Pharmacokinetics and Safety of Dolutegravir in Neonates Exposed to HIV-1 (IMPAACT 2023)

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On behalf of the IMPAACT 2023 Team

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ANNUAL MEETING
2024

Dolutegravir (DTG) Dosing in Pediatrics

- DTG is an HIV-1 integrase strand transfer inhibitor (INSTI) indicated for the treatment of HIV-1 in adults and children aged at least 4 weeks (3 kg and above).
- DTG is hepatically metabolized via glucuronidation, with the majority of metabolism (85%) mediated by UGT1A1 and minor contributions from CYP3A.
- Two approved DTG formulations
  - ✓ Dispersible tablet (DT)
  - ✓ Film coated tablet (FCT)

Recommended dosage of DTG DT in Infants (Aged ≥4 Weeks and Weighing ≥3 kg), Children, and Adolescents

Weight Band (kg)	Once Daily Dosing	Number of 5-mg DT
3 to <6	5 mg DT	1 DT
6 to <10	15 mg DT	3 DT
10 to <14	20 mg DT	4 DT
14 to <20	25 mg DT	5 DT
≥20	30 mg DT	6 DT

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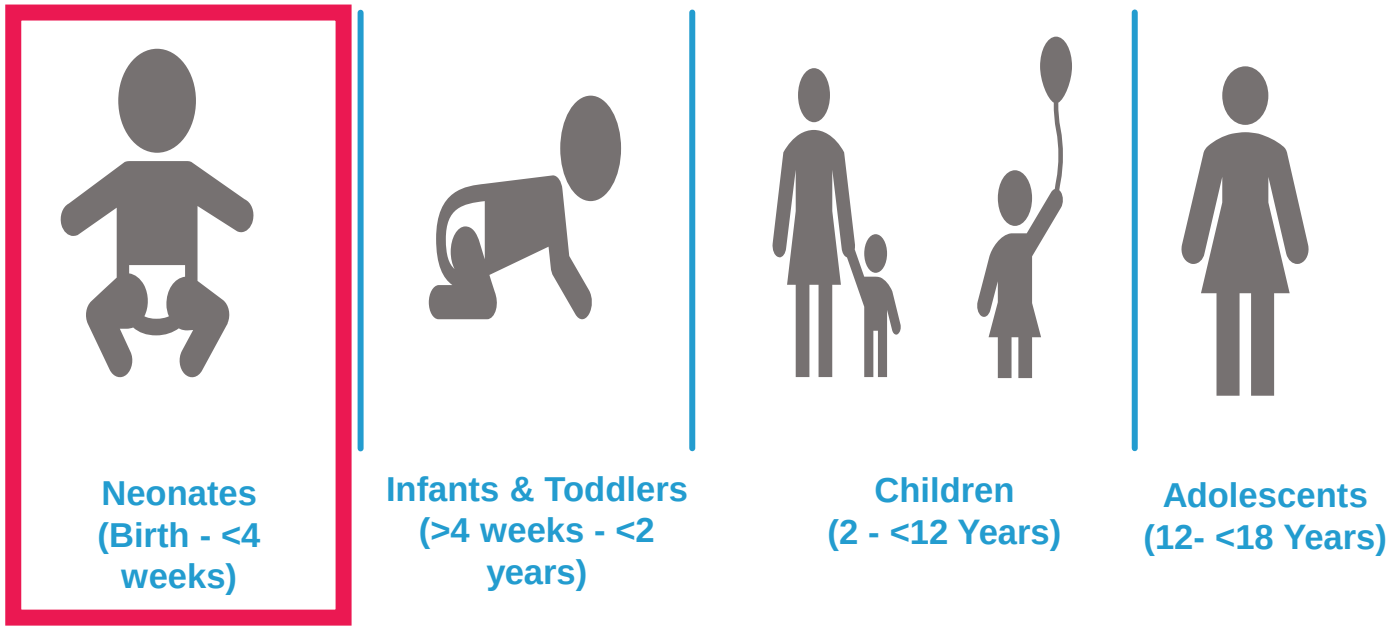
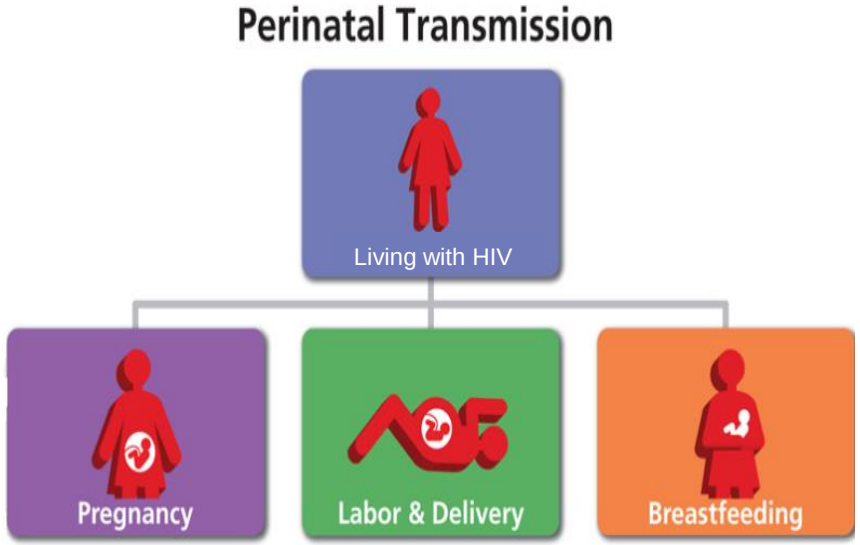
Only Remaining DTG Dose Gap is in Neonates





Infants born to mothers living with HIV should receive antiretroviral (ARV) drugs beginning as close to the time of birth as possible, preferably within 6 hours of delivery[1]

1. https://clinicalinfo.hiv.gov/en/guidelines/perinatal/management-infants-arv-hiv-exposure-infection

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IMPAACT 2023: Model-Informed Study Design

Dosing regimen for both DTG-exposed (mother receiving DTG) and DTG-naïve (mother not receiving DTG) is critical for prevention of HIV transmission and for early treatment of infants who acquire HIV.

Cohort 1

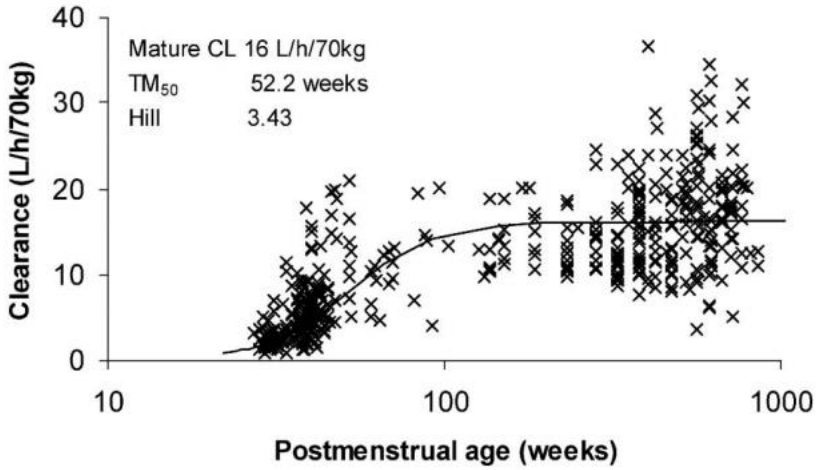
Two single doses of DTG

Stratum 1A: Naïve, Liquid Suspension (0.5 mg/kg)
Stratum 1B: Exposed, Liquid Suspension (0.5 mg/kg)
Stratum 1C: Naïve, Dispersible Tablet (5 mg)

Cohort 2

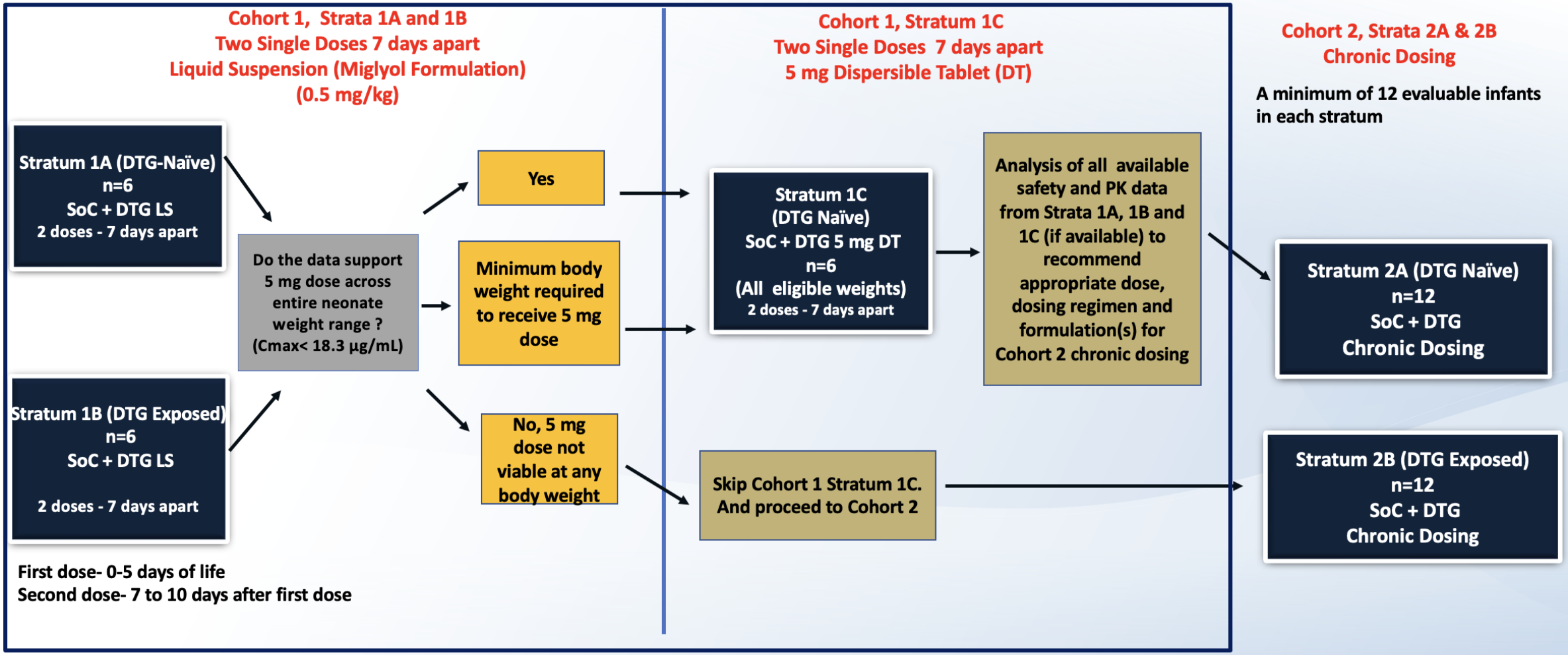
Chronic dosing

PK and safety analysis (including modeling & simulation) of Cohort 1 data to inform chronic dosing regimen in DTG-Naïve & DTG-Exposed neonates



Maturation of UGT1A1 clearance described using a sigmoid hyperbolic function. *Drug Metab Pharmacokinet*. 2009;24(1):25-36.

IMPAACT 2023 Study Design



Abbreviations: LS- liquid suspension DT – dispersible tablet; DTG – dolutegravir; µg – microgram; mg – milligram; mL – milliliter; SoC – standard of care

https://www.impaactnetwork.org/studies/impaact2023

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Objectives

- Characterize the pharmacokinetics (PK) and safety of DTG in neonates born to mothers living with HIV-1.

- Use two single doses PK data Cohort 1 (Strata 1A, 1B, and 1C) to develop a DTG population pharmacokinetic (PopPK) model.

- Use model for simulations to select chronic dosing regimen(s) for Cohort 2 to achieve:
  - ***C_{trough} : Target population geometric mean (GM) of 0.995 µg/mL (0.697-2.260 µg/mL)***
  - ***$AUC_{0\text{-}tau}$: Target population exposure (GM) of 46 µg*h/mL (37-134 µg*h/mL)***
  - ***C_{max}: Below 18.35 µg/mL (5 times adult GM Cmax)***

- Evaluate safety and grade adverse events (AEs) using the Division of AIDS Table for Grading the Severity of Adult and Pediatric Adverse Events (DAIDS AE Grading Table) through 4 weeks of life.

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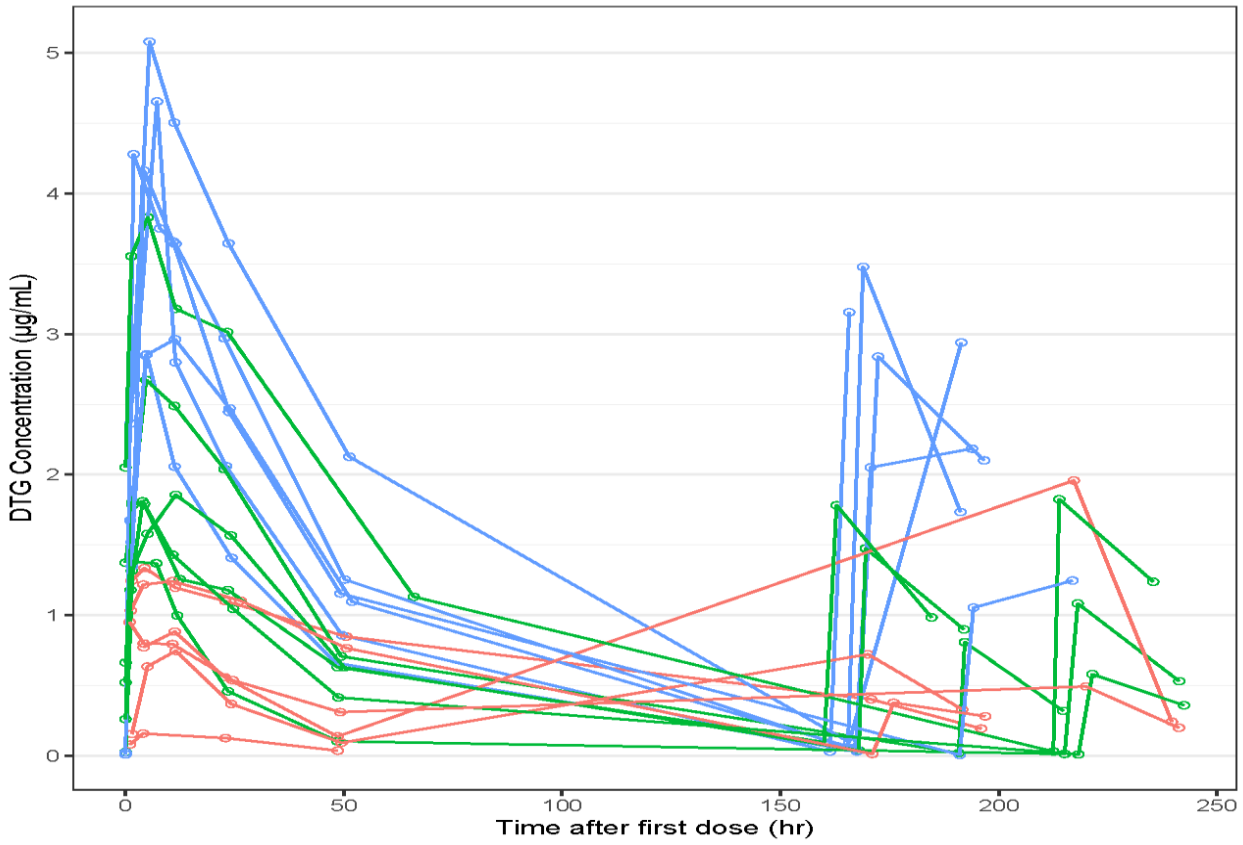
Participant Demographics (Cohort 1)

	Statistic	Strata 1A DTG-Naïve (0.5 mg/kg LS)	Strata 1B DTG-Exposed (0.5 mg/kg LS)	Strata 1C DTG-Naïve (5 mg DT)	Overall
Number of Participants (%)	.	6 (33.3)	6 (33.3)	6 (33.3)	18
Baseline Age (Days)	Mean (SD)	2.3 (1.2)	2.8 (1.5)	3.8 (1.0)	3.0 (1.3)
	Median (Min-Max)	2.5 (1.0 - 4.0)	2.5 (1.0 - 5.0)	3.5 (3.0 - 5.0)	3.0 (1.0 - 5.0)
Baseline Weight (kg)	Mean (SD)	2.88 (0.352)	3.05 (0.197)	3.08 (0.294)	3.10 (0.308)
	Median (Min-Max)	2.94 (2.30-3.24)	3.08 (2.68-3.26)	3.18 (2.68-3.40)	3.14 (2.30-3.54)
Sex N (%)	Male	1 (16.7)	4 (66.7)	3 (50)	8 (44)
	Female	5 (83.3)	2 (33.3)	3 (50)	10 (56)
Race N (%)	Black	4 (66.7)	1 (16.7)	3 (50)	8 (44)
	Asian	2 (33.3)	5 (83.3)	3 (50)	10 (56)
Ethnicity N (%)	Non-Hispanic/Latino	6 (100)	6 (100)	5 (83.3)	17 (94)
	Hispanic/Latino	.	.	1 (16.7)	1 (6)

Abbreviations: LS- liquid suspension DT – dispersible tablet

DTG Disposition was Similar in Naïve and Exposed Neonates



1A- Naïve (0.5 mg/kg LS) , 1B-Exposed (0.5 mg/kg LS), 1C-Naïve (5 mg DT)

- Two doses given within first 15 days of life.
- Maximum observed C_{max} in Stratum 1A (DTG-naïve neonates): **1.34 µg/mL**.
- Maximum observed C_{max} in Stratum 1B (DTG-exposed neonates): **3.83 µg/mL** .
- Pre-dose concentration ranged from **0.025 to 2.05 µg/mL** in Stratum 1B participants.
- Maximum observed C_{max} in Stratum 1C (DTG-naive neonates receiving 5 mg DT): **5.08 µg/mL.**

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No Unexpected Safety Events Occurred

- Safety data collected for first 4 weeks of life.
- No AEs reported were classified as serious adverse events (SAEs).
- No AEs were life-threatening or caused death, led to the temporary or permanent discontinuation of the study drug, were Grade 3 or higher, or were assessed as related to the study drug.
- The doses evaluated in Cohort 1 (0.5 mg/kg liquid suspension and 5 mg DT) passed safety guidelines.

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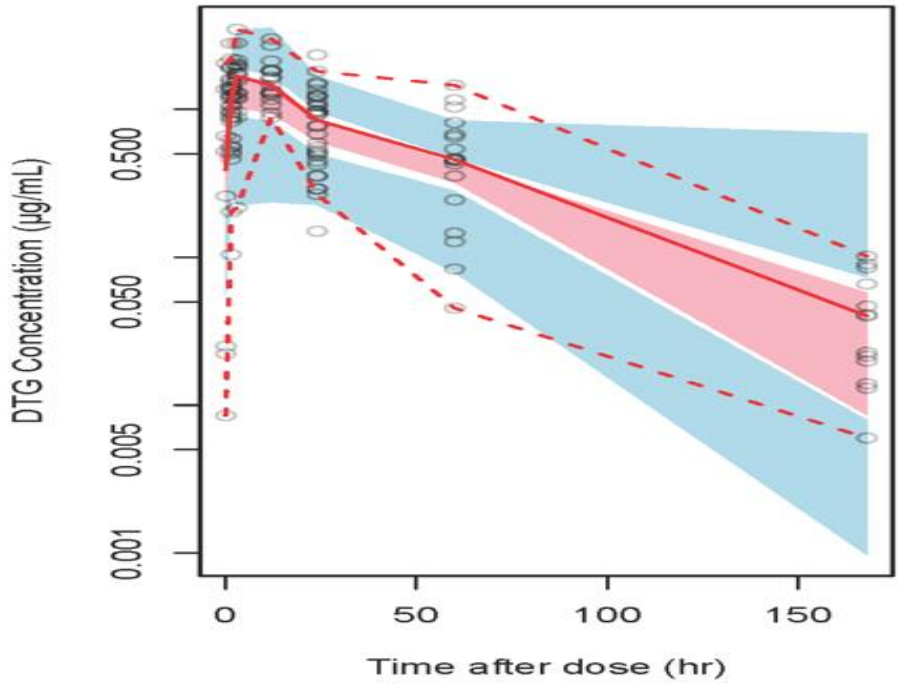
Population Modeling to Characterize PK of DTG in Neonates

Neonate PK Model Parameter Estimates			
Parameter [Units]	Point Estimate	95% CI	%RSE
CL/F [L/h]	1.34	1.29 – 1.40	2.16
V/F [L]	14.6	11.8 – 18.2	11.2
KA (DT)	2.00	1.31 – 3.07	21.7
Baseline (ug/mL)	0.356	0.244 – 0.521	19.3
F Fixed to DT value	1.53	-	-
CL/F~WT	0.608	0.549 – 0.667	4.92
V/F~WT	0.592	0.518 – 0.666	6.42
TM_{50} [week]	52.2 FIX	-	-
Hill	3.43 FIX	-	-

CL/F, apparent clearance; V/F, apparent volume; KA, absorption rate constant; Baseline, pre-dose DTG concentration estimate in DTG exposed neonates; TM_{50}, age at 50% of maturation for UGT1A1; Hill, Hill coefficient describing the steepness of the maturation process; CI, confidence interval; %RSE, percent relative standard error of the estimate.

No observed difference in bioavailability of liquid formulation compared to the DT formulation in this model with limited (n=6) data with DT



Open Circle: Observed Concentrations, Solid and dashed lines are observed median, 5th and 95th percentile. Shaded region represents the predicted exposures.

Simulated Chronic Dosing Regimens with DTG 5 mg Dispersible Tablet (Naïve & Exposed Neonates)

Regimen Number	Neonate Week of Life			
	Week 1	Week 2	Week 3	Week 4
1	Every 48 hours (Q2D)		Every 24 hours (QD)	
2	Every 48 hours (Q2D)			Every 24 hours (QD)
3	Every 48 hours (Q2D)			

- 200 participants (100 male and 100 female) were generated for a single simulation.
- Each neonate trial was simulated 1000 times within NONMEM using parameter estimates from the final model including the variability from inter-subject, inter-occasion, and residual errors.
- Total 200,000 (200 x 1000) neonates simulated, and PK parameters ($AUC_{0\text{-}tau}$, C_{max}, C_{trough}) were determined by non-compartmental methods.
- First DTG DT 5 mg dose immediately after delivery.

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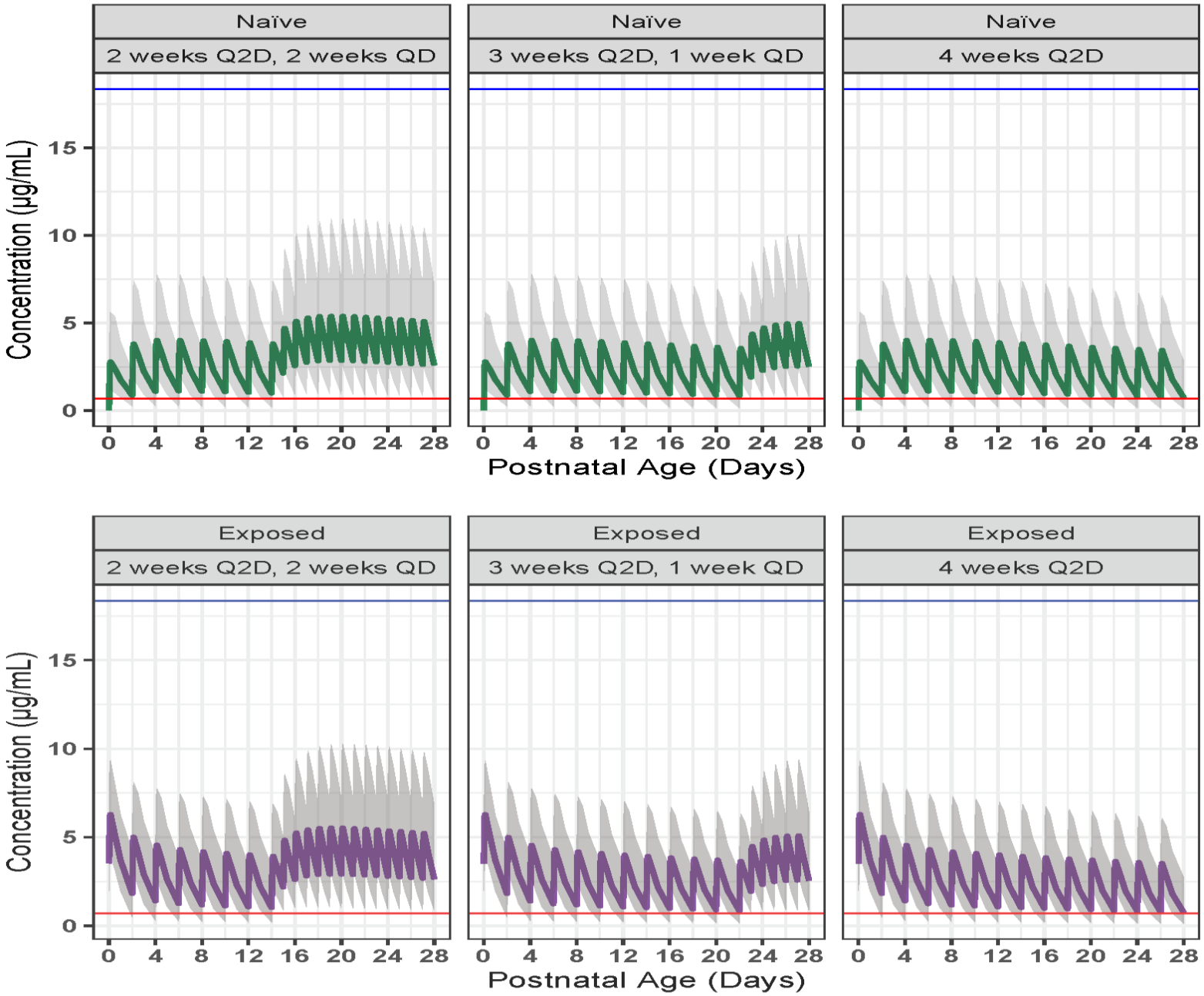
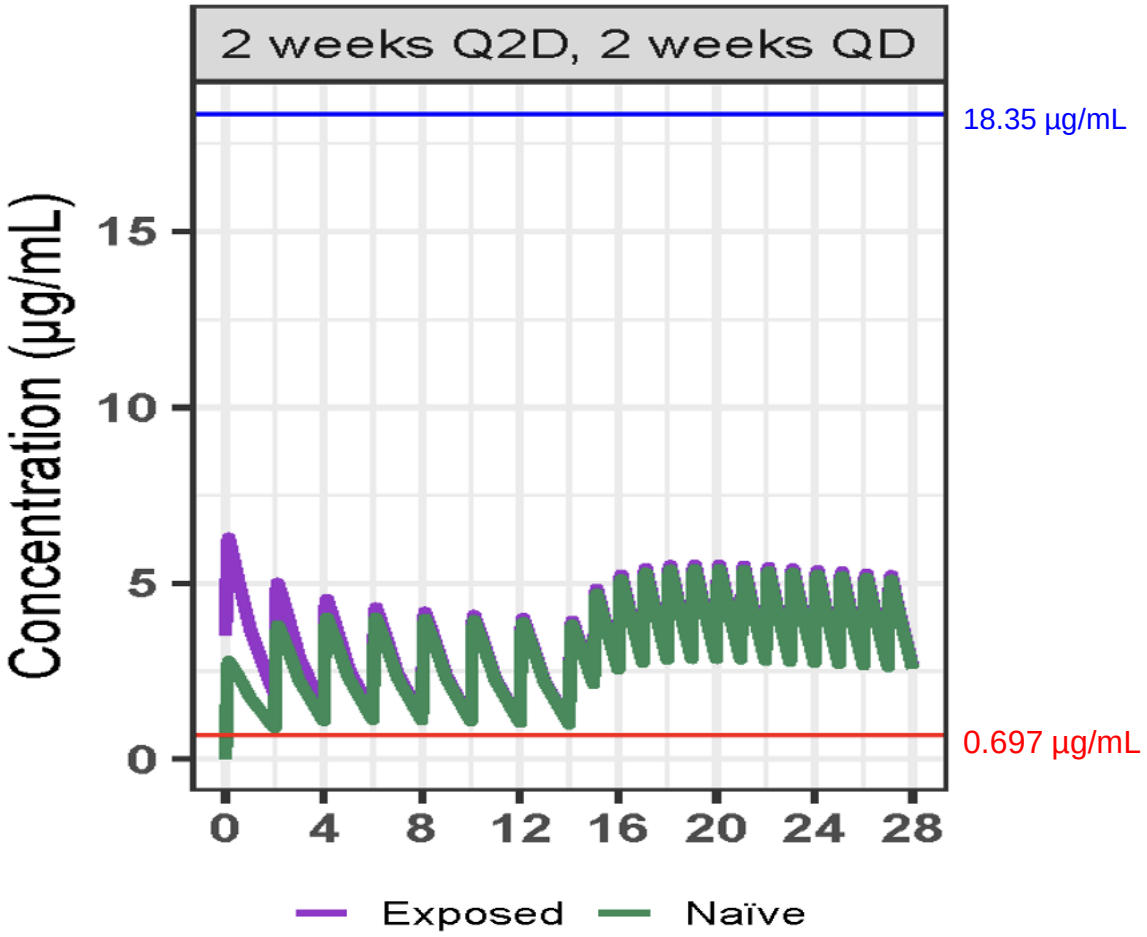
Simulated DTG Concentration versus Time Profiles

Chronic Dosing Regimens using DTG 5 mg Dispersible Tablet (Naïve & Exposed Neonates)



Simulated exposures presented as GM (solid lines) and 90% prediction intervals (gray shaded area). Red line represents target C_{trough} GM of 0.697 µg/mL and blue line represents upper limit C_{max} target 18.35 µg/mL.

Predicted Exposures are Nearly Identical After ~1 Week in Naïve & Exposed Neonates With Chronic Dosing (2 weeks Q2D followed by 2 Weeks QD).



Regimen is recommended for further study in Cohort 2

Geometric Mean Profiles

Conclusions

- Two single doses of DTG, on top of SoC ARV prophylaxis, were well-tolerated with no unexpected adverse events in neonates exposed to HIV-1.
- Each simulated regimen is predicted to provide exposures well below the upper limit C_{max} target of 18.35 µg/mL.
- Simulations show that for both DTG-naïve and DTG-exposed neonates, a 5 mg DT dose Q2D for two weeks, followed by 5 mg QD, is predicted to achieve and maintain target exposures.
- This chronic DTG dosing regimen is under evaluation in a subsequent cohort (Cohort 2) of IMPAACT 2023.

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