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Research paper

Pharmacokinetics and predicted neutralisation coverage of VRC01 in HIV-uninfected participants of the Antibody Mediated Prevention (AMP) trials

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ABSTRACT

The phase 2b AMP trials are testing whether the broadly neutralising antibody VRC01 prevents HIV-1 infection in two cohorts: women in sub-Saharan Africa, and men and transgender persons who have sex with men (MSM/TG) in the Americas and Switzerland. We used nonlinear mixed effects modelling of longitudinal serum VRC01 concentrations to characterise pharmacokinetics and predict HIV-1 neutralisation coverage. We found that body weight significantly influenced clearance, and that the mean peripheral volume of distribution, steady state volume of distribution, elimination half-life, and accumulation ratio were significantly higher in MSM/TG than in women. Neutralisation coverage was predicted to be higher in the first (versus second) half of a given 8-week infusion interval, and appeared to be higher in MSM/TG than in women overall. Study cohort differences in pharmacokinetics and neutralisation coverage provide insights for interpreting the AMP results and for investigating how VRC01 concentration and neutralisation correlate with HIV incidence.

1. Research in context

1.1. Evidence before this study

We searched PubMed for prior related work using various combinations of the following search terms: "monoclonal antibody", "broadly neutralising antibody", "passive infusion", "passive administration", "passive immunisation", "HIV", "clinical trial", "VRC01", and "population pharmacokinetics". We placed no filters on study year or language.

Three previous phase 1 studies have characterised the safety and pharmacokinetics of passively administered VRC01 in adults. Two of these were dose-escalation studies, each conducted at a single site in the United States: one in healthy, HIV-uninfected adults aged 18–50 (n = 29) and one in clinically stable HIV-infected adults aged 18–50

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(for dose escalation) or 18−70 (for enrolment of viremic HIV-infected adults) (n = 27). The third phase 1 study was conducted at six sites in the United States in healthy, HIV-uninfected, low-risk adults aged 18−50 (n = 88) and examined different doses, schedules, and routes of administration. We also found one phase 1 study, conducted in the United States, Zimbabwe, and South Africa, that characterised the safety and pharmacokinetics of passively administered VRC01 in HIV-exposed infants (n = 40).

We found two published studies of population pharmacokinetic modelling of VRC01: One study used 1117 longitudinal VRC01 serum concentrations from 84 participants in the third phase 1 study mentioned above to construct a population pharmacokinetics (popPK) model that characterised serum VRC01 concentrations over time. In addition, the popPK model developed in this study was validated using data from the first phase 1 study mentioned above. The other popPK study of VRC01 used 1475 VRC01 longitudinal VRC01 serum concentrations across the three adult and one infant clinical trials (n = 40 infants, 60 adults) to construct a popPK model aimed at guiding dose selection for clinical trials in infants.

1.2. Added value of this study

This study is the first to systematically characterise and compare the pharmacokinetics of an HIV broadly neutralising mAb, VRC01, in two different populations of healthy adults who are at risk of HIV acquisition: predominantly black, sub-Saharan African women, and predominantly non-black men and transgender persons in the Americas and Switzerland who have sex with men. In addition, this study presented unique data of the predicted VRC01 neutralisation coverage of circulating strains of HIV-1 based on the modelled VRC01 serum concentration in each population.

1.3. Implications of all the available evidence

First, our findings could facilitate the interpretation of the AMP trial efficacy results. For example, if the prevention efficacy of VRC01 is lower in HVTN 703/HPTN 081 than in HVTN 704/HPTN 085 as predicted in our simulations, then our neutralisation coverage analysis would be validated by empirical data from the AMP studies, suggesting that the differential efficacy could be attributable to the differing PK characteristics and/or neutralisation sensitivity of the circulating strains to VRC01 in the two study populations. Second, given the differing PK characteristics between the two study populations, it suggests that the sampling of uninfected control participants for the case-control study should be stratified by study. Third, given that participant body weight significantly influenced VRC01 clearance in both study populations, it suggests that the popPK modelling of the case-control concentration data should adjust for study and body weight. Fourth, the correlates analysis to assess whether VRC01 serum concentration associates with risk of HIV infection should also adjust for study and body weight as potential confounding factors. Lastly, the PK features studied in this article, including elimination half-life, steady state volume of distribution etc., could be evaluated as potential correlates of risk of HIV infection.

2. Introduction

With an estimated 38 million people living with HIV and 690,000 deaths due to AIDS-related causes in 2019 [1], the global HIV pandemic continues to deal a devastating blow to public health. Advances such as antiretroviral therapy and pre-exposure prophylaxis (PrEP) have significantly reduced AIDS-related morbidity and mortality and HIV acquisition, but challenges in access, uptake and adherence continue [2]. In addition, the rollout of PrEP has had a variable effect on HIV acquisition, particularly in the absence of a supporting comprehensive combination prevention program [3]. An international commission of global experts and stakeholders recently concluded that “existing HIV tools and strategies are insufficient” to end the HIV pandemic [4], highlighting the need for new and complementary preventive interventions.

Monoclonal broadly neutralising antibodies (bnAbs) against HIV-1 are a promising new avenue for HIV-1 prevention [5]. VRC01 is a human IgG1 monoclonal bnAb that targets the conserved CD4 binding site on the HIV-1 envelope (Env) surface glycoprotein [6], demonstrates breadth of neutralisation of clinical HIV-1 isolates [7,8], and prevents simian HIV infection in nonhuman primates [9,10,11,12,13,14,15]. In addition, it has been shown to be safe and well-tolerated in phase 1 trials in healthy HIV-uninfected adults at low-risk of HIV-1 acquisition in the United States when administered subcutaneously or intravenously (IV) in 4-weekly to 8-weekly doses [16,17]. Population pharmacokinetic (PK) modelling of these trials [18] demonstrated that following intravenous administration, VRC01 PK was best described by an open 2-compartment disposition model with first-order elimination from the central compartment, which accounts for reversible monoclonal antibody (mAb) transfer between the central and peripheral compartments [19]. VRC01 half-life estimates were consistent between the two phase 1 clinical trials conducted in the US[16,17] and VRC01 PK features were relatively stable across the multiple doses [17]. The pharmacokinetics of mAbs is such that biodistribution is mainly in the vascular and interstitial spaces [20], and is dependant on extravasation into tissue spaces, distribution in the interstitial fluid, mAb binding to tissue components, and clearance from the tissues [19]. Moreover, due to their relatively large size (molecular weight approximately 150 kDa), mAbs cannot be eliminated from the kidneys and are instead eliminated mainly through intracellular proteolytic catabolism by lysosomes to amino acids and smaller peptides that are then reused for new protein synthesis [19,20].

VRC01 is the first bnAb being tested for efficacy for the prevention of HIV-1 infection in humans in the proof-of-concept Antibody Mediated Prevention (AMP) trials [21], with primary results expected in Q4 2020. The safety and efficacy of ten 8-weekly IV infusions of VRC01 are being assessed in AMP in two study populations at risk of HIV-1 acquisition through predominantly different transmission routes: women in sub-Saharan Africa who have sex with men (HVTN 703/HPTN 081; ClinicalTrials.gov #NCT02568215) and men and transgender persons in Brazil, Peru, Switzerland, and the United States who have sex with men (MSM/TG) (HVTN 704/HPTN 085; ClinicalTrials.gov #NCT02716675) [21]. The major HIV-1 subtypes also differ between the two trials, with clade C predominating in sub-Saharan Africa and clade B predominating in the Americas and Switzerland [22].

One key secondary objective of AMP is to assess, through a case-control study, marker correlates (or predictors) of instantaneous HIV-1 risk (see [21] and [23] for further details), e.g. VRC01 serum concentration and serum neutralisation titre to panels of HIV-1 isolates. If validated, such a concentration or neutralisation biomarker will aid HIV vaccine development by setting a benchmark biomarker value for the required potency of a vaccine-induced neutralising antibody response to putatively achieve a high level of protection against HIV infection. This could help define study endpoints in phase 1 and 2 trials that vet candidate HIV vaccines for advancement into efficacy trials.

In preparation for the AMP case-control correlates study, we conducted a PK pilot study amongst a subset of VRC01 recipients in the AMP trials who remained HIV-uninfected until the end of the study and were not taking PrEP during the study. The objectives were to develop a population PK (popPK) model to characterise the PK features of VRC01 in more diverse HIV risk settings and populations than the phase 1 trials, over 10 administrations rather than the three to four administrations previously considered, and to identify factors that may influence these PK features. Consequently, this popPK pilot

study provides a technique for simulating serum concentrations for all VRC01 recipients and for inferring neutralisation coverage of participants' sera against the circulating strains in the AMP trials. A similar technique will be used to estimate VRC01 concentrations for individual participants in the case-control cohort at any given day during follow-up, which constitutes a critical data component in the AMP case-control correlates study. Importantly, findings from this PK pilot study are expected to aid the interpretation of the final AMP trial results on prevention efficacy, and to inform the sampling design of the case-control correlates study.

3. Methods

3.1. Study procedures

The AMP trials are being conducted in two distinct study populations: HVTN 703/HPTN 081 (ClinicalTrials.gov #NCT02568215) in sub-Saharan Africa (Botswana, Kenya, Malawi, Mozambique, South Africa, Tanzania, and Zimbabwe) in cisgender women who have sex with men (n = 1924), and HVTN 704/HPTN 085 (#NCT02716675) in Brazil, Peru, Switzerland, and the United States in MSM/TG (n = 2699). Participants were randomised (1:1:1) to receive ten 8-weekly infusions of 10 mg/kg VRC01, 30 mg/kg VRC01, or placebo (further details of the trial design and statistical considerations are given in [21]). Specimens are collected for HIV diagnosis and biomarker measurements at 25 time-points throughout the trial, including at 5 days after the second infusion (day 61), every 4 weeks from week 0 until week 80, and at weeks 88, 96 and 104.

We analysed serum concentration data collected at the above time-points from a total of 47 randomly selected VRC01 recipients, 23 from HVTN 703/HPTN 081 (women) and 24 from HVTN 704/HPTN 085 (MSM/TG), with 11 or 12 from each dose group per study (Table 1). Participants were eligible for sampling into the pilot study, irrespective of the number of infusions received and the timing of infusions, if they had remained HIV-1 uninfected until at least week 88, had not permanently discontinued infusions during trial follow-up, and were inferred to have not used PrEP. The HVTN 704/HPTN 085 (MSM/TG) participants were determined to be non-PrEP users based on self-report and dried blood spot data; HVTN 703/HPTN 081 (women) were determined to be non-PrEP users based on self-report data given the low frequency of PrEP use in the region (see Text S1 for details). For each sampled participant, serum samples from all available stored sample time points were assayed for VRC01 levels through week 104.

3.2. Serum concentration measurements

Enzyme-linked immunosorbent assay (ELISA) methods were developed to quantify bnAb concentration in human serum [16,24]. Quantification of VRC01 concentrations in participant serum was performed in 96-well plates on a Beckman Biomek-based automation platform according to the VRC/NVITAL Standard Operating Procedure "5500-Automated ELISA on SCARA Core System." The VRC01 anti-idiotype, Fab-specific 5C9 monoclonal antibody (manufactured by the Vaccine Research centre, National Institutes of Health) was coated onto Immulon-4HXB microtiter plates overnight at 4 °C at a concentration of 3·5 μg/mL (concentration is determined for each lot). Plates were then washed and nonspecific binding sites were blocked (10% foetal bovine serum in phosphate-buffered saline) for 2 h at room temperature. Duplicate serial 3-fold dilutions covering the range of 100 - 24,300 of the test sample were incubated for 2 h at 37 °C, followed by incubation with horseradish peroxidase-labelled goat anti-human antibodies (1 hour, 37 °C) and 3,3′,5,5′-tetramethylbenzidine substrate (15 min, room temperature). colour development was

Table 1
Characteristics of AMP participants at enrolment included in the PK pilot study.

		HVTN 703/HPTN 081 (women)	HVTN 704/HPTN 085 (MSM/TG)	HVTN 703/HPTN 081 and HVTN 704/HPTN 085 pooled
Dose	10 mg/kg VRC01	12 (52%)	12 (50%)	24 (51%)
	30 mg/kg VRC01	11 (48%)	12 (50%)	23 (49%)
Sex assigned at birth	Female	23 (100%)	1 (4%)	24 (51%)
	Male	0 (0%)	23 (96%)	23 (49%)
Gender	Cisgender woman	23 (100%)	0 (0%)	23 (49%)
	Cisgender man	0 (0%)	23 (96%)	23 (49%)
	Transgender man	0 (0%)	1 (4%)	1 (2%)
Race	Black	22 (96%)	6 (25%)	28 (60%)
	White	0 (0%)	15 (63%)	15 (32%)
	Other	1 (4%)	3 (13%)	4 (9%)
Age (y)	Median (range)	25 (19, 37)	31 (19, 50)	26 (19, 50)
Body mass index (kg/m2)		25·6 (20·3, 37·1)	25·8 (19·7, 37·6)	25·7 (19·7, 37·6)
Body weight (kg)		64·8 (47·0, 92·6)	75·2 (59·9, 130·2)	69·9 (47, 130·2)
Temperature (°C)		36·6 (35·7, 37·3)	36·6 (36·0, 37·1)	36·6 (35·7, 37·3)
Pulse rate (beats/min)		83 (58, 108)	76·5 (51, 101)	80 (51, 108)
Diastolic blood pressure (mmHg)		76 (64, 86)	74 (59, 89)	75 (59, 89)
Systolic blood pressure (mmHg)		119 (103, 128)	122 (109, 136)	120 (103, 136)
Respiratory rate (breaths/min)		18 (12, 24)	16 (12, 24)	18 (12, 24)
Alanine aminotransferase (units/L)		14 (9, 63)	20 (8, 87)	15 (8, 87)
creatinine clearance (l/day)		135·5 (96·5, 211·4)	126·2 (80·8, 212·3)	135·46 (80·8, 212·3)
Haematocrit (%)		40 (35, 46·5)	43·55 (39·9, 48)	42·2 (35, 48)
Haemoglobin (g/dl)		13·5 (11·4, 15·7)	14·6 (12·8, 15·6)	14·1 (11·4, 15·7)
Erythrocyte mean corpuscular volume (fL)		87 (73·7, 91)	90·35 (80, 100·3)	89 (73·7, 100·3)
Platelets (10^3/mm^3)		268 (183, 463)	229·5 (148, 335)	249 (148, 463)
Leukocytes (10^3/mm^3)		5·6 (3·2, 10·8)	5·9 (4·2, 9·8)	5·62 (3·2, 10·8)
Neutrophils (cells/mm^3)		3223 (1360, 5740)	3191·5 (1712, 5988)	3223 (1360, 5988)
Lymphocytes (cells/mm^3)		2158 (1395, 4070)	1932 (1043, 3058)	2033 (1043, 4070)
Monocytes (cells/mm^3)		360 (160, 790)	455 (211, 740)	400 (160, 790)
Eosinophils (cells/mm^3)		100 (22, 386)	101 (38, 380)	100 (22, 386)
Basophils (cells/mm^3)		31 (8, 72)	30·5 (0, 140)	31 (0, 140)

stopped by addition of sulfuric acid (stop solution 5% H_2SO_4), after which the absorbence of each well at 450 nm was measured within 30 min using a Molecular Devices Paradigm plate reader. Final sample concentrations were based upon dilution-corrected concentrations estimated from linear regression of a standard curve covering the range of 5 to 125 ng/mL. Concentration values below the limit of quantification (LoQ=1·0 μg/mL) were replaced by 0·5 μg/mL in all calculations. Sensitivity analyses were performed to evaluate the effect of this censoring value on the modelling results. If there were consecutive measurements below the LoQ, only the first one was included in the modelling.

4. Statistics

4.1. Population pk (popPK) modelling

PopPK modelling is a powerful approach where drug concentration data from multiple individuals are evaluated simultaneously using a nonlinear mixed-effects model, which incorporates both fixed effects (that are constant) and random effects (that vary across individuals or over time).

4.1.1. Structure model

VRC01 concentrations over time were analysed using nonlinear mixed effects modelling with the NONMEM software system (Version 7·4, ICON Development Solutions). The stochastic approximation of expectation-maximisation (SAEM) algorithm was used for the estimation of model parameters. An open 2-compartment disposition model with first-order elimination from the central compartment was parameterised in terms of clearance from the central compartment in L/day (CL), volume of the central compartment in L (Vc), inter-compartmental distribution clearance in L/day (Q), and volume of the peripheral compartment in L (Vp).

4.1.2. Variability popPK model

The statistical model considered three primary sources of variability around the structure population mean model: inter-individual variability (IIV), inter-occasion variability (IOV), and residual variability (RV) remaining after controlling for other sources of variability in the data. IOV was investigated by considering each infusion as an occasion to account for PK parameter changes between infusions due to, for example, changing number of doses or changing participant characteristics over time that may impact the underlying PK process. For both IIV and IOV, an exponential between-individual and between-occasion random effects model was considered such that the distribution of PK parameters is log-normally distributed, but the random effect is normally distributed. Further details are given in Text S1.

Regarding RV, the additive, proportional, and combination proportional + additive residual error models were all considered and compared. Further details are given in Text S1. The percentage coefficient of variation (%CV) of the error terms and the resulting fit of the different error models based on likelihood ratio tests of the objective function value (OFV) (minus twice the log likelihood of the data, with smaller value indicating better fit) were used in determining the final error model. Statistical significance of a hypothesis testing result is noted based on a 2-sided p-value $< 0{\cdot}05$.

4.1.3. Covariate model

Identification of baseline covariates predictive of PK variability was performed to better understand the sources of observed inter-individual variability. The baseline covariates that were screened for this analysis were pre-defined, including study (HVTN 703/HPTN 081 or HVTN 704/HPTN 085) and dose group (10 mg/kg or 30 mg/kg) as well as demographic variables: age (years), sex assigned at birth (male or female), body weight (kg), race (black or other), body mass index (kg/m^2); clinical variables: pulse rate (beats/min), respiratory rate (breaths/min), diastolic blood pressure (mmHg), systolic blood pressure (mmHg), temperature (°C); and safety lab variables: Cockcroft-Gault creatinine clearance (L/day), erythrocyte mean corpuscular volume (fL), alanine aminotransferase (units/L), haematocrit (%), haemoglobin (g/dL), platelets (10^3/mm^3), leucocyte count (10^3/mm^3), lymphocyte count (cells/mm^3), monocyte count (cells/mm^3), neutrophil count (cells/mm^3), basophil count (cells/mm^3), and eosinophil count (cells/mm^3). These covariates were screened and selected based on their performance in explaining the observed inter-individual variabilities of the PK parameters using a similar model selection procedure as described in Huang et al. [18]. where the IOV random effect term was not included (see Text S1). The IOV term was later evaluated in the final popPK model.

4.2. Simulations of serum concentration and prediction of neutralisation coverage

Serum concentrations were simulated both over the course of 8 weeks after a single dose and over the course of ten 8-weekly doses for AMP VRC01 recipients based on their body weight and treatment assignment information using the final popPK model without IOV. We graphed predicted neutralisation coverage against clade C viruses for HVTN 703/HPTN 081 and clade B viruses for HVTN 704/HPTN 085 using data from the Compile, analyze and Tally NAb Panels (CATNAP) database[25]; we predicted that an individual's serum at a specified time point would achieve "neutralisation coverage" of a virus if ID50 serum neutralisation titre was $\geq$ 100, i.e., the geometric mean serum concentration of VRC01 was at least 100-fold greater than the viral in vitro inhibitory concentration 50% (IC50) values, as measured in vitro, e.g. via the TZM-bl target cell assay [26]. We based the 100-fold estimate on the nonhuman primate simian human immunodeficiency virus (SHIV)-challenge model, where protection is achieved by CD4 binding-site bnAbs if serum antibody concentrations are approximately 50 to 100-fold higher than the measured IC50 of the challenge virus [14]. We considered viruses to be resistant to neutralisation (i.e., neutralisation coverage not achieved) if the IC50 was greater than 10 μg/mL.

4.3. Comparison of pk features between groups with covariate-adjustment

Seven individual-level PK features – CL, Vp, steady state volume of distribution, steady state area under the time-concentration curve (AUC), distribution half-life, elimination half-life, and accumulation ratio estimates aggregated over all infusion occasions – were derived from the base popPK model. For comparing non-randomised groups of interest, such as the two AMP trials, to reduce confounding bias the targeted minimum loss-based estimation (TMLE) method [27,28] was used to estimate the mean of each feature for each group, adjusted for potential predictors of PK variability: age, body weight, race, creatinine clearance and dose group (implemented in the *tmle* R package [29]). TMLE is an alternative to standard linear or nonlinear regression that can have improved robustness and efficiency. All TMLE estimation results of means were averaged over 20 runs with a fixed random seed on top of the leave-one-out cross-validation estimation procedure to ensure stability of the estimates. The set of learning algorithms used by TMLE for estimating the mean outcome conditional on baseline covariates are listed in Text S1. In addition, to account for variability and co-variability of the individual-level estimates for each PK feature due to the fact that they were derived from a common popPK model, a bootstrap procedure based on 250 datasets was used to calculate the empirical variances of the estimates for each group and to derive the 95% confidence interval, as well as to test for a non-zero mean difference between the two groups. The Holm method [30] was used to adjust for multiple comparisons.

5. Ethics statement

The AMP trials were approved by all relevant Institutional Review Boards and Ethics Committees. All other layers of review, such as national regulatory review agencies, were also completed when required.

6. Role of the funding source

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7. Results

Study population descriptions The characteristics of the 47 AMP pilot PK study participants are summarised in Table 1. Overall, 24 of the 47 participants were assigned female sex at birth, 28 were black, and the median age was 26 (range 19 to 50). In HVTN 703/HPTN 081, all 23 participants were assigned female sex at birth, 22 were black, and the median age was 25 years (range 19 to 37). In HVTN 704/HPTN 085, 23 of the 24 participants were assigned male sex at birth, 6 were black, and the median age was 31 years (range 19 to 50).

Forty-five (95·7%) of the 47 pilot study participants received the planned 10 infusions of VRC01. In HVTN 703/HPTN 081 (women), the average interval between two consecutive infusions was 59·7 days (range 48·7 to 103) with one participant in the 30 mg/kg dose group who missed all infusions starting from the 4th; in HVTN 704/HPTN 085 (MSM/TG), the average infusion interval was 57·7 days (range 48·1 to 106) with one participant in the 30 mg/kg dose group who missed the 9th infusion (Figure S1). Given that baseline serum concentration measurements were all negative at week 0 (serving as assay quality control), and only one participant had a detectable level at week 96 (Figure S2), the popPK modelling excluded data at weeks 0, 96 and 104, and included 1003 VRC01 serum concentrations between week 4 through 88 from the 47 participants (Fig. 1).

Base popPK models Dosing at 10 mg/kg or 30 mg/kg did not influence any of the PK parameters when dose is evaluated as a covariate in the popPK models, thereby verifying the linear PK assumption regarding PK parameters having the same value across dose levels and allowing a single PK model to be used to describe data for both dose groups. In the base two-compartment model, the combination proportional + additive error model was chosen for its significantly improved objective function value (OFV=3156) over the proportional (OFV=3313) and additive (OFV=4373) models. IIV was observed primarily for CL and Vp with%CV of 20−21% and 24−26%, respectively, with and without IOV being considered (Table S1). However, after IOV was considered, residual errors were considerably reduced, and the precision of the fixed effects and the constant error term were considerably improved (Table S1). Therefore, PK features including CL, Vp, half-life, steady state AUC and accumulation ratio were estimated from the base model with IOV considered. Of note, despite the considerable level of IOV, the individual-level CL, Vp and half-life estimates did not obviously increase or decrease as the infusion numbers progressed (Fig. 2).

Final popPK models Clinical and demographic variables were assessed for their potential role in explaining the observed inter-individual variability according to the model selection process described. Further details on the construction of the final popPK model are given in Text S1. As shown in Table S2, when IOV was included, the model fit significantly improved (OFV = −1434·42 vs. OFV = 3064·36), suggesting that IOV will likely need to be considered in the estimation of concentrations for the AMP case-control correlates study. Overall, the popPK model diagnostic results suggested that the modelling assumptions were reasonable, and the final model with IOV included provides a reliable description of the data (Figures S5 and S6).

Based on the final popPK model, the population mean estimate for CL was 0·383 (95% CI: 0·357, 0·409) L/day for individuals with a body weight of 68·8 kg (median body weight over both studies), with an estimated 0·611 (95% CI: 0·350, 0·872) log increase of CL per kg of body weight. The population mean estimate for Vp was 3·17 L (95% CI: 2·87, 3·47) for individuals in HVTN 703/HPTN 081 (MSM/TG), estimated to be 0·428 (95% CI: 0·270, 0·586) fold higher for individuals in HVTN 704/HPTN 085 (women). After accounting for body weight and study cohort, the inter-individual variability of CL and Vp decreased from 20·0 to 15·8%CV, and from 23·6 to 13·5%CV, respectively.

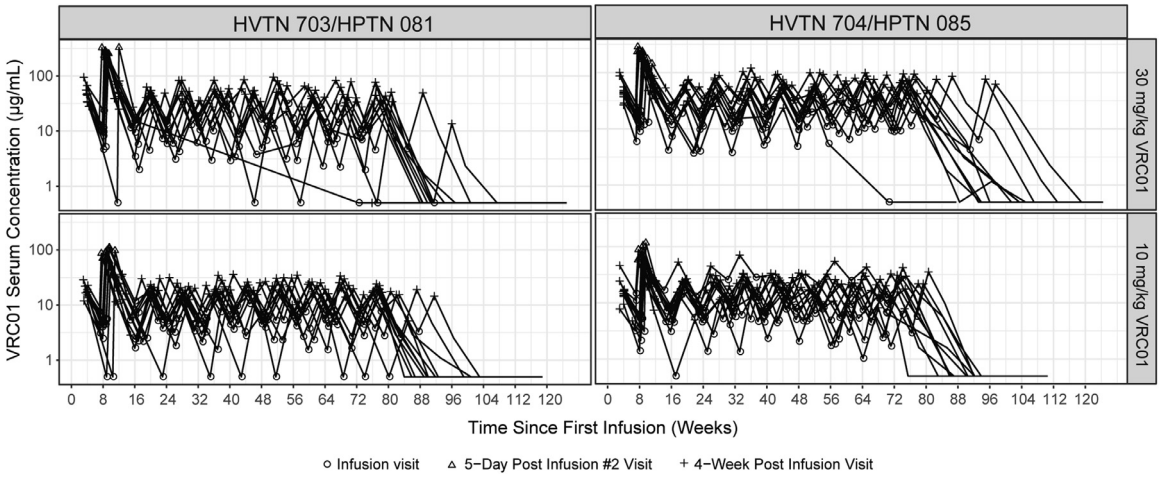

Fig. 1. Individual-level VRC01 serum concentration (log_{10}-scale) over time in HVTN 703/HPTN 081 (women) (n = 23), and HVTN 704/HPTN 085 (MSM/TG) (n = 24). "+" indicates the observed concentration at a 4-week post infusion visit, an open circle indicates the observed concentration at an infusion visit, and a triangle indicates the observed concentration at the 5-day post infusion #2 visit.

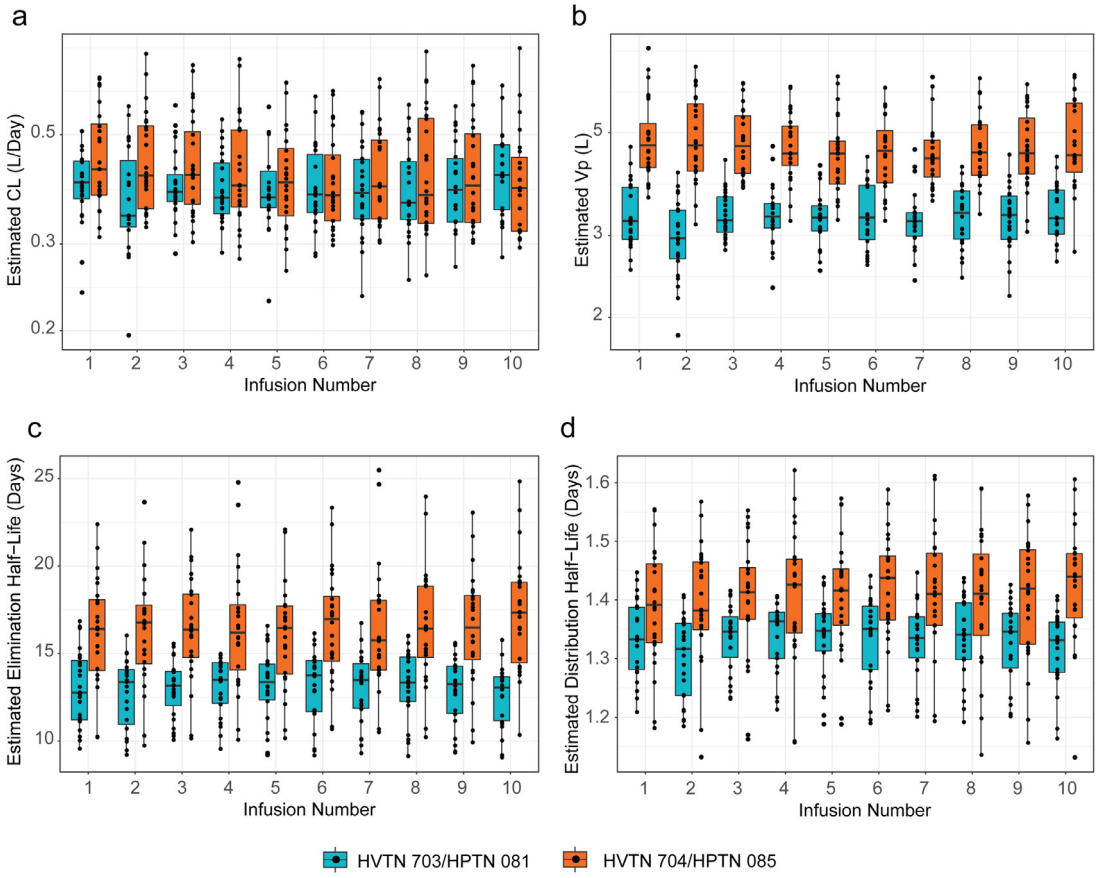

Fig. 2. Distributions of individual-level PK parameter estimates of VRC01 over the 10 infusions in HVTN 703/HPTN 081 (women) and HVTN 704/HPTN 085 (MSM/TG). a) Clearance (CL), and b) volume of the peripheral compartment (Vp), c) distribution half-life, and d) elimination half-life estimates are shown. Estimates are based on the inter-occasion variability-included base model described in Table S1. Panels a and b are shown on a log10 scale since both CL and V_p show a log-normal distribution, while panels c and d are shown on a linear scale.

In addition, the terminal half-life of VRC01estimated to be 12·33 and 16·43 days, distribution half-life 1·24 and 1·33 days, and steady state volume of distribution 5·26 and 6·62 L in HVTN 703/HPTN 081 (women) and HVTN 704/HPTN 085 (MSM/TG), respectively, based on the final popPK model. In the 10 mg/kg dose group, the final model resulted in an estimated accumulation ratio of 1·04 and 1·09 for the average 60 days of dosing interval in the study, and steady state AUC of 1796·35 and 1796·35 mg*day/mL in HVTN 703/HPTN 081 (women) and HVTN 704/HPTN 085 (MSM/TG), respectively, for individuals with a body weight of 68·8 kg. In the 30 mg/kg dose group, the final model resulted in an estimated accumulation ratio of 1·04 and 1·09, and steady state AUC of 5389·03 and 5389·03 mg*day/mL in HVTN 703/HPTN 081 (MSM/TG) and HVTN 704/HPTN 085 (women), respectively.

Predicted neutralisation coverage To visualise the expected concentrations in the two AMP trials, Fig. 3 and Figure S7 display simulated concentrations over 8 weeks after a single dose for the two dose groups. These concentrations were simulated based on the final popPK model accounting for body weight of actual AMP trial participants. Fig. 3 also displays the predicted coverage of VRC01 after a single dose based on known IC50 values in each trial population. The predicted coverage of VRC01 appears to be higher in HVTN 704/HPTN 085 (MSM/TG) compared to HVTN 703/HPTN 081 (women), for both dose groups after a given dose (Figs. 3 and S7) and over the course of 10 doses (Figure S8). Alternative posology analyses showed that with a higher dose level at 15 mg/kg (instead of 10 mg/kg) and 45 mg/kg (instead of 30 mg/kg), the neutralisation coverage in HVTN 703/HPTN 081 increased to a similar level as that in HVTN 704/HPTN 081 (Figure S9). As expected, coverage is predicted to be considerably higher in the first 4 weeks post-infusion compared to in the second 4 weeks [for 10 mg/kg groups: 43% vs 14% in HVTN 704/HPTN 085 (MSM/TG), 34% vs 7% in HVTN 703/HPTN 081 (women); for 30 mg/kg groups: 68% vs 35% in HVTN 704/HPTN 085 (MSM/TG), 56% vs 22% in HVTN 703/HPTN 081 (women)].

7.1. Covariate-adjusted study effects on PK features estimated from the base popPK model and TMLE

Seven individual-level PK features: CL, Vp, dose-normalised steady state AUC, steady state volume of distribution, distribution half-life, elimination half-life and accumulation ratio, were estimated from the base popPK model. The distributions of these estimates by study are shown in Figures S10 and S11. Comparisons of these PK features between the two studies adjusted for age, body weight, race, creatinine clearance and dose group using the TMLE approach are shown in Figs. 4 and 5. We found that the estimated mean of Vp, steady state volume of distribution, elimination half-life, and accumulation ratio were significantly higher in HVTN 704/HPTN 085 (MSM/TG) than in HVTN 703/HPTN 081 (women): estimated means of Vp 4·86 L and 3·21 L ($p < 0·001$, adjusted $p < 0·001$), steady state volume of distribution 7·49 L and 5·58 L ($p < 0·001$, adjusted $p < 0·001$), elimination half-life 17·29 and 12·64 days ($p = 0·005$, adjusted $p = 0·027$) and accumulation ratio 1·11 and 1·04 ($p = 0·008$, adjusted $p = 0·031$) respectively (Table 2, Fig. 4, Fig. 5).

8. Discussion

This popPK modelling work of VRC01 is the first of its kind to systematically characterise and compare PK of an HIV broadly

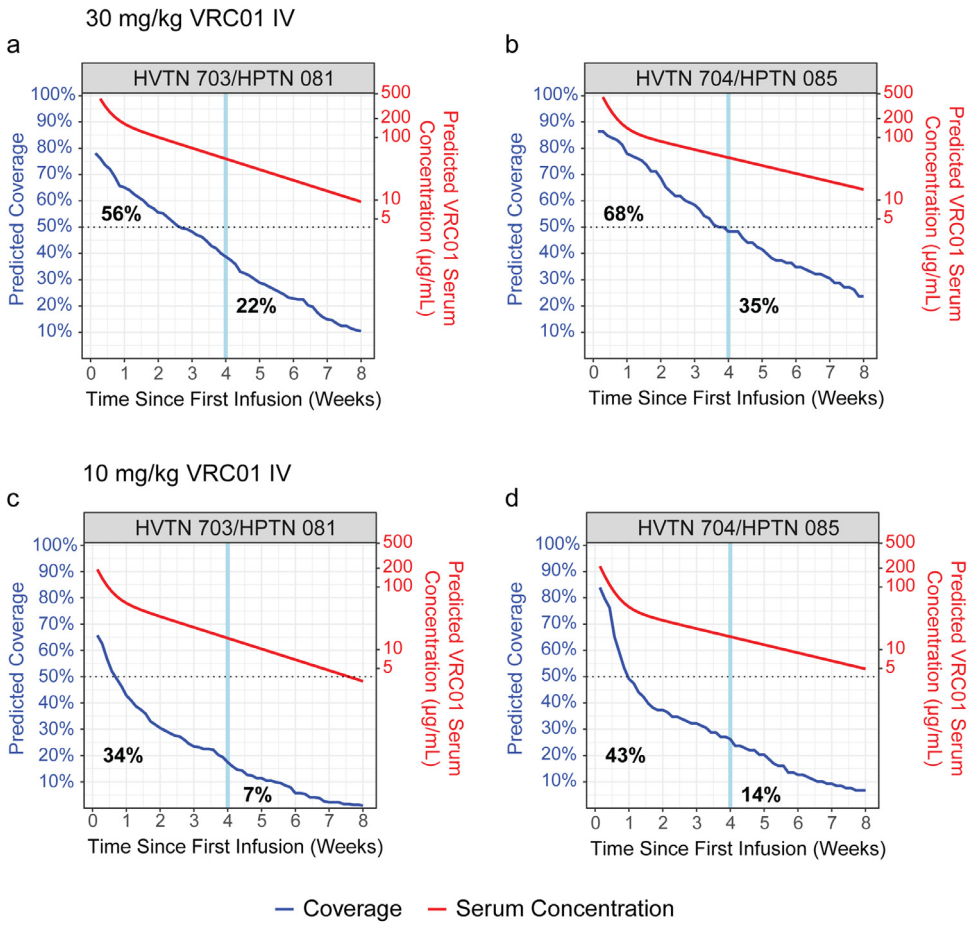

Fig. 3. Predicted VRC01 neutralisation coverage and serum concentration by time since first infusion. a (30 mg/kg), c (10 mg/kg) in HVTN 703/HPTN 081 (women): Percent of 315 clade C isolates on CATNAP that would be sensitive to VRC01 neutralisation if the geometric mean serum concentration at the given time-point was at least 100-fold greater than the viral in vitro inhibitory concentration 50% (IC50), i.e., ID50 serum neutralisation titre is ≥100. b (30 mg/kg), d (10 mg/kg) in HVTN 704/HPTN 085 (MSM/TG): Percent of 118 clade B isolates on CATNAP that would be sensitive to VRC01 neutralisation if the geometric mean serum concentration at the given time-point was at least 100-fold greater than the viral in vitro inhibitory concentration 50% (IC50), i.e., ID50 serum neutralisation titre is ≥100. Within each plot, the left-most bolded percentage corresponds to the average coverage in the first 4 weeks post-first infusion and the right-most bolded percentage corresponds to the average coverage in the second 4 weeks post-first infusion.

neutralising mAb in healthy adults who are at risk of HIV acquisition in two distinct study populations: predominantly black, sub-Saharan African women (AMP HVTN 703/HPTN 081), and predominantly non-black men and transgender persons in the Americas and Switzerland who have sex with men (MSM/TG) (AMP HVTN 704/HPTN 085). Based on VRC01 serum concentration data collected longitudinally over 10 infusions at two different doses from a subset of AMP participants, we constructed a popPK model accounting for baseline participant characteristics, variabilities of PK features across individuals, as well as variabilities across repeated product infusions. We found that participants' body weight significantly influenced VRC01 clearance in both AMP study populations with a faster clearance for heavier

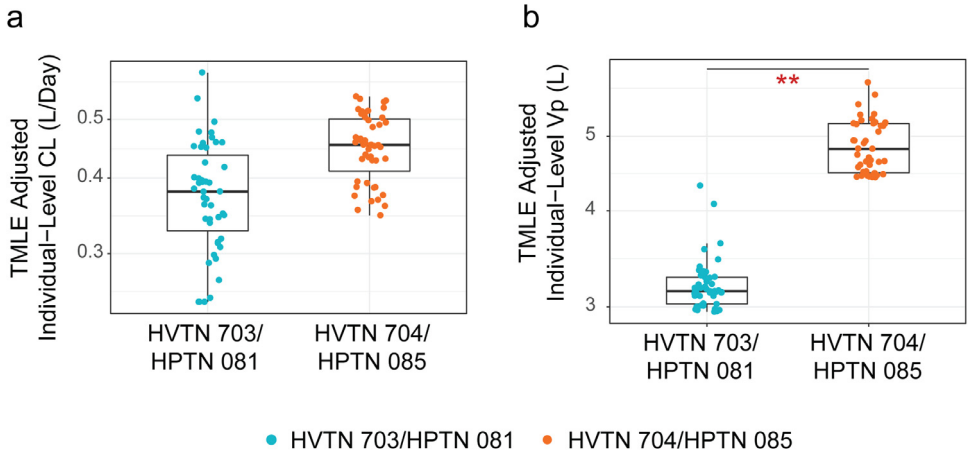

Fig. 4. Distributions of covariate-adjusted individual-level PK parameters of VRC01 in HVTN 703/HPTN 081 (women) and HVTN 704/HPTN 085 (MSM/TG). a) Clearance (CL) and b) volume of the peripheral compartment (Vp). All estimates were adjusted for dose, age, body weight, race, and creatinine clearance via targeted minimum loss-based estimation (TMLE) as presented in Table 2. **, two-sided adjusted p-value < 0.001.

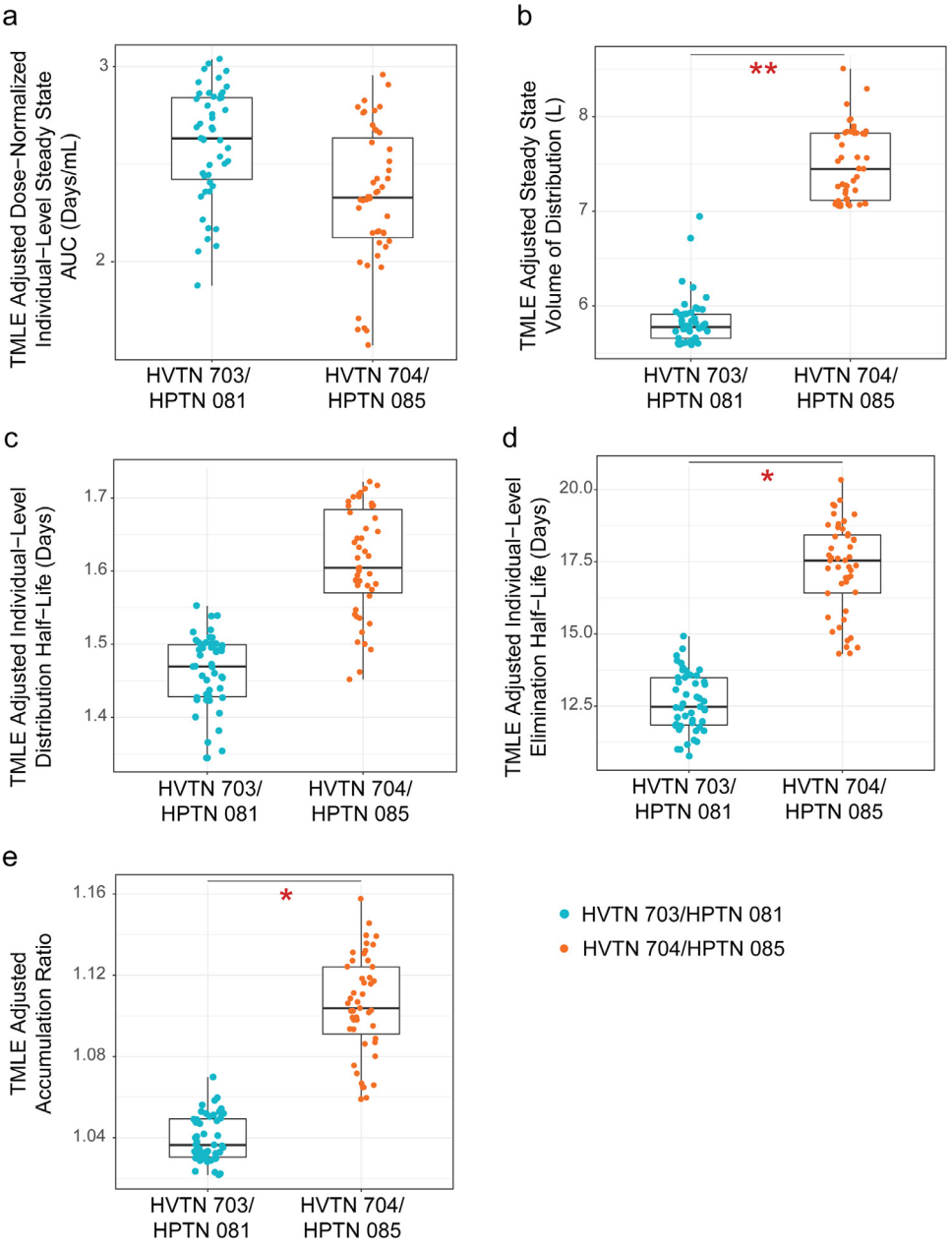

Fig. 5. Distributions of covariate-adjusted individual-level PK parameters of VRC01 in HVTN 703/HPTN 081 (women) and HVTN 704/HPTN 085 (MSM/TG). a) Steady state AUC, b) steady state volume of distribution, c) distribution half-life, d) elimination half-life, and e) accumulation ratio. All estimates were adjusted for dose, age, body weight, race, and creatinine clearance via TMLE as presented in Table 2. *, two-sided adjusted p-value < 0.05; **, two-sided adjusted p-value < 0.001.

individuals, consistent with findings from previous PK studies of VRC01 in the US and of multiple other mAbs [31]. Mechanisms of underlying PK differences by body weight that should be considered in interpreting these findings include decreased lymph flow rates in obese patients, which may influence the rate and extent of mAb distribution in tissues; increased protein endocytosis and catabolism in underweight patients, which affects clearance; and the correlation of body size with plasma and interstitial fluid volumes, which affect distribution [31].

We identified four PK features of VRC01 (peripheral volume of distribution, steady state volume of distribution, elimination half-life, and accumulation ratio) that were significantly different between the two study cohorts even after adjusting for potential confounding factors including dose, age, race, body weight, and creatinine clearance. This finding suggests that these differences in PK features are likely due to other factors that differ between the two study cohorts, e.g. sex assigned at birth, exposure to pathogens, or genetics. The many cohort differences make it difficult to identify the exact causes of the observed differences in PK features.

There is a paucity of data assessing study population effects on pharmacokinetics of mAbs. Similar PK were observed in American Caucasians and Asian people from Japan and China for evolocumab, a mAb for prevention of hypercholesterolaemia-related heart attack and stroke [32]. Likewise, there was no significant difference in genotype frequencies of Fcγ-receptor IIA (receptor-mediated endocytosis via Fcγ receptors may contribute to elimination of some mAbs [19]) between Caucasians and African-Americans [33]. However, to our knowledge, there is no literature comparing PK responses between black Africans and other racial/ethnic groups. As nearly 70% of all people living with HIV globally [34] and over 60% of all new HIV infections are in sub-Saharan Africa [34], there is a particularly pressing need for safe and efficacious HIV prevention and treatment

Table 2
Covariate-adjusted comparisons of PK features between HVTN 703/HPTN 081 (women) and HVTN 704/HPTN 085 (MSM/TG). All comparisons were adjusted for dose, age, body weight, race, and creatinine clearance.

PK feature	Trial	Mean[a]	95% CI[b]	2-sided raw p-value[b]	2-sided adjusted p-value[c]
CL (L/day)	HVTN 703/HPTN 081	0.380	(0.379, 0.381)	0.248	0.497
	HVTN 704/HPTN 085	0.451	(0.450, 0.452)		
Vp (L)	HVTN 703/HPTN 081	3.206	(3.157, 3.254)	<0.001	<**0.001**
	HVTN 704/HPTN 085	4.861	(4.812, 4.909)		
Steady state AUC[d] (day/mL)	HVTN 703/HPTN 081	2.571	(2.527, 2.614)	0.496	0.497
	HVTN 704/HPTN 085	2.306	(2.263, 2.350)		
Steady state volume of distribution (L)	HVTN 703/HPTN 081	5.584	(5.789, 5.886)	<0.001	<**0.001**
	HVTN 704/HPTN 085	7.492	(7.444, 7.541)		
Distribution half-life (day)	HVTN 703/HPTN 081	1.462	(1.462, 1.463)	0.033	0.098
	HVTN 704/HPTN 085	1.612	(1.611, 1.612)		
Elimination half-life (day)	HVTN 703/HPTN 081	12.640	(11.616, 13.664)	0.005	**0.027**
	HVTN 704/HPTN 085	17.287	(16.263, 18.311)		
Accumulation ratio[e]	HVTN 703/HPTN 081	1.040	(1.039, 1.040)	0.008	**0.031**
	HVTN 704/HPTN 085	1.105	(1.1046, 1.1054)		

[a] Covariate-adjusted mean by targeted minimum loss-based estimation (TMLE) (See Methods for more details).
[b] Confidence intervals and p-values based on empirical variances estimated via the bootstrap procedure.
[c] P-values adjusted by the Holm method to control for family-wise error rate.
[d] Area under the time-concentration curves divided by dose amount.
[e] Accumulation ratio calculated for an infusion interval of 56 days.

interventions in this region. It is thus a major strength of our study that we characterised PK responses to bnAb infusions in a sub-Saharan African population.

Another difference between the study populations that may have influenced PK features is sex assigned at birth. Although early phase trials evaluating other mAbs for prevention of viral infections, including cytomegalovirus in renal transplant recipients [35] and post-exposure prophylaxis of rabies [36], have not reported any differences in PK responses by sex assigned at birth, this may not be translatable to HIV-1 where sexual acquisition occurs in tissues with significant sex-based physiological differences: vaginal versus rectal. Our study showed that the female assigned at birth participants in HVTN 703/HPTN 081 had a smaller Vp than the predominantly male assigned at birth participants in HVTN 704/HPTN 085. Smaller Vp could be indicative of higher peripheral concentration that may influence efficacy. Further evaluation of VRC01 or similar mAbs for HIV prevention may warrant physiologically based pharmacokinetic (PBPK) modelling to understand PK features at the target tissue-level [37].

We also observed low VRC01 accumulation ($\leq$10%) over the 10 study infusions in both study populations and across both dose groups, although there appeared to be noticeable variabilities of CL and Vp over infusion intervals. Because there was no specific trend in CL and Vp over infusion intervals, these variabilities are more likely due to fluctuation of individual participant characteristics over time, rather than systematic change of the PK features due to repeated dosing. Given the apparent increase in the precision of the inter-individual variability of CL and Vp after incorporating variabilities over infusion intervals, it will be important to account for both types of variability for a more accurate estimation of concentration at time of infection in the future AMP case-control correlates study.

In addition, we presented unique data of the predicted VRC01 neutralisation coverage of circulating strains of HIV-1. These plots provide a way to predict the proportion of HIV-1 strains to which trial participants in the geographic areas of each trial may be exposed that would be expected to be neutralised based on the modelled VRC01 serum concentration in each target population. While VRC01 exhibits relatively broad neutralisation activity, its neutralisation coverage varies across clade, with clade C viruses generally neutralised less well than clade B viruses [38,39]. This observation was borne out in our predicted coverage plots, where the predicted VRC01 neutralisation coverage against the clade C panel was always less than the predicted VRC01 neutralisation coverage against the clade B panel, within each dose group, and within the same post-infusion time window (weeks 1–4 vs. weeks 4–8). As serum neutralising titre against a given exposing virus (calculated by dividing the serum concentration of the bnAb on the day of exposure by the known in vitro titre of that bnAb against the exposing virus) has been shown to be strongly correlated with protection against SHIV acquisition in non-human primate challenge studies [40], these results suggest that, while VRC01 serum concentration levels over time are similar across the two trials, neutralisation coverage against circulating HIV-1 strains in the specific region may be slightly higher in HVTN 704/HPTN 085 (MSM/TG) compared to HVTN 703/HPTN 081 (women), suggesting slightly higher predicted efficacy of VRC01 in the former study.

We also quantified the greater predicted neutralisation coverage in the first 4 weeks post-first infusion compared to in the second 4 weeks. An implication is that the time elapsed from the first infusion until the point of exposure is a major factor that could influence whether the infused VRC01 can provide protection against the circulating strains, and that participants who are exposed in the first 4 weeks post-first infusion are more likely to be protected than participants who are exposed in the second 4 weeks. These results also suggest that the overall VRC01 exposure (i.e. AUC of the time-concentration curve) may not be lower in HVTN 703/HPTN 081 (women) vs. HVTN 704/HPTN 085 (MSM/TG), although other PK features may be.

Our findings are important not only for gaining a preliminary understanding of the PK characteristics of VRC01 in the AMP study populations, which is expected to aid the interpretation of the primary efficacy results (expected in Q4 2020), but also for informing the sampling design of serum concentration and other markers of VRC01 for the AMP correlates study. Specifically, if, for example, the prevention efficacy of VRC01 is indeed lower in HVTN 703/HPTN 081 than in HVTN 704/HPTN 085 as predicted in our neutralisation coverage analysis, then our findings suggest that the differential efficacy could potentially be attributable to the differing PK characteristics or neutralisation sensitivity of the circulating strains to VRC01 in the two study populations. If AMP demonstrates that VRC01 is partially efficacious for the prevention of HIV-1, then the estimated serum VRC01 concentration at the time of HIV-1 acquisition, combined with statistical methods for estimating the day of HIV-1 infection [41], can be used to estimate the association of serum concentration with risk of HIV-1 acquisition, and similarly to estimate the association of neutralising antibody titre to a panel of HIV-1 strains with risk of HIV-1 acquisition. Such correlates of risk could set a benchmark for the required potency of a vaccine-induced neutralising antibody

response to achieve a high level of protection against HIV infection [21], informing optimal dose-regimen selection for the next-generation of mAbs or mAb combinations with cost-saving implications. Given the potentially differing PK characteristics between the two study populations and the impact of participant body weight on PK, our findings suggest that the sampling of controls for the case-control study should be stratified by study, and both study and body weight should be considered as potential covariates to adjust for in the correlates analyses. Moreover, in addition to VRC01 serum concentration and sensitivity to VRC01-mediated neutralisation of Env-pseudotyped viruses derived from HIV-1 infected trial participants, the PK features studied here could be evaluated as potential correlates of risk, depending on their a priori biological plausibility and the presence of sufficient inter-individual variability.

Our study is limited by the lack of data on anti-drug antibodies, which are known contributors to increased elimination of mAbs [42]. We were also unable to assess the effect of albumin concentration, which is inversely associated with mAb clearance [19]. However, since participants were required to be healthy with no malignancies, autoimmune conditions or history of renal or hepatic dysfunction, it is less likely that albumin levels would be a significant contributor to mAb clearance in the AMP trials. Other limitations of our study are that our prediction neutralisation coverage analyses are based on the premise that clade-specific HIV-1 sequences retrieved from the CATNAP database represent to some degree the sequences of the HIV-1 viruses to which participants in each trial are exposed. However, it is difficult to ascertain how accurately the HIV-1 sequences in CATNAP represent contemporaneously circulating viruses. For example, a study of recently transmitted clade C viruses documented antigenic drift at VRC01 target sites, and found that the clade C viruses became significantly less sensitive to VRC01-mediated neutralisation over the last 20 years [38]. Therefore, it is possible that HVTN 703/HPTN 081 (women) participants are exposed to clade C viruses that have naturally acquired a greater level of resistance to VRC01 than is apparent by using HIV-1 sequences from the CATNAP database. In such a scenario, VRC01 coverage in the HVTN 703/HPTN 081 trial would be expected to be even lower than predicted, potentially leading to decreased prevention efficacy. In addition, for simplicity, we used clade C CATNAP viruses to represent the circulating strains to which HVTN 703/HPTN 081 participants were exposed during the trial, and clade B CATNAP viruses to represent the circulating strains to which HVTN 704/HPTN 085 participants were exposed during the trial. While these clades comprise the majority of circulating strains in the two respective trials, it is worth noting that clades A and D predominate in East Africa, and clades C and F also circulate in South America [43], and these differences would also affect actual VRC01 neutralisation coverage. Lastly, our study is of a relatively small sample size. Therefore, further investigation is needed in the larger case-control study when those data become available from the AMP study, to validate the described results of this pilot study. Nevertheless, these results provide initial understanding of the potential predictors of VRC01 PK and provide useful knowledge for the design of the case-control study.

9. Contributors

Literature search: YH, LN, LNC, SK, PBG, KM, EL. Study concept and design: YH, JL, MMGL, DB, AD, MJ, JM, SE, NM, MC, LC, PA, SK, PBG. Data generation and collection: LN, PG, AM, SE, NM, KM, EL. Data management and analysis: YH, LZ, ER, AR. Data interpretation: all authors. Drafting of the manuscript: YH, LN, LNC, PA, SK, PBG, KM, EL. Review and finalisation of the manuscript: all authors.

Data sharing statement

Upon acceptance, the data underlying the findings of this manuscript will be made publicly available at the public-facing HVTN website (https://atlas.scharp.org/).

Declaration of Competing Interest

Dr. Huang, Ms. Zhang, Dr. Carpp, Ms. Rudnicki, Dr. Randhawa, Dr. DeCamp, Dr. Juraska, Dr. Corey, Dr. Karuna, and Dr. Gilbert report grants from the National Institute of Allergy and Infectious Diseases of the National Institutes of Health during the conduct of the study. Dr. Edupuganti reports grants from Fred Hutch/NIH during the conduct of the study. Dr. Mascola has a patent E-300−2009: Isolation of Novel Broadly Neutralizing Monoclonal Antibodies Against HIV-1 Using Epitope Specific Glycoprotein Probes to Identify HIV-1 Specific B-Cells, VRC01 issued. Dr. Cohen reports Advisory Board travel expenses from Merck, outside the submitted work. Dr. Mngadi reports grants from The Aurum Institute during the conduct of the study and grants from the HIV Vaccine Trial Network Research and Mentorship Programme outside the submitted work. Dr. Mngadi is a non-voting member of the HVTN Scientific Governance Committee. Review editor for Frontiers Reproductive Health, HIV and STI's Journal, a member of the Trial Steering Committee for the PrEPVACC study, a member of the Safety Monitoring Committee for the IAVI C100 study, and Protocol Co-Chair for the HVTN 705/VAC89220HPX2008 and HVTN 107 studies. All other authors have nothing to disclose.

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Supplementary materials

Supplementary material associated with this article can be found, in the online version, at doi:10.1016/j.ebiom.2020.103203.

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