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Model Informed Development of VRC01 in Newborn Infants Using a Population Pharmacokinetics Approach

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Abstract

VRC01 is a first-in-class, potent, broadly neutralizing antibody that targets the CD4 binding site of gp120 on HIV-1 viruses, and is under development as a novel HIV therapeutic. This study utilized population pharmacokinetic modeling to characterize VRC01 pharmacokinetics to guide dosing selection for ongoing phase 2 clinical trials in pediatric patients. Combining VRC01 pharmacokinetic data from 3 adult and 1 infant clinical trials, a total of 1475 VRC01 serum concentrations from 100 participants were used in the analysis (40 infants, 60 adults). VRC01 was administered either intravenously (IV) or subcutaneously (SC) (1 – 40 mg/kg). All infants received SC doses as compared to 13% SC and 87% IV in adults. The data were well described by a two-compartment model. Clearance was 37% higher in adults with HIV infection and 83% lower in infants than adults. Subcutaneous bioavailability was 55% in adults. Rapid absorption was seen in infants indicating therapeutic levels could be achieved quickly. Monte Carlo simulations were used to determine optimal dosing and demonstrated 40 mg/kg SC at weeks 0, 2, 6, and 10 would maintain VRC01 levels at the suppressive target concentration of 50 μg/mL for the first 14 weeks of life in infants. The current analysis provides new insight into differences in monoclonal antibody pharmacokinetics between infants and adults and demonstrates the utility of a population pharmacokinetic approach in informing drug development for infant populations.

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Author Contributions

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Keywords

HIV-1; neonates; VRC01; population pharmacokinetics; broadly neutralizing antibody; mother-to-child transmission of HIV

Introduction

Antiretroviral therapy (ART) has dramatically reduced vertical transmission of HIV. However, many infants are newly infected each year, with an estimated 160,000 acquiring HIV globally in 2018 (1). Factors including late diagnosis of maternal HIV, incomplete adherence to ART, infection with ART-resistant virus, and breastmilk transmission account for the majority of current new infections (1). Broadly neutralizing antibodies (bNAb) are a novel class of therapies characterized by long half-lives which require infrequent dosing and can improve compliance; thus have the potential to improve HIV treatment and prophylaxis for infants and young children.

VRC01 is a novel, first-in-class IgG1 bNAb that targets the highly conserved CD4 binding site of gp120 on HIV-1 viruses (2). VRC01 is both potent and has wide coverage as demonstrated by in-vitro neutralization of 94% of viruses in a 3-clade panel of tier-2 viruses at ≤50 micrograms per milliliter (μg/mL) (3). In clinical studies, VRC01 was well tolerated when administered intravenously (IV) or subcutaneously (SC) at 3 or 4-week intervals in adults and infants, and anti-drug antibodies (ADA) were undetectable when adults were assessed through 16 weeks. A trough concentration of >50 μg/mL has been targeted to maintain viral suppression in HIV-infected patients because that is the level at which >90% of a multiclade panel of tier-2 viruses are neutralized (4, 5).

VRC01 pharmacokinetics (PK) have been characterized in HIV-exposed infants, healthy adults, and HIV-infected adults, with half lives of approximately 20, 15, and 11 days (4–8). A two-compartment popPK model reported a clearance of approximately 0.0167 L/hour in HIV-uninfected adults, with only body weight considered a significant covariate that was predictive of clearance and volume of distribution (7). However, no popPK model has been reported for VRC01 in infants. The current study aimed to use population PK modeling to characterize the factors affecting VRC01 disposition to provide rational dosing recommendations for VRC01 infant clinical trials.

Methods

Patient Population

VRC01 data was combined from 4 previously published clinical trials in adults and infants. The adult data was comprised of two studies in HIV-infected (VRC601, NCT01950325) and HIV-uninfected (VRC602, NCT01993706) adults conducted by the Vaccine Research Center (VRC), National Institute of Allergy and Infectious Diseases, National Institutes of Health (NIH), and one study in HIV-infected adults (A5340, NCT02463227) conducted by the AIDS Clinical Trials Group and NIH (5, 6, 8). The study in HIV-exposed, uninfected infants (P1112, NCT02256631) was conducted by the International Maternal Pediatric Adolescent AIDS Clinical Trials (IMPAACT) Network (4). The studies were approved by the

institutional review board for each participating site, and written informed consent was obtained from participants, parents, or guardians for all participants in the studies. Guidelines of the Department of Health and Human Services governing experimentation in human subjects were followed.

Drug Administration and Pharmacokinetic Sampling

VRC601 was a phase 1, dose-escalation study examining the safety and pharmacokinetics of VRC01 in HIV-positive adults (8). Participants received VRC01 intravenously (IV) at 1–40 mg/kg or subcutaneously (SC) at 5 mg/kg as either a single dose or as two doses with the second dose administered 4 weeks after the first dose. PK sampling consisted of up to 18 post-dose samples between the completion of the infusion and up to 140 days after the end of each infusion.

VRC602 was a phase 1, dose-escalation study examining the safety and pharmacokinetics of VRC01 in healthy, HIV-uninfected adults (5). Participants received 5–40 mg/kg VRC01 IV or 5 mg/kg SC, as either a single dose or as two doses with the second dose administered 4 weeks after the first dose. PK sampling consisted of up to 13 samples between the completion of the infusion and up to 56 days after the end of each infusion.

A5340 was a phase 1 study investigating the feasibility of achieving sustained suppression of plasma viremia in HIV-positive adults by means of multiple infusions of VRC01 after the discontinuation of antiretroviral therapy (ART) (6). Participants received 40 mg/kg VRC01 IV every 3 weeks for up to 3 doses. PK sampling consisted of weekly samples between the completion of infusion and 3 weeks after the end of each infusion.

P1112 was a phase 1, multi-center dose-escalation study examining the safety and pharmacokinetics of SC VRC01 and another anti-HIV neutralizing monoclonal antibody (VRC01LS) in HIV-exposed newborn infants within the first 72 hours of life (4). Infants in dose groups 1 and 2 received a single dose of 20 or 40 mg/kg VRC01 SC, respectively. Infants in dose group 3 were being breastfed by mothers living with HIV, so the infants received multiple doses of SC VRC01, with an initial dose of 40 mg/kg, followed by multiple doses of 20 mg/kg monthly while being breastfed for at least 24 weeks and no more than 72 weeks. PK sampling for dose groups 1 and 2 consisted of up to 9 samples after the dose between the completion the infusion and 48 days after the infusion. PK sampling for dose group 3 consisted of up to 7 samples between the completion of the first infusion and 24 weeks, followed by one sample every 12 weeks until completion of the study.

Pharmacokinetic Analysis

Quantification of VRC01 concentrations in subject serum was performed in 96-well plates on a Beckman Biomek-based automation platform utilizing the monoclonal antibody 5C9 for VRC01 detection. Four-parameter logistic curve regression of a standard curve of VRC01 covering the range from 0.98 to 1000 ng/mL was utilized to quantitate sample concentrations based upon the average of sample dilutions within the range of the assay as previously described (5, 8).

Using the computer program NONMEM (version 7.3) with a GNU Fortran G77 compiler, concentration time data were fitted using first-order conditional estimation method (FOCE) with interaction. A two-compartment pharmacokinetic structural model (ADVAN4, TRANS4 subroutine) with zero order input followed by first order absorption was used to describe the data. The two compartment model had the following parameters: clearance (CL), inter-compartmental clearance (Q), volume of distribution for the central compartment (Vc), volume of the peripheral compartment (Vp), first-order absorption into the central compartment (KA), bioavailability (F1), and dose-normalized rate of zero order input (R1). An exponential-normal distribution error model was used for inter-subject variability. Due to the lack of IV data in infants, SC bioavailability in infants was assumed to be the same as in adults.

Pharmacokinetic parameters were scaled by subject size prior to evaluation of other potential covariates. Due to the 20-fold difference in average weights between infants and adults, an allometric approach was used to scale CL and Q by weight ($WT^{0.85}$) and both Vc and Vp by weight ($WT^{1.0}$) (9). Time-varying body weight was used for infants to account for their rapid growth that occurred during the study. Age, dose, dose number, sex, HIV status, and split dosing in infants (one vs. two SC injections) were evaluated as potential covariates for CL, V, and R1. Due to the importance of maturation effects on PK, the age covariate was explored using several parameterizations; specifically:

1. Categorical age model (adult vs. infant ≥6 months vs. infant <6 months) that assumes specific cutoffs for significant age groups;

$$\text{Parameter} = \text{Parameter}_{\text{Adult}} * \theta_1(\text{if infant} < 6 \text{ months}) * \theta_2(\text{if infant} \geq 6 \text{ months})$$

2. Continuous, linear age model that assumes a constant effect of age in infants;

$$\text{Parameter} = \text{Parameter}_{\text{Adult}} * \left(\frac{\text{Age}}{\text{Median Age}}\right)^{\theta} (\text{if infant})$$

3. Continuous, E_{max} age model that assumes a continuous effect that plateaus after a certain amount of time.

$$\text{Parameter} = \text{Parameter}_{Adult} * \frac{\theta_1 * \text{Age}}{\theta_2 + \text{Age}} (\text{if infant})$$

Potential covariates were added to the model one at a time as a linear or categorical function, with covariates that improved the model fitting at a statistically significant level ($p < 0.05$; change in objective function of 3.84 for a single covariate) being retained in the initial covariate screen. A forward addition approach was utilized in the multivariate assessment. Covariates found to improve the model fitting at a statistically significant level ($p < 0.005$; change in objective function of 7.88 for addition of a single degree of freedom) were retained in the final model.

Empiric Bayesian estimates of the individual pharmacokinetic parameters were generated from the final model using POSTHOC routine. A 1000 sample bootstrap assessment of the

final model was performed using Wings for NONMEM. Monte Carlo simulations of 1000 virtual HIV-infected infants were conducted to optimize dosing for treatment of HIV-infected infants. We simulated dosing regimens in HIV-infected infants using median infant body weights based on CDC growth charts and targeted VRC01 trough concentrations above 50 μg/mL. Three key dosing regimens tested were: 1) 40 mg/kg SC followed by 20 mg/kg SC every 4 weeks (Q4W), 2) 40 mg/kg SC Q4W, and 3) 40 mg/kg SC on weeks 0, 2, 6, and 10.

Results

Patients

A total of 1475 VRC01 pharmacokinetic serum samples were used for the population PK model. PK sampling was obtained from 40 infants and 60 adults. A total of 37 adults had HIV and no infants acquired HIV. Of the 37 adults with HIV, only 6 had viral loads over 1,000, the highest of which was 27,090. All 40 infants received subcutaneous (SC) VRC01 while 8 adults received SC VRC01 and 52 IV VRC01. Two or more doses of VRC01 were administered to 46 adults and 13 infants. Table 1 summarizes participant characteristics at first PK visit and study designs. Average infant weights increased from 3.0 kg at birth to 6.7 kg at week 16. Dose-normalized concentration profiles of VRC01 after the first SC dose for infants and adults are shown in Figure 1.

Population Pharmacokinetic Analysis

A two-compartment structural model described the data well. Attempts to simplify the model to one compartment resulted in a poor fit to the data. Covariate analysis was conducted as a univariate screen followed by multivariate evaluation after allometric scaling for weight. The univariate screen found age (represented by infant status), dose, sex, and HIV status as predictors of clearance (CL) while age (represented as a variable with 3 categories: adult, infant <6 months, and infant ≥6 months) and dose had effects on Vc and Vp; age (represented by infant status), sex, and dose number had effects on the rate of zero order input (R1). Age for CL, Vc, Vp, and R1; and HIV status for CL were significant covariates retained in the final model (Table 2). Although attempts to stratify the age effect for infants on clearance further did not result in an improvement in the model, the 6-month cutoff stratification on Vc and Vp significantly improved the model. An age effect was also tested on bioavailability instead of CL, Vc and Vp with a significantly worse fit to the data. Between subject variability was assessed for CL and R1, and a single between subject variability was assessed for Vc and Vp. A combined additive and proportional error were used to characterize residual error.

The final population pharmacokinetic model described the data without significant bias as shown in Figure 2A–D. Shrinkage estimates for inter-subject variability were low for CL (2.5%) and Vc and Vp (5.8%), but higher for R1 (53%). Final model parameters and variance estimates are shown in Table 2. Bootstrap evaluation of the final model successfully converged 89.3% of the time and estimation results are summarized in Table 2. The final parameter estimates of the model fall within the 95% confidence interval and deviate minimally from the median estimates, which suggests the final model represents the

populations well. Weight-normalized Vc and Vp were 40% lower in infants <6 months and 70% lower in infants ≥6 months relative to Vc and Vp in adults. Weight-normalized clearance in infants was 83% lower than in adults, while weight-normalized clearance in HIV positive subjects was 37% higher than that of HIV negative subjects. Dose-normalized rate of zero order input for SC administration was 2.79 times higher in infants than adults. Since the model fit the data well, more complicated models (i.e. nonlinear PK models) were not attempted. To confirm no potential confounding between route of administration and population, infant and adult data were modeled separately; the models identified covariates and parameters that were consistent with the final model.

Monte Carlo Simulations

Monte Carlo simulations of 1000 virtual HIV-infected infants were conducted to guide dosing recommendations for pediatric clinical trials investigating the effect of early, aggressive VRC01 therapy. Simulations based on median infant body weights are presented in Figure 3 and Table 3. The P1112 study dosing regimen predicted less than 95% of patients would maintain trough concentrations >50 μg/mL on weeks 8, 12, and 16. The 40 mg/kg Q4W regimen improved target attainment and predicted at least 95% of patients would maintain trough concentrations >50 μg/mL throughout the first 16 weeks of treatment. Finally, the 40 mg/kg on weeks 0, 2, 6, and 10 regimen also predicted >95% of patients would maintain trough concentrations >50 μg/mL on weeks 2, 6, 10, and 14.

Discussion

The development of novel therapies for infants and young children can be challenging (10). Characterizing the PK of a drug in infants is especially difficult, as studies in infants often have limited blood sampling due to their smaller blood volume. Direct extrapolation of adult to infant PK through simple allometry is often unreliable, as rapid growth and maturation in infants can lead to dramatic physiological changes in a short amount of time (11). Population PK modeling that combines rich adult PK data with limited pediatric data can allow for better characterization of the disposition of novel therapies in infants and young children, which in turn allows for optimization of dosing to streamline pediatric clinical trials.

The current analysis combined VRC01 data from infants and adults to create a popPK model to inform development of VRC01, a first-in-class bNAb for HIV-1 in infants. At doses of 20–40 mg/kg SC in infants, VRC01 is rapidly absorbed and achieves suppressive plasma concentrations within the first day of dosing. Infants had 83% lower weight-normalized CL and 2.79 times faster SC absorption than adults, and HIV-infected adults had 37% higher CL than HIV-uninfected patients.

In the initial stages of development, VRC01 target trough concentrations started as low as 10 μg/mL, and over time have increased to 50 μg/mL (2). At 50 μg/mL, VRC01 was shown to neutralize 91% of viral isolates from a panel of 190 strains representing all major circulating HIV-1 genetic subtypes (2). This target appears sufficient for HIV-prophylaxis, as no infants in dose group 3 of study P1112 have acquired HIV (4). However, little is known about the optimal VRC01 trough target for HIV-treatment. In HIV-infected adults, viral rebound

occurred despite maintaining plasma VRC01 concentrations between 50–100 μg/mL (6). Furthermore, even less is known about VRC01 treatment in HIV-infected infants, as IMPAACT 2008 will be the first study of VRC01 in this population. Thus, while 50 μg/mL target is effective for prophylaxis and can serve as a benchmark for the minimum acceptable trough concentration, targeting higher trough concentrations may be necessary for early, aggressive treatment to prevent establishment of viral reservoirs in HIV-infected infants.

Monte Carlo simulations were conducted to optimize VRC01 dosing for the treatment of HIV-infected infants. Since HIV-infected infant data were not available, these simulations leveraged HIV-infected adult data to evaluate VRC01 PK in HIV-infected infants. Additionally, since safety data in infants only exists for doses up to 40 mg/kg, no single dose was to exceed 40 mg/kg. While maintenance doses of 20 mg/kg in HIV-exposed uninfected infants maintained trough concentrations >50 μg/mL in P1112, initial simulations using the P1112 regimen predicted less than 95% of HIV-infected infants would maintain trough concentrations >50 μg/mL on weeks 8, 12, and 16. This suggested subsequent VRC01 doses higher than 20 mg/kg were needed to maintain trough concentrations above the 50 μg/mL target. The subsequent 40 mg/kg Q4W simulation predicted >95% of HIV-infected infants should maintain trough concentrations above the target. However, while this regimen was satisfactory in maintaining the 50 μg/mL target, relatively low troughs at week 4 were concerning. Thus, to maximize early VRC01 trough concentrations, the final regimen of 40 mg/kg at weeks 0, 2, 6, and 10 was tested. This regimen predicted VRC01 concentrations would not only achieve trough concentrations above the target for >97% of patients, but also that plasma concentrations would be maintained at high levels throughout the first 6 weeks of life. This dosing regimen is currently being evaluated in a clinical trial of HIV-infected infants to evaluate the safety, PK, and effect of early intensive VRC01 treatment (IMPAACT 2008, NCT03208231) (12).

VRC01 possesses many desirable characteristics for an anti-HIV agent to address the existing challenges of traditional ART in infants, including a long plasma half-life to allow infrequent administration to increase adherence, high potency, ability to be formulated at high concentrations for SC administration, a wide breadth of HIV coverage, and a novel mechanism of action to prevent cross-resistance with conventional ART. This allows combining VRC01 with ART with minimal risk of drug-drug interactions as is being done in current clinical trials. Additionally, VRC01 has limited to no self-reactivity, a good safety profile, and capacity for parenteral administration (3, 5, 6, 8). VRC01's excellent safety profile in adults allowed a rapid transition to studies in infants for prevention of vertical HIV transmission. Its SC administration is an advantage for treating infants, as it is well tolerated, feasible to scale up and has favorable pharmacokinetics. These advantages have been noted by researchers, as VRC01 is currently being studied for pre-exposure prophylaxis as an alternative to the current standard of care, and drugs with even longer half-lives are being explored for HIV therapy and prophylaxis in infants, children, and adults (13–16). Given VRC01 is the most studied antibody in this class, the abundance of PK data can be used to characterize differences in anti-HIV bNAb PK between infants and adults and guide the development of similar antibodies in the future.

The results from our analysis are reflective of previous VRC01 PK analyses. Our popPK approach estimated a median VRC01 half-life of 24 days in infants, which is similar to a noncompartmental analyses that estimated a median half-life of approximately 21 days (4). Our model estimated median clearance and half-life of VRC01 in healthy, HIV-uninfected adults was 0.0168 L/hour and 14.3 days, respectively, which is consistent with a previous popPK model that reported 0.0167 L/hour and 15 days (7). Finally, our model estimated a shorter half-life of 10.5 days in HIV-infected adults, which is consistent with a previous analysis (8).

Our model showed adults with HIV had 37% higher CL than adults without HIV. The higher clearance in adults with HIV than healthy adults was also seen for another bNAb, 10–1074, where serum half-life of was 12.8 days in adults with HIV and 24.0 days in healthy adults (17). While the underlying mechanisms are not well understood, studies suggest both the metabolic microenvironment and the innate and adaptive immune systems are altered in patients with HIV. Individuals with HIV are known to experience chronic immune activation and inflammation (18). This may lead to an upregulation in various metabolic pathways, including the reticuloendothelial system that is responsible for IgG antibody degradation. While we assumed these differences would be similar in HIV-infected infants for our simulations, this still needs to be validated in an HIV-infected infant cohort.

Development of novel therapeutics for infants requires characterizing CL over the first year of life. An estimated increase in clearance over time for infants may be due to a dilutional effect from rapid growth rather than a direct change in clearance. Furthermore, for therapeutic agents such as monoclonal antibodies where metabolites cannot be directly measured, it is almost impossible to distinguish whether the lower drug concentrations are due to the dilutional effect of growth or direct drug metabolism. An allometric exponent of 0.75 has been historically used to scale clearance and volume, but may be less ideal for therapeutic proteins and when the pediatric population is very young (19–21). The 0.75 exponent was established based on blood-flow driven small molecule PK, which is different from antibody clearance that is linked to both blood and lymph flow. We utilized an allometric scaling exponent of 0.85 for clearance, which was based on data from 13 monoclonal antibodies tested in cynomolgus monkeys that demonstrated a fixed exponent of 0.85 for CL and 1.0 for volume reasonably predicted human concentration-time profiles of antibodies (9). To assess the difference between the allometric exponents, we used the final model and changed the 0.85 exponent to 0.75. No clinically meaningful difference in the PK parameters was detected when testing the 0.75 exponent. Therefore, we used the 0.85 exponent as this value was estimated from monoclonal antibody PK data.

This is only the second study that combines adult and infant data for a popPK model for a monoclonal antibody. The results from our study are reflective of a prior combined adult and infant popPK model of palivizumab, a humanized IgG monoclonal antibody (22). Palivizumab is administered intramuscularly (IM), so the rate of IM absorption was estimated for both infants and adults. While SC and IM administration exhibit different absorption kinetics, both absorption processes are dependent on lymph flow (23). Our estimated 2.79 times faster SC absorption of VRC01 in infants than adults is identical to intramuscular (IM) palivizumab which was absorbed 2.7 times faster in infants than adults.

Our popPK model also estimated infants had lower weight-normalized CL than adults. A similar trend in CL was seen in the popPK model of palivizumab in adults and children where post-hoc baseline CL appeared higher in adults than in infants (22). The slower CL in infants seen in both studies may be explained by infants' higher weight-normalized FcRn concentrations, which protects IgG antibodies from lysosomal degradation through the reticuloendothelial system (24).

Our study has several limitations. First, all infants in study P1112 were HIV-exposed, but due to a lack of information regarding clinically relevant physiological characteristics of HIV-exposed infants, all subjects from P1112 were modeled as healthy infants in this analysis based on the assumption that HIV-exposed infants have similar characteristics to healthy infants. Second, due to the sparse sampling for infants in dose group 3 receiving multiple VRC01 doses, we could not characterize a continuous maturation effect on VRC01 PK in infants between birth to 80 weeks of age. The sparse sampling for infants also made it difficult to estimate between subject variability on Q. Third, due to the sparse sampling for all infants within the first day of dosing, there were issues characterizing the SC absorption rate variability, as demonstrated by the shrinkage on R1. However, simulations of the model predict infants achieve suppressive concentrations of VRC01 within the first day of administration, so the variability on SC absorption rate should not be clinically relevant. Fourth, since VRC01 was only administered SC in infants, we could not determine if potential age differences in CL/F were solely due to immature clearance or if differences in bioavailability contributed to the age effect. However, infant and adult data modeled separately identified covariates and estimated parameters that were consistent with the final model for each population, confirming no potential confounding between route of administration and the population. Lastly, our dataset contained limited covariate data that could be used to characterize PK variability. Particularly, we lacked albumin data, which has been shown to affect antibody clearance and distribution.

In conclusion, we developed a population PK model for VRC01 using infant and adult data to inform dosing in an infant trial. HIV infection increased clearance while infant status decreased clearance. Simulations of the final model allowed for a rational and mechanistic approach to optimize dosing of this novel therapeutic in ongoing clinical trials. The model demonstrates the differences in monoclonal antibody PK between infants and adults can only partially be explained by allometry alone, and popPK modeling can be used effectively guide optimal dosing for pediatric clinical trials.

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Study Highlights

What is the current knowledge on the topic?

Little is known about the absorption and metabolism of HIV bNAbs in infants and changes that occur with age. Some HIV bNAbs demonstrate higher clearance and shorter half-life in HIV-infected individuals compared to HIV-uninfected individuals.

What question did the study address?

What are the PK differences of VRC01 between infants and adults?

What does this study add to our knowledge?

This is the first popPK analysis of an anti-HIV bNAb combining both adult and infant data in a single analysis. Subcutaneous bNAb administration may result in significantly different absorption for infants. Additionally, bNAb metabolism is significantly slower in infants than adults, and rapid growth in infants has a dilutional effect on bNAb concentrations.

How might this change clinical pharmacology or translational science?

This analysis suggests leveraging adult pharmacokinetic data to inform pediatric models can be used to informing dosing recommendations in pediatric clinical trials. This also suggests further exploration is needed to assess changes in PK in the pediatric population, as allometry alone does not explain the complex differences between the two populations.

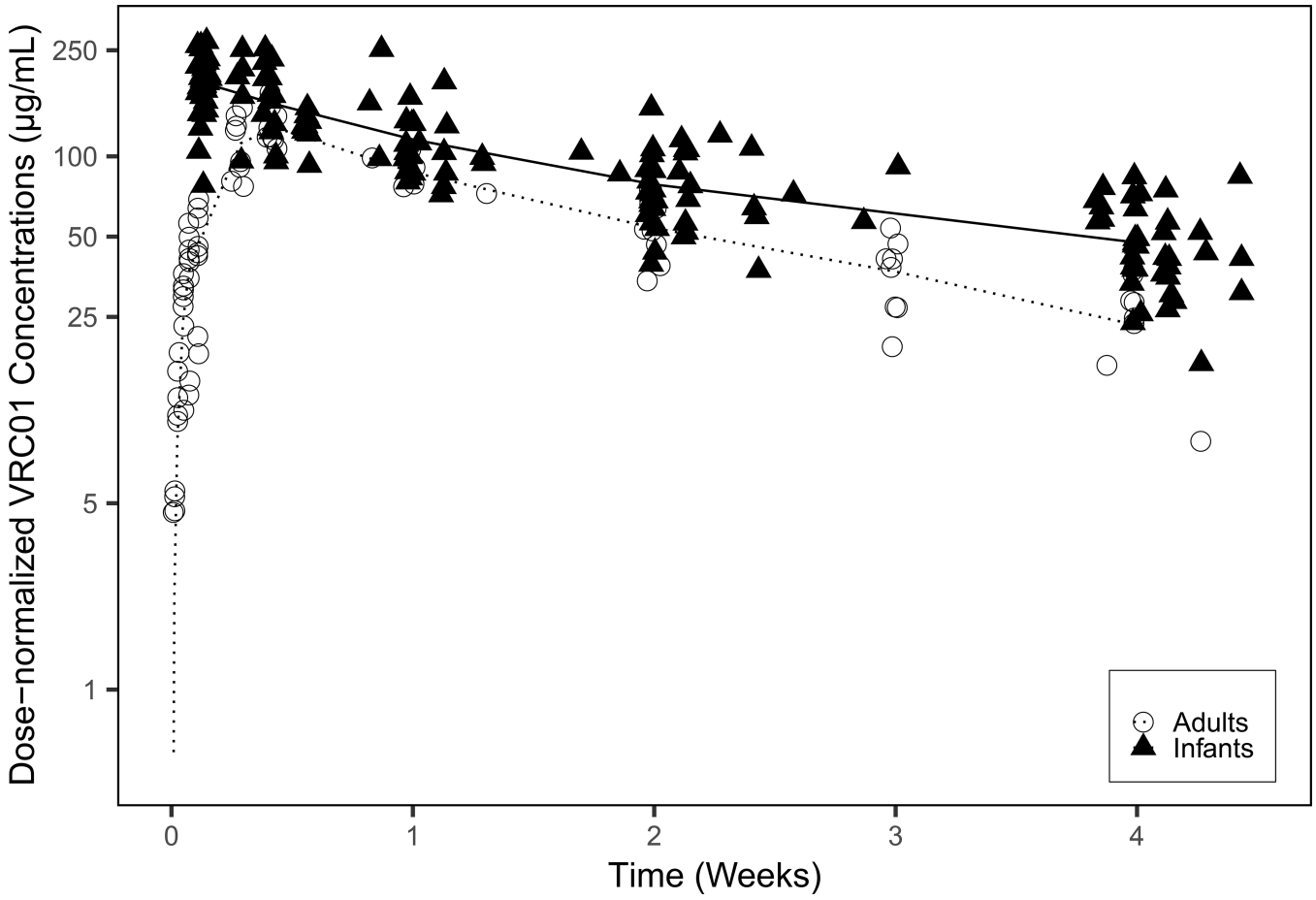

Figure 1.

Dose-normalized to 20 mg/kg subcutaneous VRC01 concentrations in infants and adults after first administration. Solid and dotted lines represent median concentrations for infants and adults, respectively. Data suggest infants absorb subcutaneous VRC01 more rapidly than adults.

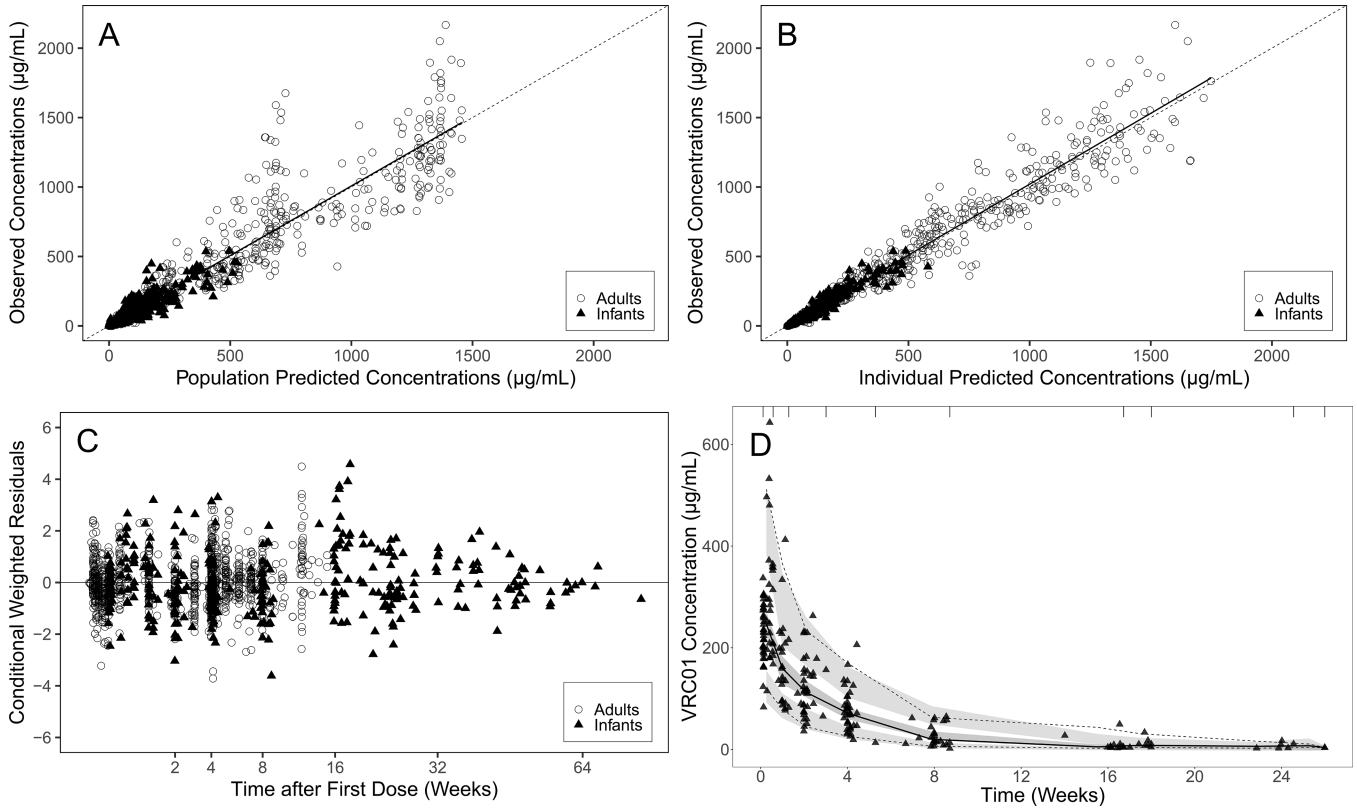

Figure 2.

Diagnostic plots for final population PK model. A: Population predicted VRC01 concentrations vs. observed concentrations. B: Individual predicted VRC01 concentrations vs. observed concentrations. Dashed line represents line of unity. Solid line represents linear regression line. C: Conditional weighted residuals vs. time (weeks). D: Visual predictive check of single dose VRC01 concentration over time. Solid and dashed lines represent the median and 2.5–97.5 percentiles of the observed data, respectively. Shaded areas represent the 95% confidence intervals around the predicted median and 2.5–97.5 percentiles. Overall model represents the data without bias.

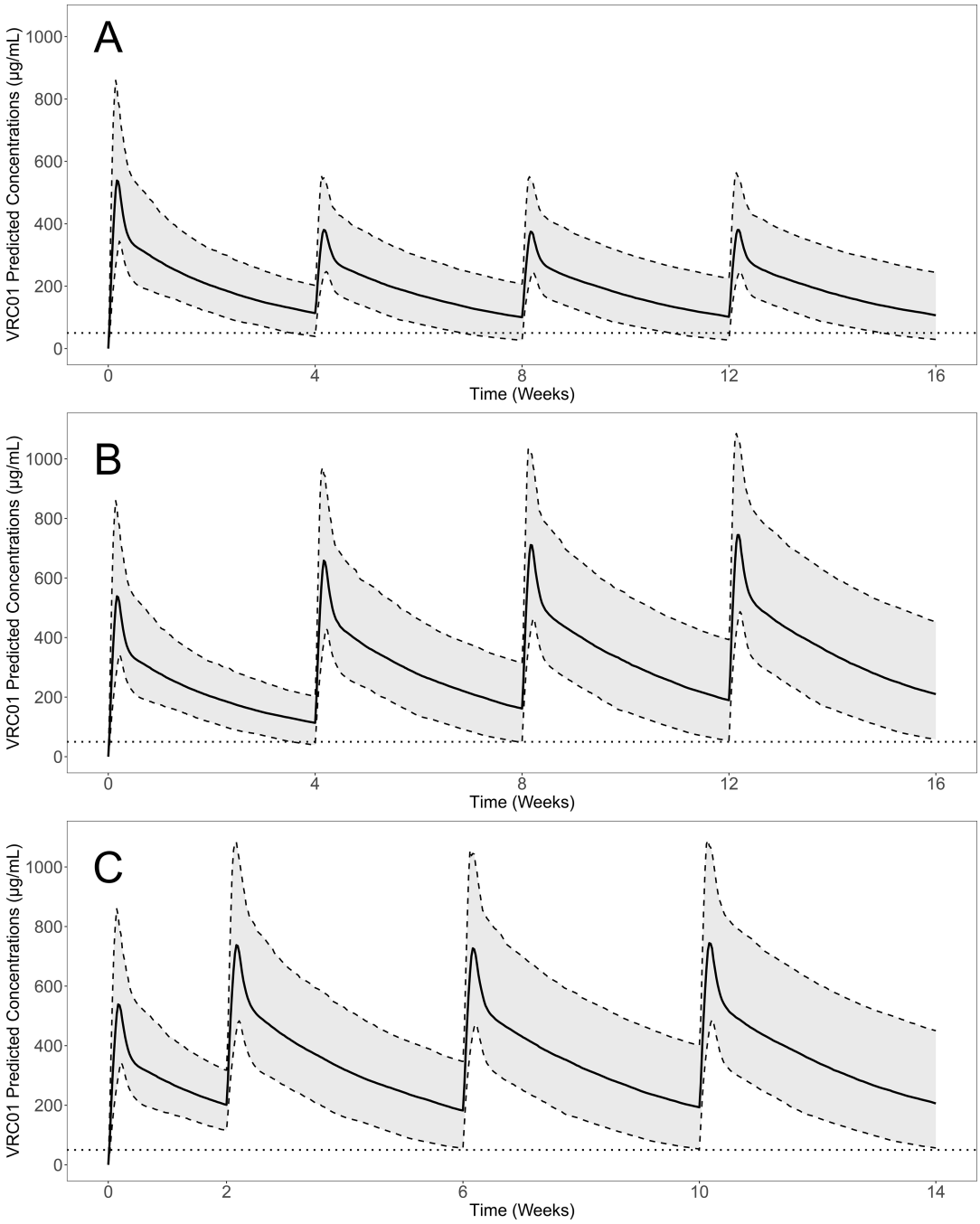

Figure 3.

Monte Carlo simulations of VRC01 PK in HIV-infected infants using the final model. Infant weights are based on median male infant weights from the CDC growth tables. A. The 40 mg/kg followed by 20 mg/kg Q4W dosing regimen (P1112 study) predicts less than 95% of patients will maintain trough concentrations >50 µg/mL on weeks 4, 8, 12, and 16. B. The 40 mg/kg Q4W dosing regimen predicts at least 95% of patients will maintain trough concentrations >50 µg/mL on weeks 4, 8, 12, and 16. C. The 40 mg/kg on weeks 0, 2, 6, and 10 dosing regimen (IMPAACT 2008 study) predicts at least 95% of patients will maintain

trough concentrations >50 μg/mL on weeks 2, 6, 10, and 14. Data represent median and 95% (2.5–97.5) prediction intervals. Horizontal dotted lines at 50 μg/mL represent pharmacodynamic target.

Table 1:

Baseline Demographics and Study Design

Adults			
Study	VRC601	VRC602	A5340
IV Administration dose (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)	40 mg/kg Q3W (14)
SC Administration dose (N)	5 mg/kg (3)	5 mg/kg (5)	None
Doses Received (N = 1 | 2 | 3)	10 | 13 | 0	3 | 20 | 0	1 | 6 | 7
PK Sampling	Hours: 0, 1, 2, 4, 8, 12, 24; Days: 2, 3, 7, 14, 21, 28, 35, 42, 49, 56 *, 85 *, 140 *	Hours: 0, 1, 2, 4, 8, 12, 24 Days: 2, 3, 7, 14, 21, 28, 56 *	Weekly
Age ** (years)	31 (21, 64)	34 (21, 48)	39 (27, 53)
Weight ** (kg)	83.8 (57.6, 115.0)	77.6 (58.5, 104.0)	85.8 (60.3, 114.8)
Sex (N = Male | Female)	19 | 4	18 | 5	14 | 0
Infants Study P1112			
SC Administration dose *** (N)	20 mg/kg single dose	40 mg/kg single dose	40 mg/kg once + 20 mg/kg Q4W for at least 24 weeks but no more than 72 weeks
Doses Received **	1 (1–1)	1 (1–1)	6 (1–16)
PK Sampling	Days: 1, 3, 7, 14, 28 Weeks: 8, 16, 24, 48	Days: 1, 3, 7, 14, 28 Weeks: 8, 16, 24, 48	Day: 1, 14, 28 Weeks: 8, 16, 20, 24, and every 12 weeks thereafter
Age ** (days)	2 (0, 3)	2 (0, 3)	2 (1, 5)
Baseline weight ** (kg)	3.0 (2.3, 4.5)	3.2 (2.6, 3.6)	2.9 (2.3, 4.3)
Sex (N = Male | Female)	9 | 4	6 | 8	8 | 5

* PK sample drawn only after second dose administration

** Data represent median (range)

*** Doses > 100 mg were split into 2 SC injections into the thigh

Abbreviations: IV = intravenous, SC = subcutaneous, mg = milligram, kg = kilogram

Table 2:

Final Population PK Model Parameters and Bootstrap Estimates with Equations.

	Final Parameter Estimates	Relative Standard Error (%)	Bootstrap Estimates* Median (95% CI)
Θ_1 (Vc; L)	1.99	3.92	1.99 (1.84, 2.16)
Θ_2 (Vp; L)	4.33	4.20	4.33 (3.97, 4.72)
Θ_3 (CL; L/h)	0.0154	5.33	0.0154 (0.0137, 0.0172)
Θ_4 (Q; L/h)	0.0514	5.16	0.0513 (0.0462, 0.0569)
Θ_5 (KA; h^{-1})	0.445	30.11	0.443 (0.1343, 0.899)
Θ_6 (F1)	0.55	8.80	0.56 (0.450, 0.714)
Θ_7 (R1; %/h)	0.627	13.95	0.63 (0.489, 0.876)
Θ_8 (Infant CL)	0.173	12.54	0.176 (0.136, 0.236)
Θ_9 (Infant <6 Mo V_C+V_P)	0.597	12.41	0.603 (0.5452, 0.833)
Θ_{10} (Infant ≥6 Mo V_C+V_P)	0.298	13.12	0.302 (0.229, 0.421)
Θ_{11} (Infant R1)	2.79	15.88	2.88 (1.86, 3.78)
Θ_{13} (HIV CL)	1.37	6.88	1.37 (1.19, 1.58)
Variability (η)			
IIV on V_C+V_P (%)	29.4	20.90	29.1 (22.6, 34.8)
IIV on CL (%)	35.9	16.51	35.1 (29.4, 41.1)
IIV on R1 (%)	28.9	58.66	26.3 (0.3, 42.5)
Error (ε)			
Proportional (%)	21.6	0.9	21.4 (19.8, 23.2)
Additive (μg/mL)	1.1	0.14	1.04 (0.79, 1.43)

*Bootstrap successfully converged 89.3% of the time

Abbreviations: V_C=central volume of distribution, V_P=peripheral volume of distribution, CL=clearance, Q=intercompartmental clearance, KA=first-order absorption, F1=bioavailability, R1=zero-order input

$$CL\left(\frac{L}{Hour}\right) = 0.0154 \times \left(\frac{WT}{70}\right)^{0.85} \times 0.173 \text{ (if infant)} \times 1.37 \text{ (if HIV positive)} \quad R1\left(\frac{\%\ Dose}{Hour}\right) = 0.627 \times 2.79 \text{ (if infant)}$$

$$V_C + V_P\ (L) = (6.32) \times \left(\frac{WT}{70}\right) \times 0.597 \text{ (if infant} < 6 \text{ months)} \times 0.298 \text{ (if infant} \geq 6 \text{ months)}$$

Table 3:

Monte Carlo Simulations of 1000 Virtual HIV-infected Infants for Three Different VRC01 Dosing Regimens

A. 40 mg/kg + 20 mg/kg Q4W (IMPAACT P1112)				
Trough Time (Week)	4	8	12	16
Median (95% PI)	114 (39–202)	100 (27–207)	102 (27–225)	107 (29–244)
Percentage >50 μg/mL	95.4	87.2	87.2	88.8
B. 40 mg/kg Q4W				
Trough Time (Week)	4	8	12	16
Median (95% PI)	114 (39–202)	162 (49–314)	190 (54–393)	210 (58–453)
Percentage >50 μg/mL	95.4	97.2	97.8	98.0
C. 40 mg/kg on Weeks 0, 2, 6, and 10 (IMPAACT 2008)				
Trough Time (Week)	2	6	10	14
Median (95% PI)	210 (115–318)	182 (55–347)	193 (53–401)	205 (56–449)
Percentage >50 μg/mL	100	97.8	97.8	97.9

Abbreviations: IMPAACT= International Maternal Pediatric Adolescent AIDS Clinical Trials Group, PI=prediction interval