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Pharmacokinetics of Daily Nevirapine in Neonates at High Risk of HIV Acquisition

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Background

- InInfants born to HIV-infected women with no or a short duration of antiretroviral treatment during pregnancy are at high-risk of perinatal transmission.
- Nevirapine (NVP) is a key component of antiretroviral (ARV) prophylaxis for newborns at high risk of intrapartum HIV infection.
- For infants diagnosed HIV positive at birth, 'therapeutic' dosing of nevirapine is necessary
- Thus, it is important to determine the optimal prophylaxis dose of NVP in newborns at High Risk of HIV Acquisition and the therapeutic dose for HIV-infected infants identified at birth

Objective

- To develop a population pharmacokinetic (PK) model to describe NVP concentrations in infants from birth through the first 2 weeks of life.

Study Design & Methods

Study Design and Population

- Infants were enrolled in an adaptive single-arm, multicenter trial in Thailand assessing 'Perinatal Antiretroviral Intensification' to prevent mother-to-child transmission of HIV in pregnant women with <8 weeks of triple ARV treatment prior to delivery (ClinicalTrials.gov NCT01511237).

ARV Prophylaxis

- Intensification consisted of maternal single-dose NVP (sd-NVP) during labor and an infant 2-week course of AZT+3TC+ NVP, followed by AZT+3TC for 2 weeks. NVP dosing was 2 mg/kg for 7 days, then 4 mg/kg for 7 days.

PK Sampling

- Infant blood samples were draw from the umbilical cord at birth, on the first day of life and at 2 weeks.

Drug Level Measurement and PK analysis

- Measurement of NVP plasma drug levels were performed by a validated HPLC assay (lower limit of quantitation of 0. 050 mg/L)
- Population means and variances of NVP PK parameters were estimated using non-linear mixed effects regression models (NONMEM Version VII).
- Infant characteristics (weight, sex, age, postnatal age) were evaluated for their inclusion in the model.
- The validity of the final model was evaluated using a visual predictive check and bootstrap re-sampling techniques (400 Bootstrap analyses).
- Monte Carlo simulations were performed to estimate the probability of achieving target NVP trough concentrations (C24) for prophylaxis (>0.10 mg/L) and for therapeutic efficacy (>3.0 mg/L) during the first 2 weeks of life.

The study was approved by the Ethics Committees (EC) at the Ministry of Public Health, Thailand; the Faculty of Associated Medical Sciences, Chiang Mai University, and local hospital ECs.

Results

- Sixty two infants were included in this analysis:

Table 1: Infant Characteristics at Birth

Median (range)	(n=62)
Gender	
Male	35 (56%)
Female	27 (44%)
Race/Ethnicity: Asian	62 (100%)
Gestational Age at Birth (wks)	38.6 (35.7-41.7)
Weight (kg)	2.9 (2.3-3.7) kg

Nevirapine Population Pharmacokinetic Model

- NVP pharmacokinetics was best described by a one compartment model with first order absorption and elimination.
- Body weight influenced NVP apparent oral clearance (CL/F) and volume of distribution (Vd/F).
- Goodness of fits plots of the NVP model are shown in Figure 1 and evaluation by visual predictive check is shown in Figure 2
- Final population estimates of NVP are presented in Table 2

Figure 1: Goodness-of-fit plots of the final NVP model

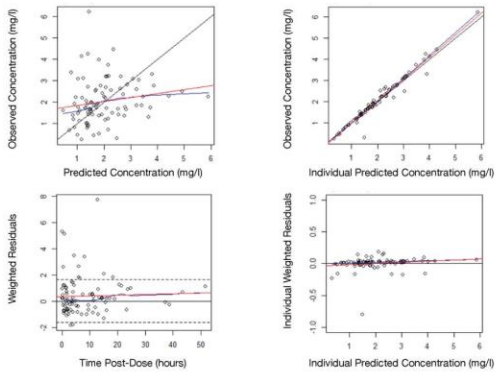


Figure 2: Visual predictive check for NVP population PK model. Lines represent the predicted population 5%, 50% and 95% percentiles and shaded areas are the 90% CIs. Observed concentrations from the infants are superimposed.

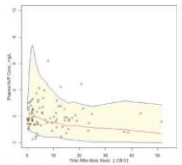


Table 2: Final NVP population pharmacokinetic parameter estimates

	Final Model		Bootstrap^	
NVP PK Parameters	**Estimate**	**RSE (%)**	**Median**	**5th - 95th percentile**
CL/F (L/h/3kg)	0.144	10.2	0.147	0.114 - 2.02
θ_{WT-CL}	4.00	21.1	3.93	2.62 - 5.70
Vd/F (L/3kg)	3.67	30.8	3.51	1.90 - 6.69
θ_{WT-Vd}	4.59	25.7	4.66	2.00 - 8.10
Ka (h^{-1})	0.23	55.1	0.21	0.10 -0.79
Inter-individual variability (IIV)				
IIV (CL/F)	0.51	12.3	0.52	0.40 – 1.02
IIV (Vd/F)	1.48	16.1	1.32	0.70 – 2.05
IIV (Ka)	1.00	49.3	1.00	0.01 – 2.2
Residual Variability				
σ (Proportional)	0.12	39.7	0.12	0.03 - 0.2

- RSE%: relative standard error (standard error of estimate / estimate*100);

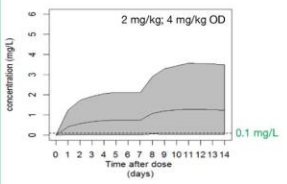
Simulation of Prophylaxis NVP dosing in Newborns

- Simulations of NVP trough concentration for a 3 kg infant receiving 2 mg/kg NVP once daily for 7 days and then 4 mg/kg for 7 days is shown in Figure 3a. Based on simulations for a 3 kg infant, without maternal sd-NVP, >88% would have a NVP C24 >0.1 mg/L after 24 hours through 2 weeks.
- Simulations of NVP trough concentration for a 3 kg infant receiving the WHO recommended 15 mg once daily dose is shown in Figure 3b; it was predicted that >92% of infants would have a NVP C24 >0.1 mg/L after 24 hours.

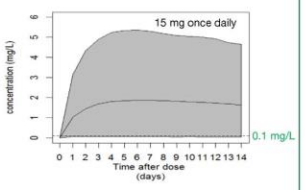
Figure 3: Simulated NVP C24h in newborns following (a) 2 mg/kg OD at birth, then 4 mg/kg OD at day 7 to 14 (PHPT-5 dosing); (b) 15 mg once daily from birth until days 14 of life (WHO guidelines).

[Note: Middle line is the 50th percentile, lower/upper solid lines represent the 5th & 95th percentiles of the simulated data]

a)



b)



Median (5th, 95th percentile) NVP C24:
At 24 hour : 0.41 (0.03-1.2) mg/L
At Day 14 : 1.24 (0.05-3.5) mg/L

Median (5th, 95th percentile) NVP C24:
At 24 hour : 1.03 (0.06-3.2) mg/L
At Day 14 : 1.62 (0.05-4.6) mg/L

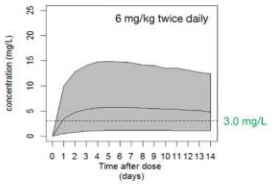
Simulation of Therapeutic dosing in Newborns

- Assuming linear kinetics, simulations of NVP trough concentration for a 3 kg infant receiving 6 mg/kg NVP twice daily for 14 days is shown in Figure 4a. It was predicted that 72% of infants would have a C24 >3.0 mg/L at 48 hours and 76% at 2 weeks.
- With 8 mg/kg twice daily the C24 was predicted to be >3.0 mg/L in 81% of in fants at 48 hours and 86% at 2 weeks (Figure 4b).

Figure 4: Simulated NVP C24h in newborns following (a) 6 mg/kg (b) 8 mg/kg twice daily from birth until days 14 of life.

[Note: Middle line is the 50th percentile, lower/upper solid lines represent the 5th & 95th percentiles of the simulated data]

a)



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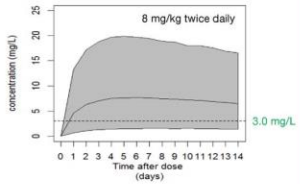

Median (5th, 95th percentile) NVP C24:
At 48 hour : 4.7 (0.8-12.9) mg/L
At Day 14 : 4.9 (1.1-12.5) mg/L

Median (5th, 95th percentile) NVP C24:
At 48 hour : 6.3 (1.0-17.1) mg/L
At Day 14 : 6.5 (1.4-16.6) mg/L

Conclusion

- The escalating NVP dose in PHPT-5 and the WHO single dose approach rapidly achieve and maintain target prophylactic concentrations over the first 2 weeks of life.
- Therapeutic NVP doses of 6 to 8 mg/kg twice daily should be studied in infants initiating treatment within the first few days of life.

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