

Randomized Clinical Trial to Assess the Impact of the Broadly Neutralizing HIV-1 Monoclonal Antibody VRC01 on HIV-1 Persistence in Individuals on Effective ART

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Background. Broadly neutralizing monoclonal antibodies (bnMAbs) may promote clearance of HIV-1-expressing cells through antibody-dependent cell-mediated cytotoxicity. We evaluated the effect of the CD4-binding site bnMAB, VRC01, on measures of HIV-1 persistence in chronically infected individuals.

Methods. A5342 was a phase 1, randomized, double-blind, placebo-controlled, parallel-arm study. Participants on effective antiretroviral therapy (ART) were randomized to receive 2 infusions of VRC01 (40 mg/kg) at entry and week 3, and 2 infusions of placebo (saline) at weeks 6 and 9; or 2 infusions of placebo at entry and week 3, and 2 infusions of VRC01 at weeks 6 and 9.

Results. Infusion of VRC01 was safe and well tolerated. The median fold-change in the cell-associated HIV-1 RNA/DNA ratio from baseline to week 6 was 1.12 and 0.83 for the VRC01 and placebo arms, respectively, with no significant difference between arms ($P = .16$). There were no significant differences in the proportions with residual plasma viremia ≥ 1 copies/mL or in phorbol 12-myristate 13-acetate/ionomycin-induced virus production from CD4⁺ T cells between arms (both $P > .05$).

Conclusions. In individuals with chronic HIV-1 infection on ART, VRC01 infusions were safe and well tolerated but did not affect plasma viremia, cellular HIV-1 RNA/DNA levels, or stimulated virus production from CD4⁺ T cells.

Keywords. bnMAB; clinical trial; HIV-1 cure; HIV-1 persistence; VRC01.

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Effective antiretroviral therapy (ART) inhibits HIV-1 replication and reduces HIV-1 plasma RNA to levels below the detection of clinical assays; however, following interruption of ART, HIV-1 RNA generally rebounds to pre-ART levels within weeks. HIV-1 is able to persist despite ART because of the establishment of latent infection in long-lived cells, including resting memory CD4⁺ T cells [1, 2]. The latent cellular reservoir decays very slowly over time ($T_{1/2}$ of 44 months) on ART alone [3]; thus alternative therapies are being explored to accelerate its decay. Monoclonal antibodies have been developed as treatment for a variety of conditions including cancer, autoimmune disorders, and infections. Such antibodies directed at the HIV-1 envelope can promote antibody-dependent cell-mediated cytotoxicity

(ADCC) and may be capable of killing HIV-1-expressing cells [4]. Several potent, broadly neutralizing monoclonal antibodies (bnMAbs) that bind to the HIV-1 envelope protein (env) have been isolated from HIV-1-infected individuals and are being developed for preventative and therapeutic use [5–7].

Studies in nonhuman primates provide evidence of the therapeutic potential of bnMAbs in HIV-1 infection. Barouch et al. [8] administered the V3 glycan loop bnMAB PGT121 alone and in combination with other bnMAbs to chronically infected, viremic (SHIV-SF162P3) rhesus macaques in a series of experiments. Rapid declines in plasma viremia were observed within 7 days of the initial infusion and were sustained until the antibody levels became undetectable. Reductions in cell-associated HIV-1 DNA in the peripheral blood, gastrointestinal mucosa, and lymph nodes have been observed in treated animals [8]. Shingai et al. reported similar results in macaques chronically infected with SHIV-AD8 using 2 bnMAbs, 1 against the CD4⁺ binding site (3BNC117) and the other against the V3 glycan loop (10–1074) of the HIV-1 envelope [9]. These observations indicate that bnMAbs can block cell-to-cell spread of simian immunodeficiency virus (SIV) in the absence of ART. In addition, analyses of viral decay kinetics suggest the clearance of virus-infected cells, possibly through ADCC [10].

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Initial clinical studies in humans have been conducted for several HIV-1 bnMAbs to evaluate safety, pharmacokinetics, and antiviral activity for antibodies targeting the CD4 binding site (3BNC117 and VRC01) and the V3-glycan (10–1074) on the HIV-1 envelope [11–16]. These trials have demonstrated that the bnMAbs are safe at doses of up to 30 to 40 milligrams per kilogram, depending on the antibody. In the absence of pre-existing bnMAB resistance, the bnMAbs demonstrated in vivo antiviral activity, leading to a decrease in plasma HIV-1 RNA on the order of 1 log₁₀ copies/mL in the absence of ART; however, evidence of bnMAB resistance was detected in some individuals at baseline, and in the majority of subjects, a return to viremia occurred as antibody levels waned [12, 14–16]. Additionally, given alone, VRC01 or 3BNC117 was not sufficient to maintain viral suppression after withdrawal of ART in individuals who initiated ART in chronic or acute infection, although some delays in rebound were observed [11, 17, 18].

To date, there are limited data describing the in vivo effect of bnMAbs on the latent viral reservoir in individuals with suppressed viremia on ART [14]. Given the evidence that bnMAbs can block cell-to-cell HIV-1 spread and potentially mediate the killing of infected cells expressing the HIV-1 envelope, there is great interest in the role of single or multiple bnMAbs, alone or in combination with latency-reversing agents, on latent HIV. We conducted a randomized controlled clinical trial to evaluate whether VRC01, a CD4-binding site bnMAB, affects the persistence of HIV-1. We measured several indicators of HIV-1 persistence, before and after VRC01 infusions, including the proportion of CD4⁺ T cells expressing HIV-1 RNA and the proportion of individuals with residual plasma viremia among chronically infected individuals on effective ART.

METHODS

Study Design and Participants

A5342 was a phase I, double-blind, randomized, placebo-controlled, parallel-arm study conducted at AIDS Clinical Trials Group (ACTG) sites in the United States (ClinicalTrials.gov Identifier: NCT02411539). Eligible participants were HIV-1-infected adults, between 18 and 65 years of age, body weight between 53 and 115 kilograms (inclusive), on continuous ART for at least 2 years and with a CD4⁺ T-cell count ≥200 per mm³, plasma HIV-1 RNA less than the limit of detection of standard clinical assays for at least 24 months and less than 40 copies/mL at screening, and acceptable laboratory parameters. Pregnant or breastfeeding women and individuals with chronic hepatitis B or hepatitis C infection, prior receipt of any humanized or human monoclonal antibody, or recent or current use of immunomodulators were excluded. Written informed consent was obtained from each study participant. The study protocol was reviewed and approved by an institutional review board at each study site.

Participants were randomized equally to 2 arms at study entry (week 0). Each participant received 2 infusions of VRC01

and 2 placebo infusions (normal saline). Arm A participants received VRC01 40 mg/kg by intravenous infusion over 30 to 60 minutes at week 0 and week 3, and saline placebo infusion at weeks 6 and 9. Arm B participants received placebo infusions at week 0 and week 3 and VRC01 infusions at weeks 6 and 9 (Figure 1). Placebo infusions were 0.9% sodium chloride and were the same volume as the VRC01 infusions. The intravenous bags were covered with an amber bag and labeled identically to maintain blinding of the participants and clinical staff.

After screening, study visits were completed at pre-entry, entry (week 0), weekly for weeks 1–12, and at weeks 15, 18, and 30. Plasma HIV-1 RNA was measured at a central laboratory at entry and weeks 3, 6, 9, 12, 18, and 30 using the Abbott M2000 assay. CD4⁺ T-cell counts were obtained at entry and weeks 6, 12, 18, and 30. Adverse events were assessed by site investigators and were graded using the National Institutes of Health Division of AIDS Table for Grading the Severity of Adult and Pediatric Adverse Events (version 2.0). In addition, adverse event attribution to study treatment was reviewed by the core team blinded to study treatment.

Specialized Laboratory Measurements

Plasma HIV-1 RNA Single-Copy Assay

The single-copy HIV-1 RNA assay (SCA) targeting integrase was performed according to published methods [19] on plasma samples obtained at screening and weeks 0, 1 (Arm A), 3, 4 (Arm A), 6, 7 (Arm B), 9, 10 (Arm B), 12. In brief, 3 to 4.5 mL of double-spun plasma was digested with proteinase K in guanidium hydrochloride and precipitated with glycogen and isopropanol, followed by a 70% ethanol wash. RNA was reverse-transcribed to cDNA, and quantitative polymerase chain reaction (qPCR) was performed targeting the integrase region of *pol*. The limit of detection of the SCA ranged from 0.4 to 1 copies/mL, depending on the volume of plasma available.

Total CD4⁺ T-Cell-Associated HIV-1 RNA and DNA

Cellular HIV-1 RNA and DNA were measured in total CD4⁺ T cells by ultrasensitive qPCR, as previously described [20]. In brief, total CD4⁺ T cells were isolated from peripheral blood mononuclear cells (PBMCs) by negative selection (Stem Cell Technologies, Vancouver, BC, Canada) and total nucleic acid

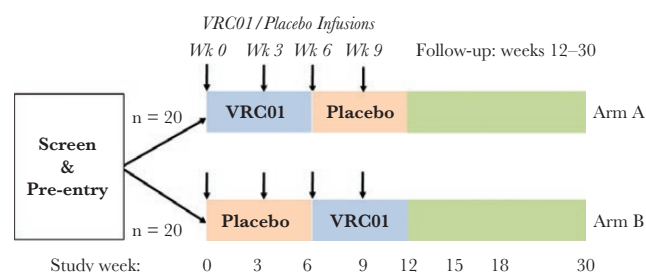


Figure 1. Study design.

extracted as described [20]. Half of the extract was used for HIV-1 DNA and CCR5 qPCR, and the other half was treated with DNase-I (Promega), reverse-transcribed, and assayed for unspliced HIV-1 RNA by qPCR targeting integrase using the same primers and probes as for SCA.

Total Virus Recovery Assay

Total CD4⁺ T cells were isolated from PBMCs (Stem Cell) and cultured (3–6 replicates of 1 million cells/well) in phenol red-free R10 media with or without phorbol 12-myristate 13-acetate (PMA)/ionomycin (Iono) for 7 days in the presence of 300 mM of efavirenz and raltegravir as previously described [21]. Total induced HIV-1 RNA was quantified in culture supernatants (pooled from replicate wells and tested in duplicate) by qPCR at pre-entry, week 6, and week 12.

VRC01 Levels

VRC01 levels in serum were measured as previously described at every visit from entry to week 30; on infusion days, samples were collected both pre-infusion and 30 to 60 minutes postinfusion [13]. Anti-VRC01 antibody was measured in serum at week 18 or week 30 as previously described [13].

Study Product

VRC01 was manufactured by the VRC Vaccine Pilot Plant, operated by Leidos Biomedical Research, Inc. (Frederick, MD) under good manufacturing practice, and purified product was vialated at a concentration of 100 ± 10 mg/mL as previously described [13].

Statistical Analysis

The co-primary objectives of the study were to assess the safety and tolerability and to determine the efficacy of 2 intravenous infusions of VRC01 administered 3 weeks apart in HIV-1-infected participants on effective ART. The primary efficacy outcome measure was the change in cell-associated HIV-1 RNA/DNA ratio in total CD4⁺ cells from baseline to week 6 and was compared between the 2 randomized arms using the Wilcoxon rank-sum test at a 10% significance level. The secondary outcome measure was change in cell-associated HIV-1 RNA/DNA ratio from pre-VRC01 dosing to post-VRC01 dosing combining participants from both arms (Arm A: from baseline to week 6; Arm B: from week 6 to week 12) and was assessed using the Wilcoxon signed rank test at a 5% significance level. Differences in medians between the 2 randomized arms and from pre-VRC01 to post-VRC01 were estimated by 95% confidence interval using Hodges-Lehmann estimate under the assumption that the 2 distributions are alike in shape and 1 distribution is shifted upward or downward by an amount relative to the other distribution. The maximal lower limit across all HIV-1 RNA SCA results was 1 copy/mL. HIV-1 RNA SCA values below the maximal detection limit were imputed with a value of half the limit (0.5 copies/mL). The proportion of participants with SCA ≥1 copies/mL was compared between the

randomized arms using the Fisher's exact test, and differences in the proportions pre- to post-VRC01 infusions were assessed using McNemar's test. Virologic outcomes were analyzed after log₁₀ transformation. Both safety and efficacy analyses used an as-treated approach restricted to randomized participants who received at least 1 dose of study treatment. All reported *P* values were nominal and not adjusted for multiple comparisons.

RESULTS

Accrual and Participant Characteristics

A total of 40 participants were enrolled and randomized between August 2015 and March 2016. The baseline characteristics of the enrolled participants are shown in Table 1, and the disposition of all study participants is displayed in Figure 2. At study entry, the median age was 52 years, and the median CD4⁺ T-cell count was 696 per mm³ (Table 1). Baseline characteristics were generally balanced between treatment arms; however, Arm B participants were older and had lower baseline CD8 counts than those in Arm A. Three participants prematurely discontinued the study: 2 participants (1 from each arm) discontinued before week 12 and did not have samples drawn for the primary efficacy assessment at week 6; and 1 Arm A participant discontinued after week 18. All participants received at least 1 infusion, and 37/40 (93%) completed all VRC01/placebo infusions per protocol.

VRC01 given as 2 intravenous doses of 40 mg/kg was safe and well tolerated. No grade 3 or higher treatment-related adverse events were reported during study follow-up. Two participants, 1 from each arm, did not complete scheduled infusions due to being off study prematurely. In total, 5 participants had mild to moderate (grade 1 and 2) clinical symptoms that were deemed possibly, probably, or definitely related to the infusions. Infusion-related adverse events were uncommon and consistent with expected monoclonal antibody infusion reactions. One VRC01 infusion was discontinued after 94% of the volume was administered due to a grade 2 rash and grade 1 pruritis, which resolved within hours; this participant again developed grade 2 rash and grade 1 pruritis with the second infusion, but the full dose was administered as elected by the participant and the site investigator. A second participant developed a grade 1 rash with the first VRC01 infusion that was determined to be possibly related; the rash did not recur with the second infusion. Three participants experienced flu-like symptoms; for 1 participant, the symptoms occurred on the day of VRC01 infusion for both doses, and for the other 2 participants, the symptoms were temporally associated with placebo. No participants experienced virologic failure during the study, defined as confirmed plasma HIV-1 RNA >200 copies/mL. CD4⁺ T-cell counts were stable throughout the study period.

VRC01 Pharmacokinetics

The serum trough concentrations of VRC01 measured 3 weeks after the first infusion ranged from 41.6 to 239.4 µg/mL (median, 112.2 µg/mL); all except 1 participant had concentrations

Table 1. Baseline Characteristics of the Study Population

	Arm A (n = 20)	Arm B (n = 20)	Total (n = 40)
Age, median (IQR), y	45 (32–54)	56 (50–59)	52 (41–58)
Male sex, No. (%)	17 (85)	20 (100)	37 (93)
Race/ethnicity, No. (%)			
White, non-Hispanic	13 (65)	14 (70)	27 (68)
Black, non-Hispanic	3 (15)	4 (20)	7 (18)
Hispanic	4 (20)	2 (10)	6 (15)
Duration of ART, median (IQR), y	7.3 (4.5–10.6)	6.9 (5.4–10.7)	6.9 (5.2–10.7)
ART regimen at entry, No. (%)			
NNRTI + NRTIs	6 (30)	5 (25)	11 (28)
PI + NRTIs	4 (20)	6 (30)	10 (25)
InSTI + NRTIs	7 (35)	6 (30)	13 (33)
Other	3 (15)	3 (15)	6 (15)
CD4 cell count, median (IQR), cells/mm ³	701 (594–952)	685 (535–843)	696 (559–889)
CD8 cell count, median (IQR), cells/mm ³	801 (490–1210)	617 (480–744)	663 (490–936)
CD4/CD8 ratio, median (IQR)	0.9 (0.7–1.2)	1.1 (0.9–1.8)	1.0 (0.8–1.4)
Cell-associated HIV-1 RNA, ^a median (IQR), log ₁₀ copies/10 ⁶ CD4	1.60 (0.90–2.09)	1.38 (0.90–2.03)	1.53 (0.90–2.04)
Cell-associated HIV-1 DNA, ^b median (IQR), log ₁₀ copies/10 ⁶ CD4	3.05 (2.42–3.20)	3.00 (2.53–3.18)	3.03 (2.42–3.18)
Cell-associated HIV-1 RNA/DNA ratio, ^a median (IQR)	0.05 (0.02–0.10)	0.03 (0.02–0.05)	0.04 (0.02–0.07)

Abbreviations: ART, antiretroviral therapy; InSTI, integrase strand transfer inhibitor; IQR, interquartile range; NNRTI, nonnucleoside reverse transcriptase inhibitor; NRTI, nucleoside reverse transcriptase inhibitor; PI, protease inhibitor.

^an = 19 for Arm A and n = 19 for Arm B.

^bn = 20 for Arm A and n = 19 for Arm B.

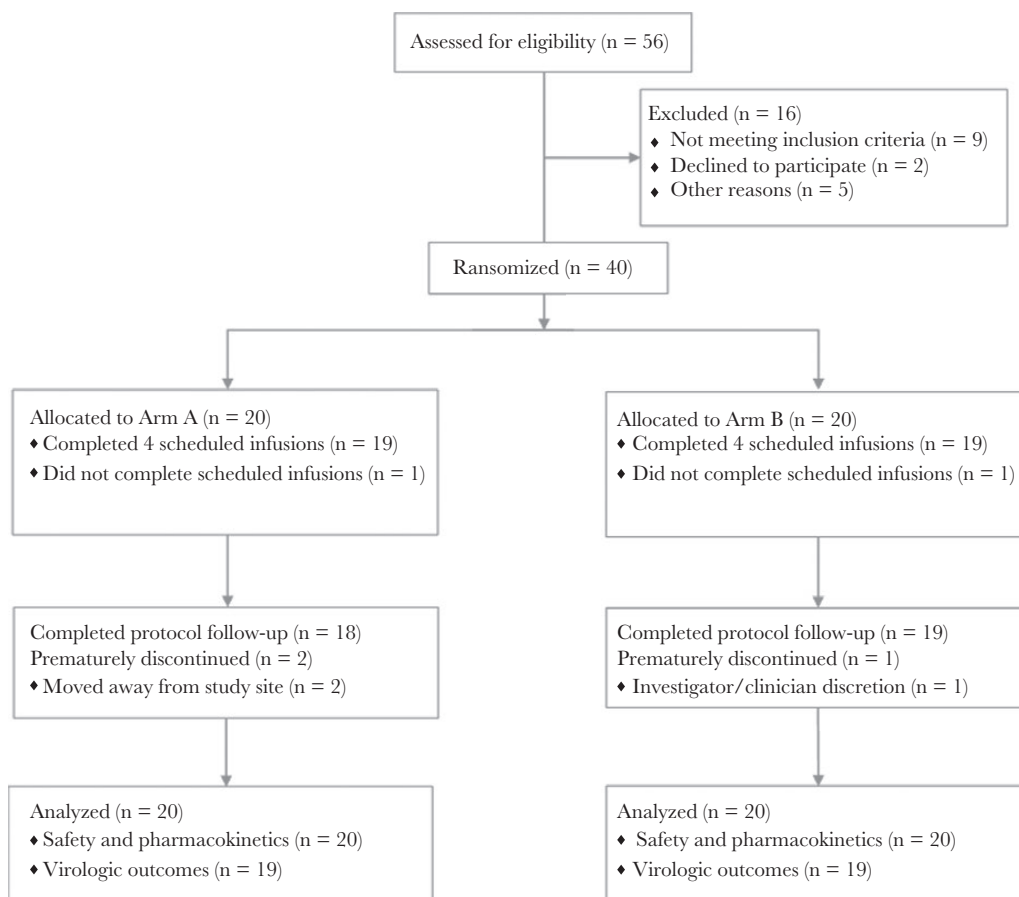


Figure 2. Consolidated Standards of Reporting Trials (CONSORT) diagram.

>50 µg/mL. The trough concentrations 3 weeks after the second dose were higher, with a range of 51.7 to 340.9 µg/mL (median, 133.5 µg/mL). All participants had detectable serum levels of VRC01 at the time point 6 weeks after the final dose, with a median level (range) of 42.1 (9.9–265.2) µg/mL. Anti-VRC01 antibody was not detected in any study participants (n = 38).

Virologic Outcomes

The median baseline (week 0) values for cell-associated HIV-1 RNA (CAR) and HIV-1 DNA (CAD) were 1.53 and 3.03 log₁₀ copies/million CD4⁺ T cells, respectively. The median ratio of CAR/CAD was 0.04 and was similar between arms (Table 1). The primary and secondary virologic outcome measures are summarized in Table 2. No significant difference was observed in the primary efficacy outcome of change in HIV-1 CAR/CAD ratio from baseline to week 6 between VRC01 and placebo (median fold-change, 1.12 vs 0.83; 95% confidence interval [CI] on the difference in median fold-change between the 2 arms, 0.75–2.42; *P* = .16). Similarly, there was no difference from pre- to post-VRC01 time points with both arms combined (median fold-change, 1.24; 95% CI, 0.83–1.69; *P* = .29).

HIV-1 plasma RNA ≥1 copies/mL was present at baseline in 22/40 (55%) participants. At week 6, there was no difference in the proportion with SCA ≥1 copies/mL between the arms (42% vs 37%; *P* = 1.0). Similarly, the proportion ≥1 copies/mL was not statistically different for the pre- to post-VRC01 time points for both arms combined (*P* = .59). No evidence of a change in the proportion of participants with SCA ≥1 copies/mL was seen at 1 and 3 weeks after each VRC01 infusion (data not shown).

The effect of VRC01 on HIV-1 persistence was also measured with an assay of PMA-ionomycin-induced HIV-1 RNA release into culture supernatants over 7 days from total CD4⁺ T cells [21]. The change in stimulated virus production (HIV-1 RNA

copies/mL in supernatants) from baseline to week 6 was not statistically different between arms (−0.13 vs 0.12 log₁₀ RNA copies/mL; *P* = .91), or from pre- to post-VRC01 time points with both arms combined (*P* = .85).

DISCUSSION

Many bnMAbs for HIV have been identified, and several are in clinical development for both the prevention and treatment of HIV-1 [5–7, 11–14, 16, 17, 22, 23]. These bnMAbs have anti-HIV-1 neutralization activity, but their impact on the persistence of HIV-infected cells and on residual viremia in ART-suppressed participants remains uncertain. In our study among individuals with chronic ART-suppressed HIV-1 infection, 2 doses of VRC01 was safe and well tolerated but did not have a measurable impact on cellular HIV-1 RNA or DNA levels, cellular HIV-1 RNA/DNA ratio, HIV-1 plasma viremia, or stimulated virus production from total CD4⁺ T cells.

Notably, even among the subset of participants (n = 22) with measurable plasma HIV-1 RNA by single-copy assay, we found no effect of VRC01 on residual viremia. Similarly, Lynch et al. also observed no effect of VRC01 infusion on residual plasma virus in 2 participants with measurable HIV-1 RNA by SCA [14]. By contrast, in HIV-1-infected individuals who were not on ART with high plasma HIV-1 RNA, both VRC01 and 3BNC117 administered as monotherapy were found to reduce plasma HIV-1 RNA by approximately 1 log₁₀ copies/mL in the absence of preexisting resistant variants [12, 14–16]. In untreated individuals, VRC01 likely lowers the abundant plasma viremia by blocking cell-to-cell spread of HIV-1 infection through its neutralization activity, rather than ADCC activity. By contrast, HIV-1 plasma RNA in individuals on long-term suppressive ART is more likely from the release of

Table 2. Virologic Outcomes

	Arm A	Arm B	<i>P</i> Value ^b	Arms A and B Combined		Change From Pre- to Post-VRC01	<i>P</i> Value ^c
	Change From Baseline to Week 6 Median (Q1, Q3)			Pre-VRC01 Values	Post-VRC01 Values		
Cell-associated HIV RNA, log ₁₀ copies/10 ⁶ CD4 cells	0.08 (−0.23, 0.32)	−0.08 (−0.26, 0.29)	.39	1.55 (0.99, 1.99)	1.48 (0.99, 2.10)	0.09 (−0.23, 0.32)	.64
Cell-associated HIV DNA, log ₁₀ copies/10 ⁶ CD4 cells	−0.06 (−0.13, 0.06)	−0.01 (−0.08, 0.13)	.30	2.93 (2.43, 3.15)	2.92 (2.51, 3.11)	−0.05 (−0.12, 0.06)	.19
Cell-associated HIV RNA/DNA ratio ^a	1.12 (0.92, 2.15)	0.83 (0.57, 2.37)	.16	0.04 (0.02, 0.08)	0.05 (0.02, 0.08)	1.24 (0.61, 2.15)	.29
Stimulated virus production from total CD4 ⁺ T cells, log ₁₀ copies/mL	−0.13 (−0.51, 0.92)	0.12 (−0.52, 0.30)	.91	2.99 (2.06, 3.37)	2.66 (2.28, 3.41)	−0.10 (−0.51, 0.44)	.85
	Week 6		<i>P</i> Value ^d				<i>P</i> Value ^e
Plasma HIV RNA ≥1 copies/mL by single-copy assay (%)	8/19 (42)	7/19 (37)	1.0	16/38 (42)	14/38 (37)	–	.59

^aChanges in RNA/DNA ratios are shown as fold-change, calculated by dividing the RNA/DNA ratio at the later time point by the earlier time point.

^bWilcoxon rank-sum test.

^cWilcoxon signed rank test.

^dFisher exact test.

^eMcNemar's test.

virus from stable reservoirs of infected cells rather than virus produced by ongoing, complete cycles of viral replication [24, 25]. The lack of effect of virus neutralization activity of VRC01 on residual viremia is consistent with numerous studies that have demonstrated the lack of effect of antiretroviral intensification on residual plasma viremia in the setting of effective ART [26–31]. In this study of individuals on effective ART, we hypothesized that VRC01 might still have an effect on persistent virus-expressing cells even in the absence of ongoing viral replication; unfortunately, we did not detect such an effect.

There are several potential explanations for the lack of response of residual HIV-1 in plasma to treatment with VRC01. First, it is possible that the residual viremia was from variants with preexisting resistance to VRC01. Prior studies have demonstrated that 90% of circulating M-type isolates were susceptible to VRC01 with a 50% inhibitory concentration of 50 µg/mL or less [32, 33]. We were not able to perform susceptibility testing of plasma virus in our study due to the very low levels of viremia, but it would be unlikely that all the participants with residual viremia would harbor HIV-1 variants in plasma that were resistant to VRC01. However, the viral variants that persist or emerge on ART may differ considerably from the variants present during untreated infection with high levels of virus production and rapid cell turnover. Viral variants that persist on ART may be inherently resistant to antibody-mediated clearance, or they may already be bound by autologous antibody that blocks binding of VRC01. Second, the residual virus in the plasma on ART may have other changes that render bnMAbs ineffective, including defective virus particles lacking envelope. In this regard, the quantity of the virus in the plasma is too low to determine whether it contains the envelope protein.

The administration of VRC01 also did not clearly impact the number or transcriptional activity of HIV-1-infected cells in blood, as measured by cell-associated HIV-1 RNA, DNA, or the ratio of RNA/DNA. It has been postulated that bnMAbs would enhance the clearance of HIV-infected cells expressing the envelope protein through ADCC [10]. Lu et al. examined the effect of the combination of the bnMAbs 3BNC117 and 10–1074 on the percentage of HIV-infected cells that persist after adoptive transfer in mice [34]. These experiments using human CD4⁺ T cells infected with primary HIV-1 isolates from 4 individuals demonstrated greater clearance of infected cells in the bnMab-treated mice compared with an isotype control [34]. There are several possible reasons why a reduction in cell-associated HIV DNA or RNA was not observed in the current human clinical trial. Additionally, Cohen et al. have similarly reported a lack of effect of 3BNC117 infusions on the viral reservoir in 9 individuals, as measured by viral outgrowth from CD4 T cells [35]. The capacity for antibody binding to infected CD4 T cells varies among the bnMAbs. In vitro experiments performed by Mujib et al. and others have shown low levels of infected cell binding and ADCC for CD4 binding site antibodies, including VRC01

and 3BNC117 [10, 36]. The clearance of infected cells by antibody requires the expression of envelope on the cell surface; however, only a small fraction of HIV-infected cells in blood express unspliced HIV-1 RNA [37]. It is not known what fraction of cells express HIV-1 envelope protein, but it is expected to be low as not all transcripts are translated, some transcripts are from defective proviruses, and even for intact, fully expressed proviruses, HIV-1 envelope expression on the cell surface is likely transient and mostly occurs before budding [38]. In addition, even if expressed on the cell surface, the envelope target density may be too low for VRC01 to have a measurable effect on the number of infected cells [38]. Finally, it is possible that VRC01 did not penetrate to the sites of potential virus production, such as lymph node germinal centers.

Although high-dose VRC01 did not have a discernable effect on multiple measures of HIV-1 persistence, it was safe and well tolerated. Moreover, the activity of more potent and broader bnMAbs with longer half-lives and enhanced Fc-mediated effector functions should continue to be studied, alone and in orthogonal combinations of bnMAbs to enhance HIV-1 variant coverage. Clinical trials of combinations of bnMAbs and of bispecific antibodies will help define the role of antibody therapeutics in reducing or controlling HIV-1 reservoirs [39].

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