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Background

- ODYSSEY (*ClinicalTrials.gov*; NCT02259127) is an ongoing international randomised trial evaluating dolutegravir (DTG)-based antiretroviral therapy (ART) versus standard-of-care in HIV-infected children starting first- or second-line ART.
- Pediatric DTG film-coated tablets (FCTs) of 10mg and 25mg are unavailable in low- and middle income countries (LMIC) where most HIV-infected children live.
- Adult DTG 50mg FCTs are produced by generic manufacturers at low-cost, are well-tolerated, and already available in many high- and LMICs.
- Within ODYSSEY pharmacokinetic (PK) substudies were undertaken to assess PK and safety data for a simplified paediatric DTG dosing approach using WHO weightbands 25 to <30kg and 30 to <40kg and once daily 50mg adult DTG doses.

Aims

- To compare DTG PK parameters in children to historical PK parameters achieved in HIV-positive adults, taking DTG 50mg film-coated tablets once daily [1] and twice-daily [2], as this is the highest approved dose that has a reassuring safety profile.
- Additionally, we considered the proportion of individuals with C_{trough} levels <0.32 mg/L, which equals the dolutegravir in vivo EC_{90} , the effective concentration at which 90% of maximal viral inhibition is achieved.

Methods

- This was a within-subject, 2-period, fixed-order PK study conducted in four ODYSSEY sites in Uganda and Zimbabwe. The PK study was approved by local ethics committees. Informed consent was obtained for all children.
- A child first completed 24 hours intensive PK sampling after observed intake of the stringent regulatory approved (SRA) paediatric dolutegravir dose of 25mg FCT in weightband 25 to <30 kg or 35mg (one 10mg and one 25mg FCT) in weightband 30 to <40 kg under steady-state conditions. A second 24 hours PK profile was taken at least one week after switch to a daily 50mg FCT.
- DTG plasma concentrations were measured using a validated UPLC-MS/MS method with a lower limit of quantification of 0.01 mg/L. Non-compartmental PK analysis was performed to determine and calculate PK parameters with Phoenix WinNonlin 64 (version 8.1) software.
- Laboratory and clinical safety were evaluated at 2, 4 and 12 weeks, and then every 12 weeks. Adverse events up to 30 weeks are reported.

Table 1. Patient demographics at time of dose initiation.

WHO weight band	25 to <30kg, n=17		30 to <40kg, n=11	
Sex male	13 (76%)		4 (36%)	
Dose (mg)	25	50	35	50
Age (years)	10.4 (7.2-15.4)	10.7 (7.5-15.9)	10.9 (9.8-17.7)	11.3 (9.8-17.8)
Weight (kg)	26.4 (25.0-28.4)	27.4 (25.0-30.7)	30.2 (28.5-37.6)	31.0 (29.9-38.7)

Table entries are n(%) or median (range).

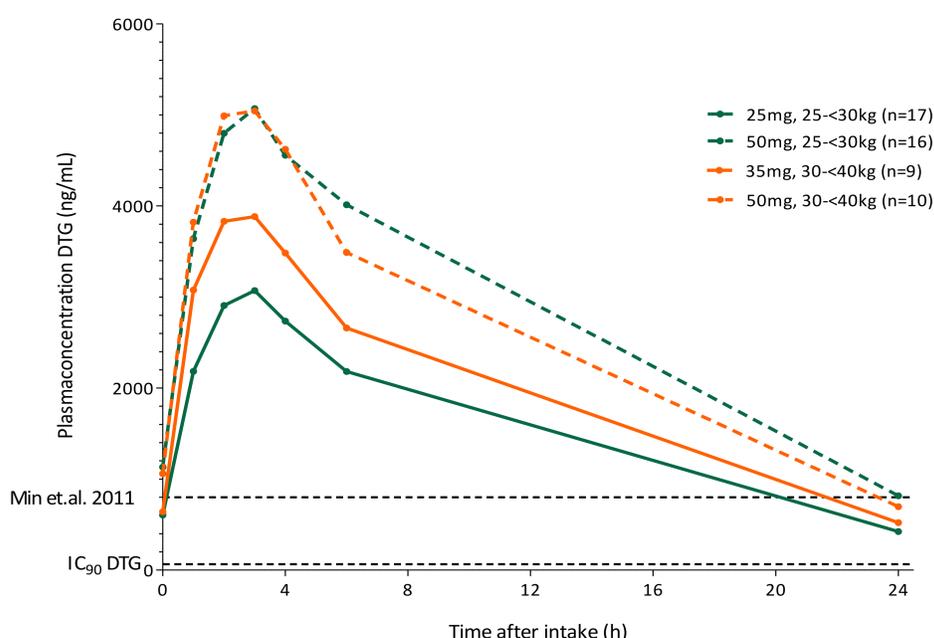


Figure 1. Mean plasma concentration versus time profile per weight band. Dotted lines indicate 50mg FCT.

Results I

Demographics

- This PK substudy included 28 black-African children from Uganda and Zimbabwe in the PK and safety analysis (Table 1).

Table 2. Main PK parameters for DTG in the ODYSSEY PK substudy and published reference PK parameters in adults.

	ODYSSEY PK study				Reference adults	
	25 to <30 kg	30 to <40 kg	30 to <40 kg	30 to <40 kg	≥ 40 kg [1]	>40 kg [2]
WHO weightband	25 to <30 kg	30 to <40 kg	30 to <40 kg	30 to <40 kg	≥ 40 kg [1]	>40 kg [2]
N	17	16	9	10	10	24
Dose (mg)	25	50	35	50	50	50 BID
Dose (mg/kg)	0.9 (0.8-1.0)	1.8 (1.6-2.0)	1.1 (0.9-1.2)	1.6 (1.3-1.7)	-	-
C_{trough} (mg/L)	0.39 (48)	0.77 (43)	0.46 (63)	0.63 (49)	0.83 (26)	2.72 (70)
N (%) below EC_{90}	5 (29%)	0 (0%)	3 (33%)	0 (0%)	-	-
AUC_{0-24h} (mg*h/L)	33.1 (23)	58.6 (28)	40.3 (35)	53.5 (32)	43.4 (20)	93.4 (50)
C_{max} (mg/L)	3.16 (24)	5.41 (25)	3.98 (28)	5.22 (25)	3.34 (16)	5.41 (40)

Pharmacokinetic parameters are expressed as geometric mean with coefficient of variation (%). Dose (mg/kg) is expressed as mean (range). Doses represent once daily doses unless otherwise indicated.

Results II

Pharmacokinetics

- On once daily SRA-doses in children 25 to <30 kg (25mg) and 30 to <40 kg (35mg) geometric mean (GM, with coefficient of variation; CV%) $C_{troughs}$ were 0.39 (48), and 0.46 (63) mg/L, respectively; 54% and 45% below adult GM C_{trough} (Table 2).
- On 50mg FCT C_{trough} was close to the adult reference, with total exposure (AUC_{0-24h}) in between reference values in adults dosed once and twice-daily, where safety data are reassuring. Additionally, no child had a C_{trough} below the dolutegravir EC_{90} (Table 2).

Safety data

- After follow-up of 24 weeks on the 50mg FCT dose, there were 3 reportable adverse events. These included one serious adverse event (SAE), which was cryptococcal meningitis (WHO stage 4/DAIDS grade 4), one asymptomatic anaemia (grade 3 laboratory event) and one asymptomatic neutropenia (grade 3 laboratory event).
- None of the adverse events were considered by the reporting clinician and endpoint review committee to be related to dolutegravir exposure and no events resulted in modification of ART.

Conclusions

The results of this PK study will allow implementation of simplified and readily available dolutegravir-based ART for children ≥ 25 kg using adult tablets. This will enable alignment with adult WHO-preferred ART regimens in LMIC. WHO has released new pediatric dosing guidelines in response to these results.

References

- [1] Min et al. AIDS 2011; 25(14):1737-45.
 [2] ViiV Healthcare. A Pilot Study Assessing the Integrase Inhibitor GSK1349572 in HIV-infected Persons With Virus Resistant to Raltegravir. Study Results. 2013. <https://clinicaltrials.gov/ct2/show/results/NCT00950859?term=dolutegravir&recrs=e&cond=Hiv&outc=AUC&age=1&draw=4&rank=30>.

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<https://www.eahp.eu/25-NP-003>

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