Pharmacokinetics of once-daily DTG/3TC FDC in children living with HIV: D3/PENTA21 sub-study

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BACKGROUND

- There is an increasing emphasis on reducing toxicity and improving acceptability of HIV-1 treatment.
- Two-drug regimens are recommended as an alternative to standard three-drug regimens in adults.
- The two-drug regimen with dolutegravir and lamivudine (DTG/3TC) is included in a number of adult treatment guidelines.
- This pharmacokinetic (PK) sub-study nested within the D3/Penta21 randomized controlled trial (#NCT04337450) aims to evaluate pharmacokinetics, safety and tolerability of new fixed-dose DTG/3TC combinations (dispersible tablets (DT) and adult film-coated tablets (FCT)) in children weighing <40 kg using WHO weight band-aligned dosing.

PARTICIPANTS AND METHODS

PK substudy inclusion

- Participants weighing 10-<40 kg in the DTG/3TC arm of the D3 trial (fig 1) at PK sites in Uganda and South Africa were enrolled.
- Children were dosed once-daily by weight band (WB): 10-<14 kg (20/120mg DT); 14-<20 kg (25/150mg DT); 20-<25 kg (30/180mg DT or 50/300 FCT); 25-<40 kg (50/300mg FCT).
- We aimed for at least 8 evaluable PK curves per weight band/formulation.

Pharmacokinetics

- Seven blood samples were taken at steady-state after an overnight fast at time=0, and 1, 2, 3, 4, 6 and 24 hours post dosing.
- PK parameters for DTG and 3TC (non-compartmental analysis) were compared with DTG in ODYSSEY and 3TC in IMPAACT 2019 studies.
- The number of children with DTG C_{trough} below EC90 (0.32 mg/L) and PA-IC90 (0.064 mg/L) were summarized.
- For DTG C_{trough} levels are correlated with efficacy; for 3TC we use $AUC_{0\text{-}24h}$ to assess exposures.

Safety analysis

- Serious adverse events (SAEs), adverse events (AEs) of grade 3 or above and ART-modifying AEs of any grade to end of week 24 visit window (210 days) from first DTG/3TC dose were analyzed in all PK participants.

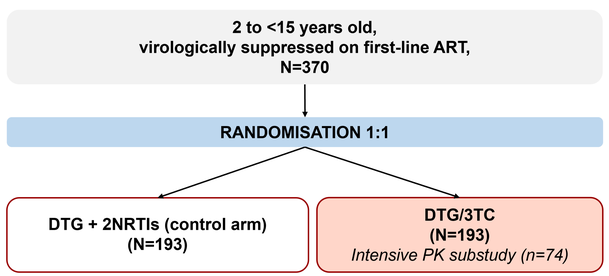

Figure 1: Flowchart of D3/Penta21 trial

DTG and 3TC PK concentrations in virologically suppressed children living with HIV, weighing 10 to <40kg, who were switched to dual DTG/3TC FDC tablets were comparable with PK results from previous paediatric studies.

For ART simplification we investigated the adult 3TC dose (300mg) for children weighing 20-<25 kg using single film-coated tablets; as expected 3TC exposures were higher on this dose/formulation than using lower dose dispersible tablets (180mg).

Safety data across all weight bands raised no concerns.

RESULTS

- 73/74 children who had a PK visit had an evaluable PK curve; median weight 21.6 kg (IQR 17.0-24.4); median age 7.1 years (IQR 5.2-10.0); 62 (85%) from Uganda and 11 (15%) from South Africa.
- PK parameters $AUC_{0\text{-}24h}$, C_{trough}, C_{max} and $T_{1/2}$ for DTG (table 1) and 3TC (table 2) were comparable to parameters from two representative studies (DTG C_{trough} shown for ODYSSEY[1] and 3TC $AUC_{0\text{-}24h}$ for IMPAACT2019[2]). Geometric means (GM) for each WB were within recommended GM ranges used previously for regulatory approvals in paediatrics (for Tivicay & Triumeq): DTG GM C_{trough} range 0.67 to 2.97 mg/L; 3TC GM $AUC_{0\text{-}24h}$ range 6.3 to 26.5 h*mg/L.
- 3/73 children had DTG C_{trough} level below EC90 (0.32 mg/L): one (0.26 mg/L) in the 10-<14 kg WB (20 mg DT DTG); two (0.25 and 0.30 mg/L) in the 25-<40 kg WB (50 mg FCT DTG). All children had C_{trough} above PA-IC90 (fig 2).
- In the 20-<25kg WB, 3TC AUC0-24h GM was 1.5 times higher in children receiving the adult 50/300mg FCT versus 30/180mg DT (fig 3).
- Over 24 weeks from first DTG/3TC dose, 2/74 children (both in 14-<20kg WB at the time of event) experienced an AE of grade 3 or above (cerebral malaria, grade 4 SAE; diarrhoea, grade 3 AE); both events were judged unrelated to ART and resolved with no treatment change. There were no other SAEs and no AEs that led to ART modifications.

[1] Bollen PDJ et al. (2020); Waalewijn H et al. (2022) & [2] Brooks KM et al. (2023)

Table 1: DTG PK parameters by WB in D3

	N	$AUC_{0\text{-}24h}$ (h*mg/L)	C_{trough} (mg/L)	ODYSSEY C_{trough} (mg/L)	C_{max} (mg/L)	$T_{1/2}$ (h)
10 kg - <14 kg (20 mg DT) ‡	10	61.65 (40)	**0.74 (64)**	**0.77 (57)**	6.38 (30)	7.71 (16)
14 kg - <20 kg (25 mg DT)	17	63.40 (30)	**0.70 (42)**	**0.87 (64)**	6.68 (28)	7.27 (15)
20 kg - <25 kg (30 mg DT)	14	68.93 (32)	**0.94 (38)**	**0.76 (73)**	6.59 (45)	9.54 (72)
20 kg - <25 kg (50 mg FCT)	14	72.95 (35)	**0.90 (66)**	**0.75 (44)**	6.95 (28)	7.65 (23)
25 kg - <40 kg (50 mg FCT)	18	65.75 (40)	**0.84 (61)**	**25-< 30 kg: 0.77 (43) 30-<40 kg: 0.63 (49)**	6.10 (33)	7.89 (17)
Total	**73**	**66.52 (35)**	**0.82 (54)**	**0.77[§]**	**6.52 (33)**	**7.95 (33)**

Table 2: 3TC PK parameters by WB in D3

	N	$AUC_{0\text{-}24h}$ (h*mg/L)	IMPAACT 2019 $AUC_{0\text{-}24h}$ (h*mg/L)	C_{trough} (mg/L)	C_{max} (mg/L)	$T_{1/2}$ (h)
10 kg - <14 kg (120 mg DT) ‡	10	**12.29 (28)**	**14.20 (24)**	0.06 (23)	2.88 (30)	5.22 (18)
14 kg - <20 kg (150 mg DT)	17	**13.51 (31)**	**13.00 (16)**	0.05 (35)	2.93 (39)	4.69 (17)
20 kg - <25 kg (180 mg DT)	14	**13.56 (64)**	**14.50 (17)**	0.06 (23)	2.81 (91)	6.01 (156)
20 kg - <25 kg (300 mg FCT)	14	**23.20 (29)**	**-**	0.07 (40)	4.76 (24)	4.24 (14)
25 kg - <40 kg (300 mg FCT)	18	**19.92 (27)**	**21.70 (26)**	0.07 (45)	3.37 (31)	4.22 (12)
Total	**73**	**16.29 (45)**	**15.5[§]**	**0.06 (37)**	**3.30 (50)**	**4.78 (55)**

Data in Table 1 and 2 are presented as geometric mean (percentage of coefficient variation).
‡ One participant was 14.1 kg on PK day and was dosed according to 10-<14kg WB. [§]Pooled across WBs.

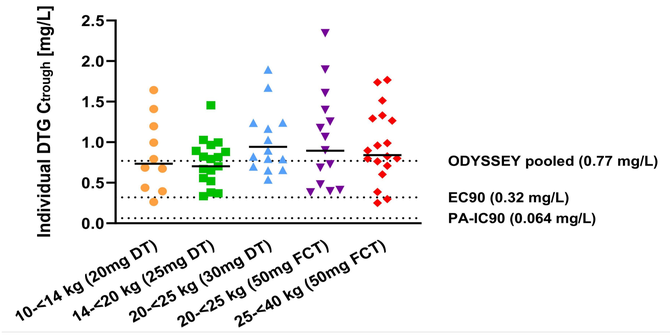

Figure 2: Individual DTG C_{trough} levels within D3 by WB

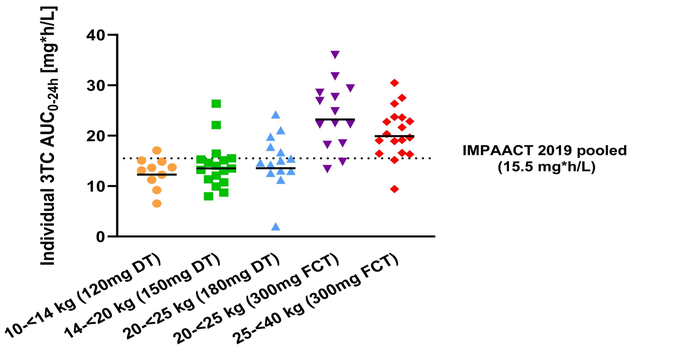

Figure 3: Individual 3TC $AUC_{0\text{-}24h}$ levels within D3 by WB

Horizontal black lines represent GM Ctrough (DTG)/AUC0-24h (3TC) levels per WB

CONCLUSIONS

- DTG PK concentrations and parameters were comparable to those seen in ODYSSEY (children on 3-drug DTG-based ART), with DTG GM Ctrough within recommended GM range for each WB after switch to DTG/3TC FDC in virologically suppressed children in D3.
- 3TC PK concentrations and parameters in D3 were comparable to those seen in the IMPAACT2019 paediatric study comparing with those in the same WBs receiving the same doses and formulations, and 3TC GMs AUC0-24h were within recommended GM range for each WB.
- The higher adult 3TC dose (300 mg) in children on FCT in the 20-<25kg WB led to higher 3TC exposures compared with children on dispersible tablets (180 mg) in the 20-<25kg WB in D3 and IMPAACT 2019.
- Safety data across the weight bands raised no concerns. Overall, no new safety issues were identified in children and adolescents in this study.

FUNDING

- The D3 trial is sponsored by Fondazione Penta Onlus (Penta) and funded by ViiV Healthcare

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