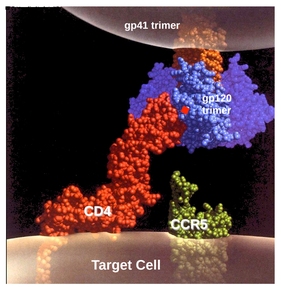
Population Pharmacokinetics (popPK) Analysis of VRC01, a Broadly Neutralizing HIV-1 Monoclonal Antibody, in Healthy Adults

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Background

VRC01 Blocks HIV-1 Attachment to CD4





- **CD4 binding site on HIV-1 gp120 is functionally conserved: All viruses must bind CD4**
- **VRC01 neutralizes 80-90% of HIV-1 viral isolates from multiple clades at levels of less than 50 mcg/ml**

Ref: Zhou et al, 2010&2013, Wu et al, 2010 & 2011, Scheid et al 2011, Li et al. 2011, West et al 2012

HVTN104 and VRC602: Safety and Drug-Level Studies of Intravenous (IV) or Subcutaneous (SC) VRC01 in Healthy Adults

- **In VRC602, 23 HIV-uninfected adults received VRC01 (Ledgerwood et al., 2015)**
  - 1 or 2 infusion(s) 4-weeks apart at 5, 20 and 40 mg/Kg dose level, or
  - 2 SC injections 4-weeks apart at 5 mg/Kg dose level
  - VRC01 serum levels measured pre-dose and 0, 1, 2, 4, 8, 12, 24, 72 (SC only) hours, and 2, 7, 14, 21, 28 and 56 (after the 2nd dose) days post-dose
- **In HVTN104, 84 HIV-uninfected adults received multiple-dose VRC01**
  - 3-6 IV infusions every 4 or 8 weeks at 10, 20, 30 or 40 mg/Kg dose-level, or
  - 11 SC injections every 2 weeks at 5 mg/Kg dose-level
  - VRC01 serum levels measured pre-dose, 1-hour, 3-days, 2, 4 and/or 8 weeks post-dose
  - Last serum level at 32 weeks (since enrollment), or 8-16 weeks after the final infusion/injection
- **HVTN104 data were used to construct the popPK model; VRC602 data were used to validate the model**

Figure 1: Study schema and VRC01 serum concentration sampling schedule in HVTN104

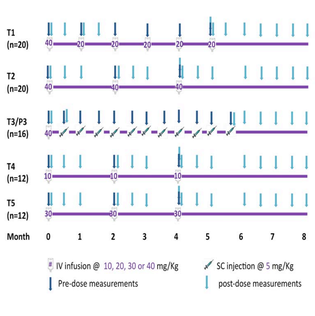
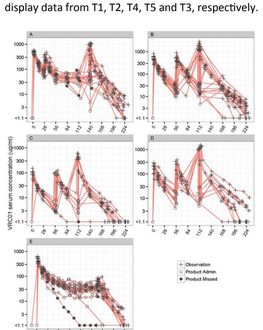


Figure 2: Individual-level concentration (log-scale)-time curves for VRC01 recipients in HVTN104. Panels A – E display data from T1, T2, T4, T5 and T3, respectively.



Antibody Mediated Prevention (AMP) study: Two Harmonized Phase 2b Efficacy Trials of IV VRC01 in Healthy Adults

- **First efficacy study of a bnAb (VRC01) for HIV-1 prevention launched in 2016**
  - HVTN703/HPTN081 in sub-Saharan African women (n=1500)
  - HVTN704/HPTN085 in American/Swiss MSM & transgender persons (n=2700)
- **Within each cohort, 1:1:1 allocation to receive a total of 10 VRC01 IV infusions 8-weekly at 10 mg/Kg, 30 mg/Kg, or placebo**
- **To assess:**
  - Prevention Efficacy (PE) -- whether IV VRC01 prevents HIV-1 infection
  - Correlates of Risk -- whether and how VRC01 serum concentration (or other VRC01 effector function markers) over time is associated with the rate of HIV infection

Motivations/Objectives of popPK Analysis of VRC01

Motivations:
- **Select dose-regimens based on predicted concentration profiles for future efficacy trials of similar bnAbs**
- **Provide a technique for inferring VRC01 concentrations over time for AMP correlates of risk analyses**

Objectives:
- **To construct and evaluate a popPK model, based on IV and SC VRC01 data from HVTN104 and VRC602**
  - concentration-time curves of VRC01
  - inter-individual variabilities of various PK parameters
  - effects of covariates on systemic drug exposure

Methods

- **VRC01 Serum Concentration were measured by an Enzyme-linked immunosorbent assay (ELISA) using anti-idiotype monoclonal antibodies**
- **Nonlinear mixed effects models were used to fit the popPK model in NONMEM**
  - 2-compartment disposition model with first-order elimination from the central compartment
  - A depot compartment with a first-order absorption rate constant for SC VRC01
  - The model was parameterized in terms of clearance (CL), central volume of distribution (Vc), peripheral volume of distribution (Vp), inter-compartmental clearance (Q), and absorption rate constant (ka)
  - The absolute bioavailability (F1) was estimated for SC administration relative to IV administration
- **Candidate covariates:** age, gender, body weight, body mass index, Creatinine clearance, alkaline phosphatase, alkaline aminotransferase, aspartate aminotransferase, hemoglobin, platelets, lymphocyte, neutrophil, and white blood cell counts

popPK Modeling Process. *FOCEi*: first-order conditional estimation method with interaction. *%CV*: percent coefficient of variation. *LLoQ*: lower-limit of quantification (of the ELISA assay). IIV: inter-individual variability

1. Base model of IV + SC or IV only groups (FOCEi & exponential random effects)
- Error model: exponential, proportion, proportion+ constant → %CV & AIC/BIC criteria
- LLoQ: sensitivity analysis → predicted concentration vs. observed in IV groups

↓

2. Covariate Screening
- Covariates → IIV of PK parameter est. vs. covariates; select if spearman correlation > 0.3 for continuous and Wilcoxon rank sum test p < 0.05 for categorical variables
- Visual check of functional form: linear, exponential or power → PK parameters est. vs. covariate

↓

3. Stepwise Covariate Model Selection (Likelihood ratio tests)
- Forward selection: include if P < 0.05
- Backward selection: exclude if P < 0.01

↓

4. Final PK Model
- Fine tune the model (for prediction purpose)
  - PK parameter correlation > 0.85 → shared random effects scaled by a factor
- Remove random effects terms if corresponding %CV < 15% in simulations

Results

Table 1: **popPK parameter estimates of VRC01 based on the modeling of all IV infusion and SC injection groups in HVTN104.** %RSE: relative standard error of the fixed effects estimate, calculated as (SE/ Estimate)*100. %CV: coefficient of variation for random effect estimates, calculated as * 100. R: correlation coefficient between random effect estimates.

Parameter (units)	Fixed effects: Population Parameter		Random effects: Inter-individual/ Covariance/ Residual error	
	Estimate	%RSE	Estimate (%CV)	%RSE
F1 (-) – bioavailability after SC administration	0.74	5.75	0.00	
ka (1/day) - absorption rate constant	0.26	14.6	0.00	
CL (L/day): clearance from the central compartment	0.40	2.95	0.067 (26.0)	17.8
Vc (L): volume of the central compartment	1.94	5.67	0.028 (16.6)	49.8
Q (L/day): inter-compartmental distribution clearance	0.84	4.92	0.063 (25.0)	57.5
Vp (L): volume of the peripheral compartment	4.90	4.35	0.120 (34.6)	23.5
Body weight influence on CL fold increase (/Kg)	0.012	16.1	--	--
Body weight influence on Vc fold increase (/Kg)	0.01	22.6	--	--
Body weight influence on log Q (/Kg)	0.69	31.0	--	--
Body weight influence on log Vp (/Kg)	0.82	22.4	--	--
Covariance between CL and Q	--	--	0.034 (R=0.52)	46.8
Covariance between CL and Vp	--	--	0.050 (R=0.56)	26.6
Covariance between Q and Vp	--	--	0.082 (R=0.95)	37.2
σ_1^2 (proportional)	--	--	0.042 (20.4)	11.8
σ_2^2 (additive)	--	--	0.456	23.7

Figure 3: Goodness-of-fit plots for the final model of IV infusion (red) and SC injection (blue) groups in HVTN104. Panels A-C are model diagnostic plots; Panels D-F are visual prediction check (VPC) plots. In the VPC plots, lines show medians, and shaded areas show bands covered by the 2.5th and 97.5th percentiles for simulated concentrations.

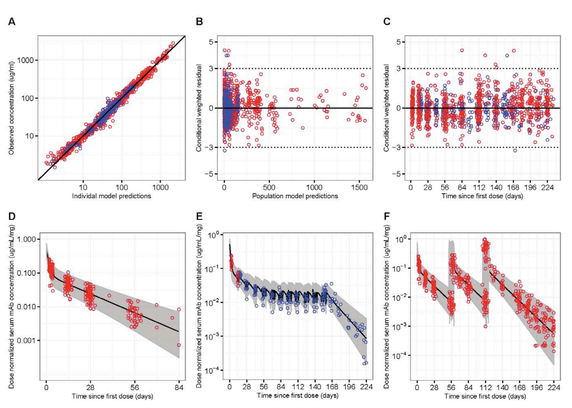


Figure 4: Observed vs. individual-predicted concentrations with an identity line in VRC602 based on the final HVTN 104 model of both the IV infusion (red) and SC injection (blue) groups.

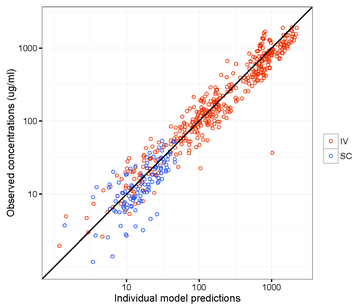
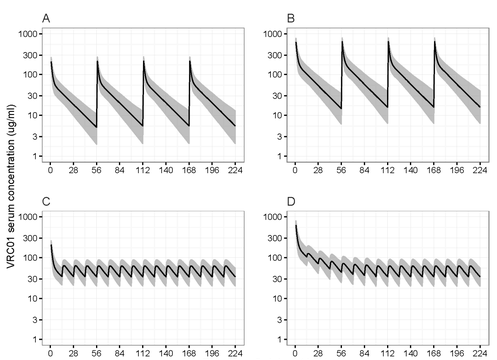


Figure 5: Simulated VRC01 serum concentrations after steady state is reached under different regimens of multiple-dose IV or SC VRC01. Panels A and B are for the 8-weekly 10 mg/Kg and 30 mg/Kg IV VRC01 regimens, respectively; Panels C and D are for the 2-weekly 5 mg/Kg SC VRC01 regimens, with an IV loading dose of 10 mg/Kg and 30 mg/Kg, respectively. Lines show medians, and shaded areas show bands covered by the 2.5th & 97.5th percentiles, simulated from 1000 trials w/weight=74.5kg.



Conclusions

- For the first time a robust popPK model of VRC01 was constructed and evaluated
  - Excellent goodness-of-fit characteristics
  - Reasonable prediction accuracy based on an external PK dataset of IV VRC01.
- VRC01 is best delivered in weight-dependent dosing regimens
- The resulting popPK model enables critical evaluation of various dose-regimens of VRC01 or its derivatives for future efficacy trials
  - IV VRC01 regimens at 10 and 30 mg/Kg 8-weekly were predicted to maintain concentration > 1 mcg/mL throughout the 32-week follow-up period for over 95% of individuals with a median steady state trough of 5.54 and 15.9 mcg/mL, respectively
  - SC VRC01 regimen 5 mg/Kg 2-weekly was predicted to maintain a median SS trough of 34.10 mcg/mL
  - Confirmed the potential of VRC01 in providing protection against HIV infection
  - Observed reasonable inter-individual variabilities in concentrations over time, supporting future correlates studies in AMP
- The developed popPK modeling process and results provide key techniques for guiding the characterization of other bnAbs, and for investigating correlates of HIV infection in ongoing and future efficacy trials of bnAbs

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