

**Population Pharmacokinetics
(Pk) of Low Dose Nevirapine
(NVP) for Prevention of Breast
Milk HIV Transmission in
Infants from Birth through 6
Months of Age**

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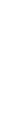
Background

- Mother to infant HIV transmission via breast milk remains a major problem in areas of the world where safe alternatives to breast feeding are not available
- Antiretroviral prophylaxis in nursing mothers or their infants has been proposed
- Use of 3TC and NVP administered to nursing infants whose mothers were HIV infected has been reported (*Vyankandondera J et al. IAS Meeting, Paris France 2003*)

- NVP elimination is slow immediately after birth, increases to a peak at 1-4 years, then decreases

	t $\frac{1}{2}$ (hours)
Transplacental washout	45
First week of life (single dose)	37
2 months to 1 year	32
1 to 4 years	21
4 to 8 years	18
>8 years	28

- Few NVP pk available during chronic dosing in infants < 6 months of age to facilitate design of low dose regimen that will provide continuous protective NVP concentrations in nursing infant



Methods

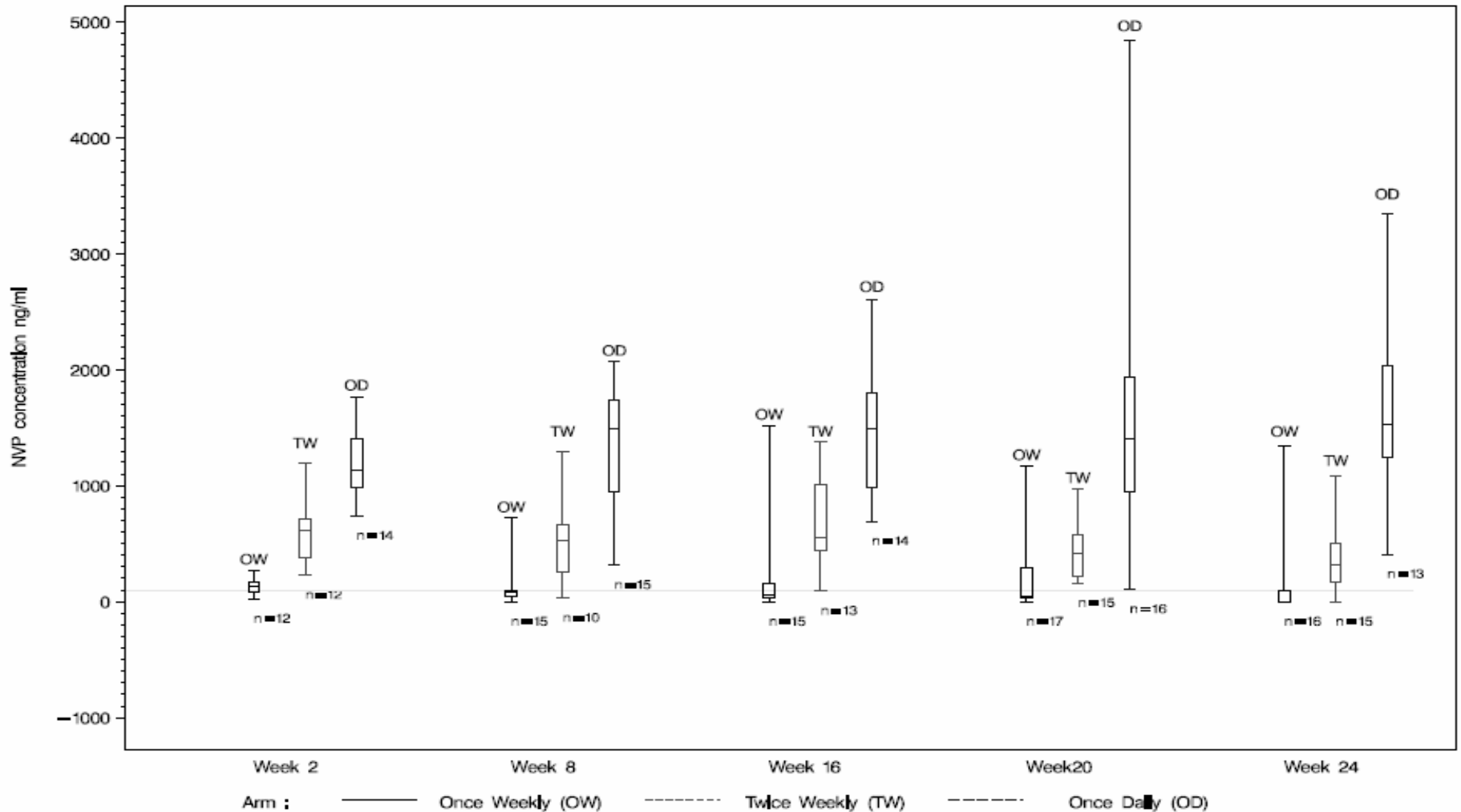
- HIVNET 023 was a phase I/II open label randomized trial of 3 NVP dosing regimens from birth through age 6 months
 - Daily dosing: 2 mg/kg through age 2 weeks, then 4 mg/kg
 - Twice weekly dosing: 4 mg/kg through age 2 weeks, then 8 mg/kg
 - Weekly dosing: 4 mg/kg through age 2 weeks, then 8 mg/kg

- 2 study sites:
 - Chitungwiza, Zimbabwe
 - Durban, South Africa
- Mothers were eligible to enroll if:
 - HIV infected
 - Over 18 years old
 - Had no major pregnancy complications
 - No evidence of clinical AIDS or other serious illness
 - No prior NNRTI use
 - Intended to breast feed

- Eligible women were enrolled at 30-38 weeks
- Single 200 mg NVP dose prescribed for home use at start of labor – no postnatal maternal NVP use
- After delivery, infants were breast fed and mother was encouraged to wean by 6 months
- Infants randomized to one of 3 dosing arms if:
 - Weighed over 2.5 kg
 - Initiated breast feeding by 48 hours of life
 - Had no severe congenital malformations
 - No condition incompatible with life
 - No hyperbilirubinemia requiring exchange transfusion

- Plasma sampling schedule:
 - Within 48 hours after birth and just before first infant dose
 - weeks 2, 8 and 20:
 - predose
 - 4 hours after the dose
 - either just before the next dose (daily dosing arm) or 2-3 days post dose (twice weekly and weekly dosing arms)
 - weeks 16 and 24: predose
- NVP assay by HPLC with LLQ of 25 ng/ml

Predose concentrations have been previously presented (*Shetty, et al. JAIDS 2003;34:482-90*)



Patient Population

- 57 infants contributed 486 concentrations

- Maternal characteristics:

Maternal age: 26.4 +/- 5.7 years

Maternal CD4 count at enrollment: 294 +/- 206 cells/cc

Route of delivery: 48 vaginal, 9 caesarean section

Intrapartum NVP: Given at home = 25

Received on arrival = 27

Not given = 5

- Infant characteristics:

Mean birth weight: 3018 +/- 388 gm

Gestational age: 38.8 +/- 1.4 weeks

Sex distribution: 31 female, 26 male

NONMEM Analysis

- Population pk parameters determined using **NONMEM** (*NON*linear *Mixed Effects Modeling*) Version V
- Individual variation in drug disposition explained by individual differences in fixed effects (age, gender, etc) and random error
- Model selection was based on the impact of covariate inclusion on residual plots, improvement in parameter estimate confidence intervals and changes in the model objective function (MOF) with a change of -3.8 considered to be a significant improvement in the fit of the model ($p < 0.05$).
- 3 step process
 - Development of an initial model
 - Evaluation of the influence of patient characteristics
 - Development of final model

Initial Model

- Advan2 Trans2 (one compartment, oral absorption)
 - Cl/F , Vd/F , Ka , absorption lag modeled
 - transplacentally acquired NVP modeled as zero-order bolus dose administered at birth with variable rate
- Combined additive/proportional error model
- Best fit - no lag, scale Cl/F and Vd/F for weight

Evaluation of Patient Characteristics

- Evaluated effect of gender, dosing cohort, study site and age on Cl/F and Vd/F
- Model fit significantly improved when effect of age on Cl/F and Vd/F added

Reduction in MOF with Addition of Single Characteristics to Cl/F and Vd/F

<i>Covariate</i>	<i>Cl/F</i>	<i>Vd/F</i>
Gender	NS	NS
Dosing Cohort	NS	NS
Site	NS	NS
Age: Washout vs < 6 wks vs > 6 wks	88.1	29.9
Linear [X + (Y*age)]	NS	NS
E max [X+(Y*age)/(Z+age)]	89.7	NS

Verification of Patient Characteristics

- Patient characteristics verified by adding the 2 significant characteristics to model, then removing them one at a time
- Removal of age effect for V_d/F did not significantly affect model fit
- Modeling effect of age on Cl/F with division into 3 age cohorts (washout, < 6 wks, > 6 wks) or with Emax model were not significantly different

Final Model

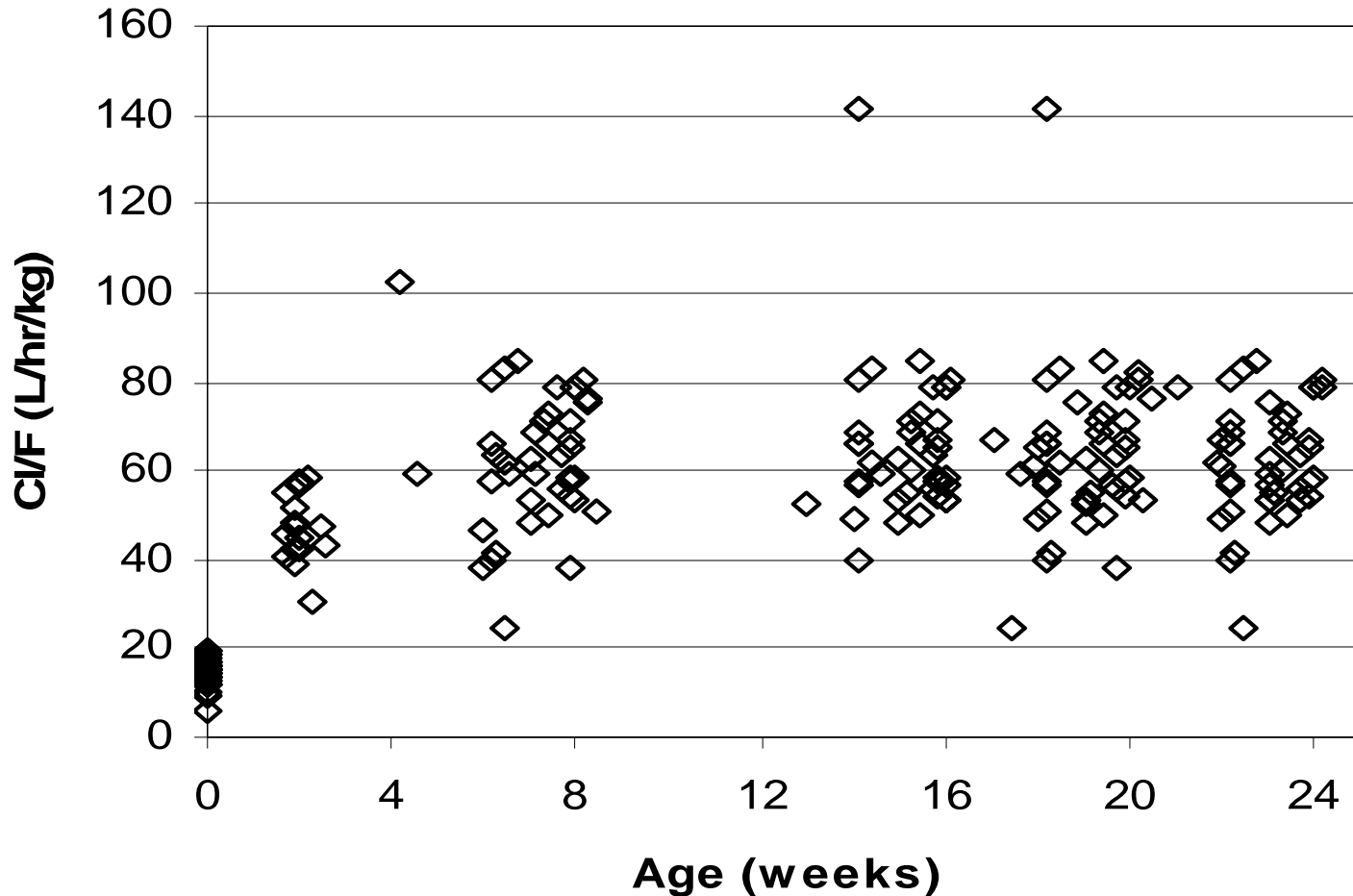
- Cl/F and Vd/F scaled for weight
- Cl/F scaled for 3 age cohorts – washout, < 6 weeks, > 6 weeks
- Combined additive and proportional error model
- Parameters estimated with first order conditional estimation
- Empirical Bayesian post hoc analysis used to estimate Cl/F for each individual at each time sampled

Final Parameter Estimates: Cl/F Scaled by Age Cohorts

Parameter		Population Mean		Interpatient Variability (%CV)	
		Final Estimate	%SEM	Final Estimate	%SEM
Vd/F (L/kg)	Θ_1	3.01	8.6%	32.7	68.4%
Cl/F (ml/hr/kg)	Θ_2	14.8	12.8%	20.3	27.6%
	Θ_3	44.6	4.8%		
	Θ_4	61.6	4.4%		
Ka	Θ_5	.976	58.0%	-----	-----
R2	Θ_6	.0318	30.3%	54.8	59.7%
Residual Variability (%CV)	Proportional	80.2	68.4%		
	Additive	56000	105.7%		

Parameters modeled as: $Vd/F = \Theta_1 * Wt$, $Cl/F = \Theta_2 * Wt$ if washout, $\Theta_3 * Wt$ if < 6 weeks old, $\Theta_4 * Wt$ if 6 weeks to 6 months old

NVP CI/F vs Age From Bayesian Post Hoc Analysis of Final Model



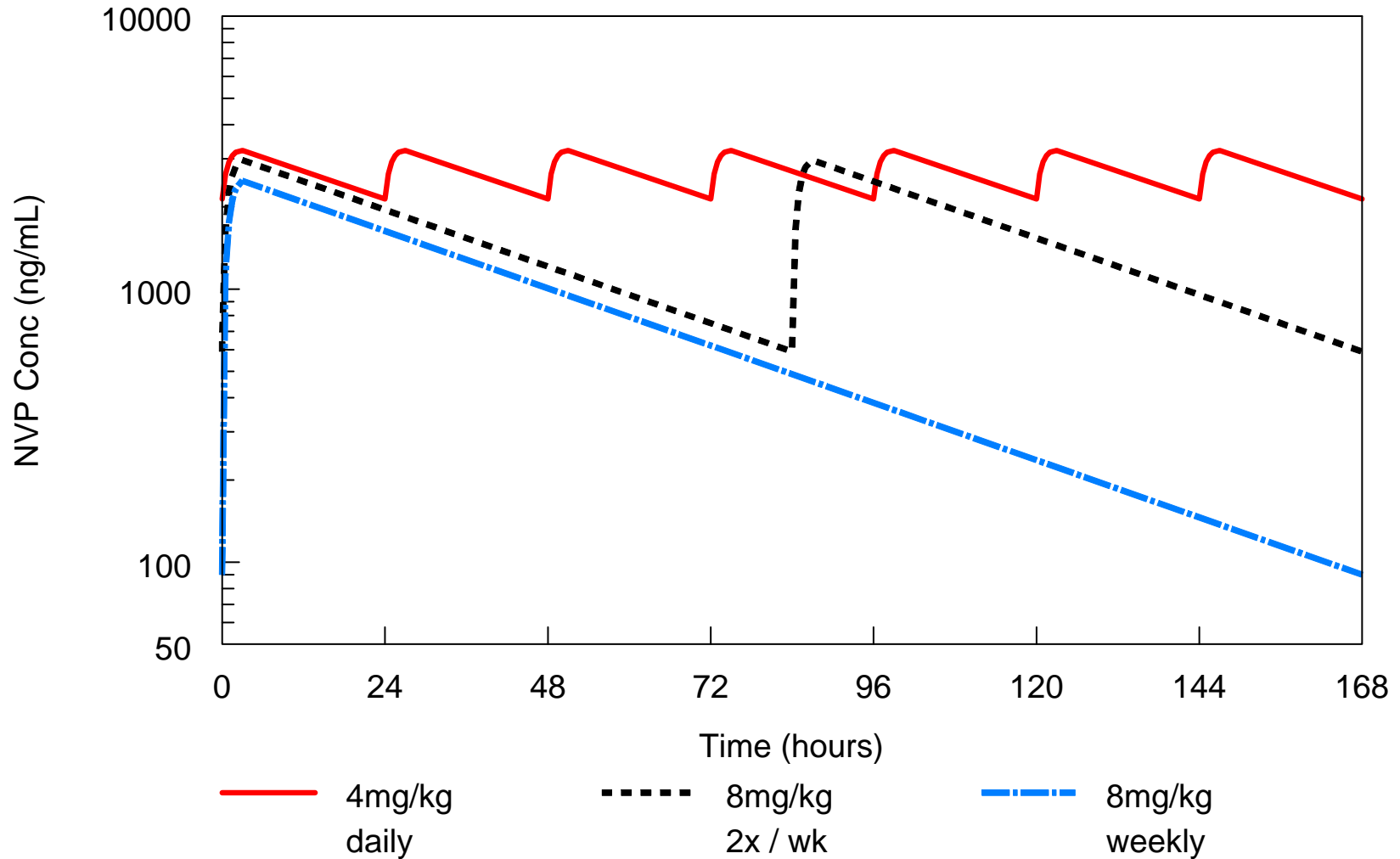
Conclusions

Population Average NVP Elimination Parameters:

	Cl/F (ml/hr/kg)	t^{1/2} (hrs)
Transplacental Washout	14.8	139.1
< 6 weeks	44.6	46.3
6 weeks- 24 weeks	61.6	33.6

Nevirapine Concentrations

Infants Greater than 6 Weeks of Age



Conclusions

- NVP elimination is slow immediately after birth but rises over the first months of life
- Use of the daily or twice weekly regimens maintained NVP plasma concentrations above the 100 ng/ml target throughout the dosing interval during the first 6 months of life

- Although these data suggest NVP C1/F plateaus after 6 weeks of life, data from older infants demonstrate continued increase in NVP C1/F
- Incorporation of these data into an analysis with those of older infants will be necessary to accurately delineate the developmental changes in NVP elimination during the first years of life