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

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on behalf of
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Dolutegravir (DTG) Metabolism and Dosing in Pediatrics

- DTG is a 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.

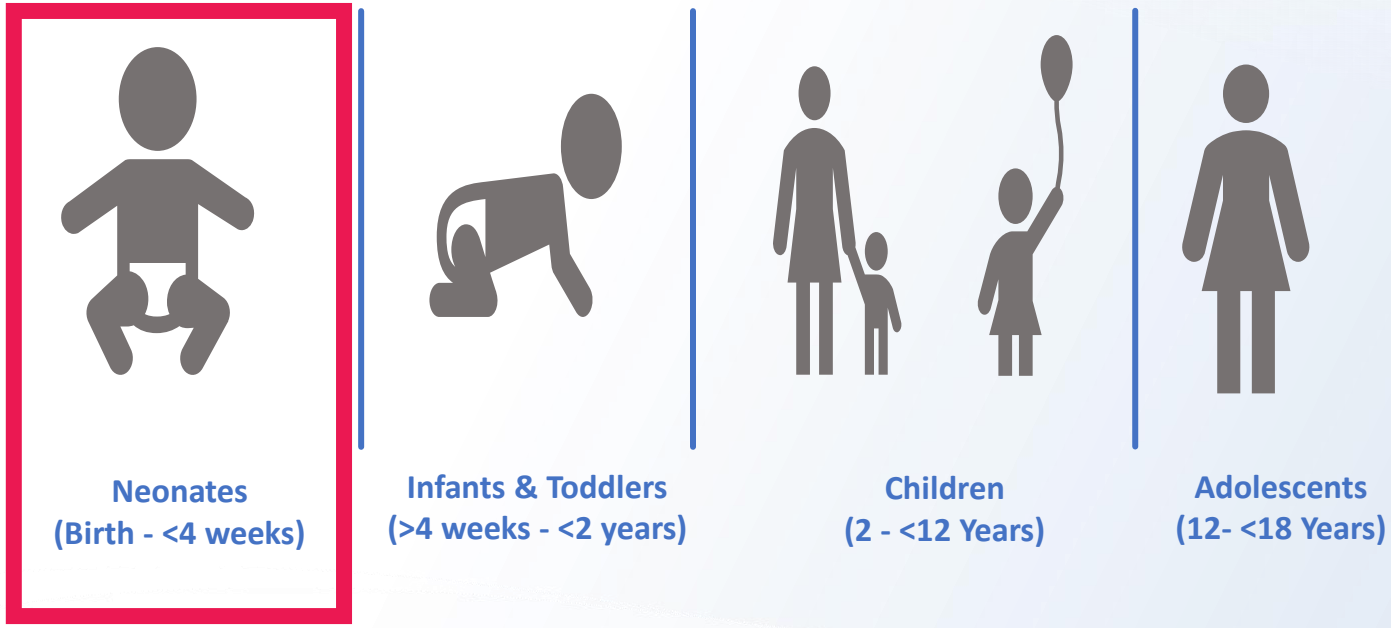
- Two approved DTG formulations
  - ✓ Dispersible tablet (DT)
  - ✓ Film coated tablet (FCT)

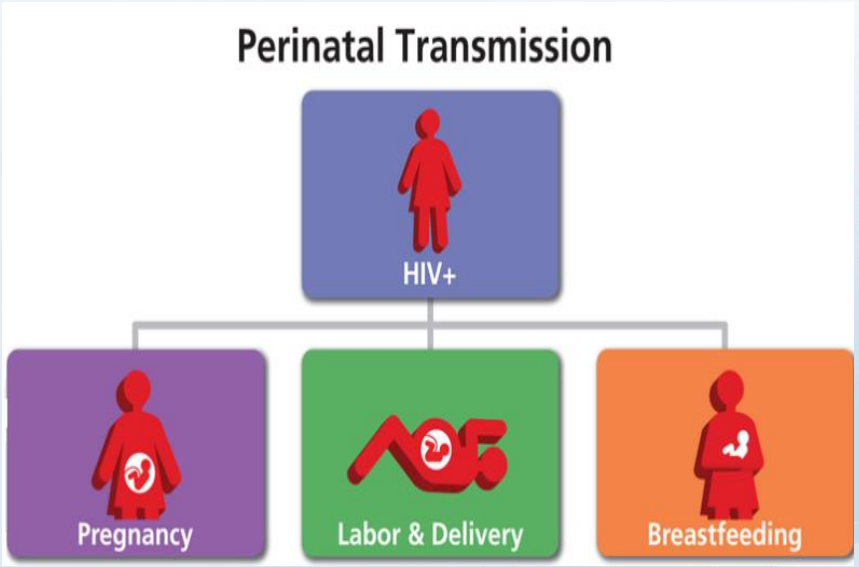
Weight Bands (kg)	Once Daily Dosing	Number of Tablets
3 to <6 (≥ 4 Weeks)	5 mg DT	1 DT
6 to <10	15 mg DT	3 DT
10 to <14	20 mg DT	4 DT
14 to <20	25 mg DT	5 DT
>20	30 mg DT or 50 mg FCT	6 DT or 1 FCT

The bioavailability of DT is ~1.6-fold that of FCT

Reference: Tivicay USPI

The Only Remaining DTG Dose Gap is in Neonatal Population





- 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.

- DTG could play a role as a valuable new ARV for inclusion in neonatal prophylaxis regimens.

Model-Informed DTG Neonate Study Design

Dosing regimen for DTG exposed (mother on DTG based ARVs) and DTG naïve (mother taking other ARVs) is critical for use of DTG in neonates for prevention of HIV transmission and for early treatment of infected infants.

Cohort 1

Two Single Doses within first 15 days of life

(DTG Naïve & DTG Exposed- Liquid Suspension) & Dispersible Tabl

Naïve only)

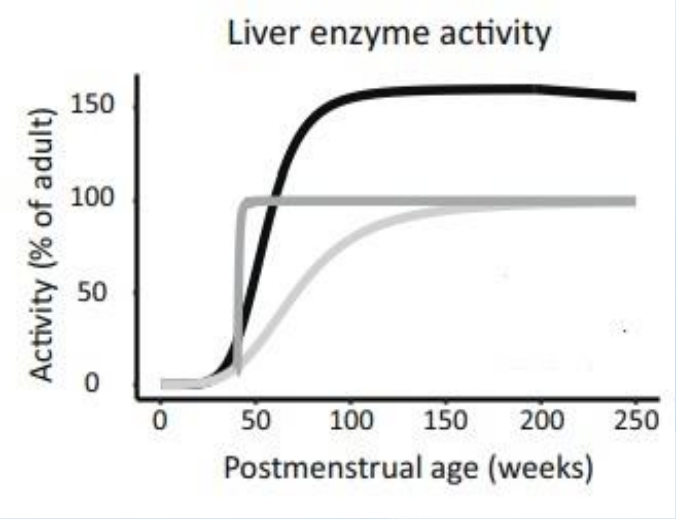
Learn With Two Single Doses & Confirm with M&S

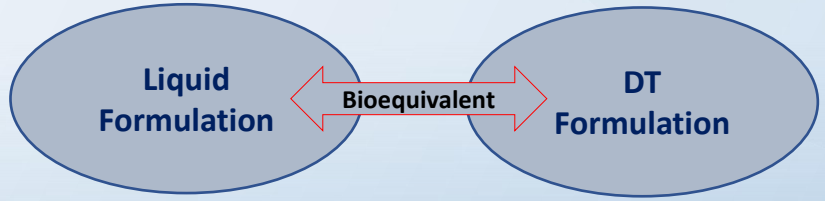
Cohort 2

Modeling & Simulation

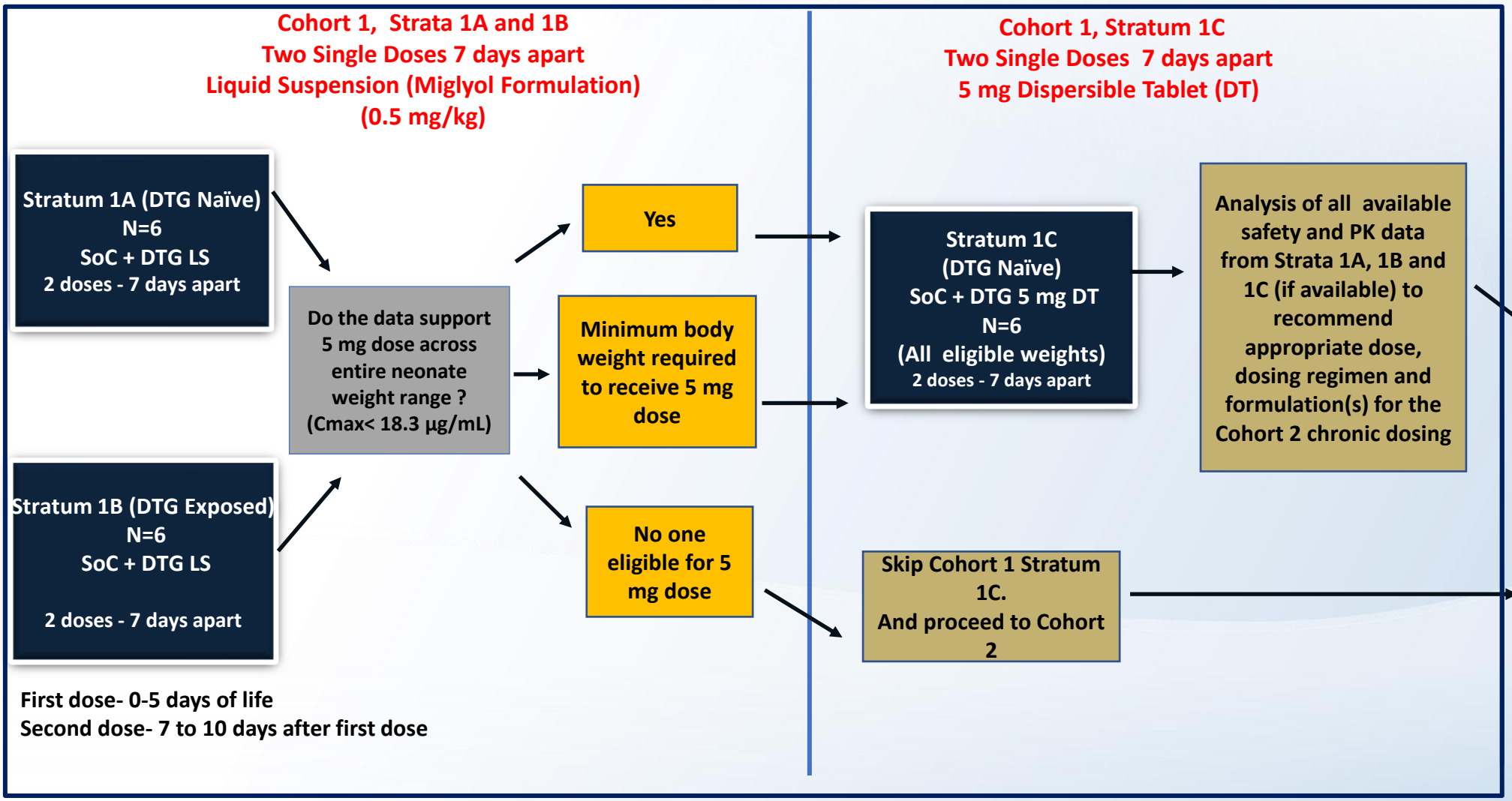
to recommend Chronic Dosing

DTG Naïve & DTG Exposed





IMPAACT 2023 Study Design



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

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

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 regimens 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}: Exposure below 18.35 µg/mL (5 times of adult GM Cmax)***

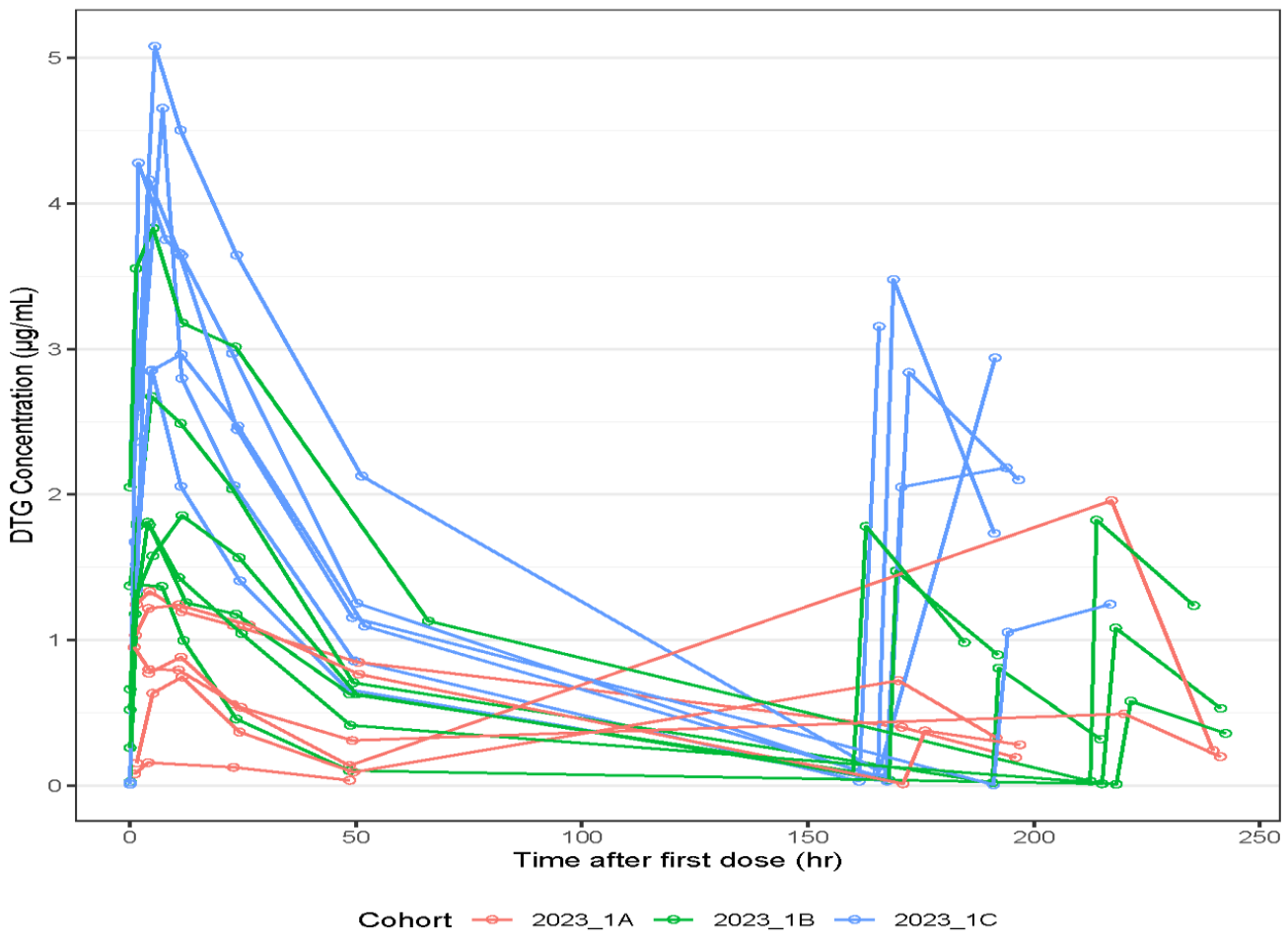
- Evaluate safety and grade adverse events (AEs) using the Division of AIDS Table for Grading the Severity of Adult and Pediatric Adverse Events (DAIDS AE Grading Table) through 4 weeks of life.

Participant Demographics in Cohort 1

Covariate	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)
Gender 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

Disposition of DTG was Similar in Both 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 Cmax in Stratum 1A-Naïve neonates - **1.34 µg/mL**.
- Maximum observed Cmax in Stratum 1B-Exposed neonates - **3.83 µg/mL** .
- Pre-dose concentration ranges from **0.025 to 2.05 µg/mL** in Stratum 1B participants.
- Maximum observed Cmax in Stratum 1C – Naïve neonates- **5.08 µg/mL.**

No Unexpected Safety Events Occurred

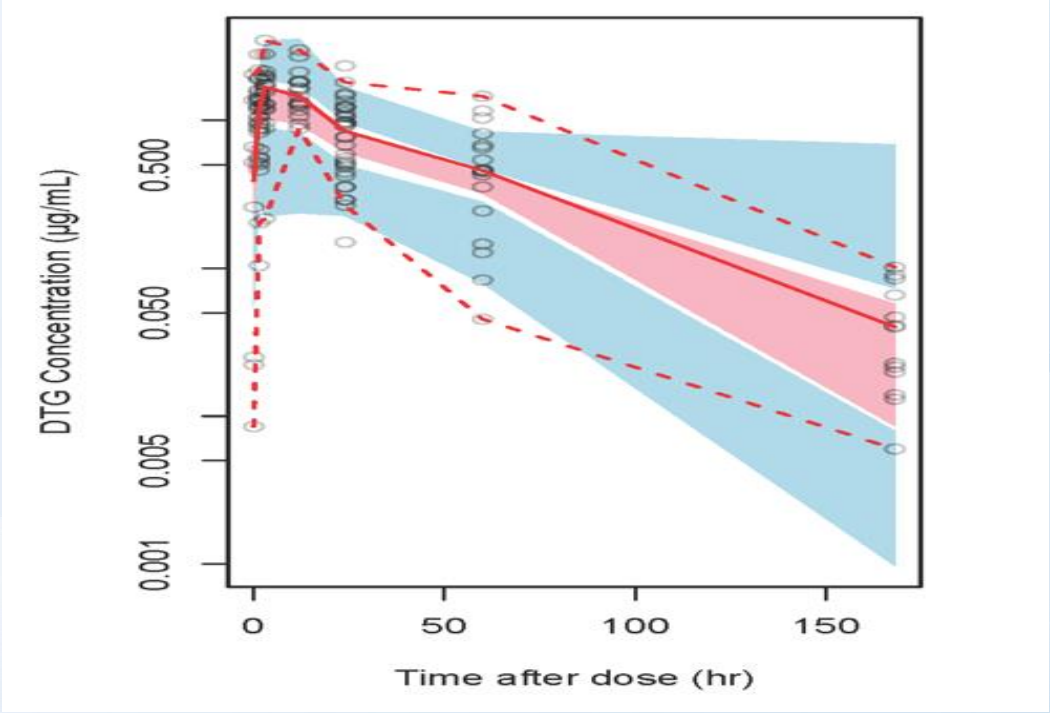
- Safety data collected for first 4 weeks of life.
- No AEs reported were classified as serious adverse events (SAEs).
- No AEs were life-threatening or caused death, led to the temporary or permanent discontinuation of the study drug, were Grade 3 or higher, or were assessed as related to the study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

Population Pharmacokinetic Model Able to Describe DTG PK 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	-	-

CI, confidence interval; CL/F, apparent clearance; V/F, apparent volume; KA, absorption rate constant; Baseline, pre-dose concentration estimate in DTG exposed neonates; Hill, Hill coefficient related to the slope of this maturation process; TM50 [week], maturation half-time; %RSE, percent relative standard error of the estimate.

- No difference in bioavailability of liquid formulation compared to the DT formulation in this model with limited n=6 data with DT.



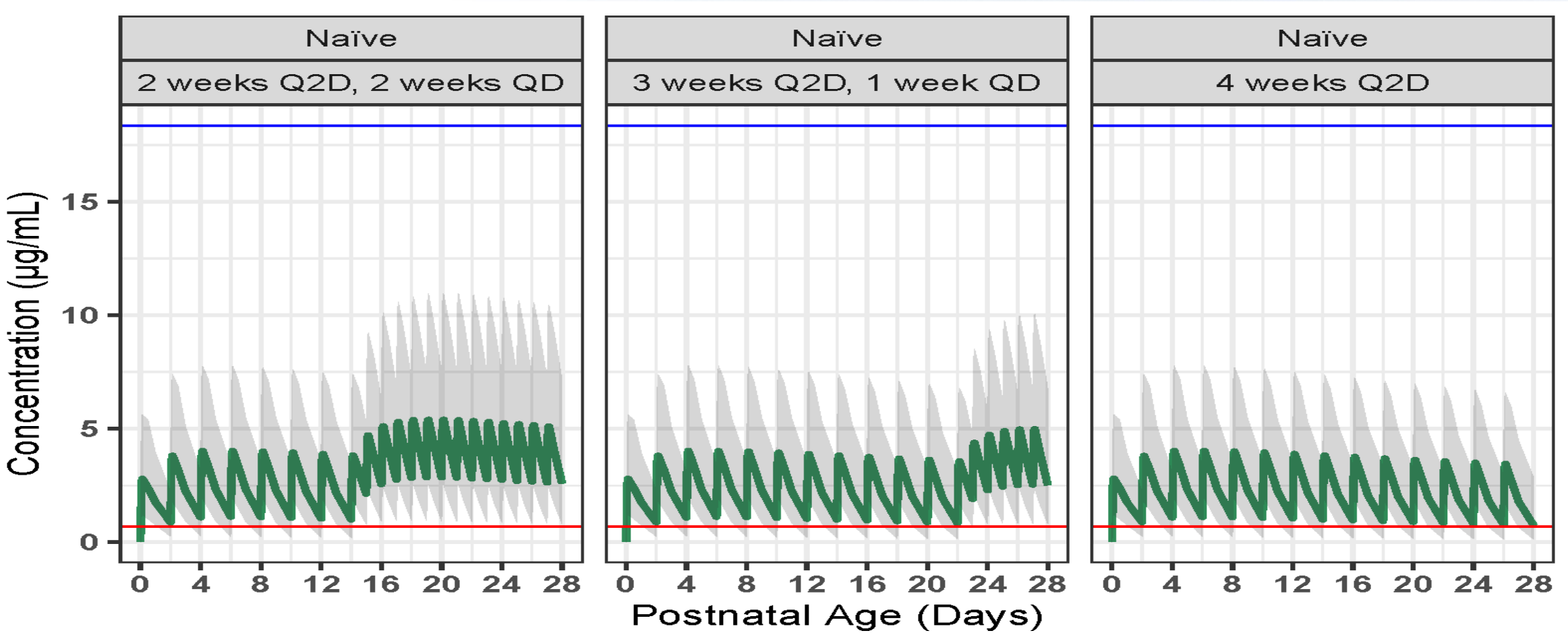
Open Circle: Observed Concentrations, Solid and dashed lines are observed median, 5th and 95th percentile. Shaded region represents the predicted exposures.

Dosing Regimens for Simulations (Naïve & Exposed)- Considering First DT (5 mg) Dose Immediately Upon Delivery

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)			

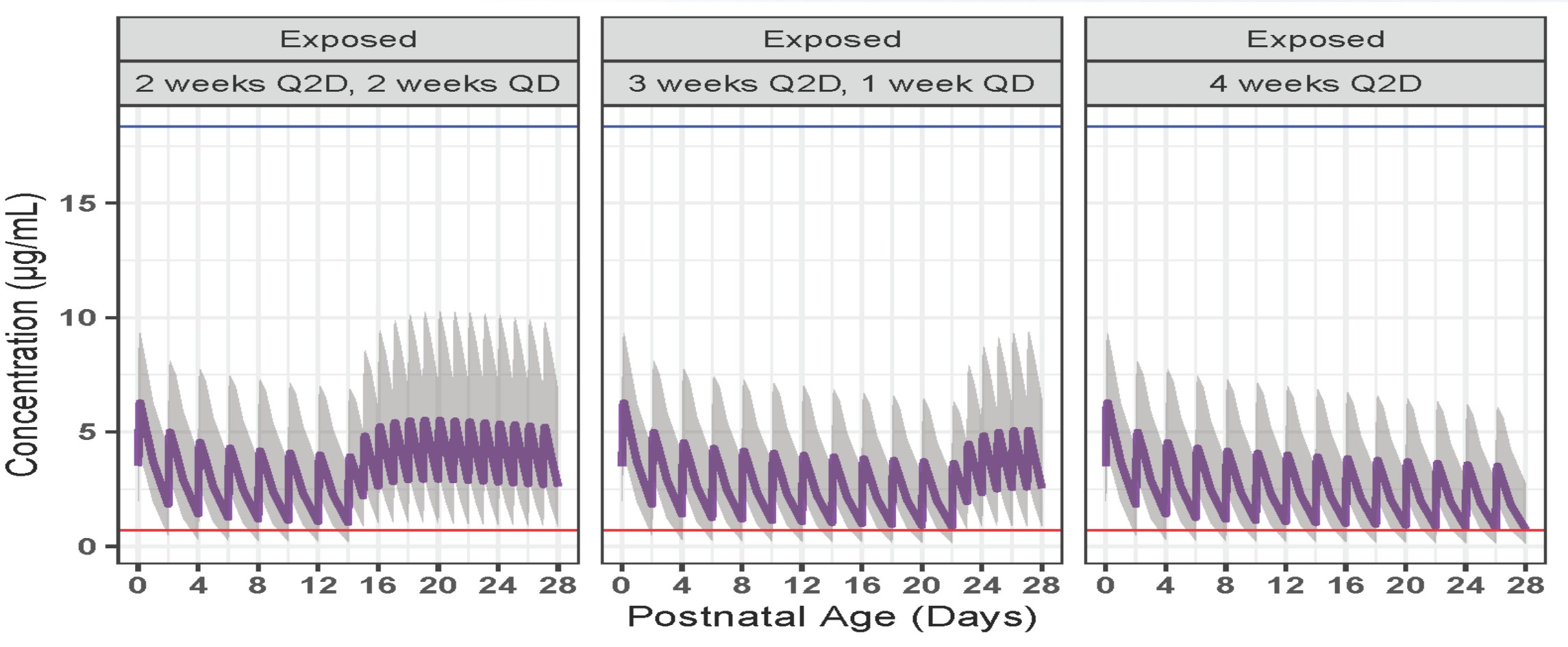
- 200 participants (100 males and 100 females) were generated for a single simulation.
- Each neonate trial was simulated 1000 times within NONMEM using parameter estimates from the final model including the variability from inter-subject, inter-occasion and residual errors.
- Total 200,000 (200 x 1000) neonates simulated, and PK parameters (AUC0-τ, Cmax, Cτ) were determined by non-compartmental methods.

DTG-Naïve Neonates- Best Regimen 2 Weeks Q2D, then 2 Weeks QD



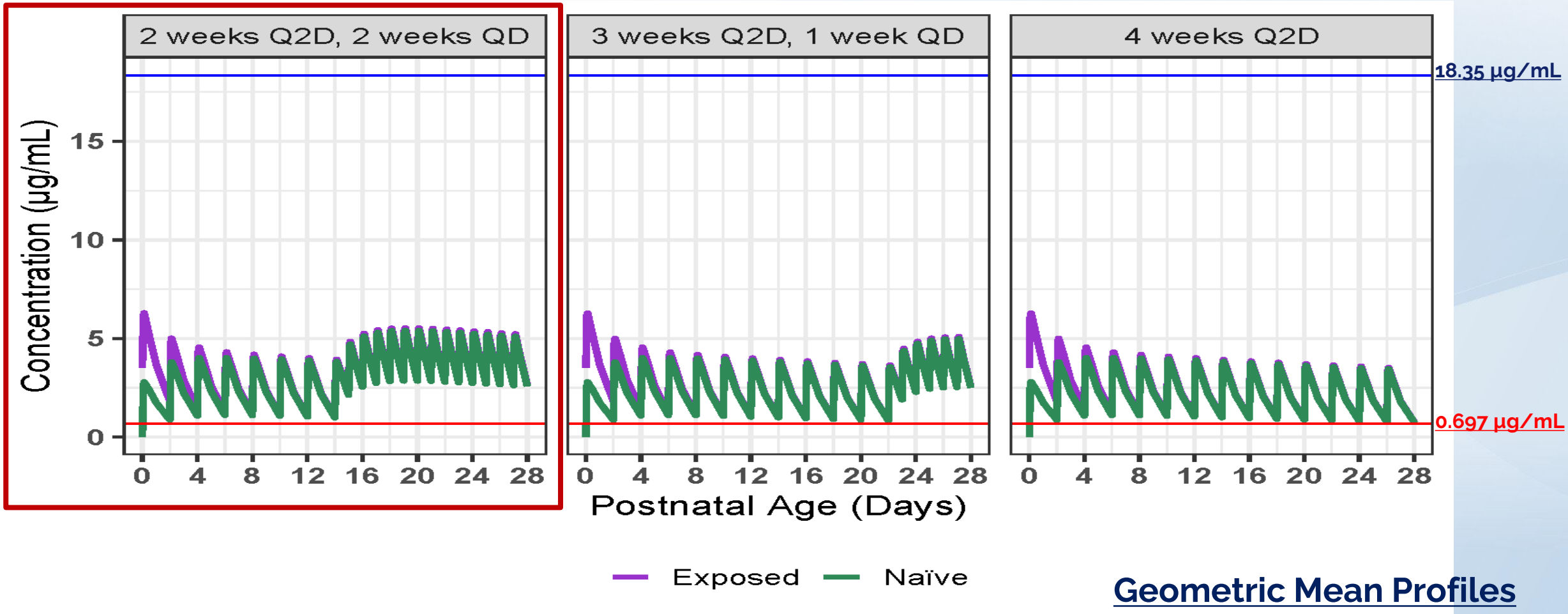
Simulated exposures presented as GM (solid green line) and 90% prediction intervals (gray shaded area). The red solid line represents target C_{trough} GM 0.697 µg/mL and blue solid line represents upper limit C_{max} target 18.35 µg/mL

DTG-Exposed Neonates- Not much different from DTG Naïve, Best Regimen Still 2 Weeks Q2D, then 2 Weeks QD



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

No Difference in Predicted Exposures in Naïve & Exposed With Chronic Dosing (2 weeks Q2D and 2 Weeks QD). Recommended For Further Study in Both Naïve & Exposed Neonates



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.

- 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 target exposures.

- Each regimen is predicted to provide exposures well below the upper limit C_{max} target of 18.35 µg/mL.

- This chronic DTG dosing regimen will be evaluated in a subsequent cohort 2 of IMPAACT 2023 study.

Acknowledgment

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