Safety and pharmacokinetics of VRC07-523LS administered via different routes and doses (HVTN 127/HPTN 087): A Phase I randomized clinical trial

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Abstract

Background

Broadly neutralizing antibodies (bnAbs) are a promising approach for HIV-1 prevention. In the Antibody Mediated Prevention (AMP) trials, a CD4-binding site targetting bnAb, VRC01, administered intravenously (IV), demonstrated 75% prevention efficacy against highly neutralization-sensitive viruses but was ineffective against less sensitive viruses. VRC07-523LS is a next-generation bnAb targeting the CD4-binding site and was engineered for increased neutralization breadth and half-life. We conducted a multicenter, randomized,
TR004406 (CLG), JAGB, LLP, and WC are/were Medical Officers with the National Institute of Allergy and Infectious Diseases (NIAID)/NIH and ABM, BF, LG, and JCM are/were Staff Scientists with NIAID/NIH. The funder had no other role in the study design, data collection and analysis, decision to publish, or preparation of the manuscript.

Competing interests: SRW has conducted clinical trials funded by Janssen Vaccines, Moderna, Pfizer, Vir, Worcester HIV Vaccine, and Sanofi Pasteur, and serves on Independent Data Monitoring Committees for Janssen Vaccines and BioNTech; SRW’s spouse is an employee of Regeneron Pharmaceuticals and may hold stock and/or stock options. CLG has received research support from Gilead and ViiV Healthcare and support from Gilead and ViiV Healthcare and conducted clinical trials funded by Moderna and Novavax. MEA has received research support from Janssen, Be Bio, and Moderna.

Abbreviations: ADA, antidrug antibody; AE, adverse event; AMP, Antibody Mediated Prevention; AUC, area under the curve; BAMA, binding antibody multiplex assay; BicC, Bayes information criterion corrected; bnAb, broadly neutralizing antibody; CI, confidence interval; CRS, clinical research site; ELISA, enzyme-linked immunosorbent assay; FcRn, neonatal Fc receptor; GM, geometric mean; GMT, geometric mean titer; HRP, horseradish peroxidase; HIV, HIV Vaccine Trials Network; IM, intramuscular; IV, intravenously; LLoQ, lower limit of quantification; LMIC, low- and middle-income country; Luc, luciferase; mAb, monoclonal antibody; MB, magnitude-breadth; MB-AUC, Magnitude-Breadth Area Under the Curve; MFI, median fluorescent intensity; MITT, modified intent-to-treat; PE, prevention efficacy; PK, pharmacokinetic; PPE, preferred product characteristics; PrEP, preexposure prophylaxis; RLU, relative luminescence unit; SAE, serious adverse event; SAEM, Stochastic Approximation Expectation Maximization; SC, subcutaneous; SMB, Safety Monitoring Board; SPA, study product administration; WHO, World Health Organization.

partially blinded Phase I clinical trial to evaluate the safety and serum concentrations of VRC07-523LS, administered in multiple doses and routes to healthy adults without HIV.

Methods and findings
Participants were recruited between 2 February 2018 and 9 October 2018. A total of 124 participants were randomized to receive 5 VRC07-523LS administrations via IV (T1: 2.5 mg/kg, T2: 5 mg/kg, T3: 20 mg/kg), subcutaneous (SC) (T4: 2.5 mg/kg, T5: 5 mg/kg), or intramuscular (IM) (T6: 2.5 mg/kg or P6: placebo) routes at 4-month intervals. Participants and site staff were blinded to VRC07-523LS versus placebo for the IM group, while all other doses and routes were open-label. Safety data were collected for 144 weeks following the first administration. VRC07-523LS serum concentrations were measured by ELISA through Day 122 in all participants and by binding antibody multiplex assay (BAMA) thereafter in 60 participants (10 per treatment group) through Day 784. Compartmental population pharmacokinetic (PK) analyses were conducted to evaluate the VRC07-523LS serum PK. Neutralization activity was measured in a TZM-bl assay and antidrug antibodies (ADAs) were assayed using a tiered bridging assay testing strategy.

Injections and infusions were well tolerated, with mild pain or tenderness reported commonly in the SC and IM groups, and mild to moderate erythema or induration reported commonly in the SC groups. Infusion reactions were reported in 3 of 20 participants in the 20 mg/kg IV group. Peak geometric mean (GM) concentrations (95% confidence intervals [95% CIs]) following the first administration were 29.0 μg/mL (25.2, 33.4), 58.5 μg/mL (49.4, 69.3), and 257.2 μg/mL (127.5, 518.9) in T1-T3 with IV dosing; 10.8 μg/mL (8.8, 13.3) and 22.8 μg/mL (20.1, 25.9) in T4-T5 with SC dosing; and 16.4 μg/mL (14.7, 18.2) in T6 with IM dosing. Trough GM (95% CIs) concentrations immediately prior to the second administration were 3.4 μg/mL (2.5, 4.6), 6.5 μg/mL (5.6, 7.5), and 27.2 μg/mL (23.9, 31.0) with IV dosing; 0.97 μg/mL (0.65, 1.4) and 3.1 μg/mL (2.2, 4.3) with SC dosing, and 2.6 μg/mL (2.05, 3.31) with IM dosing. Peak VRC07-523LS serum concentrations increased linearly with the administered dose. At a given dose, peak and trough concentrations, as well as serum neutralization titers, were highest in the IV groups, reflecting the lower bioavailability following SC and IM administration. A single participant was found to have low titer ADA at a lone time point. VRC07-523LS has an estimated mean half-life of 42 days across all doses and routes (95% CI: 40.5, 43.5), over twice as long as VRC01 (15 days).

Conclusions
VRC07-523LS was safe and well tolerated across a range of doses and routes and is a promising long-acting bnAb for inclusion in HIV-1 prevention regimens.

Trial registration
ClinicalTrials.gov/ NCT03387150 (posted on 21 December 2017).
Author summary

Why was this study done?

- Broadly neutralizing antibodies (bnAbs), which can block HIV-1 infection in laboratory settings, have considerable promise for HIV-1 prevention in people.
- In the Antibody Mediated Prevention (AMP) trials, a CD4-binding site (CD4bs) targeting bnAb, VRC01, was found to have 75% prevention efficacy against highly neutralization-sensitive viruses. Most circulating isolates of HIV-1 are less sensitive, and VRC01 was ineffective against those viruses.
- Our clinical trial was done to assess the safety and drug levels of another CD4bs bnAb called VRC07-523LS, which has been engineered for improved breadth, potency, and a longer half-life.

What did the researchers do and find?

- We administered VRC07-523LS to healthy volunteers without HIV using multiple routes (intravenous [IV], subcutaneous [SC], and intramuscular [IM]) and at doses ranging from 2.5 mg/kg to 20 mg/kg.
- VRC07-523LS was safe and well tolerated over more than 30 months of follow-up.
- At any given dose, peak and trough concentrations, as well as serum neutralization titers, were highest in the IV groups, reflecting the lower bioavailability following SC and IM administration.
- VRC07-523LS has a half-life of about 42 days, which is over twice as long as VRC01 (15 days).

What do these findings mean?

- VRC07-523LS was safe and well tolerated across a range of doses and routes and is a promising long-acting bnAb for inclusion in HIV-1 prevention regimens.
- The main limitations of our study are the small sizes of the individual groups and missing blood draws at the later time points due to COVID-19 restrictions, both of which lead to uncertainty in our estimates of drug levels and pharmacokinetic parameters.

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Introduction

Despite the proven effectiveness of behavioral and pharmacological methods of preventing HIV-1 [1–3], worldwide over 1.5 million individuals are estimated to acquire HIV yearly [4], suggesting a need for additional prevention methods [5]. Accordingly, long-acting and well-
tolerated biomedical prevention approaches such as passive immunization using broadly neutralizing antibodies (bnAbs) are a promising new approach for HIV-1 prevention [6,7] that would be more discreet than many comparator methods [5]. In the only efficacy trials of a bnAb against HIV-1 conducted to date, the Antibody Mediated Prevention (AMP) trials, overall efficacy was not demonstrated [8]. Importantly, however, the AMP studies provided proof of concept that passive immunization with a bnAb could confer protection against HIV-1 infection and identified neutralization as a correlate of protection [9]. Despite overall low efficacy, viruses that were highly sensitive to neutralization by VRC01 (IC_{50} < 1 μg/mL) were successfully blocked in vivo [8,9]. This result suggests that bnAbs with increased breadth and increased potency might provide increased protection.

Toward this aim, another antibody (VRC07) was identified from the same donor as VRC01, cloned, and then engineered to increase its neutralization potency and breadth [10]. Additional mutations (Met428Leu and Asn434Ser; -LS) were made to the Fc portion of the antibody to increase the antibody’s binding affinity for the neonatal Fc receptor (FcRn), resulting in increased recirculation and, therefore, a longer half-life in vivo [11,12]. The resultant antibody, VRC07-523LS, was 5- to 8-fold more potent than VRC01 and considerably broader in vitro, with an IC_{50} < 1 μg/mL against 92% of HIV-1 pseudoviruses across circulating HIV-1 isolates from multiple clades [10]. In a first-in-human, dose-escalation study (VRC 605), VRC07-523LS administered intravenously (IV) to healthy volunteers without HIV was safe, well tolerated, and found to have a half-life of 38 days at 1, 5, 20, and 40 mg/kg doses and 33 days with a 5-mg/kg subcutaneous (SC) administration, more than twice the half-life of 15 days with VRC01 [13].

The increased potency and durability of VRC07-523LS relative to VRC01 may help address a key question regarding bnAbs as a potential HIV prevention tool, namely, the feasibility of their administration. More potent and longer-acting bnAbs can be administered less frequently and at lower doses and, thus, at lower cost. The route of administration is another important feasibility consideration, influenced by both dose and volume. In the AMP studies, the necessary dose and volume of the less potent VRC01 required IV administration. While IV administration was well tolerated in the AMP studies, the World Health Organization (WHO)’s 2022 target product profile for HIV prevention bnAbs reflects a preference for SC or intramuscular (IM) injection, particularly for broad programmatic deployment in low- and middle-income countries (LMICs) [14].

In planning for an eventual efficacy trial with combination bnAb administration, we conducted a Phase I study to comprehensively assess the safety and pharmacokinetics of VRC07-523LS at a range of doses and via 3 different routes of administration.

**Methods**

**Participants and study design**

HVTN 127/HPTN 087 is a multicenter, randomized, partially blinded Phase I clinical trial to evaluate the safety and serum concentrations of VRC07-523LS, administered in multiple doses and routes to healthy adults without HIV (Table 1). Participants received 5 administrations of the assigned dose and route every 4 months at Weeks 0, 16, 32, 48, and 64 and were followed on study through Week 112. The product was vialled at a concentration of 100 mg/mL and volume considerations limited the SC route to a maximum of 5 mg/kg and the IM route to 2.5 mg/kg.

Participants were enrolled at 7 clinical research sites (CRSs): Brigham & Women’s Hospital (Boston, MA), the Fenway Institute (Boston, MA), the University of North Carolina (Chapel Hill, NC), the University of Alabama (Birmingham, AL), Ponce de Leon CRS (Atlanta, GA),
Columbia University (New York, NY), and the Centre Hospitalier Universitaire Vaudois (Lausanne, Switzerland). Volunteers were eligible if they were between 18 and 50 years of age, without HIV-1, in good overall health, and unlikely to acquire HIV during the study period based on behaviors reported within the 12 months prior to enrollment [15]. The study was approved by the Institutional Review Boards of each participating CRS, and all participants provided written informed consent. The HIV Vaccine Trials Network (HVTN) Safety Monitoring Board (SMB) provided safety oversight. The trial was registered with ClinicalTrials.gov (NCT03387150).

Participants were randomized through an internet-based randomization system in blocks. Group 6 (IM route) was added via an amendment after enrollment of Groups 1 to 5 began. Participants and study staff were unblinded to group assignment (Groups 1 through 6) but blinded to antibody versus placebo (normal saline) within Group 6. Randomization was performed in blocks to ensure balanced randomization across Groups 1 through 5 first, and then using proper weights to accelerate enrollment in Group 6 relative to Groups 1 through 5, which had opened earlier so that enrollment would progress concurrently in all arms. The subset of participants assessed by BAMA and nAb activity were randomly selected within each treatment group.

A power analysis was carried out to evaluate the ability of the trial to identify safety concerns with study product administration (Primary Objective 1), particularly the probability of detecting serious adverse events (SAEs) among study arms, either alone or pooled together, for a range of possible true SAE rates, and the width of 95% confidence intervals (95% CIs) for the true rate of an SAE. The power analysis also evaluated the precision with which a true mean concentration of VRC07-523LS could be estimated (Primary Objective 2), assuming sample sizes of \( n = 16, 18, \) and 20 per arm to reflect an attrition rate of 20%, 10%, and 0% for a planned treatment group size of 20 participants.

### Safety assessments

Following the first study product administration (SPA), participants were monitored for at least 60 minutes to assess for solicited local and systemic adverse events (AEs), including pain/tenderness at the infusion or injection site, fever, malaise, myalgia, headache, chills, arthralgia, nausea, urticaria, nonexertional dyspnea, nonexertional tachycardia, generalized pruritus, facial flushing, and unexplained diaphoresis. If no reactions occurred after the first administration, in-clinic monitoring after subsequent SPAs could decrease to 30 minutes. For the 3 IV groups, the infusion rate for a 30-minute infusion could range from 10 to 20 mg/kg/hour for the lowest dose group (2.5 mg/kg) to 80 to 160 mg/kg/hour for the highest dose group (20 mg/kg). For the 2 SC and 1 IM groups, the product was administered by a needle and syringe.

### Table 1. Study schema.

<table>
<thead>
<tr>
<th>Group</th>
<th>N</th>
<th>Dose</th>
<th>Route</th>
<th>Month 0</th>
<th>Month 4</th>
<th>Month 8</th>
<th>Month 12</th>
<th>Month 16</th>
</tr>
</thead>
<tbody>
<tr>
<td>T1</td>
<td>19</td>
<td>2.5 mg/kg</td>
<td>IV</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
</tr>
<tr>
<td>T2</td>
<td>19</td>
<td>5 mg/kg</td>
<td>IV</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
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<td>T3</td>
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<td>20 mg/kg</td>
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<td>X</td>
<td>X</td>
<td>X</td>
</tr>
<tr>
<td>T4</td>
<td>21</td>
<td>2.5 mg/kg</td>
<td>SC</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
</tr>
<tr>
<td>T5</td>
<td>20</td>
<td>5 mg/kg</td>
<td>SC</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
</tr>
<tr>
<td>T6</td>
<td>21</td>
<td>2.5 mg/kg</td>
<td>IM</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
</tr>
<tr>
<td>P6</td>
<td>3</td>
<td>Placebo</td>
<td>IM</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
</tr>
</tbody>
</table>

IM, intramuscular; IV, intravenous; SC, subcutaneous.

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Participants completed daily symptom diaries to document solicited AEs for 3 days following each infusion or injection. Symptom-targeted physical exams and laboratory assays (complete blood count with differential, creatinine, alanine aminotransferase, urine dipstick, pregnancy testing, and HIV testing) were performed for safety monitoring at prespecified intervals throughout the study. Unsolicited AEs were collected throughout the study. AEs were graded according to the Division of AIDS Table for Grading the Severity of Adult and Pediatric Adverse Events, Version 2.1 (https://rsc.niaid.nih.gov/sites/default/files/daidagradingcorrectedv21.pdf). An immediate safety pause was to occur if a Grade 4 or 5 SAE occurred that was deemed related to the study product by site investigators. In addition, Grade 3 SAES and Grade 3 or 4 AEs deemed related to study product would trigger a safety review by the Protocol Safety Review Team to consider a pause.

Pharmacokinetics studies

Enzyme-linked immunosorbent assay (ELISA). An ELISA assay developed by the study product developer (Dale and Betty Bumpers Vaccine Research Center) was used to measure serum concentrations of VRC07-523LS between the first and second SPA. These concentrations were quantified in 96-well plates on a Beckman Biomek–based automation platform. The monoclonal antibody (mAb) 5C9 was coated onto Immulon-4HB microtitre plates overnight at 4°C. Plates were then washed and blocked (10% FBS in PBS) for 2 hours at room temperature. Duplicate serial 3-fold dilutions covering the range of 1:100 to 1:24,300 of the test sample were incubated 2 hours at 37°C followed by horseradish peroxidase (HRP)—labeled goat antihuman antibody (1 hour at 37°C) and TMB substrate (15 minutes at room temperature). Color development was stopped by addition of sulfuric acid and plates were read within 30 minutes at 450 nm via the Molecular Devices Paradigm plate reader. Linear regression of a standard curve of VRC07-523LS covering the range from 0.91 to 5 ng/mL was utilized to quantify sample concentrations based upon the average of sample dilutions within the range of the assay. The lower limit of quantification (LLOQ) of the ELISA assay was 1 μg/mL. Serum concentration data from 121 volunteers were measured by the ELISA assay on Target Visit Days 0, 3, 6, 28, 56, 84, and 112 (second SPA).

Binding antibody multiplex assay (BAMA). For programmatic reasons, the BAMA assay performed in an HVTN laboratory (Duke Human Vaccine Institute) was used to measure serum concentrations of VRC07-523LS in samples collected after the second SPA in a subset of participants enrolled in each treatment group. Serum VRC07-523LS concentrations were measured on a Bio-Plex instrument (Bio-Rad) using a validated assay designed to measure infused VRC07-523LS by its ability to bind anti-idiotype antibody captured on fluorescent magnetic beads. This assay was derived from a standardized custom HIV-1 Luminex assay [16–19]. The Bioplex software provides 2 readouts: a background-subtracted median fluorescent intensity (MFI), where background refers to a plate level control (i.e., a blank well containing antigen-conjugated beads run on each plate), and a concentration based on a standard curve using a 5PL curve fit. Each sample was run in duplicate.

VRC07-523LS was titrated and combined to create a standard curve used to determine concentration of the diluted samples. The negative controls were CH58 (an irrelevant mAb) and blank beads. Samples with VRC07-523LS concentrations below 0.01 μg/mL at a dilution of 1:100 were truncated at 0.01 μg/mL for plotting purposes. All samples are shown in the plot, including concentrations below the LLOQ. Samples with concentrations above the LLOQ at a 1:100 dilution were further tested at various dilution factors to obtain MFIs in the linear range of the standard curve, and the in-well concentration closest to the EC_{50} of the 5PL standard curve was reported.
Several criteria were used to determine if data from an assay were acceptable and could be statistically analyzed. The standard curve EC\textsubscript{50} values and MFI values were tracked against historical data in Levey Jennings and points with an MFI > 100 must have had a %CV < 20% between replicates. Any sample without at least 2 observed concentrations in agreement with each other, or with baseline MFI > 1000 was repeated to obtain an accurate measurement. The physiological LLoQ of the BAMA assay was 0.0457 \mu g/mL. Serum concentrations were measured using BAMA in 60 of 121 participants who received the study product (10 randomly selected participants for each treatment group) in samples collected at target visit days 168, 224, 280, 336, 448, 504, 560, 616, 672, 728, and 784.

**Neutralization activity.** Neutralizing antibody activity against HIV-1 was measured as a function of reduction in Tat-regulated luciferase (Luc) reporter gene expression in TZM-bl cells as described [20,21]. The assay performed in TZM-bl cells measured neutralization titers against Env-pseudotyped viruses sensitive to the bnAb (i.e., bnAb-specific viruses) in each group and a magnitude-breadth panel of Env-pseudotyped viruses. The assay tested neutralization of a panel of Tier 2 viruses isolated from placebo recipients in the AMP studies [22] that exhibit a range of known sensitivities to VRC07-523LS (S1 Table), which are H703_0646_051sN, H703_1471_190s, H703_1750_140Es, H704_0726_080sN, H704_1535_030sN, H704_2544_140eN01, PVO.4 [22], and a negative control Env-pseudotyped virus (SVA-MLV). Serum neutralization titer was defined as the serum dilution that reduced relative luminescence units (RLUs) by 50% and 80% (ID\textsubscript{50} and ID\textsubscript{80}) relative to the RLU in virus control wells (cells + virus only) after subtraction of background RLU (cells only).

**Antidrug antibodies.** Antidrug antibodies (ADAs) were assayed and characterized using a tiered bridging assay testing strategy, in which ADAs act to bridge labeled drug product and are detected in an electrochemiluminescent assay, as previously described [23]. In Tier I, a sensitive binding assay determined if samples may have ADA present. In Tier II, the response was confirmed by establishing the specificity of the response by competition with free drug. In Tier III, the ADA response magnitude was characterized by titration. The presence of ADA was assayed at 3 prespecified time points (baseline [Month 0], Month 8, and Month 16) as well as on samples from participants who experienced infusion reactions.

**Statistical methods**

**Endpoints.** The first primary endpoint was the safety and tolerability of different doses of VRC07-523LS administered IV, SC, and IM by repeat dosing every 16 weeks for a total of 5 administrations. The second primary endpoint was the serum concentrations of VRC07-523LS administered IV, SC, and IM over 6 different dose/route regimens. The safety data analyses included data from all enrolled participants regardless of how many study product administrations they received. The analysis was a modified intent-to-treat (MITT) analysis in that individuals who were randomized but not enrolled did not generate any safety data and were excluded from the statistical analysis. The concentration data from enrolled participants were analyzed according to the initial randomization assignment regardless of how many administrations they received. The analyses reported herein included data from 121 participants who received VRC07-523LS (data from the 3 placebo recipients were excluded).

**Statistical approaches.** Magnitude-breadth (MB) curves [24] were constructed by study week for ID\textsubscript{50} and ID\textsubscript{80} separately. All statistical analyses were carried out using R version 4.0.

**Population pharmacokinetics analysis.** The population pharmacokinetic (PK) analysis was conducted according to a MITT analysis in which data from enrolled participants were included regardless of how many administrations they received. The PK profile of VRC07-
523LS in serum was described using compartmental models. The analysis considered and compared PK models with 1, 2, and 3 compartments. These candidate models were fitted to observed serum concentrations using a nonlinear mixed effects approach, including random effects to account for interparticipant variability in PK parameters. The conditional variance of the error term, given the random effects, was assumed to include 2 additive terms: One term was proportional to the conditional expectation of the concentration; the second term was a constant. Participant-specific (individual) PK parameters were assumed to follow log-normal distributions. The variance-covariance matrix of the random effects was fully unstructured. Additionally, PK parameters were adjusted for the assay (ELISA or BAMA) used to measure concentrations. The model was fitted using the method of maximum likelihood, implemented using the Stochastic Approximation Expectation Maximization (SAEM) algorithm. The significance of the difference in each PK parameter between the 2 assays was evaluated using Wald tests. Comparison of models with 1, 2, and 3 compartments was carried out using a corrected Bayes information criterion (BICc) [25]. Participant-specific PK parameters were predicted using their empirical Bayes estimates, defined as the most probable value of the participant-specific PK parameters, given the estimated population parameters and the data from the corresponding participant. These participant-specific PK parameters were used to predict the most probable trajectory of the serum concentration for each participant. Association between predicted participant-specific PK parameters and covariates (weight, BMI, age) were evaluated using Spearman’s rank correlation coefficients. Modeling assumptions were evaluated using weighted conditional residuals plotted as a function of study day. Model-based predicted participant-specific (most probable) serum concentration trajectories were plotted as a function of study day and compared to the observed serum concentrations. To assess the precision of point estimates, 95% Wald CIs were constructed. All compartmental PK analyses were conducted using MonolixSuite Version 2019R2 [26].

The area under the curve (AUC) of the VRC07-523LS serum concentration of each individual study participant after 1 study product administration was computed by summing the estimate of the AUC between Days 0 and 112 computed using the trapezoidal method applied to untransformed serum concentrations and the estimate of the AUC after Day 112 computed as \( \exp(a + 112 \cdot b) / \exp(b) \) where \( a \) and \( b \) are the intercept and slope of a linear regression model describing log-serum concentration as a function of time since baseline and fitted to serum concentrations measured in the log-linear portion of the pharmacokinetics of VRC07-523LS. Dose-normalized AUCs were computed by dividing the AUC by the administered dose.

**Neutralization activity.** Key secondary objectives included determining whether serum neutralizing activity is maintained at consistent levels after each product administration and to determine whether serum neutralizing activity agreed with measured serum concentrations. A response to a given pseudovirus was considered positive if the corresponding ID\(_{50}\) or ID\(_{80}\) value was >10 or 20, depending on the starting dilution of the sample. The assay measured neutralization titers against 7 Env-pseudotyped viruses to determine bnAbs activities against specific viruses (S1 Table).

**Results**

**Participant characteristics and demographics**
 Participants were recruited between 2 February 2018 and 9 October 2018. A total of 124 participants enrolled between 28 February 2018 and 9 October 2018 at 6 sites in the United States and 1 in Switzerland (Fig 1). A total of 75 participants (60%) were assigned female sex at birth; 7 participants reported that they were gender nonconforming. A total of 71 participants (57%) identified as white, 28 (23%) as black/African American, and 12 (10%) as Hispanic (Table 2).
Fig 1. CONSORT diagram (A) and study schema (B).

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### Table 2. Participant demographics.

<table>
<thead>
<tr>
<th>2.5 mg/kg IV T1 (N = 19) n (%)</th>
<th>5 mg/kg IV T2 (N = 19) n (%)</th>
<th>20 mg/kg IM T3 (N = 21) n (%)</th>
<th>2.5 mg/kg SC T4 (N = 21) n (%)</th>
<th>5 mg/kg SC T5 (N = 20) n (%)</th>
<th>2.5 mg/kg IM T6 (N = 21) n (%)</th>
<th>Placebo IM (N = 3) n (%)</th>
<th>Total (N = 124) n (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Assigned Sex at Birth</strong></td>
<td></td>
<td></td>
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<td></td>
<td></td>
</tr>
<tr>
<td>Male</td>
<td>5 (26.3%)</td>
<td>11 (57.9%)</td>
<td>10 (47.6%)</td>
<td>6 (28.6%)</td>
<td>7 (35.0%)</td>
<td>10 (47.6%)</td>
<td>0 (0.0%)</td>
</tr>
<tr>
<td>Female</td>
<td>14 (73.7%)</td>
<td>8 (42.1%)</td>
<td>11 (52.4%)</td>
<td>15 (71.4%)</td>
<td>13 (65.0%)</td>
<td>11 (52.4%)</td>
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<td>1 (5.3%)</td>
<td>1 (4.8%)</td>
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<td>1 (4.8%)</td>
<td>0 (0.0%)</td>
</tr>
<tr>
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<tr>
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<td>3 (15.8%)</td>
<td>5 (23.8%)</td>
<td>2 (9.5%)</td>
<td>0 (0.0%)</td>
<td>2 (9.5%)</td>
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</tr>
<tr>
<td>Not Hispanic or Latino/a</td>
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<td>16 (84.2%)</td>
<td>16 (76.2%)</td>
<td>19 (90.5%)</td>
<td>20 (100%)</td>
<td>19 (90.5%)</td>
<td>3 (100%)</td>
</tr>
<tr>
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<td>White</td>
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<td>10 (52.6%)</td>
<td>13 (61.9%)</td>
<td>10 (47.6%)</td>
<td>11 (55.0%)</td>
<td>12 (57.1%)</td>
<td>3 (100%)</td>
</tr>
<tr>
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<td>4 (21.1%)</td>
<td>2 (9.5%)</td>
<td>5 (23.8%)</td>
<td>6 (30.0%)</td>
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<td>1 (5.0%)</td>
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</tr>
<tr>
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<td>0 (0.0%)</td>
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<tr>
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<td>0 (0.0%)</td>
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</tr>
<tr>
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<td>1 (4.8%)</td>
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</tr>
<tr>
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<td>2 (9.5%)</td>
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</tr>
<tr>
<td><strong>Age (Years)</strong></td>
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<tr>
<td>18–20</td>
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<td>3 (15.8%)</td>
<td>4 (19.0%)</td>
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<td>2 (9.5%)</td>
<td>0 (0.0%)</td>
</tr>
<tr>
<td>21–30</td>
<td>6 (31.6%)</td>
<td>7 (36.8%)</td>
<td>11 (52.4%)</td>
<td>11 (52.4%)</td>
<td>17 (85.0%)</td>
<td>13 (61.9%)</td>
<td>1 (33.3%)</td>
</tr>
<tr>
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<td>6 (31.6%)</td>
<td>7 (36.8%)</td>
<td>4 (19.0%)</td>
<td>3 (14.3%)</td>
<td>3 (15.0%)</td>
<td>3 (14.3%)</td>
<td>2 (66.7%)</td>
</tr>
<tr>
<td>41–50</td>
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<td>2 (10.5%)</td>
<td>2 (9.5%)</td>
<td>6 (28.6%)</td>
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<td>3 (14.3%)</td>
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<td>Over 50</td>
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<td>0 (0.0%)</td>
<td>0 (0.0%)</td>
<td>0 (0.0%)</td>
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<tr>
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<td>Median (Range)</td>
<td>25.3 (20.5, 43.0)</td>
<td>25.2 (19.0, 36.1)</td>
<td>27.3 (19.7, 38.4)</td>
<td>26.9 (19.9, 41.7)</td>
<td>25.2 (20.4, 38.9)</td>
<td>25.7 (20.2, 36.8)</td>
<td>35.5 (25.7, 36.2)</td>
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<td><strong>SPA Frequencies</strong></td>
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<tr>
<td>V2/Week</td>
<td>0</td>
<td>19 (100%)</td>
<td>19 (100%)</td>
<td>21 (100%)</td>
<td>21 (100%)</td>
<td>20 (100%)</td>
<td>21 (100%)</td>
</tr>
<tr>
<td>V8/Week</td>
<td>16</td>
<td>18 (94.7%)</td>
<td>18 (94.7%)</td>
<td>19 (90.5%)</td>
<td>21 (100%)</td>
<td>19 (95.0%)</td>
<td>20 (95.2%)</td>
</tr>
<tr>
<td>V10/Week</td>
<td>16</td>
<td>18 (94.7%)</td>
<td>17 (89.5%)</td>
<td>18 (85.7%)</td>
<td>19 (90.5%)</td>
<td>18 (90.0%)</td>
<td>20 (95.2%)</td>
</tr>
</tbody>
</table>

(Continued)
The median age of participants at enrollment was 28 years. A total of 95 participants (77%) received all 5 injections or infusions. The final SPA occurred on 10 January 2020, prior to the arrival of COVID-19 in the US or Switzerland; however, pandemic restrictions had a considerable impact on follow-up visits. To ensure that sites could collect safety information, remote visits were permitted to be conducted, but no samples could be collected until local safety restrictions allowed in-person visits. The final study visit occurred on 4 December 2020. Sample availability is shown in Fig 1.

Safety and tolerability

VRC07-523LS was safe and generally well tolerated at all doses and via all routes administered (Fig 2). Mild to moderate injection site pain and/or tenderness was noted by most participants randomized to receive VRC07-523LS by the SC or IM routes. Erythema and/or induration at the injection site was noted by most participants in the SC groups but was generally mild to moderate. Malaise/fatigue and headaches were the most common systemic solicited AEs. The majority (98 [79%]) of participants experienced at least 1 unsolicited AE during the study, but the vast majority (357 of 373 [96%] AEs) were deemed unrelated to VRC07-523LS administration and most were mild (158 [42%]) or moderate (203 [54%]). Of the 16 unsolicited AEs deemed related to VRC07-523LS, 4 began as solicited AEs that continued past the diary period and 9 (7% of participants) were isolated symptoms or combinations of symptoms suggestive of infusion-related reactions, similar to those seen with VRC01 administration [27]. These symptoms included generalized pruritis, facial flushing, chills, myalgia, arthralgia, nausea, headache, and diaphoresis. In 3 participants in the 20 mg/kg IV group, these combinations of symptoms were deemed to be consistent with infusion reactions. Of these 3 participants, 1 received paracetamol (acetaminophen) and diphenhydramine in the clinic, 1 self-administered ibuprofen at home, and 1 received paracetamol (acetaminophen) and diphenhydramine in the clinic. No pregnancies or HIV acquisitions were reported during the study. There were 3 SAEs all deemed unrelated to VRC07-523LS: staphylococcal infection, pyrexia in a returned traveler, and urinary calculus.

Participants completed acceptability surveys at every SPA visit to assess their opinions on elements of the administration including discomfort, overall time commitment, and willingness to receive products via their specific route (S2 Table). In general, participants reported that the discomfort, pain, and anxiety related to the SPA was acceptable, although participants in the 2 SC groups were more likely to say that these were unacceptable (S2A-S2C Tables). The time required for SPA was considered acceptable by most participants (>87% across all visits and groups; S2D Table). Most participants were very (>77%) or somewhat (>4%) willing to use the same method to prevent a serious illness (S2E Table) and most would recommend that method to a friend at risk of HIV, but this recommendation was lowest for participants in the SC groups at the final SPA (77.4% yes; S2F Table). Four participants

Table 2. (Continued)

<table>
<thead>
<tr>
<th>Treatment</th>
<th>2.5 mg/kg IV T1 (N = 19) n (%)</th>
<th>5 mg/kg IV T2 (N = 19) n (%)</th>
<th>20 mg/kg IM T3 (N = 21) n (%)</th>
<th>2.5 mg/kg SC T4 (N = 21) n (%)</th>
<th>5 mg/kg SC T5 (N = 20) n (%)</th>
<th>2.5 mg/kg IM T6 (N = 21) n (%)</th>
<th>Placebo IM (N = 3) n (%)</th>
<th>Total (N = 124) n (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>V12/Week 48</td>
<td>15 (78.9%)</td>
<td>17 (89.5%)</td>
<td>17 (81.0%)</td>
<td>18 (85.7%)</td>
<td>15 (75.0%)</td>
<td>17 (81.0%)</td>
<td>3 (100%)</td>
<td>102 (82.3%)</td>
</tr>
<tr>
<td>V14/Week 64</td>
<td>13 (68.4%)</td>
<td>16 (84.2%)</td>
<td>15 (71.4%)</td>
<td>17 (81.0%)</td>
<td>14 (70.0%)</td>
<td>17 (81.0%)</td>
<td>3 (100%)</td>
<td>95 (76.6%)</td>
</tr>
</tbody>
</table>

Note that participants were not required to answer demographic questions and several questions allowed multiple selections; therefore, counts/percentages may not match the total number of participants.

BMI, body mass index; SPA, study product administration.

https://doi.org/10.1371/journal.pmed.1004329.t002
Fig 2. Solicited AEs reported by participants after product administration. Local (A) and systemic (B) solicited AEs were collected for 3 days following each administration of VRC07-523LS or placebo. P6 = placebo IM; T1 = 2.5 mg/kg IV; T2 = 5 mg/kg IV; T3 = 20 mg/kg IV; T4 = 2.5 mg/kg SC; T5 = 5 mg/kg SC; T6 = 2.5 mg/kg IM. AE, adverse event; IM, intramuscular; IV, intravenously; SC, subcutaneous.

https://doi.org/10.1371/journal.pmed.1004329.g002
reported adverse social impacts [28] as a result of their participation, mostly in the realm of their interpersonal relationships.

Antidrug antibody

The presence and magnitude of ADA in serum were measured using a tiered "bridging assay" to detect ADA from serum samples obtained at Months 0, 2, 4, 8, and 16. A total of 124 participant samples were tested from Month 0, 1 from Month 2, 2 from Month 4, 114 from Month 8, and 96 from Month 16. A single participant enrolled in Group 4 (SC route, 2.5 mg/kg VRC07-523LS) exhibited a confirmed ADA response at Month 8 (4 months after the second SPA) with a low titer of 1:9 but was ADA negative at Month 16 (4 months after the fourth SPA).

Serum concentrations

At a given dose, peak and trough concentrations were highest in the IV groups and lowest in the SC groups. Peak geometric mean titers (GMTs) after the first dose, as measured by ELISA, were noted on Day 3, with GMT (95% CI) of 28.98 μg/mL (25.16, 33.39) in the 2.5 mg/kg IV group, 58.51 μg/mL (49.41, 69.29) in the 5 mg/kg IV group, 257.22 μg/mL (127.52, 518.86) in the 20 mg/kg IV group, 10.84 μg/mL (8.84, 13.3) in the 2.5 mg/kg SC group, 22.78 μg/mL (20.05, 25.88) in the 5 mg/kg SC group, and 16.35 μg/mL (14.71, 18.18) in the 2.5 mg/kg IM group (Figs 3 and S1). The lowest preadministration troughs were noted on Day 112, just before the second infusion, with GMT (95% CI) of 3.4 μg/mL (2.51, 4.61) in the 2.5 mg/kg IV group, 6.5 μg/mL (5.6, 7.54) in the 5 mg/kg IV group, 27.2 μg/mL (23.85, 31.01) in the 20 mg/kg IV group, 0.97 μg/mL (0.65, 1.44) in the 2.5 mg/kg SC group, 3.09 μg/mL (2.2, 4.33) in the 5 mg/kg SC group, and 2.61 μg/mL (2.05, 3.31) in the 2.5 mg/kg IM group (Figs 3 and S1).

We compared the AUC of the VRC07-523LS levels for the various doses and routes following the first administration. As a measure of exposure to VRC07-523LS, the AUC was higher in the 20 mg/kg IV group (S2A Fig). When corrected for the administered dose, the 3 IV groups had higher AUCs than either the SC or the IM groups (S2B Fig), reflecting the lower bioavailability of the SC and IM routes.

The subsequent 4-month postadministration troughs were slightly higher than after the first dose and quite similar between the second and fifth study product administrations (Figs 4 and S3). This result suggests that there was very little in vivo accumulation of VRC07-523LS with the 16-weekly administration schedule, at least up to 5 consecutive doses. Furthermore, the relatively consistent levels of VRC07-523LS measured between the second and fifth administrations given at a frequency of 4 months suggests that a near-steady state is established after the second administration with peaks and troughs determined by the dose and route.

Population PK analysis

We conducted a population PK analysis of VRC07-523LS serum concentrations measured in healthy participants after up to 5 SPA via the IV, SC, or IM routes at various doses. Data were collected at 19 time points between Day 0 and Day 784, covering the period from baseline up to after the fifth SPA. The BICc determined that the 2-compartment PK model was better at describing serum concentrations of VRC07-523LS than PK models with 1 or 3 compartments. The 2-compartment PK model predicted well serum concentrations across routes of administration and doses (Figs 5 and S4A–S4F). Estimated PK parameters are summarized in S3 Table.

Based on data measured between the first and second SPA using ELISA, the elimination half-life of VRC07-523LS was estimated as 42.43 days (95% CI 40.93, 43.93). Its bioavailability was estimated as 0.40 (95% CI 0.397, 0.403) after SC administration, and 0.57 (95% CI 0.51,
0.63) after IM administration, as compared with IV administration. The difference between the bioavailability after SC and IM administrations was significant \( p < 0.001 \). The average clearance of VRC07-523LS was 0.11 L/d (95% CI 0.10, 0.12).

The analyses of serum concentrations measured after the first SPA using ELISA versus after the second SPA using BAMA found significantly different PK parameters, namely, estimated clearance (0.11 L/d [95% CI 0.10, 0.12] versus 0.15 L/d [95% CI 0.14, 0.16], \( p < 0.001 \)), central compartmental volume (2.72 [95% CI 2.48, 2.96] versus 3.18 [95% CI 2.95, 3.41], \( p < 0.001 \)), peripheral compartmental volume (3.59 [95% CI 3.35, 3.83] versus 3.74 [95% CI 3.50, 3.98], \( p < 0.001 \)), and intercompartmental clearance (0.49 L/day [95% CI 0.43, 0.55] versus 1.18 L/day [95% CI 1.07, 1.29], \( p < 0.001 \)). The distribution and elimination half-lives were also significantly different (1.17 days [95% CI 0.91, 1.43] versus 4.61 days [95% CI 4.35, 4.87], \( p < 0.001 \); and 42.43 days [95% CI 40.93, 43.93] versus 42.67 days [95% CI 41.17, 44.17], \( p < 0.001 \)) following the first SPA (by ELISA) and following the second SPA (by BAMA), respectively (S5 Fig). Although these differences are statistically significant, the absolute difference is quite small and unlikely to be clinically significant. Differences between the bioavailability and absorption rate constant based on BAMA versus ELISA derived data could not be estimated due to numerical instability occurring when fitting a population PK model that allowed for differences in these parameters between the 2 assays. This instability may be due to the differences in sampling frequency between the first and second SPA versus the less frequent sampling following the second SPA.
The analysis suggested that serum concentrations of VRC07-523LS increased linearly with the dose following IV and SC administrations, as evidenced by the population PK model properly fitting data across dose levels and routes of administration (Figs 5 and S4A–S4F) and the similarity of the peak and trough levels as well as dose-normalized AUC across dose groups within a given route of administration (S1 and S2 Figs).

Significant positive associations were found between the predicted participant-level PK (clearance, volume of distribution, and peripheral volume of distribution) and weight as well as BMI (adjusted p-values ≤ 0.047); see S4 Table.

Neutralization activity

Neutralization activity was assayed at 3 time points (Weeks 8, 72, and 88 following the first infusion of study product) in a subset of approximately 10 participants in each active treatment group and 3 placebo recipients, as follows: 9 participants in Group 1, 10 in Group 2, 10 in Group 3, 10 in Group 4, 10 in Group 5, 11 in Group 6, and 3 in the Placebo group.

In the IV and SC groups, the magnitude of serum neutralizing activity increased overall with dose at a given time point (Figs 6 and S6). Overall, neutralization titers at Week 72 (8 weeks after the fifth study product administration) were either comparable to or slightly higher than those measured at Week 8 (8 weeks after the first study product administration), again suggesting limited accumulation of VRC07-523LS between the first and fifth administrations.
As expected, the lowest response magnitudes were observed at Week 88 (24 weeks after the fifth study product administration) (Figs 6 and S6).

In addition to confirming that neutralization activity of VRC07-523LS is preserved following in vivo administration, these results allow us to compare the established in vitro ID₈₀ titer with the predicted serum concentrations (g/mL) of VRC07−523LS observed or predicted by a 2-compartment pharmacokinetic model. Spearman’s rank correlation coefficient: rho = 0.99.

Fig 5. Measured serum concentrations of VRC07-523LS vs. concentrations predicted by a 2-compartment pharmacokinetic model. Spearman’s rank correlation coefficient: rho = 0.99.

https://doi.org/10.1371/journal.pmed.1004329.g005

(Figs 6 and S6).
in vivo concentration to generate a predicted protective efficacy titer (PT\textsubscript{80}) [9]. If an in vivo neutralization threshold of 200 is required for achieving potent prevention efficacy for VRC07-523LS [9], this level would only have been achieved for 3 of the 7 primary HIV-1 isolates we tested even at 8 weeks after SPA and only for participants who received the highest dose (Fig 6).

At a given dose, higher serum neutralization titers were observed after IV administrations compared to either SC or IM administrations, and this was particularly pronounced in the Magnitude-Breadth Area Under the Curve (MB-AUC) analysis (Figs 7 and 57). The MB-AUC plots also indicate that neutralization activity was higher after receiving 5.0 mg/kg of VRC07-523LS via the SC route versus a lower dose of 2.5 mg/kg of VRC07-523LS via the IV route, suggesting that the levels of neutralization achieved by IV infusions may be reached by administering higher doses via the SC route. For the 2.5 mg/kg dose, which was the only one given via all 3 routes, the neutralization titers were highest for the IV route, followed by the IM route, and lowest via the SC route. As with the neutralization titers, response rates tended to be higher in the IV groups than in the SC or IM groups when comparing responses among groups that received the same dose.

**Discussion**

This Phase I clinical trial yielded several key findings that have implications for the design of future bnAb efficacy studies. First, a human neutralizing antibody engineered for breadth,
potency, and a prolonged in vivo half-life was safe and generally well tolerated when administered across a wide dose range and via different routes of administration. Second, although the half-life of VRC07-523LS (42 days) is considerably longer than that of the VRC01 antibody (15 days) used in the AMP studies [29], the half-life of VRC07-523LS is substantially less than VRC01LS (71 days) [30]. Third, while SC and IM administration of VRC07-523LS was safe
and well tolerated and these routes have notable operational advantages [14], decreased bioavailability may have implications for achieving target concentrations, and interindividual variability in PK parameters observed must be considered in designing a combination bnAb efficacy study with VRC07-523LS.

In this study, we found that the serum concentrations of VRC07-523LS increased linearly across the dose range administered in this study. We also found that the peak and trough concentrations were highest in the IV groups and lowest in the SC groups at any given dose. There was also no clear difference in the half-life of VRC07-523LS when administered by different routes. These trends were also true for VRC01 and VRC01LS in other studies [30,31], as well as for other bnAbs [32], which likely reflects generalizable PK behavior of antiviral antibodies in unexposed hosts. Some studies noted shorter half-lives of anti-HIV-1 bnAbs in persons living with HIV [33–35], which has implications for use of these biologics in HIV treatment and cure studies.

We also found an excellent correlation between the predicted level of VRC07-523LS and the measured serum concentrations, suggesting that a 2-compartment model can predict the PK of this monoclonal antibody following repeated IV, SC, or IM administrations. This correlation was robust to dose, delivery route, and method of antibody measurement (ELISA versus BAMA). The high performance of these prediction models may allow future Phase I studies to be smaller and more efficient, in terms of the number of participants needed, the number of injections or infusions administered, and the total length of follow-up needed to develop a robust PK model. This finding, in turn, has the potential to facilitate moving bnAbs into efficacy studies.

Data from this study of a range of doses and routes have informed ongoing studies of combination bnAbs, as it is likely that combinations of bnAbs targeting complementary epitopes on Env will be necessary to provide sufficient protection in vivo [7]. VRC07-523LS has been evaluated in combination with the non-LS-mutated bnAbs PGT121, PGDM1400, and 10–1074, in the HVTN 130/HPTN 089 study [36]. PGT121 and 10–1074 target the V3 glycan epitope, whereas PGDM1400 targets the V1V2 region, and all 3, while narrower in breadth than VRC07-523LS, are considerably more potent [37]. As bnAbs with longer half-lives are likely to be more feasible for deployment [6,7], VRC07-523LS is also being evaluated in combination with an engineered version of PGT121 called PGT121.414.LS in the recently completed HVTN 136/HPTN 092 trial [NCT04212091]. In the HVTN 140/HPTN 101 study [NCT05184452], VRC07-523LS and PGT121.414.LS were tested in combination with PGDM1400.LS. In the multiphase CAPRISA 012 studies [38,39], VRC07-523LS was tested with CAP256V2LS, a V1V2 targeting bnAb, which is particularly potent against clade C isolates of HIV-1. Some of these studies include modified SC administration methods (for example, SC infusion via pump in HVTN 136/HPTN 092 [NCT04212091] and coadministration of bnAbs with hyaluronidase in CAPRISA 012 [38,39]) to try to increase the bioavailability of the SC route. Furthermore, analysis of mucosal tissue and secretion PK of VRC07-523LS at rectal and vaginal sites is ongoing in the HVTN 128 trial [NCT03735849], which is particularly relevant as the vast majority of HIV-1 infections occur at mucosal sites.

Our study has limitations, however. While all study product administrations were completed prior to the arrival of SARS-CoV-2 in the regions that participated in this study, local restrictions on conducting in-person visits led to many later study visits being done remotely, which led to some imprecision in our estimates of VRC07-523LS PK at the later time points. In addition, while our study population reflects the demographics where our clinical research sites are located, this does not represent where the burden of new HIV-1 infections occur. Recently, the correlates of risk analyses from the AMP studies were used to generate a model of protective efficacy (PTₜₐ₀) that can be used for predicting efficacy of bnAbs against
HIV-1 [9]. The PT$_{80}$ model combines in vitro IC$_{80}$ neutralization data with in vivo PK data to provide an estimate of protection against a population of viruses to which participants may be exposed [9]. This model was used to predict prevention efficacy (PE) of a hypothetical repeat of the AMP studies using the broader and more potent mAb VRC07-523LS as a single agent and suggested that PE in this case could have been approximately 79% against clade C viruses [9]. However, the PT$_{80}$ model also suggested that a high-dose 3 bnAb combination regimen including VRC07-523LS could have a PE of approximately 95% against a panel of recent clade C isolates [9]. Ultimately, large efficacy studies will need to be performed with combination bnAbs to assess their ability to prevent HIV-1 acquisition.

UNAIDS recently released their preferred product characteristics (PPC) for mAbs for HIV-1 prevention, noting that longer-acting mAbs could play an important role in future preexposure prophylaxis (PrEP) campaigns as many people may opt for an injectable product rather than antiretroviral pills or intravaginal rings [14]. Long-acting prevention methods may be desirable for key populations such as pregnant women and adolescent girls who are at high risk of HIV-1 acquisition, particularly in sub-Saharan Africa [14]. While the UNAIDS PPC expressed a preference for SC administration, as noted for other low-volume mAbs for noninfectious indications [40], the participants in our SC groups had a somewhat less enthusiastic opinion about acceptability of SC administration compared to the other groups. SC infusion via a pump or SC administration with hyaluronidase may be more acceptable, but like IV infusion, these will have increased costs that may limit deployment in resource-limited settings. Furthermore, the lower bioavailability observed for VRC07-523LS combined with the high concentrations likely needed to exceed the PT$_{80}$ for circulating strains of HIV-1 argue that IV administration is more likely to be successful for HIV-1 prevention until the technical hurdles that impact injection volume and potency are overcome.

Supporting information

S1 CONSORT Checklist. CONSORT Checklist.
(PDF)

S1 Table. In vitro IC$_{50}$ and IC$_{80}$ of the clinical lot of 2 bnAbs (VRC07-523LS and VRC01) against 7 Env-pseudotyped viruses. The env sequences are derived from isolates sequenced from incident acquisition events from the AMP studies.
(PDF)

(PDF)

S3 Table. Parameter estimates based on the 2-compartment population PK model fitted to VRC07-523LS serum concentrations in participants who received the study product via the IV (T1-T3), SC (T4, T5), or IM (T6) route. The model assumed a linearly combined error variance and a fully unstructured random effects variance-covariance matrix. SE, standard error; %RSE, relative SE, calculated as (SE/Estimate) × 100.
(PDF)

S4 Table. Pharmacokinetic parameter covariate analysis.
(PDF)
S1 Fig. VRC07-523LS levels following first study product administration (SPA). Individual measurements are shown in Panel A; note X-axis is not to scale. Numbers at the top of the panels indicate the sample size at each time point. Longitudinal per-participant levels are shown in Panel B.

S2 Fig. VRC07-523LS serum concentrations were measured following the first study product administration and the area under the curve (AUC, panel A) and AUC corrected for dose (B) were computed to characterize the pharmacokinetics of VRC07-523LS. Numbers at the top of the panels indicate the sample size at each time point.

S3 Fig. VRC07-523LS concentrations measured after product administration every 4 months at specified doses and routes. Peak levels were only assessed after the first dose. Levels following the second and subsequent doses were assessed by binding antigen multiplex assay (BAMA). Individual-level data are shown in gray, and the group median is shown in color.

S4 Fig. S4A–S4F Fig. Observed (•) and predicted (−) serum concentrations of VRC07–523LS as a function of time in individual participants (one per plot). S4A Fig. Group 1 (IV 2.5 mg/kg) is shown. S4B Fig. Group 2 (IV 5 mg/kg) is shown. S4C Fig. Group 3 (IV 20 mg/kg) is shown. S4D Fig. Group 4 (SC 2.5 mg/kg) is shown. S4E Fig. Group 5 (SC 5 mg/kg) is shown. S4F Fig. Group 6 (IM 2.5 mg/kg) is shown. The 2-compartment population PK model with fully unstructured random effects variance–covariance matrix was fitted to VRC07–523LS concentrations.

S5 Fig. Distribution (A) and elimination (B) half-life of VRC07-523LS. Values were predicted from the 2-compartment model on a per-participant basis for each dose and route group. Box and whisker plots indicate the quartiles and median of the data set.

S6 Fig. Neutralization activity of participant serum 8 weeks following their first VRC07-523LS administration against 7 HIV-1 isolates collected from incident HIV-1 acquisition events in placebo recipients in the AMP trials. ID₅₀ titer is shown.

S7 Fig. Magnitude-breadth curves for participant serum following VRC07-523LS administration against a panel of HIV-1 isolates collected from incident HIV-1 acquisition events in placebo recipients in the AMP trials. ID₅₀ titer is shown at Week 8 (A) and Week 72 (B) following first study product administration.

S1 Protocol. HVTN127 HPTN 087 Protocol.

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Disclaimer

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