Population Pharmacokinetics of VRC01LS in Term Infants and Adults

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Background

General

- **HIV Prevalence:** 37.9 million people living with HIV worldwide[1]
  - ≤ 15 years: 1.7 million children
  - Up to 90% of children are infected *via* vertical transmission during pregnancy or during birth
- Transmission can occur during breastfeeding
- Aggressive early treatment may benefit HIV-infected infants
- There are limited treatment and prophylaxis options, and a need for a pediatric friendly therapy to ensure compliance

Broadly Neutralizing Antibody

- **Broadly neutralizing antibodies** (bnAbs) against HIV are in development for prevention and treatment of HIV infection
- **VRC01LS -** First long-acting bnAb
  - Binds to CD4 binding site on HIV-1 gp120
  - Two amino acid modifications in the Fc region of the **VRC01** antibody extending the duration of its serum $T_{1/2}$ by roughly **5 folds**
- Target Serum Level[2]:
  - IC_{50} < 1 µg/mL against 72% tested isolates
  - IC_{50} < 50 µg/mL against 91% tested isolates

Prevention	Treatment
≥ ~20 mcg/mL	≥ ~50 mcg/mL

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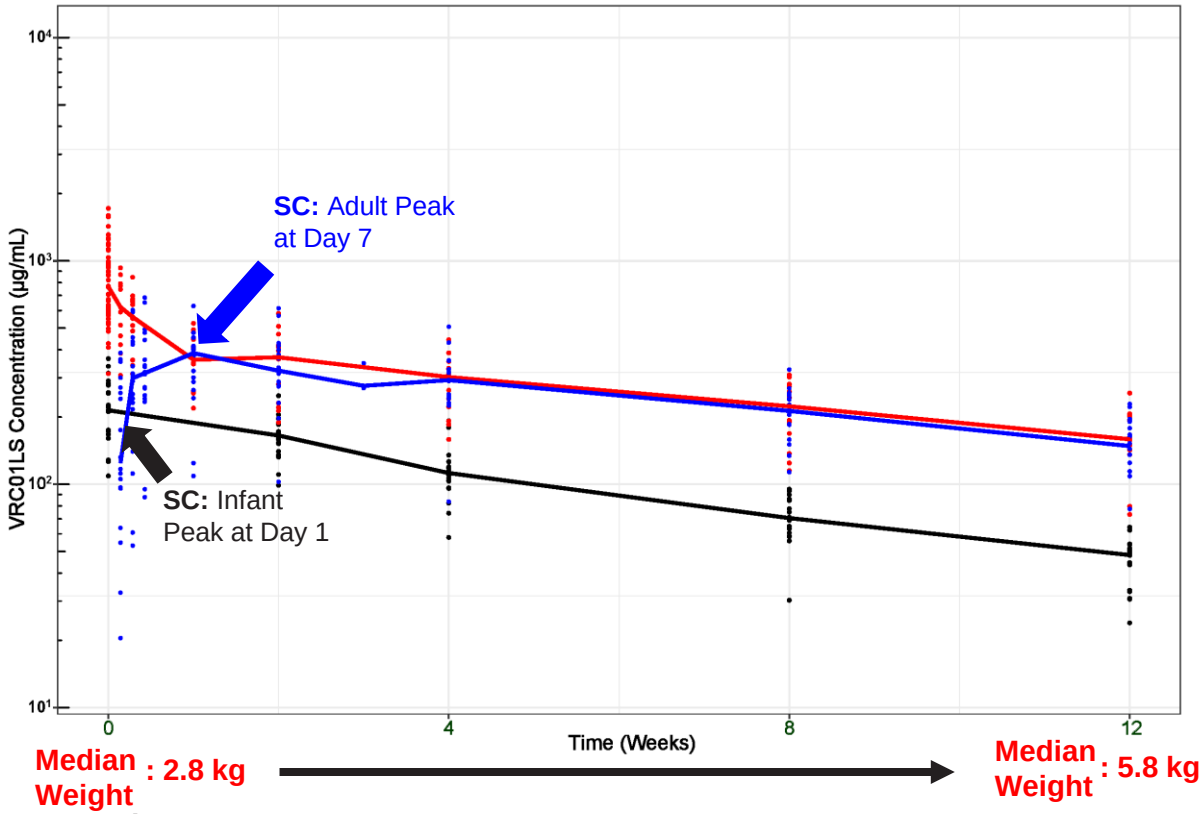
[1]*https://www.who.int/data/gho/data/themes/topics/topic-details/GHO/death;* [2]*Wu et al. 2010 Aug; 329(5993); 856-861*

VRC01LS – Study Design

Objectives: Characterize VRC01LS population pharmacokinetics (PopPK) from phase I studies in early infancy and adults to optimize dosing therapy

	VRC01LS Study	
	Vaccine Research Center (VRC) Study 606[1] *(N = 49)*	**International Maternal, Pediatric, Adolescent AIDS Clinical Trials (IMPAACT) P1112 Arm 4[2] *(N = 21)***
Study Population	**Healthy Adult**	**HIV-Exposed Infant**
IV Administration (N)	**Single Dose** 5-40 mg/kg x1 (N= 11) **Multiple Dose** 20 mg/kg IV q 12 weeks x 3 (N=10)	*N/A*
SC Administration (N)	**Single Dose** 5 mg/kg x1 (N=3) **Multiple Dose** 5 mg/kg SC q 12 weeks x 3 (N=15)	**Single Dose[Non-Breastfed]** < 4.5 kg: 80 mg; ≥ 4.5 kg: 100 mg (N=10) **Two Doses [Breastfed]** < 4.5 kg: 80 mg; ≥ 4.5 kg: 100 mg (N=11)
PK Sampling	**Day:** 1, 2, 3, 7, 14, then every 4-8 weeks	**Day:** 1, 14, then every 4-8 weeks
Median Age *(Range)*	28 years (19 – 46)	2 days (0– 4)
Median Weight (kg) *(Range)*	73.3 (46.5 – 105.9)	2.8 (2.3 – 3.8)



Methods

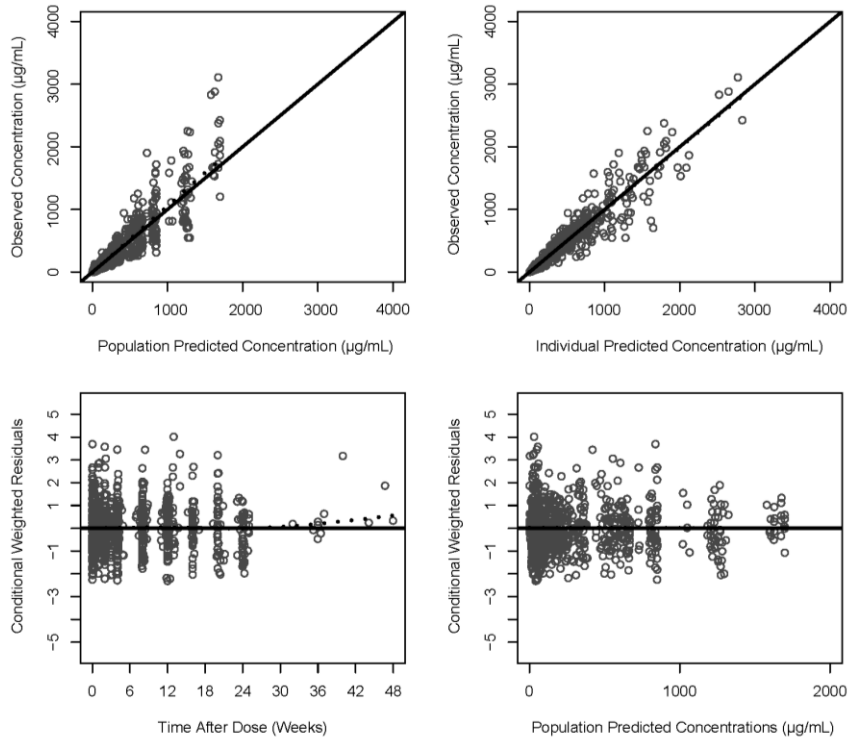
Study VRC606 → **Base PK Model (Two Compartment)** + **Study IMPAACT P1112 Arm 4** → **Base model with both adult and infant data** → **Covariate Screen** *(Forward Selection)* → **Model Validation** → **Simulation with Current Infant Dose Regimen**

[1] *Gaudinski et al. 2018 Jan; 24; 15(1); e1002493* [2] *McFarland et al. 2019 March; Conference on Retroviruses and Opportunistic Infections (CROI) [Abstract]*

Final Model

Final **Model Parameter**	Final Value	Bootstrap Estimates Median (95% CI)
Θ_1 (V1, L)	1.64	1.64 (1.47 – 1.79)
Θ_2 (CL, L/hr)	0.0015	0.0015 (0.00132 – 0.00167)
Θ_3 (V2, L)	1.89	1.88 (1.51-2.3)
Θ_4 (Q, L/hr)	0.023	0.023 (0.017 – 0.31)
Θ_5 (KA, 1/hr)	0.013	0.013 (0.009665 – 0.01855)
Θ_6 (D, hr)	8.5	10.3 (1.2 – 19.2)
Θ_7 (F, %)	0.64	0.63 (0.50-0.76)
Θ_8 (Antibody Allometric Scale)	0.85 FIXED	-
Θ_9 (Dose 1 vs 2/3 on Vss)	0.83	0.83 (0.74-0.93)
Θ_{10} (Infants on KA)	2.78	2.78 (1.87-4.19)
Θ_{11} (Infants on F1)	0.71	0.74 (0.60-0.94)
Between Participant Variability		
IIV on V_{ss}	23.8%	22.6% (15.7-28.8)
IIV on CL	26.5%	2.1% (0.3 – 30.5)
IIV on V_{ss}-CL	26.6%	24.4% (15.7-28.8)
IIV on F1	8.2%	48.1% (29.56 – 66.21)
IIV on KA	48%	79.1% (55.85 – 92.0)
Error		
Proportional	25.2%	25.1% (21.8-28.0)
Additive	0.84	0.003 (0.003-0.9971)

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



Equations:

$$CL(L/h/70kg) = 0.00148 * \left(\frac{WT}{70}\right)^{0.85}$$

$$V_1(L/70kg) = 1.64 * \left(\frac{WT}{70}\right) * 0.83 \text{ (if dose 2/3)}$$

$$V_2(L/70kg) = 1.89 * \left(\frac{WT}{70}\right) * 0.83 \text{ (if dose 2/3)}$$

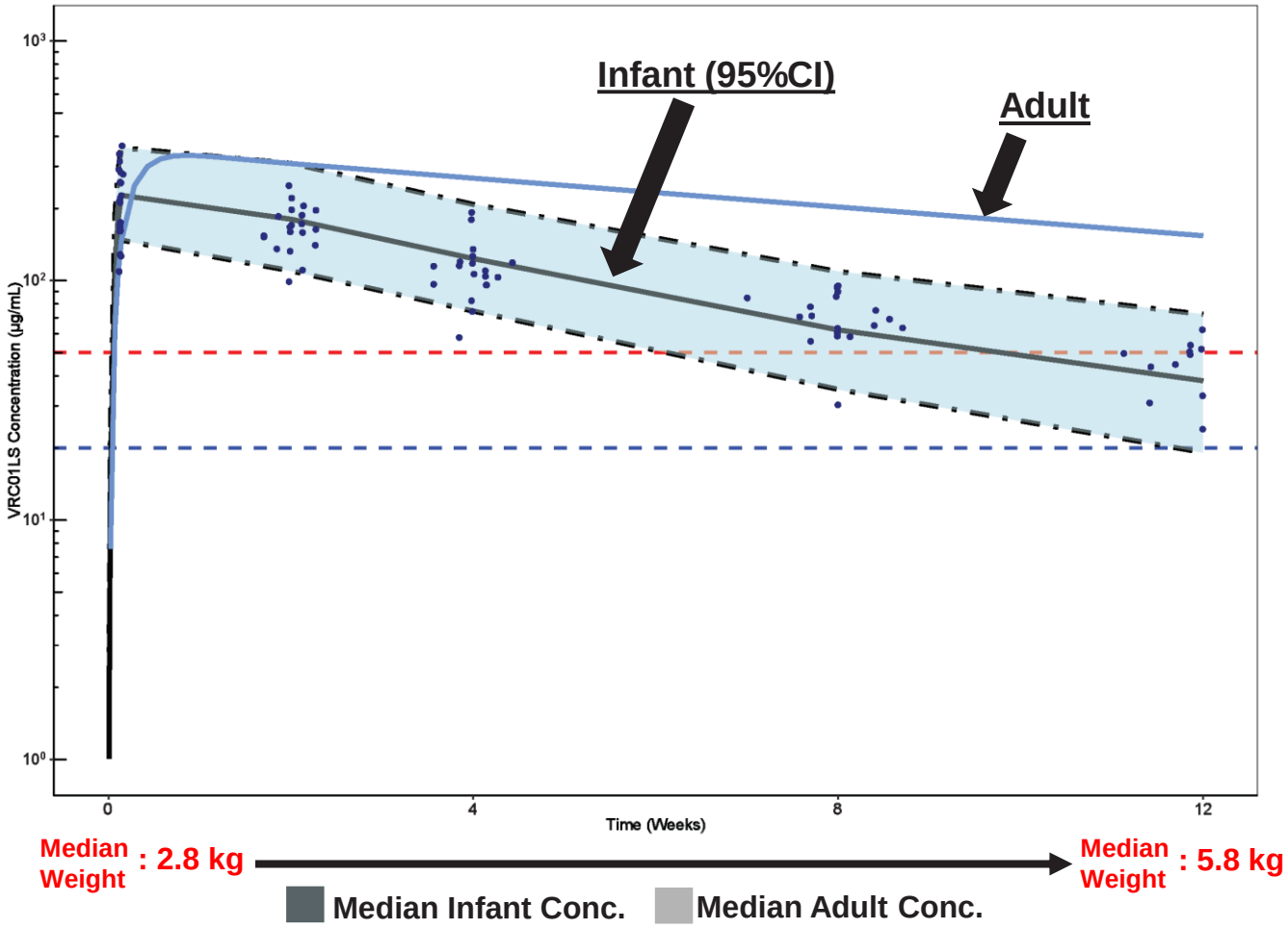
$$Q(L/h) = 0.023 * \left(\frac{WT}{70}\right)^{0.85}$$

$$D\ (h) = 8.5$$

$$F(\%) = 0.64 * 0.71 \text{ (if Infants)}$$

$$KA = 0.0129 * 2.78 \text{ (if Infants)}$$

Simulation: Infant



Simulated VRC01LS Trough Concentrations		
	Week 12	**Week 24**
Median Conc (µg/mL) (95% CI)	38.1 (20.2-69.3)	45.3 (22.8-86.4)
Prophylaxis Target (≥ ~20 mcg/mL)	96%	99%
Treatment Target (≥ ~50 mcg/mL)	9.8%	39%

Conclusions

- Current study represents the first composite PopPK evaluation of a long acting bnAb in both adults and early infancy
- Infants absorbed VRC01LS more rapidly and appeared to have lower bioavailability compared to adults
- There is a dilution effect from early growth in infants that contributes to the fall in VRC01LS concentrations
- Simulation of the current dosage studied is projected to maintain concentrations ≥20 mcg/mL for 6 months in virtually all infants for HIV prevention
- Higher dose or more frequent administration would be needed to maintain concentrations ≥ 50 mcg/mL in most of infants

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Study Team

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Sites

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