. (2023), [2]US FDA Tivicay [package insert] (2013), [3]US FDA Emtriva [package insert] (2003)

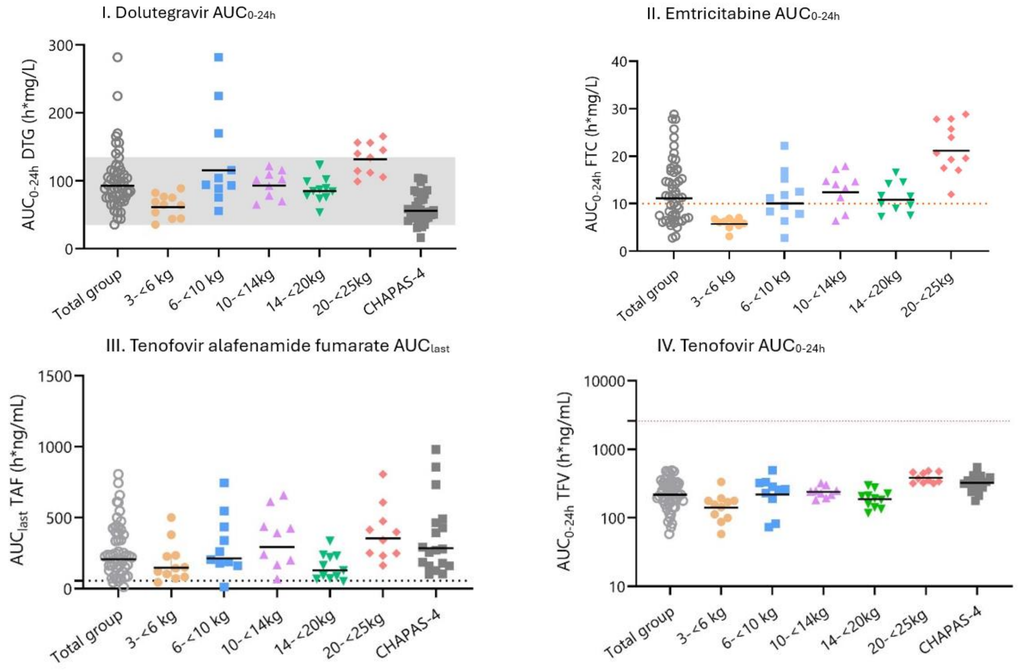


Figure 1. Individual DTG, FTC, TAF and TFV PK parameters compared with historical data.
*Solid lines indicate the geometric means. (I) Grey shading indicates the lower and upper bound of the 90% CI for geometric mean exposure associated with DTG once and twice daily in adults (37-134 h*mg/L). (II) The orange dotted line indicates the mean FTC AUC0-24h in adults taking FTC 200 mg OD. (III) The black dotted line represents the TAF AUC_{last} of 55 h*ng/mL.[4] (IV) The red dotted line represents the TFV $AUC_{0\text{-}24h}$ of 2586 h*ng/mL.[5] [4]US FDA Descovy [package insert]. (2016), [5]Saez-Llorens et al. (2015)*

- Inclusion number per WB: 3-<6 kg: 11; 6-<10 kg: 10; 10-<14 kg: 11; 14-<20 kg 11; 20-<25 kg: 10
- 51/53 children* who completed a PK visit were included in the PK analysis. Median (range) age and weight were 3.2 years (0.2-8.7) and 12.1 kg (4.4-22.6).

*Two exclusions from PK analysis: breakfast >30 min from dose (n=1); prior dose >28 h before PK day (n=1)

Table 2. Primary PK outcomes for DTG, FTC, TAF, TFV

	Total group UNIVERSAL1	Reference data
DTG		**CHAPAS-4**
$AUC_{0\text{-}24h}$ (h*mg/L)	93.1 (41)	57.1 (38)
C_{trough} (mg/L)	1.7 (55)	0.8 (64)
C_{max} (mg/L)	7.2 (44)	5.0 (42)
FTC		**Adults**
$AUC_{0\text{-}24h}$ (h*mg/L)	11.1 (60)	10.0 (3.1)
C_{trough} (mg/L)	0.06 (46)	0.09
C_{max} (mg/L)	1.6 (63)	1.8 (0.7)
TAF		**CHAPAS-4**
AUC_{last} (h*ng/mL)	207.1 (101)	285 (79)
C_{last} (ng/mL)	6.9 (180)	
C_{max} (ng/mL)	125.2 (114)	145 (91)
TFV		**CHAPAS-4**
$AUC_{0\text{-}24h}$ (h*ng/mL)	219.0 (53)	324 (29)
C_{trough} (ng/mL)	6.9 (66)	11.0 (35)
C_{max} (ng/mL)	14.4 (50)	19.6 (26)

UNIVERSAL1 and CHAPAS-4 (DTG substudy) data (children weighing ≥14 kg) are presented as geometric mean (percentage of coefficient variation). FDA registration data of FTC from adults are presented as mean values (standard deviation).

PLAIN LANGUAGE SUMMARY

This data supports a novel dose ratio of DTG/FTC/TAF for treatment of children living with HIV. This represents an important step toward harmonizing HIV treatment across pediatric and adult populations and closing the treatment gap.

Efficacy data are pending and will be reported when available.

FUNDING

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