Lamivudine (3TC) Dosing for Preterm Neonates Exposed to HIV

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BACKGROUND

- Preterm infants born to pregnant women with HIV require antiretrovirals for prevention and treatment of HIV.
- Lamivudine (3TC) is one of 3 antiretrovirals widely used in neonates but no pharmacokinetic (PK) data are available in infants <34 weeks gestational age (GA).
- 3TC is primarily renally eliminated and immature kidney function after birth significantly impacts 3TC clearance.

We developed a pragmatic 3TC twice daily dosing strategy for preterm infants, stratified by GA bands: (i) ≥27 to <30 weeks; and (ii) ≥30 to <36 weeks

METHODS

Study Population

- 3TC concentration data were combined from 8 completed studies performed in neonates and young infants receiving the liquid 3TC formulation twice daily **Table1.**

Table 1. *Summary of the 3TC concentration-time data available for development of the population PK model*

Study	Number of Children	Number of Samples	Median Age at 1st PK (weeks)
PACTG 300 (Tx)	15	67	23
PACTG 353 (PNP)	20	101	1.0
PACTG 356 (Tx)	40	268	14
PACTG 358 (PNP)	12	55	3.1
PACTG 386 (PNP)	12	63	7.3
EIT Study (Tx)	28	51	1.1
IMPAACT 1069 (Tx)	1	7	26
IMPAACT 1106 (Tx)	26	246	9.0

PACTG=Pediatric AIDS Clinical Trials Group; Tx=treatment; PNP=postnatal prophylaxis; EIT= Early Infant HIV Treatment in Botswana; IMPAACT=International Maternal Pediatric Adolescent Clinical Trials Network

Pharmacokinetic Modelling and Simulation

- A population PK model was used to describe 3TC plasma concentrations using non-linear mixed effects regression.
- Covariates assessed included, GA, postnatal age (PNA), postmenstrual age (PMA), (i.e., GA+PNA), birth weight (BWT), body weight (WT), and serum creatinine.
- Different 3TC dosing strategies were simulated in a virtual population of preterm infants from birth through 6 months of life with the goal of achieving 3TC exposures comparable to those reported in children.
- The 3TC geometric mean (GM) exposure ($AUC_{0\text{-}12}$) target range was 3.15 to 13.24 µg·hr/mL.

Proposed 3TC Preterm Dosing
based on PK modeling & simulation

Gestational Age Bands	0 - <4 Weeks of life	≥4 Weeks of life
GA 27 to < 30 weeks	2 mg/kg BID	2 mg/kg BID
GA ≥ 30 to < 36 weeks	2 mg/kg BID	4 mg/kg BID

Infants ≥3kg and aged ≥4 weeks switch to 30mg BID (per WHO)

RESULTS

- 858 3TC plasma concentrations were from 154 infants were included in the analysis; 61 (40%) infants were males and 34 (22%) were born preterm.
- At the 1st PK sampling, infants had a median PMA of 42.8 (range; 35.7-64.6) weeks, PNA of 6.3 (0.52-26.6) weeks, body weight of 3.8 (1.9-7.8) kg, and creatinine of 0.4 (0.1-1.2) mg/dL, respectively.
- 3TC concentrations were adequately described by a 1-compartment PK model, with clearance (CL/F) and volume of distribution (Vd/F) allometrically scaled to body weight. Maturation of 3TC CL/F was described using an Emax model based on PNA, which also influenced Vd/F. The prediction-corrected visual predictive check (pcVPC) of the model fitting the 3TC data is shown in **Figure 1**.
- For simulations, the final 3TC PK model was modified to account for the expected lower renal function in preterm infants by including GA as a covariate on birth CL/F. The PK parameters of the model used for simulations is shown in **Table 2**.
- Results of the model simulations for babies with GA 27-40 weeks through 6 months of life using 3TC doses between 2 to 4 mg/kg twice daily, **stratified by GA bands,** are shown in **Figure 1.**

Figure 1. *Prediction-corrected visual predictive check the final 3TC PK model*

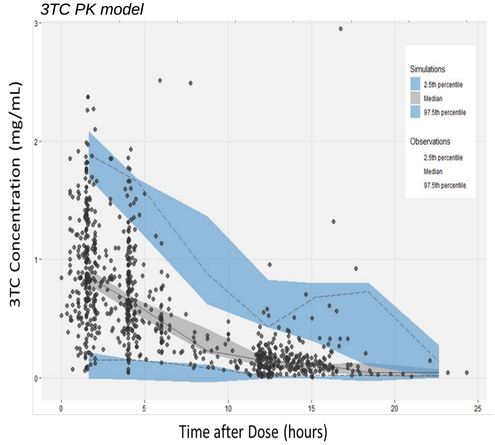


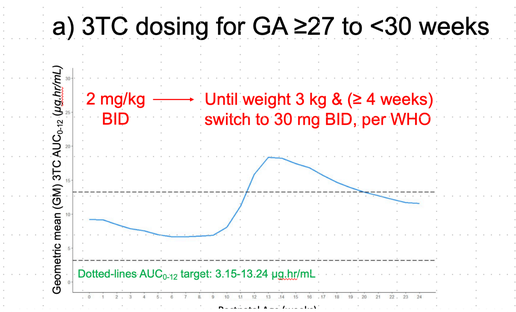
Table 2: *Final 3TC population PK parameter estimates expanded for gestational age down to 27 weeks*

	Final Model		SIR	
3TC PK Parameters	Estimate	RSE (%)	Median	2.5th-97.5th percentile
Ka (1/hr)	1.33	11	1.33	1.03-1.66
CL/F (L/hr)				
Maturation Parameters				
CL_{BL}	0.335	8	0.334	0.278-0.385
Emax	1.12	6	1.12	0.99-1.27
TM50 (days)	82.7	5	82.8	73.3-90.6
Hill	1.31 (fixed)	-	-	-
$\theta_{Tm50\text{-}GA}$	-2.35 (fixed)	-	-	-
$\Theta_{CLBL\text{-}GA}$	1.6 (fixed)	-	-	-
Vc/F (L)	2.84	5	2.84	2.53-3.14
θ_{PNA}	0.112	32	0.110	0.045-0.176
Inter-individual variability (IIV)				
ω^2CL/F	0.096	20	0.095	0.058-0.134
ω^2Vc/F	0.078	34	0.076	0.027-0.127
Residual Variability				
Proportional	0.202	7	0.203	0.174-0.232

*CL/F oral clearance; Vd, apparent volume of distribution; RSE%: relative standard error (standard error of estimate / estimate*100); SIR, sampling importance resampling.

RESULTS (continue)

Figure 1. *Predicted 3TC GM $AUC_{0\text{-}12}$ through 24-weeks of life: (a) 2 mg/kg BID from birth; (b) 2 mg/kg BID, first 4-weeks of life, then 4 mg/kg BID. Infants ≥3kg and aged ≥4 weeks switch to 30mg BID (per WHO).*



CONCLUSIONS

- We provide the first modeling and simulation-based 3TC dosing guidance for preterm (≥27 weeks) hospitalized neonates born to women living with HIV. Infants ≥3kg and aged ≥4 weeks switch to 30mg BID (per WHO).
- This pragmatic twice daily 3TC mg/kg dosing strategy, considered body weight, time after birth, and anticipated changes in renal maturation during early life.
- This proposed preterm 3TC dosing guidance is endorsed by the WHO-Pediatric Antiretroviral Working Group (PAWG) but requires clinically validation to provide reassurance of model predictions.

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