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 µg/mL, $AUC_{0\text{-}tau}$ > 37 µg*h/mL, and C_{max} <18.35 µg/mL.
- Tolerability information was collected using a questionnaire administered to caregivers.

Table 1. Participant Baseline Characteristics

	DTG-naive	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]	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 demographics 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 ≥ 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-naive infants (n=7). Solid lines represent median concentrations. Horizontal dotted line displays minimum target concentration (0.697 µg/mL).

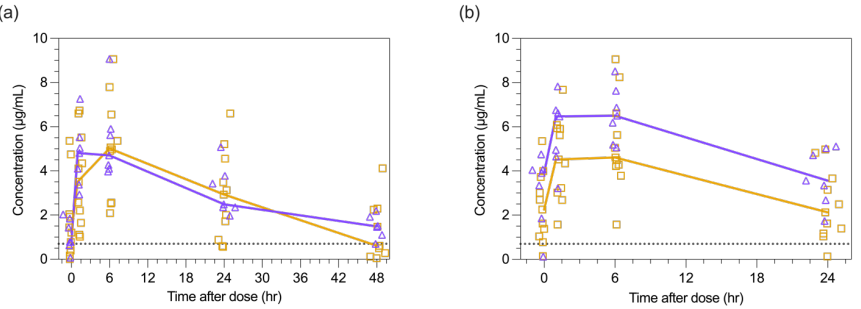

Table 2. Pharmacokinetic results

	C_{trough}	$AUC_{0\text{-}tau}$	C_{max}
	µg/mL	µg*hr/mL	µg/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 µg/mL
*$AUC_{0\text{-}tau}$ > 37 µg*h/mL*
C_{max} <18.35 µg/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

1. 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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