UC San Diego
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Population Pharmacokinetics of VRC01 in Infants and Adults

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IMPAACT
International Maternal Pediatric Adolescent AIDS Clinical Trials Network

NIH National Institute of Allergy and Infectious Diseases

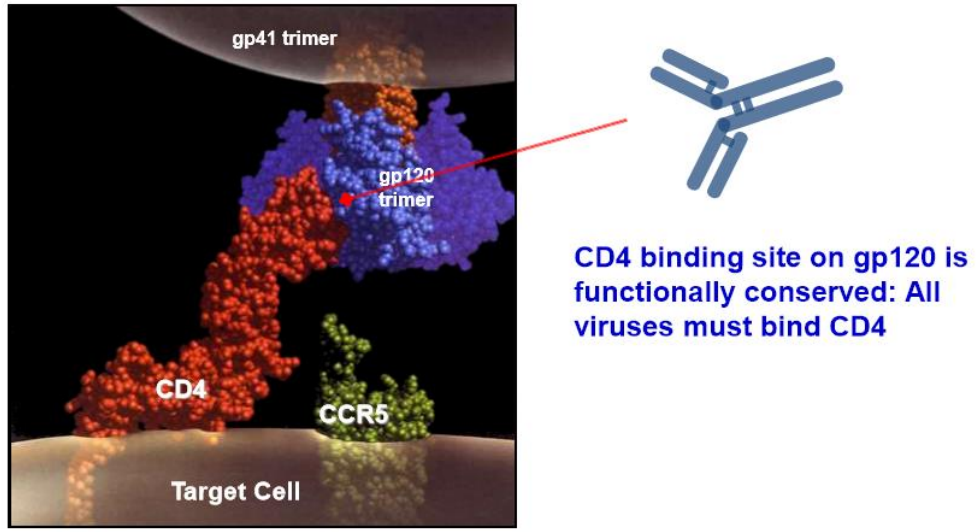
Disclosures

I have no disclosures.

The co-authors have no disclosures.

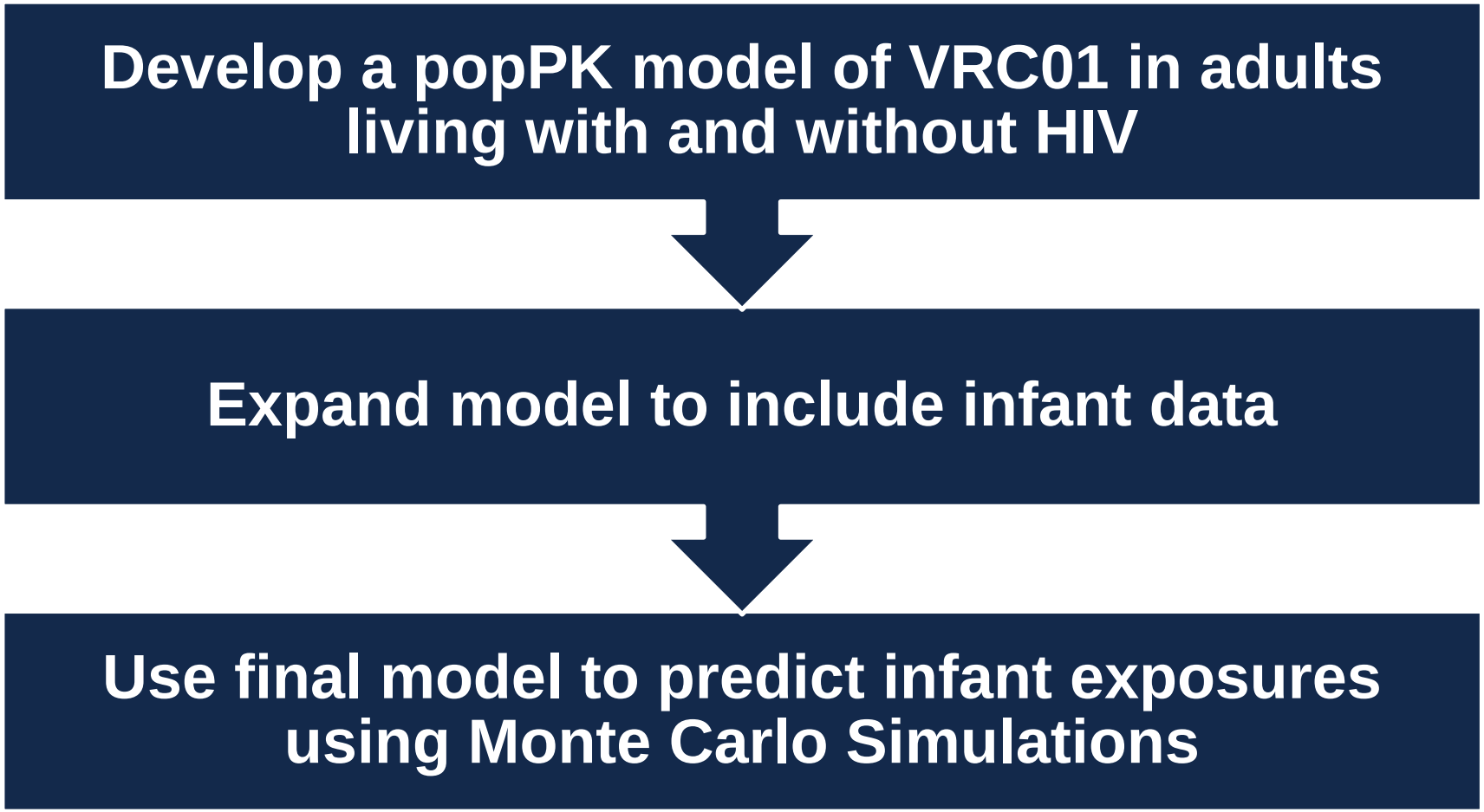
VRC01: a broadly neutralizing antibody (bNAb)

- bNAbs represent a new class of antiretroviral therapy (ART) with long plasma $t_{1/2}$ allowing infrequent administration.
- bNAbs offer advantages over existing ART in preventing HIV transmission and HIV treatment where poor adherence or highly resistant virus are present.
- VRC01 is a bNAb that binds to CD4 binding site of gp120
- VRC01 is potent
  - IC_{50} <1 mcg/mL neutralized 72% tested isolates
  - IC_{50} <50 mcg/mL neutralized 91% tested isolates



<u>Aim</u>: Develop a population PK model in infants and adults

Approach


Develop a popPK model of VRC01 in adults living with and without HIV
Expand model to include infant data
Use final model to predict infant exposures using Monte Carlo Simulations

Methods

- PK data from 3 studies were combined (VRC601, VRC602, P1112)
- NONMEM version 7.3 FOCEI method
  - 2-compartment model
  - Evaluated rate of subcutaneous (SC) absorption
  - Allometric scaling exponent was used to account for subject size on clearance and volume of distribution[1]
    - CL = $\left(\frac{WT}{70}\right)^{0.85}$; Q = $\left(\frac{WT}{70}\right)^{0.85}$; V1, V2 = $\left(\frac{WT}{70}\right)^{1}$
  - Covariates evaluated using univariate followed by multivariate assessment
  - Model validation using bootstrap with 1000 iterations
  - Monte Carlo Simulations of 1000 virtual infants were used to predict VRC01 concentrations following repeat SC administration

1. *Deng R et al. MAbs 2011*

VRC01 Studies

	VRC601[1] (N = 23)	VRC602[2] (N = 23)	P1112[3] (N = 27)
Study Population	HIV positive adults	HIV negative adults	Infants exposed to HIV
IV Administration (N)	1 mg/kg (3) 5 mg/kg (3) 20 mg/kg (3) 40 mg/kg (11)	5 mg/kg (5) 20 mg/kg (8) 40 mg/kg (5)	*N/A*
SC Administration (N)	5 mg/kg (3)	5 mg/kg (5)	20 mg/kg (13) 40 mg/kg (14)
PK Sampling	Hour: 0, 1, 2, 4, 8, 12, 24 Day: 2, 3, 7, 14, 21, 28, 35, 42, 49, 56, 85, 140**	Hour: 0, 1, 2, 4, 8, 12, 24 Day: 2, 3, 7, 14, 21, 28, 56**	Day: 1, 3, 7, 14, 28, 56, 112, 168
Doses Received (1/2)	10/13	3/20	27/0
Age*	31 years (21, 64)	34 years (21, 48)	1.7 days (0, 3)
Weight (kg)*	83.8 (57.6, 115.0)	77.6 (58.5, 104.0)	3.1 (2.2, 4.4)

Abbreviations: IV = intravenous, SC = subcutaneous, mg = milligrams, kg = kilograms
*Median (range) at enrollment
**PK sample drawn only after second dose administration

1. *Lynch RM et al. Sci Transl Med 2015*
2. *Ledgerwood JE et al. Clin Exp Immunol 2015*
3. *Cunningham CK et al. CROI 2017*

Adult VRC01 PopPK Model Parameters

	Final Parameter
Θ1 (V1)	2.30
Θ2 (V2)	5.05
Θ3 (CL)	0.0168
Θ4 (Q)	0.0548
Θ5 (KA)	0.39
Θ6 (F1)	0.612
Θ7 (R1)	0.00669
Θ8 (WTKG on V_{SS})	0.733
Θ9 (HIV on CL)	1.52
IIV on V_{ss}	21.8%
IIV on CL	24.3%
IIV on R1	47.2%
Proportional	19.7%
Additive	1.08

Abbreviations:
IIV = interindividual variability; V_{SS} = steady state volume of distribution

Equations:

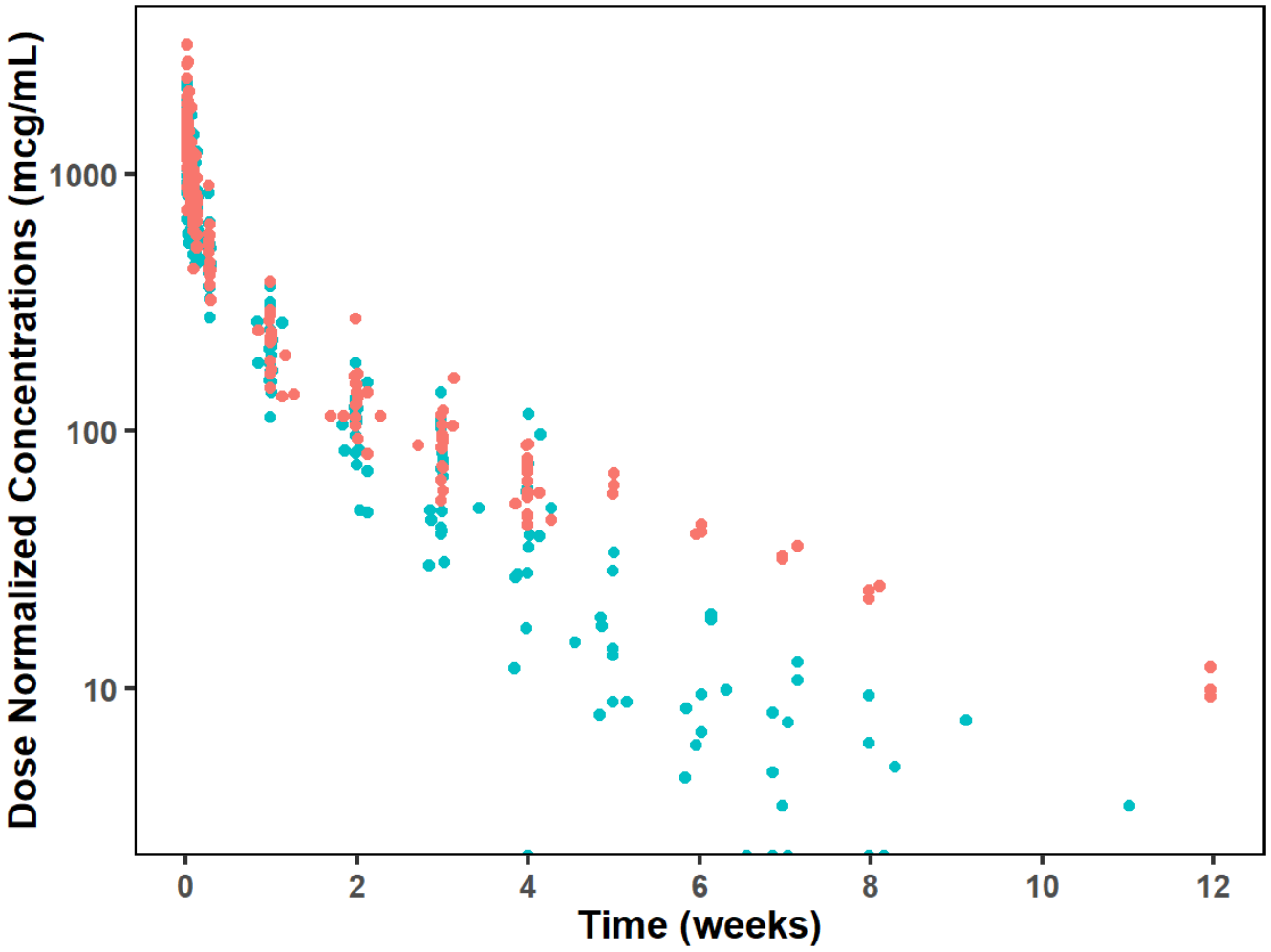
$$CL\ (L/h) = 0.0168 \times 1.52 \text{ (if HIV Positive)}$$

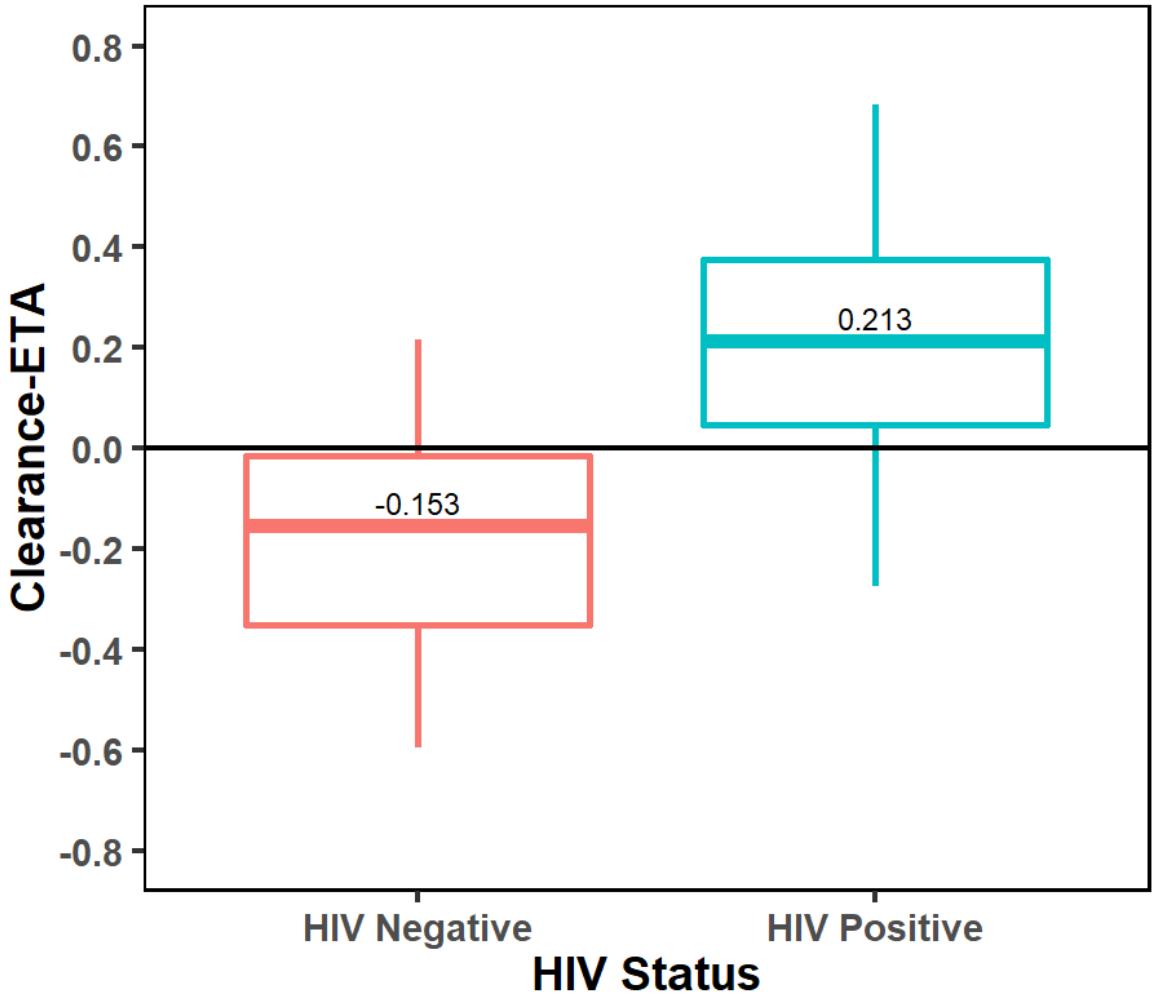
$$V_1\ (L) = 2.30 \times \left(\frac{WT}{78.5}\right)^{0.733}$$

$$V_2\ (L) = 5.05 \times \left(\frac{WT}{78.5}\right)^{0.733}$$

- HIV positive adults have higher clearance compared to HIV negative adults
- Higher weight increased the volumes of distribution

Effect of HIV Status on VRC01 PK in Adults





HIV Negative HIV Positive

Final Adult-Infant VRC01 PopPK Model Parameters

	Final Parameter ± Standard Error	Bootstrap Estimates Median (95% CI)
Θ1 (V1)	2.14 ± 0.0904	2.14 (1.93, 2.33)
Θ2 (V2)	4.72 ± 0.241	4.72 (4.16, 5.24)
Θ3 (CL)	0.016 ± 0.00080	0.016 (0.0142, 0.0176)
Θ4 (Q)	0.0483 ± 0.0023	0.0488 (0.044, 0.055)
Θ5 (KA)	0.458 ± 0.122	0.348 (0.045, 0.792)
Θ6 (F1)	0.674 ± 0.0419	0.666 (0.568, 0.762)
Θ7 (R1)	0.00702 ± 0.0011	0.0073 (0.0020, 0.031)
Θ8 (infant on CL)	0.283 ± 0.0287	0.283 (0.231, 0.344)
Θ9 (infant on R)	2.90 ± 0.507	3.55 (2.26, 9.15)
Θ10 (HIV on CL)	1.44 ± 0.115	1.44 (1.23, 1.68)
Variability (η)		
IIV on V_{ss}	23.2% ± 2.6%	22.1% (16.5%, 27.6%)
IIV on CL	30.0% ± 2.9%	29.4% (23.4%, 31.5%)
IIV on R1	28.3% ± 8.9%	32.1% (0.3%, 89.9%)
Error (ε)		
Proportional	21.7% ± 1.1%	21.8% (19.7%, 24.7%)
Additive	0.808 ± 0.144	0.812, (0.414, 1.097)

Equations:

$$CL(L/h) = 0.016 \times \left(\frac{WT}{70}\right)^{0.85} \times 0.283 \text{ (if infant)} \times 1.44 \text{ (if HIV positive)}$$

$$V_1(L) = 2.14 \times \left(\frac{WT}{70}\right)$$

$$V_2(L) = 4.72 \times \left(\frac{WT}{70}\right)$$

$$Q(L/h) = 0.0483 \times \left(\frac{WT}{70}\right)^{0.85}$$

$$R = 0.00702 \times 2.9 \text{ (if infant)} \times Dose$$

Abbreviations:
IIV = interindividual variability
V_{SS} = steady state volume of distribution;
Successful bootstrap convergence: 62.3%

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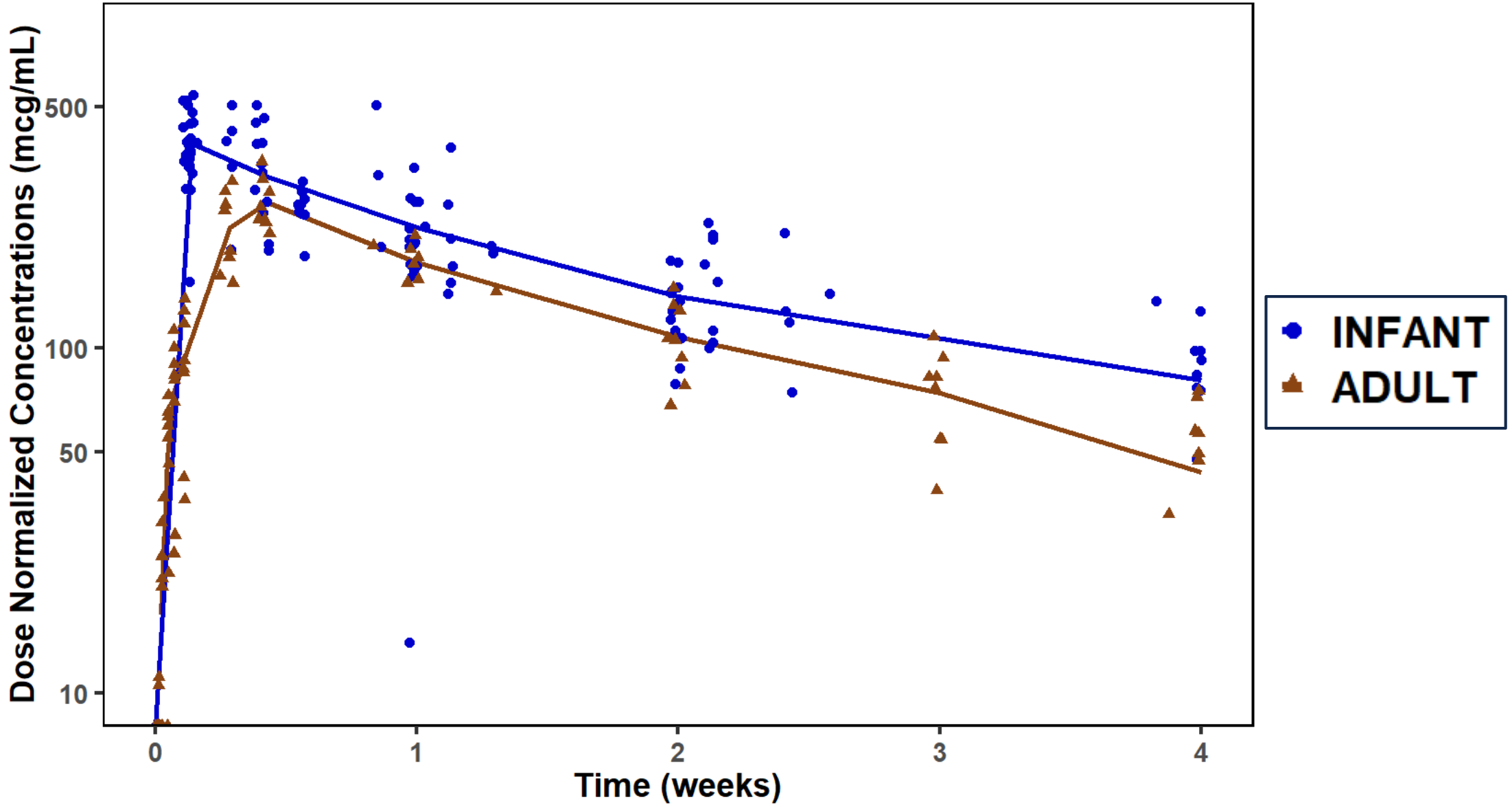
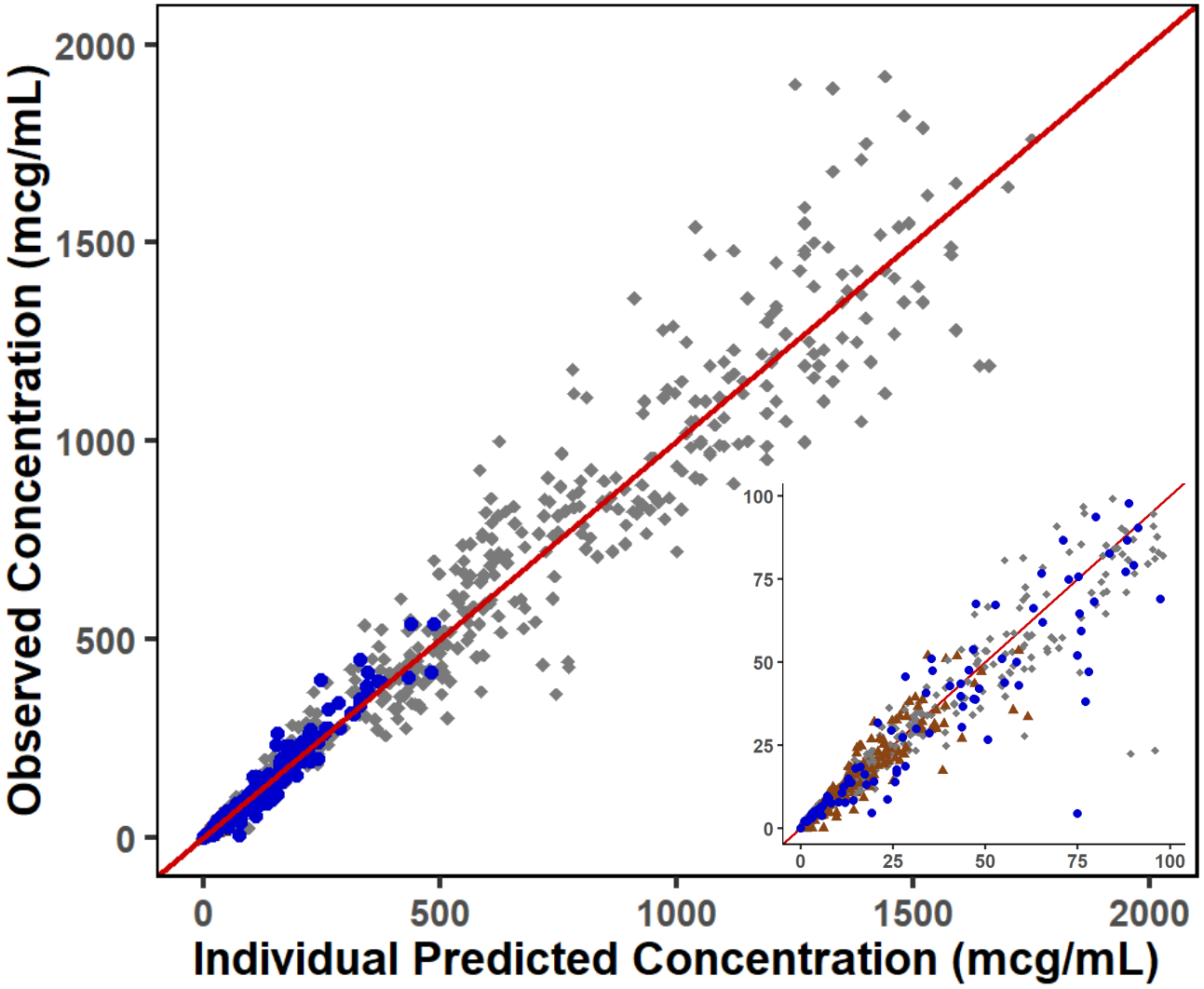
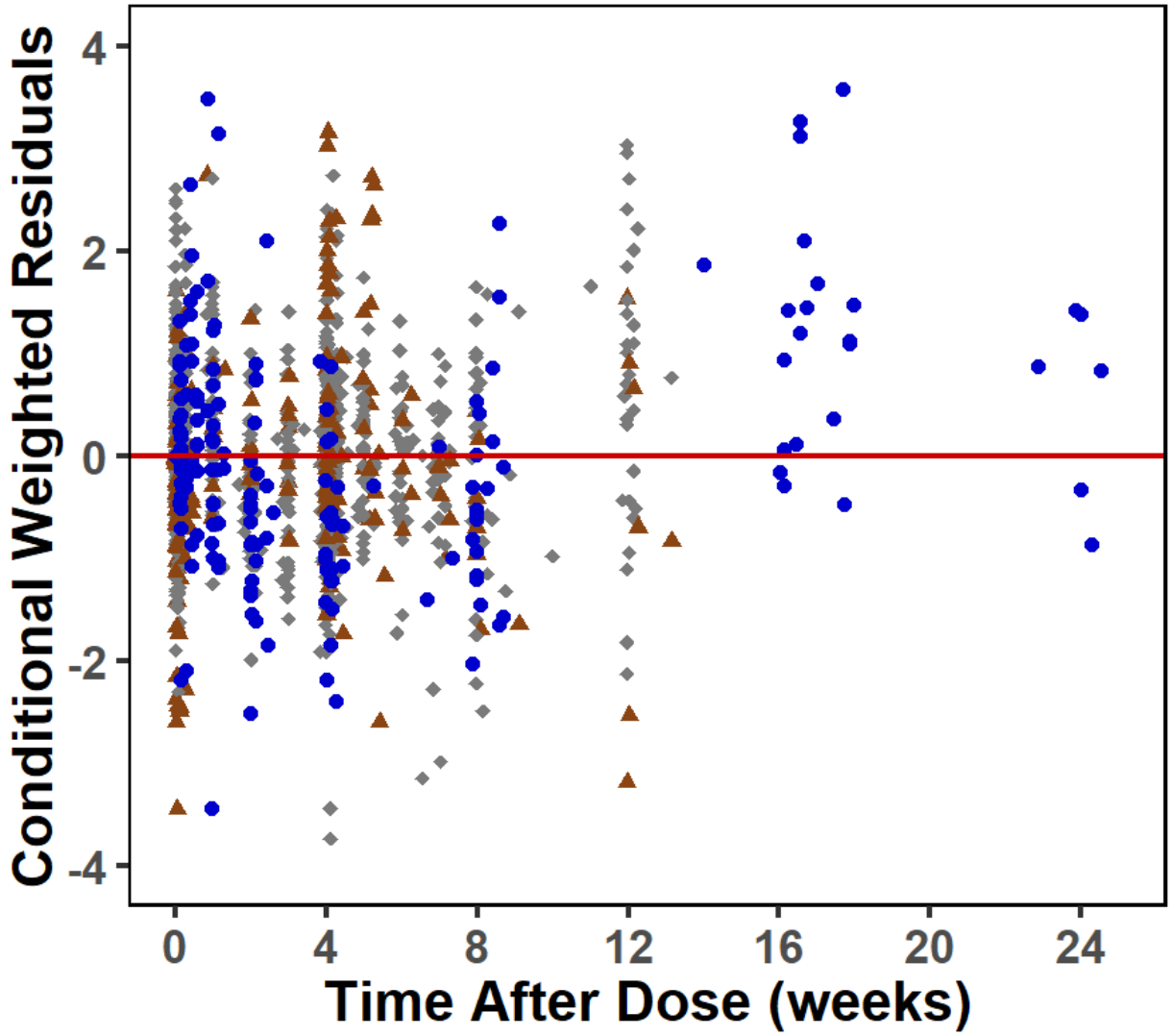
Initial VRC01 Concentrations Following SC Administration in Adults and Infants



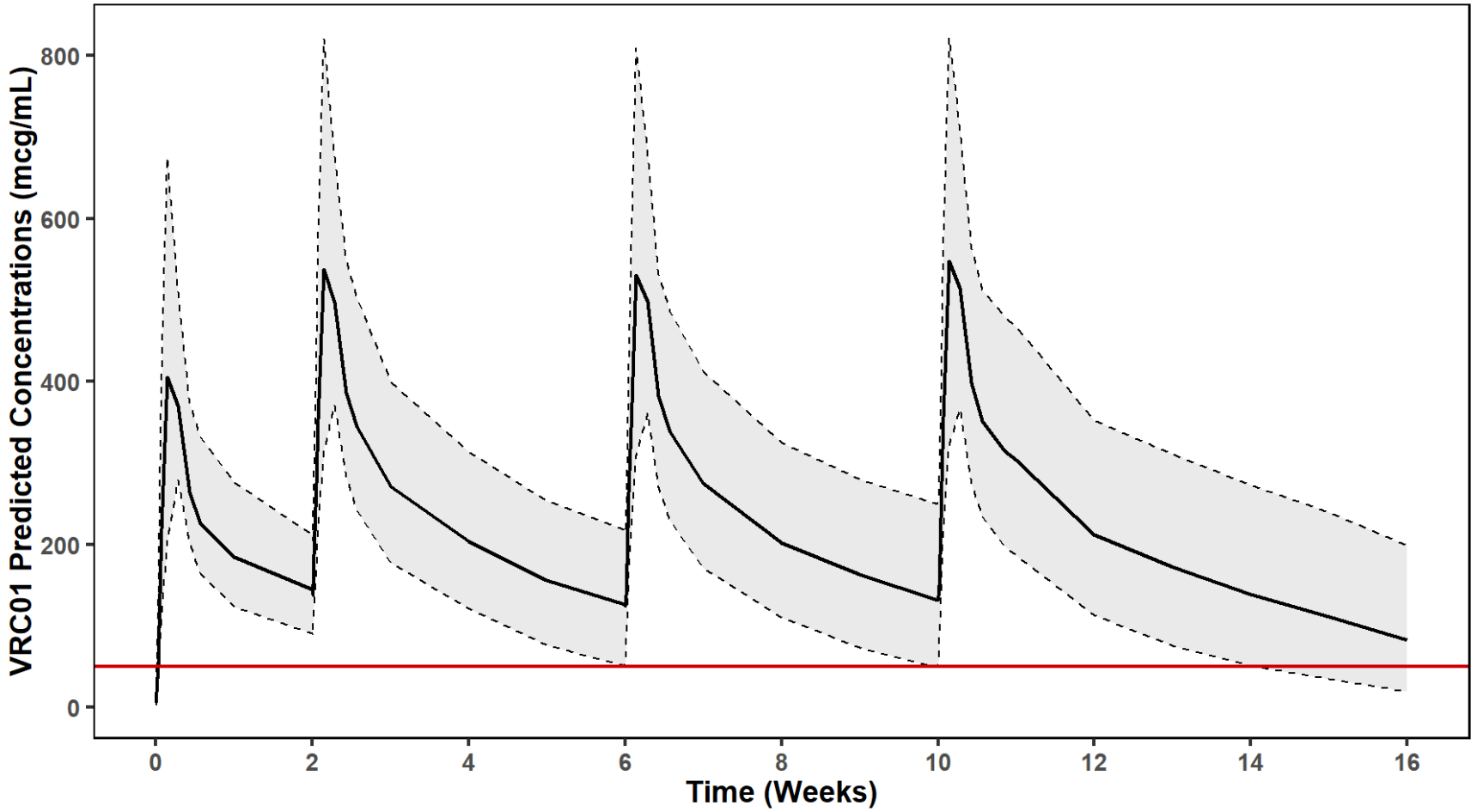
Adult-Infant VRC01 PopPK Model Goodness of Fit





Infant Adult SC Adult IV

Monte Carlo Simulation of Repeat SC Dosing in HIV Positive Infants



VRC01 dosing regimen

- 40 mg/kg SC administered at Weeks 0, 2, 6, and 10

Goal: Maintain average VRC01 concentrations above 50 mcg/mL for first 16 weeks

Simulated VRC01 Trough Concentrations (mcg/mL)				
	Week 2	Week 6	Week 10	Week 14
Median	137.7	124.8	131.9	138.5
2.5%	87.8	50.8	49.2	51.0

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Conclusions

- VRC01 demonstrated higher clearance in adults with HIV compared to adults without HIV
- VRC01 has good absorption following SC administration
- Infants have lower apparent clearance and more rapid SC absorption of VRC01 than adults
- Monte Carlo Simulations suggest an infant dose 40 mg/kg SC every 4 weeks will maintain suppressive plasma concentrations of >50 mcg/mL

Acknowledgments – Thanks to:

The International Maternal Pediatric Adolescent AIDS Clinical Trials Network

The P1112 Team

Vaccine Research Center

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Sites

Cape Town, S. Africa
Harare Family Care
Bronx-Lebanon Hospital, NY
Univ Californa, LA
Emory University
University of Puerto Rico
Jacobi Med. Ctr. , NY
Johns Hopkins University
San Juan, Puerto Rico
South Florida, Ft Lauderdale
Texas Children's Hosp.
University of Colorado
University of Florida

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