

PK and Safety of Chronic Dolutegravir Administration in Neonates Exposed to HIV-1

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BACKGROUND

- Dolutegravir (DTG) is approved for treatment of HIV-1 in adults and pediatric patients ≥ 4 weeks and ≥ 3 kg.
- We previously reported the pharmacokinetics (PK) and safety of two single doses of DTG (0.5 mg/kg administered as liquid suspension) given with standard of care antiretrovirals in the first 15 days of life among neonates exposed to HIV-1 in utero.¹
- Here, we describe preliminary PK and safety of 4-6 weeks DTG dosing using a 5-mg dispersible tablet (DT) formulation in neonates exposed to HIV-1.

METHODS

- IMPAACT 2023 is a PK, safety, and tolerability study of DTG in singleton full-term (≥ 37 weeks gestation at birth) HIV-1 exposed infants during the first 4-6 weeks of life.
- In this cohort, DTG 5 mg DT was dosed every other day until day 14 of life, followed by once daily dosing.
- Infants received their first DTG dose between 0-5 days of life.
- DTG-exposed infants were defined as those with *in utero* exposure to maternal DTG and DTG-naïve infants were defined as those without *in utero* exposure to maternal DTG.
- Intensive PK sampling was performed at 7 Days after DTG initiation and Week 4 of life.
- Adverse events (AEs) were graded using the DAIDS AE Grading Table.
- DTG exposures were evaluated according to protocol-defined target geometric mean (GM) exposures: $C_{trough} > 0.697$ $\mu\text{g/mL}$, $AUC_{0-24} > 37$ $\mu\text{g}\cdot\text{h/mL}$, and $C_{max} < 18.35$ $\mu\text{g/mL}$.
- Tolerability information was collected using a questionnaire administered to caregivers.

Table 1. Participant Baseline Characteristics

	DTG-naïve	DTG-exposed	Total
	N=7	N=11	N=18
Age at First Dose (days)	3 (0-5)	4 (1-5)	3 (0-5)
Female Sex (%)	71%	73%	72%
Gestational Age (weeks)	39.1 (38.3-39.7)	39.1 (37-42)	39.1 (37-42)
Weight (kg)	3.02 (2.68-3.63)	3.11 (2.36-3.63)	3.09 (2.36-3.63)
Breastfeeding at Entry (%)	1 (14%)	8 (73%)	9 (50%)

Data presented as median (min-max) except sex and breastfeeding at entry (%).
1. Includes already breastfeeding and planning to breastfeed

Use of DTG 5-mg dispersible tablet (every other day for two weeks until day 14 of life, followed by once daily dosing) for 4-6 weeks was well-tolerated with no unexpected AEs in neonates exposed to HIV-1.

RESULTS

- Data were available from 11 infants with maternal DTG use (DTG-exposed) and 7 DTG-naïve infants with birthweights between 2.36 – 3.63 kg and postnatal age 0 – 5 days at time of first DTG dose. Participant demographic characteristics are shown in Table 1.
- Participants were enrolled from South Africa (n=9), Thailand (n=5), and USA (n=4)
- Standard-of-care antiretroviral prophylaxis included either a single regimen of nevirapine or zidovudine, or multi-drug regimens of zidovudine and/or lamivudine, generally in combination with nevirapine.
- No clinically meaningful differences were observed in DTG exposures between DTG-exposed and DTG-naïve infants and PK results for each group were combined.
- At the 7 days post-initial dose PK visit, 15 participants received every other day DTG dosing and 3 participants received once daily DTG dosing.
- PK results are displayed in Figure 1 and Table 2.
- Five of 18 participants had trough concentrations below the target at 7 days post-initial dose while only 1 of 18 participants had a trough concentration below the target at Week 4.
- No neonates experienced $\geq$ grade 3 AEs related to study drug.

Figure 1. DTG concentrations at 7 days post-initial dose (a) and 4 weeks (b) in neonates exposed to HIV-1. Yellow squares, DTG-exposed infants (n=11). Purple triangles, DTG-naïve infants (n=7). Solid lines represent median concentrations. Horizontal dotted line displays minimum target concentration (0.697 $\mu\text{g/mL}$).

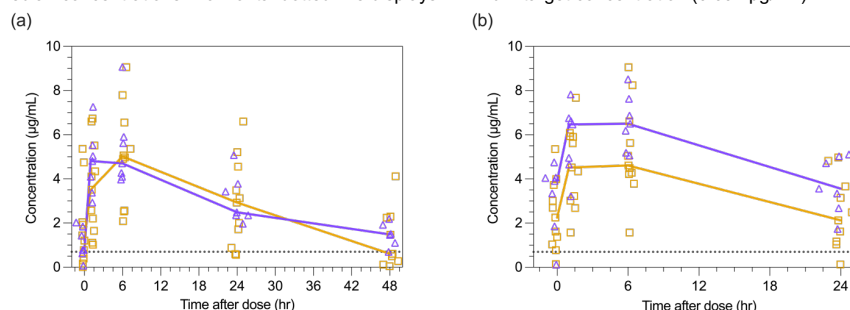


Table 2. Pharmacokinetic results

	C_{trough}	AUC_{0-24}	C_{max}
	$\mu\text{g/mL}$	$\mu\text{g}\cdot\text{h/mL}$	$\mu\text{g/mL}$
7 days post-initial dose (participants receiving Q48h dosing at time of PK sampling) (n=15)	0.87 (0.05 – 4.12)	129.6 (42.0 – 321.9)	4.9 (2.1 – 9.1)
7 days post-initial dose (participants receiving Q24h dosing at time of PK sampling) (n=3)	2.95 (2.36 – 3.49)	91.7 (75.9 – 108.8)	4.8 (4.0 – 5.5)
Week 4 (n=18)	2.31 (0.13 – 5.11)	98.6 (24.0 – 158.5)	5.5 (1.6 – 9.1)

Protocol-defined target geometric mean exposures:

$C_{trough} > 0.697$ $\mu\text{g/mL}$

$AUC_{0-24} > 37$ $\mu\text{g}\cdot\text{h/mL}$

$C_{max} < 18.35$ $\mu\text{g/mL}$

Data presented as geometric mean (min-max)

CONCLUSIONS

- Use of DTG 5-mg DT (every other day for two weeks until day 14 of life, followed by once daily dosing) for 4-6 weeks was well-tolerated with no unexpected AEs in neonates exposed to HIV-1.
- DTG exposures met GM protocol-defined targets; however, there was considerable variability in exposures.
- Continued evaluation of this DTG dosing regimen including potential sources of PK variability is ongoing in IMPAACT 2023.

REFERENCES

- Pharmacokinetics and Safety of Dolutegravir in Neonates Exposed to HIV-1 (IMPAACT 2023). International Workshop on Pediatrics & HIV. Munich, Germany. July 7, 2024.

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