Optimizing Dolutegravir Initiation in Neonates using Population Pharmacokinetic Modeling

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Introduction

- Infants exposed perinatally to HIV should receive postpartum antiretroviral drugs beginning soon after birth
- Dolutegravir (DTG) is approved by the FDA down to 4 weeks of age, but there is still a knowledge gap on when to begin dosing in the days after delivery
- To address this unmet need, population pharmacokinetic (popPK) modeling and simulation was utilized to optimize initiation of DTG in neonates

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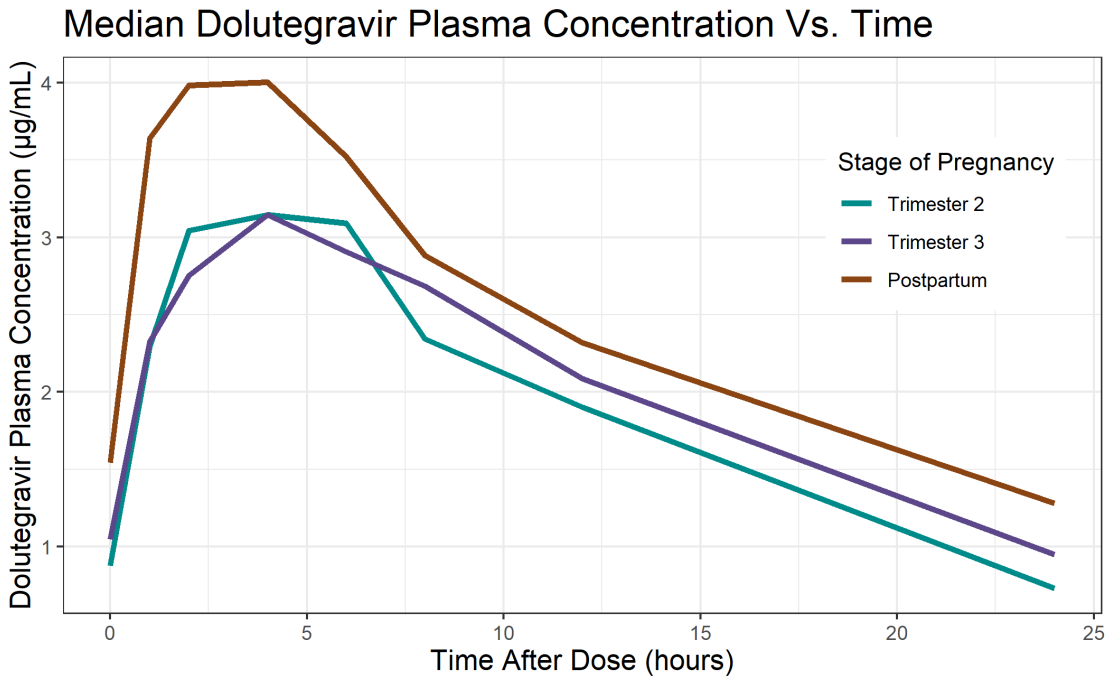
Pharmacokinetic Summary Data

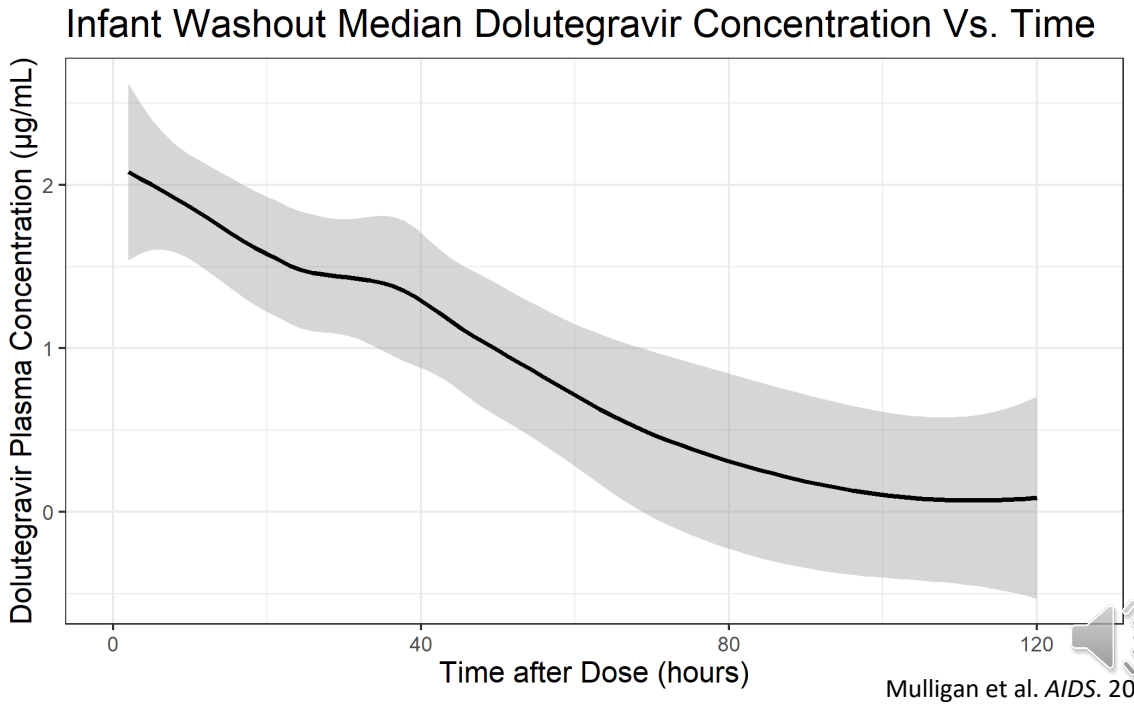
Maternal Data (n=31)

Demographic	Median	Min	Max
Age (years)	31.0	21.0	42.0
Weight (kg)	79.4	45.9	232.6
Serum Creatinine (mg/dL)	0.7	0.4	1.3

Neonatal Data (n=18)

Demographic	Median	Min	Max
Gestational Age (Weeks)	38.0	36.0	40.0
Weight (kg)	3.1	2.4	4.0
Length (cm)	50.0	44.0	54.0
Sex	Male (n=7)	Female (11)	





Mulligan et al. *AIDS*. 2018

Maternal and Neonatal Model Parameters

Maternal Model Output

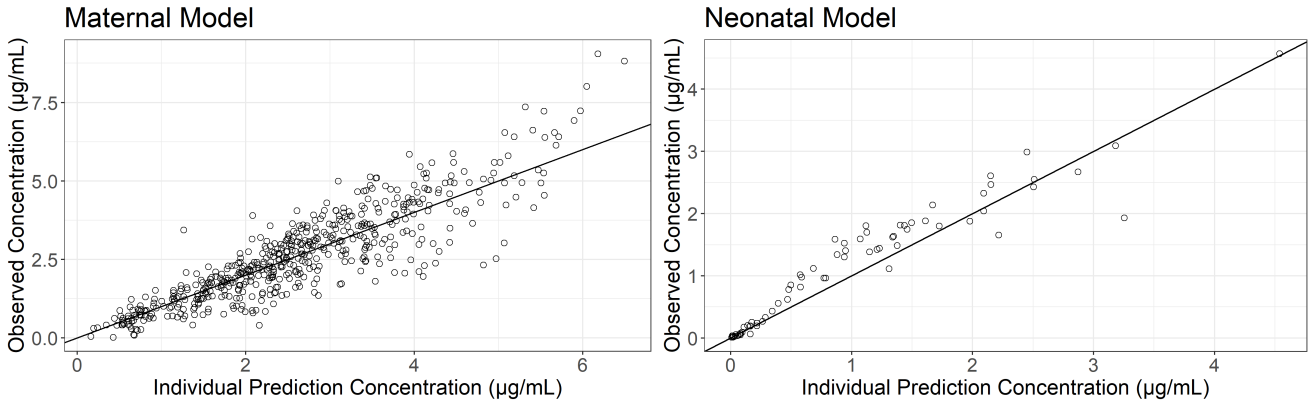
Parameter	Final Estimate	SE
CL/F (L/hr)	0.75	0.0575
Vd/F (L)	17.6	0.958
Ka (hours^{-1})	1.04	0.146
Pregnancy ~ CL	1.45	0.106
Vd ~ Weight	0.714	0.179
Between Subject Variability		
CL/F	30.7%	3.53%
V	20.5%	4.72%
Ka	76.4%	12.5%
Residual Variability		
Proportional Error	24.1%	2.96%
Additive Error	264 ng/mL	148.2 ng/mL

$$\frac{CL}{F}\left(\frac{L}{hr}\right) = 0.75 * (1.45\ if\ pregnant)$$

$$\frac{Vd}{F}(L) = 17.6 * (\frac{WTKG}{79.4})^{0.714}$$

Neonatal Model Output

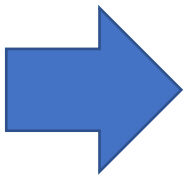
Parameter	Final Estimate	SE
Ke (hours^{-1})	0.0157	0.00162
Between Subject Variability		
Ke	43.4%	19.1%
Residual Variability		
Proportional Error	47.6%	8.74%



Simulation of Neonatal Plasma Concentrations

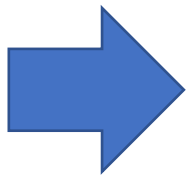
Simulated Maternal Concentrations at Delivery

DTG dosed in 3rd trimester women 6-24 hours prior to delivery



Transplacental DTG

A cord blood/maternal plasma ratio of 1.25 was used to calculate transplacental DTG administration



Simulated Neonatal Concentrations at Birth and after First Oral Dose

Neonatal dosing occurred 0-72 hours after birth

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Maternal Time from Last Dose to Delivery (hours)	Neonatal Time after Birth to 5 mg Dose (hours)			
	Birth	24	48	72
	Simulated Neonatal Median Pre-dose Concentration (µg/mL)			
6	3.42	2.20	1.48	1.04
12	2.37	1.63	1.01	0.74
24	1.06	0.78	0.50	0.33
	Simulated Neonatal Median Cmax (µg/mL)			
6	8.11	6.92	6.24	5.81
12	7.10	6.36	5.79	5.53
24	5.85	5.56	5.30	5.15

CONCLUSIONS

- Neonatal dose prior to concentration falling below 0.5 µg/mL avoids Cmax > 7.0 µg/mL
- Initiation of neonatal DTG 24-48 hr after birth is appropriate if last maternal dose given within 24 hours of delivery

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  - Sites and participants in the study

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