IMPAACT
International Maternal Pediatric Adolescent AIDS Clinical Trials Network

Viremia Accelerates VRC01 Clearance in Infants Living with HIV: Insights from IMPAACT 2008

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BACKGROUND

- **VRC01,** a **broadly neutralizing monoclonal antibody** (bNAb) targeting the **HIV-1 CD4 binding site,** is safe in adult and pediatric populations.[1]
- Subcutaneous (SC) administration and a long half-life permit **infrequent dosing**, making **VRC01 an attractive adjunct to early antiretroviral therapy (ART) in infants.**[1]
- In addition to direct viral neutralization, bNAbs may exert a "**vaccinal effect**," enhancing host immune responses through Fc-mediated mechanisms and promoting clearance of infected cells, with the potential to **limit establishment or persistence of viral reservoirs during early infection.**[2]
- Prior studies in HIV-exposed but uninfected (HEU) infants demonstrated that VRC01 was **well tolerated**, **achieved target plasma concentrations**, and did not induce anti-drug antibodies.[1]
- However, VRC01 **population pharmacokinetics** (popPK) in infants living with HIV remains **incompletely characterized**, especially with active viremia at ART initiation.[1]
- **Disease-related factors**, including HIV RNA burden, may **influence monoclonal antibody clearance and contribute to variability in VRC01 exposure** in infants.[3]

Our objective was to **characterize VRC01 popPK in infants living with HIV** and to **evaluate clinical and virologic factors associated with VRC01 clearance**.

METHODS

- **IMPAACT 2008** was a randomized, open-label, phase I/II study evaluating VRC01 administered subcutaneously with early ART in infants living with HIV in Malawi, Botswana, Zimbabwe, and Brazil.
- Infants aged ≤12 weeks initiating ART were randomized 1:1 to receive **VRC01 + ART** or **ART alone**.

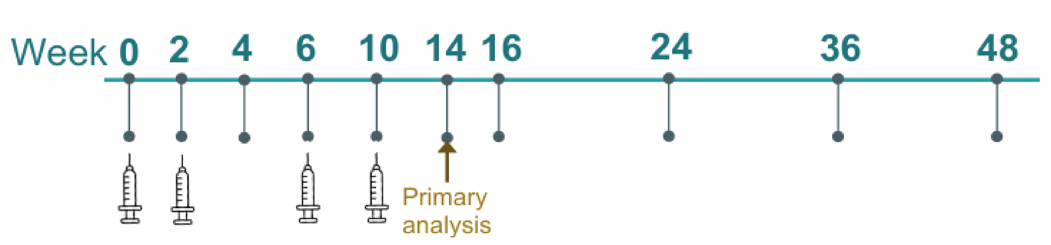

FIGURE 1. IMPAACT 2008 study design and VRC01 dosing schedule. Infants received VRC01 40 mg/kg SC at Weeks 0, 2, 6, & 10 with standard-of-care ART. PK samples were collected prior to dosing and during follow-up, with primary analysis timepoint at Week 14.

Pharmacokinetic Analysis

- A popPK analysis was performed using nonlinear mixed-effects modeling (**NONMEM v7.6**, FOCE with interaction).
- VRC01 concentration-time data from infants receiving VRC01 (n = 29 infants; 141 plasma samples) were included and described by a **two-compartment model with first-order absorption**.
  - VRC01 plasma concentrations were quantified using an immune-based assay at the NIAID Vaccine Immune T-Cell and Antibody Laboratory (NVITAL; lower limit of detection: 1 μg/mL).
- Body weight was included *a priori* using **allometric scaling** consistent with monoclonal antibodies: (CL/F ∝ $WT^{0.85}$; V/F ∝ $WT^{1.0}$).[4]
- **Covariates** were screened using a **univariate approach**, evaluating age, sex, dose number (DNUM), ART regimen, study site, and multiple HIV-1 RNA measures (baseline, Week 6, change from baseline to Week 6, and at time of PK sample [$HIVRNA_t$]), followed by **multivariable** *("all models")* **evaluation** due to variable **collinearity.**
- Model performance was assessed using **goodness-of-fit** diagnostics, and parameter uncertainty was evaluated via **bootstrap resampling** (1000 replicates; Wings for NONMEM v7.5).

Higher HIV viremia was associated with *accelerated VRC01 clearance* in infants receiving early ART, leading to **lower antibody exposure** and *highlighting the need* for **optimal bNAb dosing strategies**.

RESULTS

TABLE 1. Baseline characteristics of infants randomized to VRC01 in IMPAACT 2008. All infants received standard-of-care ART including NVP or LPV/r, and nucleoside reverse transcriptase inhibitors (3TC with either ZDV or ABC). Baseline plasma HIV-1 RNA and antiretroviral resistance profiles are shown.

	VRC01 (*N*=30)
Baseline Characteristics	
Female Sex *n* [%]	14 (47%)
Black, non-Hispanic *n* [%]	25 (83%)
Age [days]*	72 [56, 82]
Time on antiretroviral (ARV) [days]*	8 [6, 11]
Entry Plasma HIV-1 RNA [log_{10} cp/mL]*	4.1 [3.7, 5]
Plasma HIV-1 RNA <100,000 cp/mL *n* [%]	13 (87%)
Baseline Antiretroviral Therapy (ART)	
Nevirapine (NVP) regimen**	16 (53%)
Lopinavir (LPV/r) regimen**	14 (47%)
NVP resistance***	10/13 (77%)
LPV/r resistance***	0/9 (0%)

* Median (Q1, Q3). ** additional ARTs included 3TC with either ZDV or ABC. *** on ARV & with resistance results.

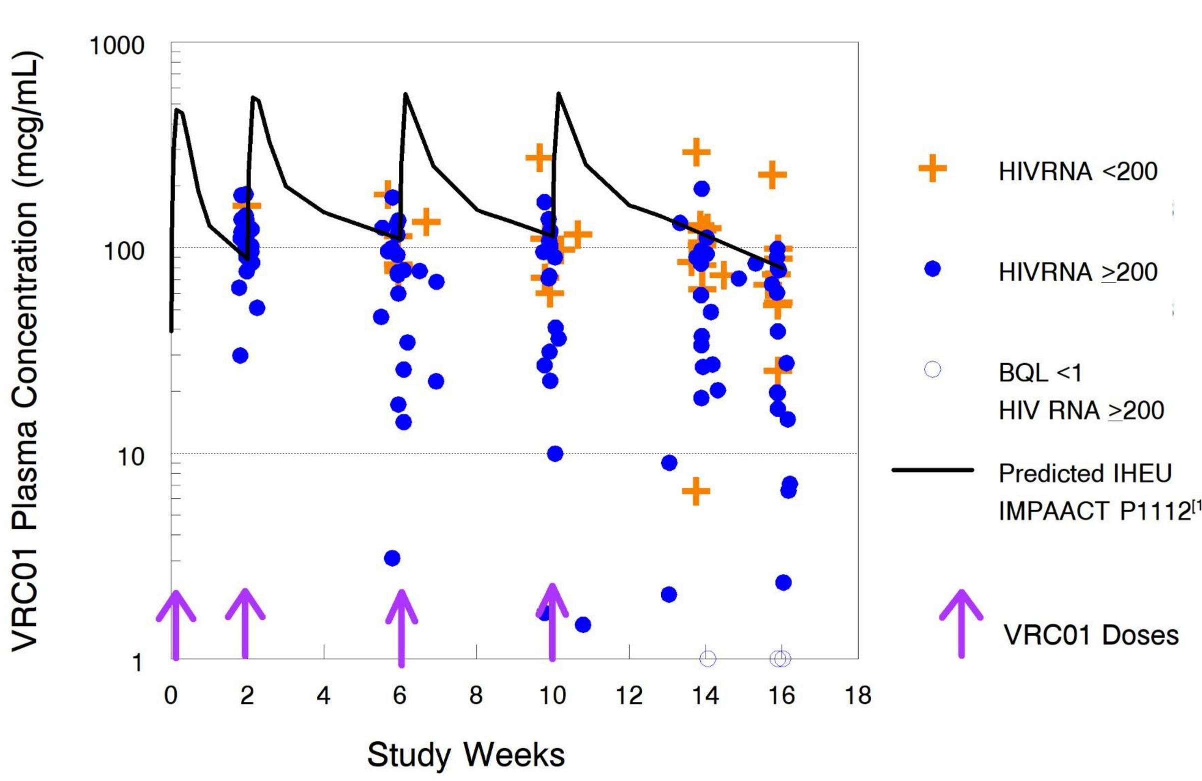

FIGURE 2. Observed VRC01 concentrations in infants living with HIV. Observed VRC01 plasma concentrations from IMPAACT 2008 are shown over time following SC dosing at Weeks 0, 2, 6, and 10. Model-predicted concentrations based on prior popPK estimates from HEU infants are overlaid for comparison.

- Univariate screening identified **dose number** (**DNUM**) and multiple **HIV RNA metrics** as potential **predictors of VRC01 clearance**.
- Due to **correlation** among HIV RNA measures, multivariate evaluation employed an "*all-models*" approach, with $\mathbf{HIVRNA_t}$ and **DNUM** retained as **significant covariates** in the final model.

TABLE 2. Final popPK parameter estimates for VRC01 in infants living with HIV. Estimates shown are typical values (± SE) and bootstrap median estimates of the parameter with 95% CI. The absorption rate constant was fixed to an estimate derived from an earlier one-compartment model developed during initial model building.

Final Model	Multivariate Estimate ± SE	Bootstrap Estimates, Median (95% CI)
Parameter		
Θ_1 (**CL/F**, L/h/70kg)	**0.0182** ± 0.0023	**0.0189** (0.0139 – 0.0236)
Θ_2 (**V2/F**, L/70kg)	**12.6** ± 1.5	**9.78** (0.05 – 14.70)
Θ_3 (**Q/F**, L/h/70kg)	**0.009** ± 0.003	**0.0380** (0.0067 – 814)
Θ_4 (**V3/F**, L/70kg)	**5.07** ± 2.69	**7.03** (2.74 – 15.40)
Vss/F (L/70kg)	**17.67** ± 4.19	**16.81** (2.79 – 30.1)
Θ_5 (**KA**, h^{-1})	**0.0156** (fixed)	**0.0156** (fixed)
Θ_6 (**DNUM**, n)	**0.507** ± 0.163	**0.400** (0.180 – 0.900)
Θ_7 ($\mathbf{HIVRNA_t}$, log_{10} cp/mL)	**0.495** ± 0.113	**0.480** (0.200 – 0.770)
Between Subject Variability (BSV)		
BSV for CL/F	**54%**	**47%** (32 – 75%)
Residual Error		
Proportional	**15%**	**15%** (7 – 30%)
Additive (μg/mL)	**8.83**	**8.44** (0.54 – 14.49)

Abbreviations: **Θ** (theta), population parameter estimate; **CL/F**, apparent clearance; **V2/F**, central volume of distribution; **Q/F**, intercompartmental clearance; **V3/F**, peripheral volume of distribution; **Vss/F**, volume of distribution at steady-state (V2/F + V3/F); **KA**, absorption rate constant; **DNUM**, dose number; $\mathbf{HIVRNA_t}$, plasma HIV-1 RNA at time of PK sample; **SE**, standard error; **CI**, confidence interval.

$$(1)\quad \frac{CL}{F}\left[\frac{L}{h}\right] = 0.0182 \times \left(\frac{WT\ [kg]}{70\ kg}\right)^{0.85} \times \left(\frac{DNUM}{2}\right)^{0.507} \times \left(\frac{HIVRNA_t}{3.31}\right)^{0.495}$$

$$(2)\quad \frac{V_{SS}}{F}[L] = 17.67 \times \left(\frac{WT\ [kg]}{70\ kg}\right)^{1.0}$$

EQUATIONS 1 & 2. Final popPK estimated model equations for VRC01. Equations describe apparent clearance (CL/F) and steady-state volume of distribution (Vss/F) as functions of body weight. HIV-1 RNA at time of PK sample collection ($HIVRNA_t$) and dose number (DNUM) are included as covariates on clearance.

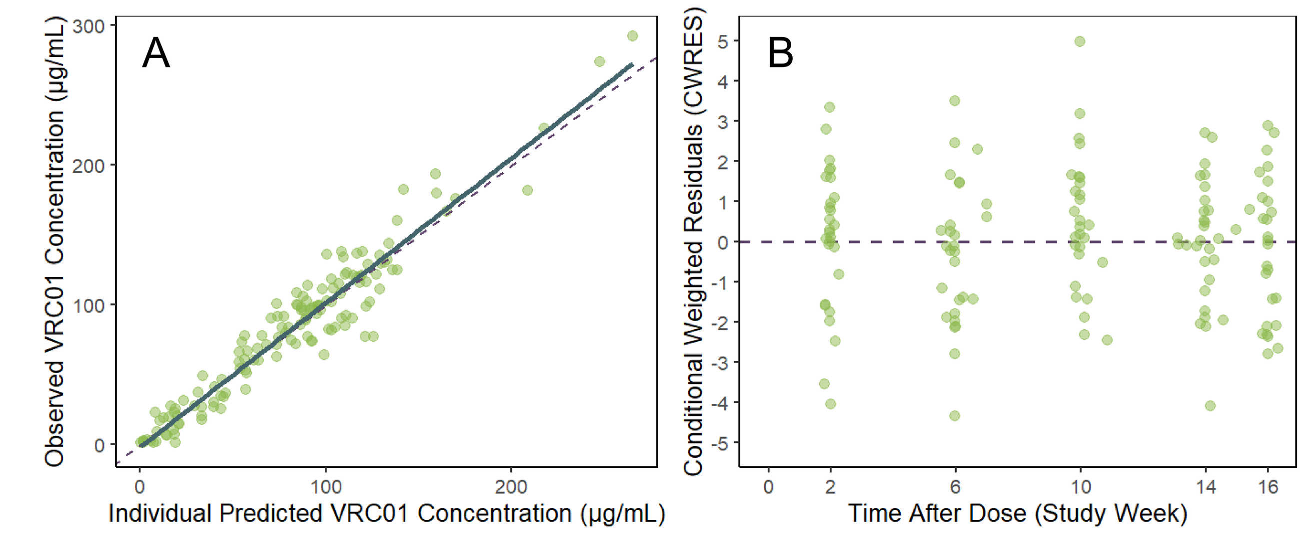

FIGURE 3. Goodness-of-fit diagnostic plots for the final popPK model. (A) Individual predicted VRC01 concentrations vs. observed concentrations (μg/mL). Dashed line represents line of unity. Solid line represents linear regression line. **(B)** Conditional weighted residuals vs. time after dose (weeks).

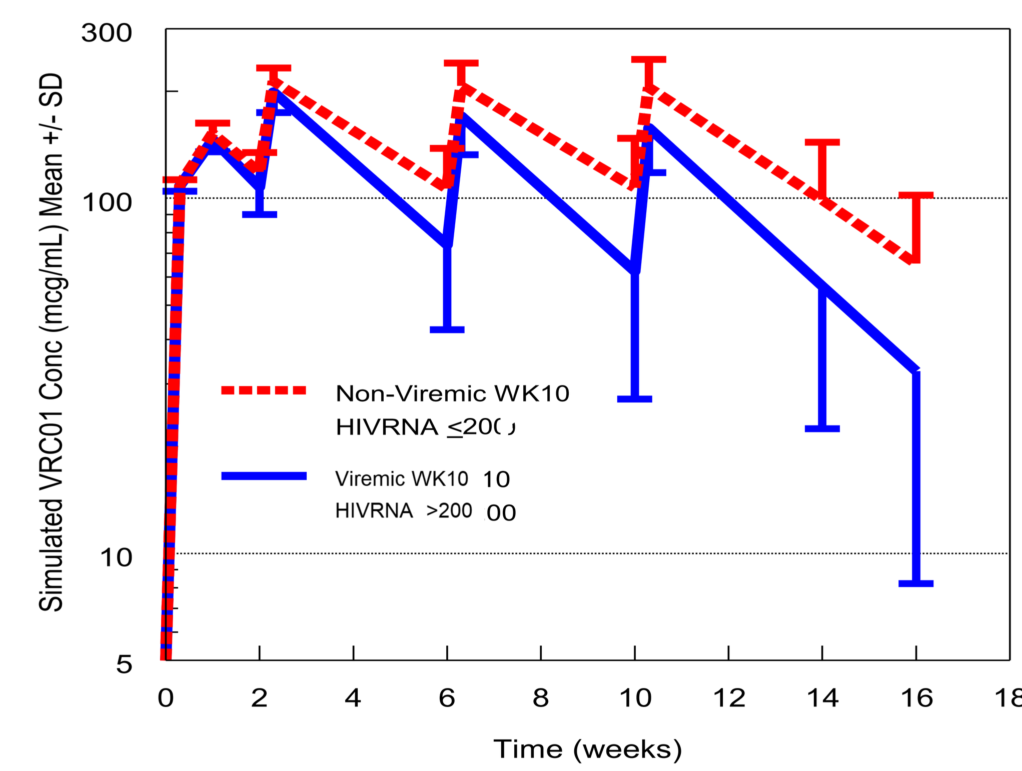

FIGURE 4. Monte Carlo simulations illustrating model-estimated VRC01 plasma levels over time, stratified by HIV-1 RNA status at Week 10 (≤200 vs >200 cp/mL). Lines represent median simulated concentrations with variability shown by error bars.

CONCLUSIONS

- Infants living with HIV who received VRC01 at ART initiation **exhibited higher apparent clearance (CL/F)** and **lower antibody exposure** than popPK models developed in HEU infants have predicted (Fig. 2).
- **Higher HIV viremia was associated with faster VRC01 clearance**, indicating that **disease burden may influence antibody disposition early treatment**.
- These findings identify **on-treatment viremia** as a clinically relevant determinant of **VRC01 exposure.**
- Results support **consideration of virologic status** when evaluating **VRC01 dosing strategies** in infants on ART.

PLAIN LANGUAGE SUMMARY

Injectable antibodies against HIV may help support treatment in infants living with HIV. We found that **infants with higher amounts of HIV** in their blood cleared the antibody more quickly, resulting in lower antibody levels, suggesting that those infants **may need higher or adjusted doses to maintain effective antibody levels for HIV treatment**.

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