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Optimizing Dolutegravir Initiation in Neonates using Population Pharmacokinetic Modeling and Simulation

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Abstract

Background: A knowledge gap exists for dolutegravir (DTG) pharmacokinetics and safety during the first 4 weeks of life, preventing safe and effective DTG use in neonates.

Setting: Population pharmacokinetic (popPK) modeling and simulation was used to assess newborn DTG dosing requirements during the first days of life as a function of maternal DTG dosing history prior to delivery.

Methods: DTG PK data were obtained from pregnant women and infants enrolled in the IMPAACT Network P1026S study. Maternal and neonate popPK models were separately developed. Monte Carlo simulations were performed to simulate neonatal concentrations following two doses of DTG after birth for infants born to mothers either receiving or not receiving DTG prior to delivery.

Results: In DTG-naïve infants, a 5 mg DTG dose at birth with a second dose after 48 hours maintained median concentrations above the lower bound of the target range (0.77 μg/mL) and below the upper bound of the target range (7.34 μg/mL representing 2-fold above the adult C_{max} value). In DTG-exposed infants, a 5 mg DTG dose at 24 hours after birth with a second dose after 48 hours maintained median concentrations within or nearly within the target range, even if the last maternal DTG dose was taken as soon as 6 hours or as long as 24 hours prior to delivery.

Conclusions: Newborn DTG dosing requirements during the first days of life depend upon maternal DTG dosing history prior to delivery. These results may inform the design of future clinical studies of DTG in the neonatal population.

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Keywords

Dolutegravir; Pharmacokinetics; Pharmacokinetic Modeling; Neonate

Introduction

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] ARV regimen selection in newborns is guided by the level of transmission risk. Sufficient neonatal pharmacokinetic and safety data are adequate to allow neonatal dosing recommendations for only a few ARVs, including zidovudine, lamivudine, nevirapine, emtricitabine, raltegravir, and maraviroc.[1]

Dolutegravir (DTG) is an integrase strand transfer inhibitor (INSTI) that is recommended in treatment guidelines as a preferred ARV drug in infants (aged ≥4 weeks and weighing ≥3 kg), children, and pregnant individuals.[1,2] DTG is approved by the U.S. Food and Drug Administration (FDA) in infants at least 4 weeks of age and weighing at least 3 kg with weight-based dosing (3 kg to <6 kg: 5 mg once daily; 6 kg to <10 kg: 15 mg once daily; 10 kg to <14 kg: 20 mg once daily).[3] However, a knowledge gap exists for DTG pharmacokinetics and safety during the first 4 weeks of life, preventing safe and effective DTG use in neonates. DTG could play an important role as an INSTI component of neonatal HIV-1 regimens both for prophylaxis and early intensive treatment. Integrase inhibitors including DTG and raltegravir block integration of viral DNA into the host cell which is a critical step in the virus lifecycle required for productive infection to occur[4]. Raltegravir is approved for use in full-term neonates but has a lower barrier to the development of resistance[5] and has a complicated neonatal dosing regimen, with three dosing changes in the first four weeks of life.

DTG is eliminated primarily by hepatic metabolism via uridine diphosphate glucuronosyltransferase-1A1 (UGT1A1)[3], which is also responsible for the conjugation of bilirubin with glucuronic acid.[6] The activity of UGT1A1 is very low at birth and increases rapidly during the first weeks of life.[7] Limited data are available on the pharmacokinetics (PK) of placentally-acquired dolutegravir in infants born to mothers receiving dolutegravir. In 16 infants with washout samples collected after birth, the median (interquartile range; IQR) half-life of DTG was 32.8 hours (25.9 – 35.9), which exceeds the half-life in adults (14 hours) and adolescents (12.9 hours).[8] Therefore, for infants exposed to HIV-1, optimized DTG dosing during the first days of life may depend upon (i) the time of the last maternal dose prior to delivery and (ii) the time of DTG initiation after birth. IMPAACT 2023 (International Maternal Pediatric Adolescent AIDS Clinical Trials Network) will be evaluating the safety, tolerability, and pharmacokinetics of DTG in neonates. The purpose of IMPAACT 2023 is to propose an appropriate dose of DTG for neonates and infants born to mothers living with HIV-1. Both DTG naïve (infants born to mothers not receiving DTG at the time of delivery) and DTG exposed (infants born to mothers receiving DTG at the time of delivery) neonates will be enrolled. The objective of the current study was to apply population pharmacokinetic (popPK) modeling and simulation to assess newborn

DTG dosing requirements during the first days of life as a function of maternal DTG dosing history prior to delivery.

Methods

Patient Population, Drug Administration, and PK Sampling

DTG PK data were obtained from pregnant women and infants enrolled in the International Maternal Pediatric Adolescent AIDS Clinical Trials (IMPAACT) Network P1026S study (NCT00042289).[9] This study was an open-label, parallel-group, multi-center, phase IV prospective study in pregnant women with HIV receiving DTG 50 mg once daily and their newborn infants. Informed consent was obtained from all participants and parents in the study. The study was approved by the institutional review boards of the participating sites and performed in accordance with the ethical standard of the 1964 Declaration of Helsinki.

Maternal intensive 24-hour PK evaluations were performed during the second trimester (20–26 weeks gestation), third trimester (30–38 weeks gestation), and 6–12 weeks following delivery. Pre-dose samples were obtained, followed by an oral DTG dose administered without regard to meals and post-dose samples drawn at 1, 2, 4, 6, 8, 12 and 24 hours. At delivery, cord and maternal blood samples were collected. Four blood samples were collected at 2–10 hours, 18–28 hours, 36–72 hours and 5–9 days after birth in the newborn infants[9]. Infants received standard of care antiretroviral prophylaxis for prevention of perinatal transmission of HIV-1. DTG was not administered to neonates as it has not yet been studied in this population.

DTG samples were analyzed at the IMPAACT Pharmacology Support Laboratory at the University of Alabama at Birmingham using a sensitive liquid chromatography tandem mass spectrometry assay validated to quantitate total DTG concentrations in human plasma samples. This method had a dynamic range of 0.005–10 mcg/mL [9].

Pharmacokinetic Analysis

Using the computer program NONMEM (version 7.3) with a GNU Fortran G77 compiler, concentration time data for maternal and neonatal data were fit separately using first-order conditional estimation method with interaction. One and two-compartment models were evaluated for the maternal structural DTG model. A one-compartment PK structural model (ADVAN2, TRANS2 subroutine) with first order absorption was selected based upon an assessment of the objective function value (OFV), visual inspection of goodness of fit plots, and precision of parameter estimates. The one-compartment model had the following parameters: oral clearance (CL/F), volume of distribution (Vd/F), and first-order absorption rate constant into the central compartment (Ka). The first neonatal concentration was used to estimate the *in utero* dose of DTG and the remaining data points were fit with a separate one-compartment structure model (ADVAN1, TRANS1 subroutine). An exponential-normal distribution error model was used for inter-subject variability for both models.

Age, weight, serum creatinine, albumin, stage of pregnancy (second trimester, third trimester, postpartum), and ethnicity, were evaluated as potential covariates for CL/F and Vd/F for the maternal model. Gestational age, weight, length, and sex were evaluated as

potential covariates for the neonatal model. Potential covariates were added to the model one at a time, with covariates that improved the model fit by a change in the objective function of at least 4.0 ($p<\sim 0.05$) being retained in the initial covariate screen. A forward selection approach was utilized for the multivariate assessment. Covariates found to improve the objective function by 10.8 ($p<\sim 0.001$) or greater were retained in the final model. Empiric Bayesian estimates of the individual PK parameters were generated from the final model using the POSTHOC routine. A 1,000-sample bootstrap assessment of each final model was performed using Wings for NONMEM for each model separately.

Monte Carlo simulations were performed to simulate neonatal concentrations following two doses of DTG after birth for infants born to mothers either taking or not taking DTG prior to delivery. For infants born to mothers taking DTG prior to delivery, the final maternal population PK model was utilized to generate DTG concentrations at delivery (last maternal dose either 6, 12, or 24 hours prior to delivery) in 1000 virtual maternal patients. The previously published paired cord blood to maternal plasma ratio 1.25 (1.07 – 1.40 [IQR]) [9] was used to generate a normal distribution of neonatal DTG concentrations at birth.

A simulation was performed to simulate neonatal concentration-time profiles following DTG dosing. A one compartment structural model (ADVAN2, TRANS2 subroutine) using the final parameters from the neonatal population PK model and a Ka fixed to the adult value of 2.24 $hours^{-1}$ was used to simulation both the first and the second doses in virtual neonates after birth. The bioavailability was assumed to be 1.0 given the lack of information in the literature regarding DTG absolute oral bioavailability. A previously published maturation function for UGT1A1-mediated clearance of raltegravir was utilized in the model to capture changes after birth in UGT1A1-mediated DTG clearance [10]:

$$Ke = \frac{\left(\left(0.077\ x\left(17.6\ x\left(\frac{3}{25}\right)\right)\right) + \left(1\ x\left(1 - e^{(-0.2x\ Age\ in\ Weeks)}\right)\right)\right) x\ \left(Body\ Weight\ (kg)^{0.75}\right)}{17.6x\left(\frac{Body\ Weight\ (kg)}{25}\right)}$$

$$Body\ Weight\ (kg) = 3.0 + 9.289 * \left(1 - e^{0.983\ *\ Age\ in\ years}\right)$$

DTG dosing in simulated neonates born to mothers taking DTG was modeled as a first oral dose of DTG 5 mg either 0, 24, 48, or 72 hours after birth and a second 5 mg dose at 24, 48, or 72 hours after the first dose (total of 9,000 virtual infants). For neonates born to mothers not taking DTG, simulations included a 5 mg DTG dose at birth followed by a second 5 mg dose at 24, 48, or 72 hours (750 total virtual infants). For all simulations, the lower bound of the target range was 0.77 μg/mL and the upper bound of the target range was 7.34 μg/mL (2-fold above the adult C_{max} value). DTG target values are consistent with targets in previous studies in older infants, children, and adolescents and are based upon exposures in adults.[11]

Results

Patients

Thirty-one maternal subjects and 18 neonates contributed data for the analysis. A total of 552 maternal DTG concentrations and 70 neonatal DTG concentrations were utilized to develop the respective popPK models. Supplemental Tables S1 and S2 summarize the maternal and neonatal demographic data. Median age for the maternal group was 31 years and the median body weight was 83.4 kg and 74.9 kg at the third trimester and postpartum, respectively. Neonatal DTG concentration data were collected for 7 males and 11 females with a median gestational age of 38 weeks and weight of 3.1 kg. Observed median concentration-time profiles of DTG for both populations are shown in Figure 1.

Population pharmacokinetic analysis

The univariate screen for the maternal model found pregnancy (second and third trimester) as an independent predictor of CL/F and weight as an independent predictor of Vd/F and were significant covariates retained in the final model (Table 1). There were no significant differences in CL/F between the second and third trimester identified by the model, thus pregnancy rather than trimester was used as a covariate for CL/F in the final model. Median CL/F in the third trimester was 1.04 L/hr which was 42% higher than post-partum.. Shrinkage estimates for inter-subject variability in the maternal model were: CL/F (0.97%), Vd/F (26.4%) and Ka (25.3%). The final model described the data without significant bias as shown in Supplemental Figure S1 (A, B). Final model parameters and variance estimates are shown in Table 1. Bootstrap evaluation of the final model successfully converged 92.4% of the time and the final parameter estimates fell within the 95% confidence interval of the bootstrap, which suggests that the model represents the population well (Table 1).

The neonatal data were initially modeled with CL and V, however the limited data led to difficulties estimating V, thus only the elimination rate constant (Ke) could be described. The final infant model had no significant covariates (Table 1). Shrinkage estimates for inter-subject variability on Ke for the neonatal model was 7.24%. The final model described the data without significant bias as shown in Supplemental Figure S1 (C, D). Final parameters and variance estimates are shown in Table 1. Bootstrap evaluation of the final model successfully converged 89.2% of the time and final parameter estimates fall well within the 95% confidence interval of the bootstrap, which suggests that the model represents the population well (Table 1).

Monte Carlo Simulations

For infants born to mothers not taking DTG, simulations were performed following a first DTG dose immediately after birth and a second dose either 24, 48, or 72 hours after birth. The median concentrations are summarized in Figure 2. C_{max} after each dose and the second dose pre-dose are presented in Supplemental Table 3. All concentrations are above the lower bound of the target range of 0.77 μg/mL. The simulated median C_{max} is below the upper bound of the target range of 7.34 μg/mL (2-fold above the adult C_{max} value) for neonates who are administered the second dose of DTG at 48 or 72 hours post-delivery.

For infants born to mothers taking DTG, simulations were performed with the last maternal dose taken 6, 12, or 24 hours prior to delivery and the first infant dose at birth, 24, 48, or 72 hours after birth. The second infant dose was simulated at 24, 48, or 72 hours after the first dose. The median concentrations are summarized in Figure 3 (first infant doses at 24 and 48 hours after birth) and Supplemental Figures S2 and S3 (first infant doses at birth and 72 hours after birth). C_{max} after each dose and the pre-dose values are presented in Supplemental Table 4. The majority of simulated median concentrations are above the lower bound of the target range (0.77 μg/mL). When the last maternal dose is taken 24 hours prior to delivery and the first infant dose is taken 24 hours after delivery, the simulated median pre-dose infant concentration is 0.7 ug/mL (9% below the target of 0.77 ug/mL). For simulations in which the infant was administered the first dose of DTG at 24, 48 or 72 hours after delivery, C_{max} concentrations were below the upper bound of the target range (7.34 μg/mL) when the second dose of DTG was administered 48 or 72 hours after the first. For simulations in which neonatal dosing occurred at delivery, only the simulation in which the second dose of DTG was administered 72 hours after the first had concentrations consistently below the upper bound.

Discussion

In this study, maternal and neonate DTG popPK models were separately developed in order to assess DTG dosing during the first days of life in infants exposed or not exposed to DTG *in utero*. Population pharmacokinetic parameter estimates of DTG were in agreement with values reported in the literature.[12–14] In DTG-naïve infants, a 5 mg DTG dose at birth with a second dose after 48 hours maintained median concentrations above the lower bound of the target range (0.77 μg/mL) and below the upper bound of the target range (7.34 μg/mL representing 2-fold above the adult Cmax value). In DTG-exposed infants, a 5 mg DTG dose at 24 hours after birth with a second dose after 48 hours maintained median concentrations within or nearly within the target range, even if the last maternal DTG dose was taken as soon as 6 hours or as long as 24 hours prior to delivery. These findings may inform the design of future clinical studies of DTG in neonates.

DTG is widely used in clinical practice for the management of HIV. The World Health Organization (WHO) recommends DTG as a first-line ARV, including for pregnant women.[15] In addition, DTG is recommended as a component of preferred ARV regimens for pediatric patients aged ≥4 weeks and weighing ≥3 kg by both the WHO and the HHS Panel on Antiretroviral Therapy and Medical Management of Children Living with HIV.[2] However, no data are available regarding dosing, efficacy or safety of DTG in newborns less than 4 weeks of age. Thus, there is a critical need to fill this knowledge gap and determine the safety, efficacy, and optimal dosing of DTG during the first weeks of life.

Drug dosing in the neonatal population is challenging in part due to rapidly changing physiology. For example, the activity of UGT1A1 is very low at birth and increases during the first weeks of life.[7,16,17] To account for developmental increases in UGT1A1-mediated glucuronidation, a maturation function was used for the neonate simulations.[18] Because the disposition of DTG is similar to raltegravir (RAL), a previously developed maturation function for RAL was adopted to describe developmental changes of DTG clearance.[10]

Notably, FDA-approved dosing for RAL in neonates indicates that if the mother has taken RAL between 2–24 hours before delivery, the neonate's first dose should be given between 24–48 hours after birth.[19] However, in contrast to RAL, cytochrome P450 3A (CYP3A) plays a minor role in DTG metabolism.[3] In neonates, CYP3A7 is the predominant CYP3A isoform[20] yet there are no *in vitro* or *in vivo* data on DTG metabolism via CYP3A7 (as opposed to CYP3A4/5).

No exposure-response relationship has been identified for DTG for safety and thus a clear upper bound for C_{max} is not available. In vitro data suggests that extremely high DTG plasma concentrations displace unconjugated bilirubin from albumin and could lead to neonatal brain injury, so that extremely high DTG plasma concentrations should be avoided in neonates.[21] The FDA has stated that a C_{max} less than 2-fold the adult value (3.67 μg/mL) is not considered to be clinically relevant based upon safety information in adults and older children.[8] From pooled analyses of the IMPAACT P1093 and ODYSSEY studies, a median C_{max} of 7.16 μg/mL (%CV 26%) was observed from pediatric patients weighing 20–25 kg receiving DTG 30 mg daily without an apparent safety signal.[8] In this study the lower bound of the target range was 0.77 μg/mL. This value has been used in other pediatric DTG trials as well as the FDA in regulatory review.

The current study has limitations. Neonate DTG washout data – from which the popPK model was developed and simulations were performed – were available from 18 infants with a median (IR) gestational age at birth of 38.9 weeks (34.9 – 42.3). A total of 2 infants were preterm (<37 weeks). Therefore, these findings should not be broadly extrapolated to preterm infants, particularly as UGT1A1 activity and DTG clearance are expected to be lower in this population who are more susceptible to bilirubin induced brain injury. Bioavailability was assumed to be 100% for infant simulations. If actual bioavailability is lower, observed concentrations in neonates will be lower than predictions. Next, although breastfeeding presents an ongoing risk of HIV exposure after birth and is not recommended in the United States, breastfeeding is common in resource-limited settings. Based on limited data, DTG is detectable in small amounts of breastmilk but not likely to contribute significantly to DTG plasma concentrations in the neonate while breast feeding infants have higher plasma bilirubin concentrations.[13,22] However, acquisition of DTG through breastmilk was not considered in this analysis. Finally, a limited range of maternal and neonatal dosing scenarios was explored. In the mother, DTG dosing was simulated at 6, 12, or 24 hours prior to delivery, yet in some clinical scenarios DTG may be taken over 24 hours prior to delivery. Further, only the first two DTG doses (at a dose amount of 5 mg) in infants were simulated. For both prophylaxis and treatment, ARV dosing will be continued for weeks or longer. A 5 mg dose was simulated to represent the lowest dose DTG dispersible tablet formulation currently commercially available and suitable for neonatal administration (5 mg TIVICAY PD tablets for oral suspension). A 5 mg dose was simulated to represent the lowest dose DTG dispersible tablet formulation currently commercially available and suitable for neonatal administration (5 mg TIVICAY PD tablets for oral suspension). This formulation cannot be used to provide accurate doses smaller than 5 mg. Development of alternative formulations (e.g. oral solutions or granules) is required in order to provide smaller doses to neonates.

In conclusion, newborn DTG dosing requirements during the first days of life depend upon maternal DTG dosing history prior to delivery. These results may inform the design of future clinical studies of DTG in the neonatal population.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Conflicts of Interest and Source of Funding:

No conflicts of interest are declared for the authors. Overall support for the International Maternal Pediatric Adolescent AIDS Clinical Trials Network (IMPAACT) was provided by the National Institute of Allergy and Infectious Diseases (NIAID) of the National Institutes of Health (NIH) under Award Numbers UM1AI068632 (IMPAACT LOC), UM1AI068616 (IMPAACT SDMC) and UM1AI106716 (IMPAACT LC), with co-funding from the Eunice Kennedy Shriver National Institute of Child Health and Human Development (NICHD) and the National Institute of Mental Health (NIMH). The content is solely the responsibility of the authors and does not necessarily represent the views of the NIH.

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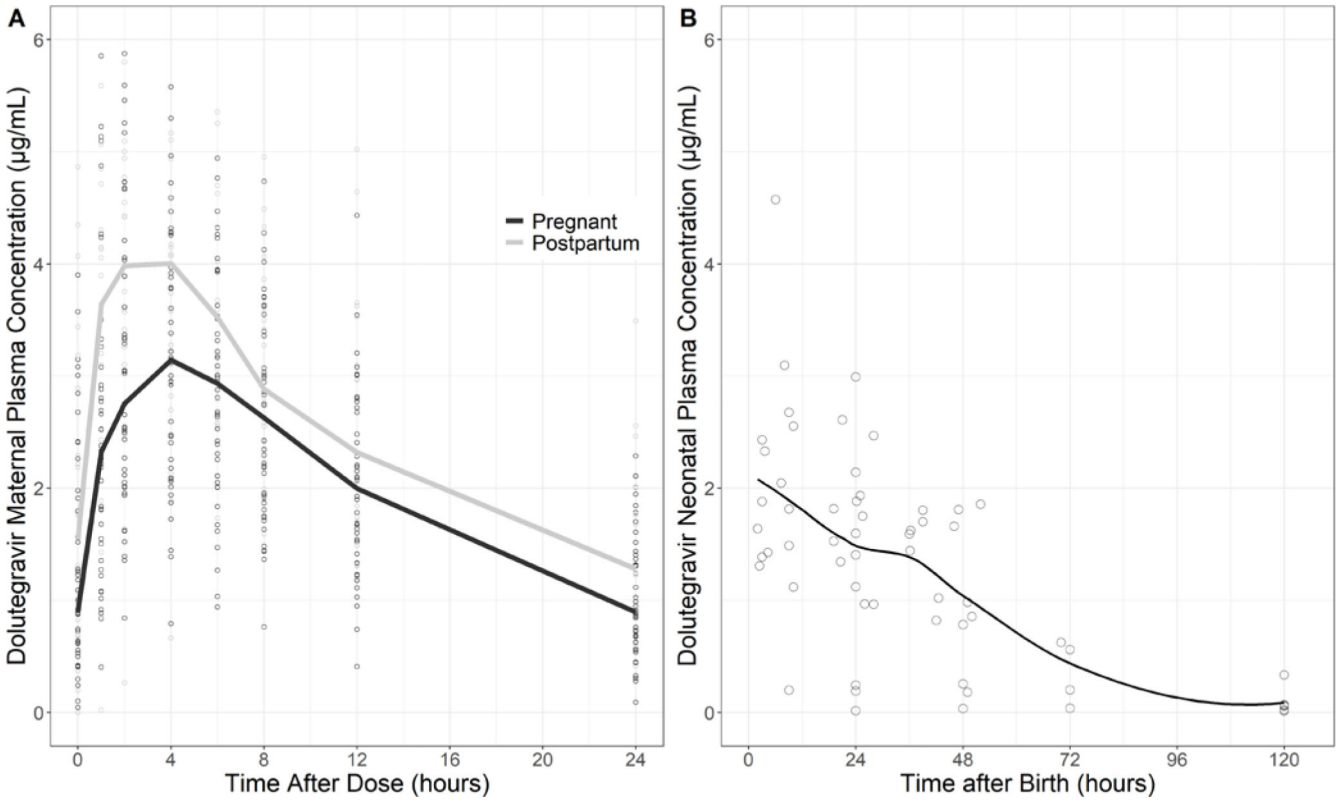

Figure 1:

Observed dolutegravir plasma concentration vs. time data for: A. Pregnant and post-partum participants and B. Neonates. Solid lines represent median concentrations.

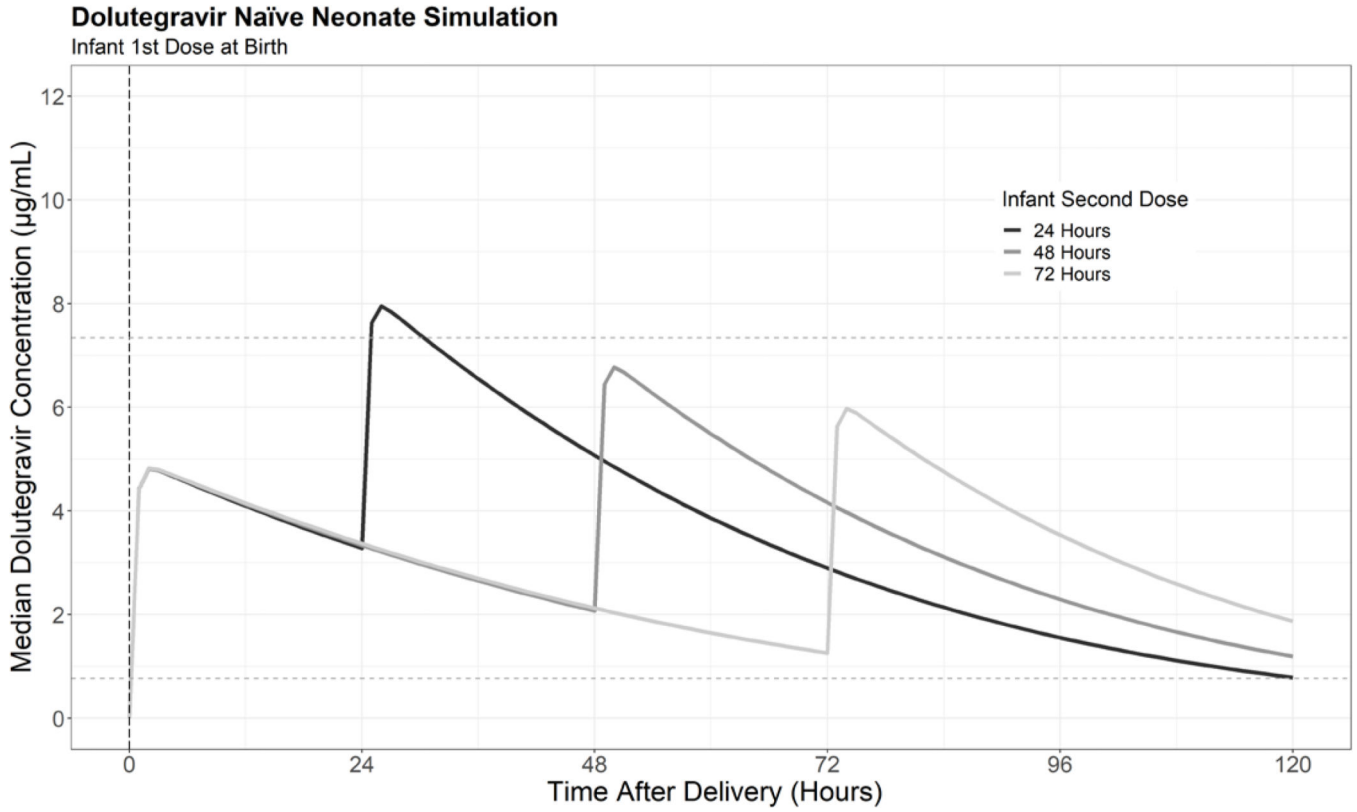

Figure 2:

Monte Carlo simulations for dolutegravir naïve neonates who received an initial 5 mg dose at delivery and second dose 24, 48, or 72 hours after delivery. The vertical black dashed line represents the time of the first dose. The horizontal dashed gray lines represent the lower and upper bounds of the target range (0.77 µg/mL and 7.34 µg/mL).

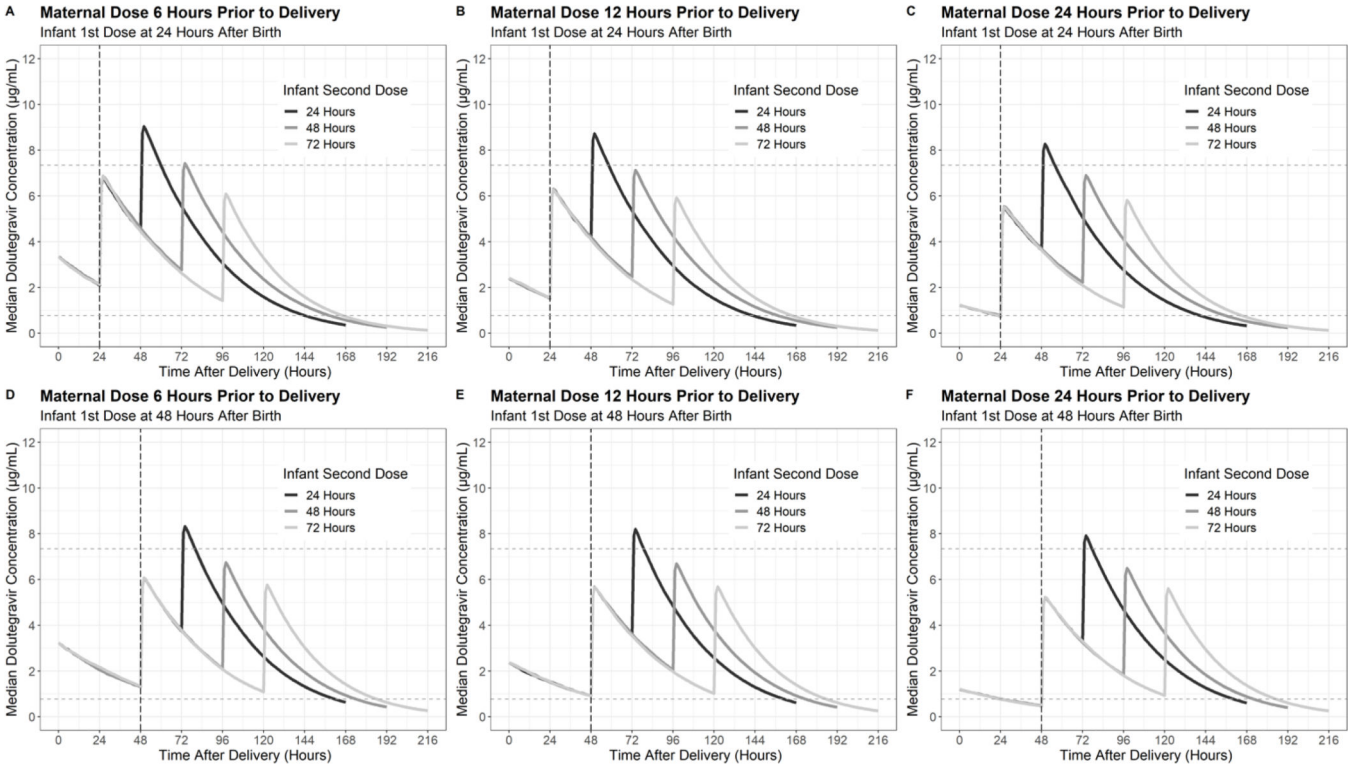

Figure 3:

Monte Carlo simulations for neonates born to mothers receiving dolutegravir 50 mg daily with last maternal doses at either 6, 12 or 24 hours prior to delivery. The initial 5 mg dose in neonates is simulated either at 24 hours after birth (A-C) or 48 hours after birth (D-F). The second neonate dolutegravir doses were simulated at 24, 48, or 72 hours after the first dose. The vertical black dashed line represents the time of the first dose. The horizontal dashed gray lines represent the lower and upper bounds of the target range (0.77 µg/mL and 7.34 µg/mL).

Table 1.

Maternal and Neonatal Population Pharmacokinetic Final Parameter Estimates

Parameter	Final Estimate	SE	Bootstrap Estimates (median and 95% CI)*
Maternal Model			
CL/F (L/hr)	0.73	0.0596	0.77 (0.667–0.899)
Vd/F (L)	18.5	1.39	18.3 (16.0–21.5)
Ka ($hours^{-1}$)	1.08	0.206	1.06 (0.768–1.48)
Pregnancy ~ CL	1.42	0.102	1.41 (1.24–1.68)
Weight ~ Vd	0.729	0.145	0.715 (0.382–1.1)
Between Subject Variability			
CL/F	29.3%	3.61%	28.7% (21.0–35.6%)
V/F	20.2%	4.36%	18.0% (4.68–26.0%)
Ka	74.3%	14.0%	73.9% (17.2–101.5%)
Residual Variability			
Proportional Error	29.1%	2.89%	28.4% (24.0–34.2%)
Additive Error**	0.45 μg/mL	-	-
Neonate Model			
Ke ($hours^{-1}$)	0.0157	0.00162	0.0154 (0.0121–0.0180)
Between Subject Variability			
Ke	43.4%	19.1%	42.8% (12.6–78.5%)
Residual Variability			
Proportional Error	47.6%	8.74%	47.5% (32.1–62.4%)

*92.4% Completed Runs for Maternal Model and 89.2% for Neonate Model

**Additive error was fixed to 0.45 μg/mL

$$Maternal\frac{CL}{F}\left(\frac{L}{hr}\right) = 0.73\ x\ \left(1.42\ if\ pregnant\right)$$

$$Maternal\frac{V}{F}(L) = 18.5\ x\ \left(\frac{Weight\ (kg)}{79.4}\right)^{0.729}$$