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HIV-1 antibody 3BNC117 suppresses viral rebound in humans during treatment interruption

Johannes F. Scheid^{1,2,*}, Joshua A. Horwitz^{1,*}, Yotam Bar-On¹, Edward F. Kreider³, Ching-Lan Lu¹, Julio C. C. Lorenzi¹, Anna Feldmann⁴, Malte Braunschweig¹, Lilian Nogueira¹, Thiago Oliveira¹, Irina Shimeliovich¹, Roshni Patel¹, Leah Burke⁵, Yehuda Z. Cohen¹, Sonya Hadrigan¹, Allison Settler¹, Maggi Witmer-Pack¹, Anthony P. West Jr⁶, Boris Juelg⁷, Tibor Keler⁸, Thomas Hawthorne⁸, Barry Zingman⁹, Roy M. Gulick⁵, Nico Pfeifer⁴, Gerald H. Learn³, Michael S. Seaman¹⁰, Pamela J. Bjorkman⁶, Florian Klein^{1,11,12}, Sarah J. Schlesinger¹, Bruce D. Walker^{7,13}, Beatrice H. Hahn³, Michel C. Nussenzweig^{1,14}, and Marina Caskey¹

¹Laboratory of Molecular Immunology, The Rockefeller University, New York, New York 10065, USA

²Massachusetts General Hospital and Harvard Medical School, Boston, Massachusetts 02114, USA

³Departments of Medicine and Microbiology, Perelman School of Medicine, University of Pennsylvania, Philadelphia, Pennsylvania 19104, USA

⁴Department of Computational Biology and Applied Algorithmics, Max Planck Institute for Informatics, Campus E1 4, 66123 Saarbrücken, Germany

⁵Division of Infectious Diseases, Weill Medical College of Cornell University, New York, New York 10065, USA

⁶Division of Biology, California Institute of Technology, Pasadena, California 91125, USA

⁷Ragon Institute of MGH, MIT and Harvard, Cambridge, Massachusetts 02139, USA

⁸Celldex Therapeutics, Inc., Hampton, New Jersey 08827, USA

⁹Montefiore Medical Center, Albert Einstein College of Medicine, Bronx, New York 10467, USA

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Correspondence and requests for materials should be addressed to M.C.N. (nussen@rockefeller.edu) or M.C. (mcaskey@rockefeller.edu).

These authors contributed equally to this work.

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¹⁰Center for Virology and Vaccine Research, Beth Israel Deaconess Medical Center, Boston, Massachusetts 02215, USA

¹¹Laboratory of Experimental Immunology, Center for Molecular Medicine Cologne (CMMC), University of Cologne, 50931 Cologne, Germany

¹²Department I of Internal Medicine, Center of Integrated Oncology Cologne-Bonn, University Hospital Cologne, 50937 Cologne, Germany

¹³Howard Hughes Medical Institute, Massachusetts General Hospital, Boston, Massachusetts 02114, USA

¹⁴Howard Hughes Medical Institute, The Rockefeller University, New York, New York 10065, USA

Abstract

Interruption of combination antiretroviral therapy in HIV-1-infected individuals leads to rapid viral rebound. Here we report the results of a phase IIa open label clinical trial evaluating 3BNC117, a broad and potent neutralizing antibody (bNAb) against the CD4 binding site of HIV-1 Env¹, in the setting of analytical treatment interruption in 13 HIV-1-infected individuals. Participants with 3BNC117-sensitive virus outgrowth cultures were enrolled. Two or four 30 mg kg⁻¹ infusions of 3BNC117, separated by 3 or 2 weeks, respectively, are generally well tolerated. Infusions are associated with a delay in viral rebound for 5–9 weeks after two infusions, and up to 19 weeks after four infusions, or an average of 6.7 and 9.9 weeks respectively, compared with 2.6 weeks for historical controls (P < 0.00001). Rebound viruses arise predominantly from a single provirus. In most individuals, emerging viruses show increased resistance, indicating escape. However, 30% of participants remained suppressed until antibody concentrations waned below 20 µg ml⁻¹, and the viruses emerging in all but one of these individuals showed no apparent resistance to 3BCN117, suggesting failure to escape over a period of 9–19 weeks. We conclude that administration of 3BNC117 exerts strong selective pressure on HIV-1 emerging from latent reservoirs during analytical treatment interruption in humans.

A fraction of HIV-1 infected individuals develops broad and potent serologic activity against the virus. Single-cell antibody cloning methods² have uncovered the source of this activity as broadly neutralizing antibodies (bNAbs), which target different sites on the HIV-1 envelope spike protein, $gp160^{1-3}$.

In animal models, bNAbs show potent prophylactic activity, suppress established viraemia, and delay viral rebound during analytical treatment interruption (ATI)^{4–8}. In humans, a phase I clinical trial showed that 3BNC117 is generally safe and effective in transiently reducing viraemia in chronically HIV-1-infected individuals⁹. A single infusion of 3BNC117 was well tolerated, rapidly decreased viral loads in viraemic individuals by an average of 1.48 log₁₀ copies per ml, with durable activity for 4 weeks⁹. In addition, 3BNC117 increased autologous antibody responses in HIV-1-infected individuals, and enhanced clearance of infected cells in humans and in humanized mice^{10,11}. VRC01, a less potent bNAb that also targets the CD4-binding site, suppressed viraemia by 1.14 log₁₀ (refs 12,13 and Fig. 1a, b).

To investigate whether 3BNC117 can suppress viral rebound from the latent reservoir during ATI in chronically suppressed HIV-1 infected humans, we conducted a phase IIa open label clinical trial. To select participants with 3BNC117-sensitive viruses in their latent reservoirs, we performed bulk viral outgrowth cultures of peripheral blood mononuclear cells (PBMCs) from individuals whose viraemia was suppressed by combination antiretroviral therapy (ART). The resulting isolates were screened for sensitivity to 3BNC117 using the TZM-bl assay (Supplementary Table 1). Of 63 individuals screened, only 11% yielded viruses that were fully resistant to 3BNC117 (IC₅₀ > 20 µg/ml), and 65% were sensitive to 3BNC117 IC₅₀ at concentrations below 2.0 µg/ml. In contrast only 29% were similarly sensitive to VRC01 (Fig. 1a and b, Extended Data Fig. 1 and Supplementary Table 1).

We enrolled HIV-1 infected individuals who were on suppressive antiretroviral therapy (ART) with plasma viral loads <50 HIV-1 RNA copies per ml for at least 12 months, had CD4 counts >500 cells per mm³, yielded 3BNC117-sensitive outgrowth viruses (IC₅₀ ≤2.0 μ g ml⁻¹), and whose viral load at screen was <20 copies per ml (Extended Data Fig. 1, Supplementary Tables 2 and 4, and Methods). Participants were enrolled in two groups: eightin group A to receive two 30 mg kg⁻¹ infusions three weeks apart, while seven in group B received up to four 30 mg kg⁻¹ infusions at two-week intervals (Fig. 1c, d, Supplementary Table 2). Two group A participants had viral loads >20 copies per ml at the time of infusion and were excluded from further analysis (Supplementary Tables 2 and 4).Participants are numbered 701–715 (Supplementary Table 2).

ATI was started 2 days after the first 3BNC117 infusion. ART was reinitiated and infusions were stopped after two consecutive plasma viral load measurements exceeded 200 copies per ml. All individuals on non-nucleoside reverse transcriptase inhibitors (NNRTIs) were switched to an integrase-inhibitor-based regimen (dolutegravir plus tenoforvir disoproxil fumarate/emtricitabine) four weeks before ATI owing to the long half-life of NNRTIs (Supplementary Table 2).

Both dosing regimens were generally well tolerated. The majority of reported adverse events were transient and grade 1 in severity (Supplementary Table 5). The mean CD4 T-cell count at baseline (day 0) was 747 cells per mm³, and the average change in CD4 T-cell counts between start of ATI and rebound was -127 cells per mm³. Although CD4T cells declined modestly during viral rebound in some participants, CD4 T-cells returned to baseline by week 12 in most participants (mean 828 cells per mm³) (Extended Data Fig. 2 and Supplementary Table 4). Of 12 individuals tested, 5 showed measurable increases in the magnitude and/or breadth of T cell responses to HIV-1 12 weeks after ATI, relative to baseline (Extended Data Fig. 3). None of the participants experienced acute retroviral syndrome during rebound, and viraemia was re-suppressed below 20 copies per ml in all participants within 2–7 weeks after restarting ART (Supplementary Table 4). We conclude that up to four 30 mg kg⁻¹ infusions of 3BNC117 during ATI are generally safe and well tolerated.

By anti-idiotype ELISA⁹ the half-life of 3BNC117 during ATI was 19.6 days among group A participants, and 14.1 days among those in group B (Fig. 1e, f and Supplementary Table

4). These measurements are similar to previously reported values for 3BNC117 in HIV-1-infected individuals on ART⁹ (Fig. 1e).

All six group A participants maintained viral loads below 200 copies per ml during the first 4 weeks, with rebound 5–9 weeks after ART interruption (Fig. 2a and Supplementary Table 4a). In group B, rebound occurred 3–19 weeks after ATI, with four out of seven (57%) participants remaining suppressed for at least 10 weeks (Fig. 2b and Supplementary Table 4b). The average time to rebound was 6.7 weeks in group A, 9.9 weeks in group B, and 8.4 weeks for all participants together, compared with 2.6 weeks for matched historical non-infused control individuals (Fig. 2c, Extended Data Fig. 4a, Supplementary Tables 4, 6 and 7). Altogether, 6 of the 13 infused individuals (46%) remained suppressed until at least 9 weeks after ATI. Relative to matched historical control individuals, the delay to rebound among all 3BNC117-infused participants was highly significant (P < 0.00001, weighted logrank test, Fig. 2c, Extended Data Fig. 4, Supplementary Tables 4, 6 and 7 and Methods). We conclude that repeated infusions of 3BNC117 are generally safe and significantly delay HIV-1 rebound from the latent reservoir during ATI.

Time to viral rebound did not correlate with pre-ATI viral culture sensitivity to 3BNC117, nor to baseline levels of cell-associated HIV-1 DNA (Fig. 2d and Extended Data Fig. 4e). Therefore the significance of viral outgrowth sensitivity as an inclusion criterion is not clear. 3BNC117 levels at rebound were also variable, ranging from 6–168 μ g ml⁻¹, but were directly correlated to the IC₈₀ of the emerging virus (Fig. 2a, b, e)

To determine whether rebound was associated with resistance to 3BNC117, we compared pre-infusion and rebound viral outgrowth cultures. A majority (8/13) of participants had rebound viruses that were more resistant to 3BNC117 (IC₈₀ > threefold higher, Fig. 3a, c, Extended Data Fig. 5a, Supplementary Table 3). Among group A participants, all but one (707) had more resistant rebound viruses; however, among group B participants, four of seven (710, 711, 712 and 715) showed similar pre-infusion and rebound sensitivity to 3BNC117 (Fig. 3a, c, Extended Data Fig. 5a, Supplementary Table 3). Among these five individuals, 711 was the earliest to rebound at 3 weeks, despite having viruses that were surprisingly sensitive to 3BNC117 as measured by IC50 (Fig. 2b, Extended Data Fig. 5a, Supplementary Tables 3 and 4). However, 100% neutralization was not achieved against 711 rebound or pre-infusion viruses, even at high (50 µg ml⁻¹) antibody concentrations, suggesting that 3BNC117 was not fully therapeutic (Extended Data Fig. 5, Supplementary Table 3). Thus, the only participant in the study to rebound within 3 weeks of ATI may have done so because of pre-existing resistance to 3BNC117 by the dominant virus in the reservoir.

The other 4 participants that showed no change between pre- and post-infusion culture sensitivity to 3BNC117, 707, 710, 712, and 715, rebounded relatively late at 9, 19, 16 and 11 weeks after ATI, respectively (Figs 2a, b, 3a, c, Extended Data Fig. 5, Supplementary Tables 3 and 4). In all of these individuals rebound was associated with relatively low antibody concentrations ranging from 6–41 μ g ml⁻¹ (mean 19.7 μ g ml⁻¹). This antibody concentration represents 9.6-fold the mean IC₈₀ for the rebounding viruses, which is consistent with previous reports on the relationship between suppressive 3BNC117 concentration and

neutralization titre in macaques¹⁴ (Fig. 2, Extended Data Fig. 5, Supplementary Tables 3 and 4).

To determine whether viral rebound during ATI was associated with resistance to other bNAbs undergoing clinical testing, we examined sensitivity to 10-1074 (ref. 15), which targets a different and non-overlapping epitope on the HIV-1 trimer (Fig. 3b, d, Extended Data Fig. 5, and Supplementary Table 3). With the exception of 703 and 711, the participants' rebound cultures did not show increased resistance to 10-1074. We conclude that rebound during ATI in the presence of 3BNC117 is infrequently associated with increased resistance to 10-1074.

To characterize viruses emerging from the latent reservoir further, we performed single genome sequencing (SGS) of viral RNA from the plasma and viral outgrowth cultures from eight individuals. Phylogenetic analysis of these sequences indicated that all of these eight trial participants were infected with epidemiologically unrelated viruses (Extended Data Fig. 6). Given the limited sampling of the pre-infusion reservoir, rebound viruses did not always fall within the radiation of pre-infusion viral isolates (Fig. 3e, f, Extended Data Figs 7 and 8, Supplementary Figs 1 and 2).

Remarkably, in five of eight participants, all rebounding virus sequences clustered within a low diversity lineage, consistent with the clonal expansion of a single recrudescent virus (Fig. 3e, f, Extended Data Figs 7 and 8, Supplementary Table 8). These data contrast with individuals undergoing ATI in the absence of antibody infusion, where virus rebound is consistently polyclonal, indicating the activation of multiple latently infected cells^{16–19}. Thus, in addition to delaying rebound, 3BNC117 appears to restrict the outgrowth of viral genotypes from the latent reservoir.

Six of eight participants sequenced had rebound viral outgrowth culture and/or plasma sequences that indicated 3BNC117 resistance. For example, in 704, all rebound viruses carried a serine at position 456 (Fig. 4a and Supplementary Figs 1 and 2), which may disrupt a highly conserved salt bridge that maintains the V5 loop's position and conformation $^{20-22}$. Similarly, in 708 and 709, nearly all rebound viruses carried atypical residues at position 282, where a lysine residue typically forms a salt bridge with 3BNC117 (Fig. 4a and Supplementary Figs 1 and 2)²³. However, documented 3BNC117 resistance mutations²⁴ were not universally identified among rebound viral strains (Fig. 4a and Supplementary Figs 1 and 2). Only a minor fraction (3 of 23) of sequences in the rebound population of participant 701 had potential resistance-conferring residues in Loop D (274F, 282R), while the remaining sequences did not (Fig. 4a and Supplementary Figs 1 and 2). Similarly, in 702 and 703, only a subset of rebound viruses carried a putative resistance-conferring A281D change^{1,23}. Nevertheless, the frequency of this change increased markedly with time in both participants, indicating continued selection for 3BNC117 resistance (Fig. 4a and Supplementary Figs 1 and 2). For participants 707 and 711, no sequence features were identified that would indicate 3BNC117 resistance.

To determine the sensitivity of rebound viruses to 3BNC117, we performed TZM-bl neutralization assays using pseudoviruses typed with SGS Env genotypes (Fig. 4b, Extended

Antibody potency and half-life are directly correlated with HIV-1 prophylaxis in pre-clinical models. For example, VRC01, a CD4bs antibody that is less potent than 3BNC117¹, is less effective than 3BNC117 in preventing SHIV_{AD8} infection in macaques^{8,25}. Consistent with these observations, clinical trials with combinations of three less-potent first-generation bNAbs showed limited effects on viral rebound in the setting of ATI in chronically infected individuals^{26,27}. In addition, selective pressure as evidenced by escape mutations was only observed for one of the three antibodies used in the combination, 2G12^{26,27}. In contrast, 3BNC117 alone significantly delayed viral rebound with nearly half of all individuals remaining below 200 copies per ml until at least 9 weeks, including four individuals who failed to develop resistance and only rebounded at low antibody concentrations. We speculate that the difference in efficacy between 3BNC117 and less potent bNAbs in the setting of ATI is due to increased potency and/or a longer half-life^{1,9,13}.

Nevertheless, the majority of the individuals we studied rebounded at high 3BNC117 serum concentrations. A single viral genotype displaying increased resistance to 3BNC117 established rebound in most cases. These viruses represent pre-existing dormant variants that emerged from the latent reservoir. The time to rebound did not correlate with the amount of viral DNA in circulating PBMCs; however, this is a poor measure of the HIV-1 reservoir, since most integrated proviruses in patients on ART are defective²⁸. Instead, the delay in viral rebound may represent a measure of the frequency of 3BNC117-resistant variants in the latent reservoir.

Combinations of drugs are needed to maintain HIV-1 suppression in effective ART regimens. Similarly, combinations of antibodies were required to suppress viraemia in humanized mice^{6,7}. We speculate that combinations of bNAbs will also be needed to increase the frequency of individuals that remain suppressed by antibody during ATI.

Whether 3BNC117 can also impact the size and composition of the latent reservoir during ATI will require additional studies.

Methods

Study design

An open-label, dose-escalation phase 2a study was conducted in HIV-1-infected participants (http://www.clinicaltrials.gov; NCT02446847). Study participants were enrolled sequentially according to eligibility criteria. Group A received 3BNC117 on days 0 and 21 at a dose of 30 mg/kg body weight at a rate of 250 ml/hour. Group B received 3BNC117 on days 0, 14, 28 and 42 at a dose of 30 mg/kg, as long as viral rebound did not occur. Antiretroviral therapy (ART) was discontinued 2 days after the first 3BNC117 infusion (day 2). Plasma

HIV-1 RNA levels were monitored weekly, and ART was resumed when viral load increased to ≥ 200 c.p.m. in two consecutive weekly measurements.

Study participants were followed for 36 weeks after the first infusion. Safety data are reported until week 36 for participants enrolled in group A and until week 14 for participants enrolled in group B. All participants provided written informed consent before participation in the study and the study was conducted in accordance with Good Clinical Practice. The protocol was approved by the Federal Drug Administration in the USA and the Institutional Review Board at the Rockefeller University.

Study participants

All study participants were recruited at the Rockefeller University Hospital, New York, USA. Eligible participants were adults aged 18-65 years, HIV-1-infected and before enrolment had plasma HIV-1 RNA levels <50 c.p.m. for at least 12 months while on combination ART and <20 c.p.m. at the screening visit, and current CD4 count >500/µl. In addition, participant-derived HIV-1 isolates produced by co-culture of participant PBMCs with HIV-uninfected donor PBMCs were required to be neutralized by 3BNC117 with an $IC_{50} \le 2 \mu g/ml$ in TZM-bl neutralization assays, as previously described³¹. An IC₅₀ of ≤ 2 ug/ml was chosen as a cut-off based on previous PK data of 3BNC117 in humans⁹ and data in macaques showing that antibody levels 10-100 times the IC₅₀ value against infecting viral strains are necessary to control viral rebound¹⁴. However, given the limited diversity and representation of the latent reservoir in outgrowth cultures (Supplementary Fig. 2) and the fact that no correlation between pre-infusion IC₅₀ and delay of viral rebound was found in this study, the significance of this criterion is unclear. Participants on an NNRTI-based ART regimen were switched to a study-provided integrase-inhibitor-based regimen (dolutegravir (Tivicay, ViiV Pharmaceuticals) + tenofovir disoproxil fumarate/emtricitabine (Truvada, Gilead Sciences) 4 weeks before treatment interruption due to the prolonged half-life of NNRTIs. Exclusion criteria included history of CD4 nadir <200 cells/µl, concomitant hepatitis B or C infections, previous receipt of a monoclonal antibody of any kind, or clinically relevant physical findings, medical conditions or laboratory abnormalities. Pregnant and breastfeeding women were not eligible.

Historical controls (ACTG trial participants)

Viral rebound data from 52 participants who participated in four ACTG ATI studies without additional interventions (ACTG 371³², A5024³³, A5068³⁴, and A5197³²) were compared with viral rebound data in this study. Historical controls were selected based on similar inclusion criteria: age 18–65, Plasma HIV-1 RNA <50 c.p.m. for at least 12 months before ATI while on combination ART, CD4 count at time of ATI >500 cells/µl, CD4 nadir >200 cells/µl, weekly viral load measurements at least until viral rebound occurred.

Study procedures

The appropriate volume of 3BNC117 was calculated according to body weight, diluted in sterile normal saline to a total volume of 250 ml, and administered intravenously over 60 min. Study participants received 3BNC117 on days 0 and 21, or 0, 14, 28, and 42 and remained under monitoring at the Rockefeller University Hospital for 4 h after each

infusion. Participants returned for frequent follow up visits for safety assessments, which included physical examination, measurement of clinical laboratory parameters such as haematology, chemistries, urinalysis, and pregnancy tests (for women). Plasma HIV-1 RNA levels were monitored weekly during the ATI period and CD4 counts were measured every other week (Supplementary Table 4). Study investigators evaluated and graded adverse events according to the DAIDS AE Grading Table and determined causality. Blood samples were collected before and at multiple times after 3BNC117 infusions. Samples were processed within 4 h of collection, and serum and plasma samples were stored at -80 °C. PBMCs were isolated by density gradient centrifugation. The absolute number of peripheral blood mononuclear cells was determined by an automated cell counter (Vi-Cell XR; Beckman Coulter), and cells were cryopreserved in fetal bovine serum plus 10% DMSO.

ART re-initiation criteria

Antiretroviral therapy was discontinued 2 days after the first 3BNC117 infusion (day 2). ART was re-initiated when HIV-1 RNA levels were found to be ≥ 200 c.p.m. and/or CD4 T cell counts decreased to <350 cells/µl and the result was confirmed with a repeat measurement.

Plasma HIV-1 RNA Levels

HIV-1 RNA levels in plasma were measured at the time of screening (within 49 days before the first infusion), day 0 (before infusion), and weekly until week 12, then at weeks 14, 24 and 36. Participants that remained virologically suppressed to <20 c.p.m. off ART beyond week 12, returned for weekly measurements of plasma HIV-1 RNA levels. HIV-1 RNA levels were determined using the Roche COBAS AmpliPrep/COBAS TaqMan HIV-1 Assay, Version 2.0, which detects between 20 and 1×10^7 c.p.m. This assay was performed at LabCorp.

CD4⁺ and CD8⁺ T cells

CD4⁺ and CD8⁺ T-cell counts were determined at screening, on day 0 (before infusion), and weeks 2, 3, 4, 6, 8, 10, 12, 14, and 36 by a clinical flow cytometry assay, performed at LabCorp. Cells were analysed by flow cytometry. Leukocytes were determined as CD45⁺ cells. Percentage of cells positively stained for CD3, CD4, CD8 as well as the CD4/CD8 ratio were analysed with the BD Multiset software (BD Biosciences).

3BNC117 study drug

3BNC117 is a recombinant, fully human IgG1κ mAb recognizing the CD4 binding site on the HIV-1 envelope¹. The antibody was cloned from an HIV-1-infected viraemic controller in the International HIV Controller Study^{1,35}, expressed in Chinese hamster ovary cells (clone 5D5-5C10), and purified using standard methods. The 3BNC117 drug substance was produced at Celldex Therapeutics Fall River (MA) GMP facility, and the drug product was fill-finished at Gallus BioPharmaceuticals (NJ). The resulting purified 3BNC117 was supplied as a single use sterile 20 mg/ml solution for intravenous injection in 8.06 mM sodium phosphate, 1.47 mM potassium phosphate, 136.9 mM sodium chloride, 2.68 mM potassium chloride, and 0.01% polysorbate 80. 3BNC117 vials were shipped and stored at 4°C.

Measurement of 3BNC117 serum levels

Serum levels of 3BNC117 were determined by a validated sandwich ELISA at Celldex Theapeutics as described previously⁹. Plates (Sigma-Aldrich PN: CLS3590 96-well, High Bind, polystyrene) were coated with 4 µg/ml of an anti-idiotypic antibody specifically recognizing 3BNC117 (anti-ID 1F1 mAb), and incubated overnight at 2–8 °C. After washing, plates were blocked for 1 h with 5% BSA. Serum samples, QCs and standards were added (1:50 minimum dilution in 5% BSA) and incubated for 1 h at room temperature. 3BNC117 was detected using an HRP-conjugated mouse anti-human IgG kappa chain specific antibody (Abcam PN: ab79115) and the HRP substrate tetra-methylbenzidine. 3BNC117 concentrations were then interpolated from a standard curve of 3BNC117 using a four-parameter logistic curve-fitting algorithm. The reference standard and positive controls were created from the drug product lot of 3BNC117 used in the clinical study.

Pharmacokinetic analysis

Blood samples were collected immediately before and at the end of infusions as well as on the day after infusion, weekly during the ATI period and at weeks 14, 24 and 36. 3BNC117 serum levels were measured by ELISA (Celldex Therapeutics).

Neutralization assay

Serum samples, viral supernatants, and control antibodies were tested against HIV-1 envelope pseudoviruses as previously described^{36,37}.

Cell-associated HIV-1 DNA

Participant's CD4⁺ T-cells were isolated from 10 million cryopreserved PBMCs by negative magnetic selection (Miltenyi). Total DNA was extracted and quantitative PCR performed using *pol*- and CCR5-directed primers as previously described⁷.

Virus cultures

Autologous virus was retrieved from HIV-1 infected individuals as previously described³¹. Briefly, healthy donor PBMCs were obtained by leukapheresis from a single donor. Cells were cultured at a concentration of 5×10^6 /ml in Iscove's Modified Dulbecco's Medium (IMDM; Gibco) supplemented with 10% fetal bovine serum (FBS; HyClone, Thermo Scientific), 1% penicillin/streptomycin (Gibco), and 1 µg/ml phytohemagglutinin (PHA; Life Technologies) at 37 °C and 5% CO₂. After 2–3 days, 5×10^6 CD8⁺ depleted cells were transferred into IMDM supplemented with 10% FBS, 1% penicillin/streptomycin, 5 µg/ml polybrene (Sigma), and 100 U/ml of IL-2. Cells were then co-incubated with 4–8 × 10⁶ CD4⁺ T cells from the study participants and 10 million irradiated healthy donor PBMCs that had been cultured together for 24 h prior in IMDM supplemented with 10% FBS, 1% penicillin/streptomycin, 100 U/ml IL-2 and 1 µg/ml PHA at 37°C and 5% CO₂. Lymphoblasts were replenished weekly by adding 3 million healthy donor PHA stimulated CD8⁺ depleted lymphoblasts. Culture supernatants were quantified using the Alliance HIV-1

p24 Antigen ELISA kit (PerkinElmer) according to the manufacturer's instructions. TCID₅₀s were determined for all HIV-1 containing supernatants^{36,37} and then tested for sensitivity against 3BNC117 and other bNAbs in a TZM.bl neutralization assay. Blood samples and leukapheresis were collected under separate IRB-approved protocols and after volunteers provided informed consent.

Sequence analysis

HIV-1 RNA extraction and single genome amplification was performed as described previously³⁸. In detail, HIV-1 RNA was extracted from plasma samples using the Qiagen MinElute Virus Spin kit (Qiagen) followed by first strand cDNA synthesis using SuperScript III reverse transcriptase (Invitrogen Life Technologies) and the antisense primer env3out 5'-TTGCTACTTGTGATTGCTCCATGT-3'. gp160 env was amplified using envB5out 5'-TAGAGCCCTGGAAGCATCCAGGAAG-3' and envB3out 5'-TTGCTACTTGTGATTGCTCCATGT-3' in the first round and second round nested primers envB5in 5'-CACCTTAGGCATCTCCTATGGCAGGAAGAAG-3' and envB3in 5'-GTCTCGAGATACTGCTCCCACCC-3'. PCRs were performed using a High Fidelity Platinum Taq (Invitrogen) at 94 °C, 2 min; (94 °C, 15 s; 55 °C 30 s; 68 °C, 4 min) × 35; 68°C, 15 min. Second round PCR was performed with 1 µl of first PCR product as template and High Fidelity Platinum Taq at 94 °C, 2 min; (94 °C, 15 s; 55 °C 30 s; 68 °C, 4 min) × 35; 68 °C, 15 min. Sequence alignments, phylogenetic trees and mutation analysis of gp160 was performed by using Geneious Pro software, version 8.1.6 (Biomatters Ltd.)³⁹. Sequence analysis was performed using Antibody database by A. West³⁰. Logograms were generated using the Weblogo 3.0 tool^{40} .

Pseudovirus generation

Selected SGS from virus culture supernatants and plasma were used to generate pseudoviruses and tested for sensitivity to bNAbs in a TZM.bl assay⁴¹. To produce the pseudoviruses, plasmid DNA containing the cytomegalovirus (CMV) promoter was amplified by PCR using forward primer 5'-GTTGACATTGATTATTGACTAG and reverse primer 5'-CTTCCTGCCATAGGAGATGCCTAAAGCTCTGCTTATATAGAC-CTC. The CMV promoter amplicon was fused to individual *env* SGS amplicons by PCR using forward primer 5'-AGTAATCAATTACGGGGGTCATTAGTTCAT and reverse primer 5'- ACTTTTTGACCACTTGCCACCCAT. Fusion PCR was carried out using the Expand Long Template PCR System (Roche) in a 60µl reaction consisting of 1 ng purified CMV promoter amplicon, 0.125 µl unpurified *env* SGA amplicon, 200 nM forward and reverse primers, 200 µM dNTP mix, 1 × Buffer 1, and 1 µl DNA polymerase mix. PCR was run at 94 °C for 2 min; 25 cycles (94 °C for 12 s, 55 °C for 30 s, 68 °C for four minutes); and 72 °C for 10 min. Resulting amplicons were analysed by gel electrophoresis, purified without gel extraction, and co-transfected with pSG3*Δenv* into HEK293T cells to produce pseudoviruses as described previously⁴¹.

Statistical analyses

Adverse events were summarized by the number of participants who experienced the event, by severity grade according to the DAIDS AE Grading Table and by relationship to 3BNC117 as determined by the investigator. PK-parameters were estimated by performing a

non-compartmental analysis (NCA) using WinNonlin 6.3. Kaplan-Meier survival curves were used to compare time to rebound in trial participants to participants in previous ATI studies conducted by ACTG²⁹. To exclude the possibility that the observed delay in rebound is confounded by clinical factors, we compared the clinical variables between the control (ACTG trial participants) and treated group using a two-sided Fisher's Exact test for categorical variables (gender and CD4 Nadir) and an unpaired Wilcoxon test (two-sided) for continuous variables (age, years on ART and CD4 count before ATI initiation) (Supplementary Table 7). Additionally, we tested for each potential confounder whether the variable is predictive for the rebound time. Therefore, we built a univariate survival regression model for each potential confounder and compared those models to a null model using a likelihood ratio test (LRT), which determines how much better the more complex model explains the data than the less complex model. Confounders were considered significant if the model with the potential confounder had an LRT *P* value of 0.05 or less, which was the case for 'years on ART' as well as 'age' for the comparison between the controls and the combined treatment group (Supplementary Table 7). We did not perform a standard Cox regression, since the proportional hazards assumption was not fulfilled for some of the variables. Rebound time was modelled using a log-normal distribution, which resulted in the best model fit as measured by Akaike information criterion (AIC) among several different distributions (Extended Data Fig. 4b-d). To determine the effect of the treatment after adjusting for the discovered confounders, we performed a weighted log-rank test⁴². Therefore, for each sample inverse probability weights based on the discovered confounders were estimated, which were used to re-weigh the variables of the log-rank statistic. We performed a bootstrapped version of the weighted log-rank test, as recommended in ref. 42 owing to the small sample size. We estimated the class probabilities using a lasso logistic regression model trained with the Matlab function lassoglm with five lambda values in a threefold cross-validation. To improve stability, the optimal lambda for the lasso logistic regression was determined only once using the original labels and used in all bootstrap runs to train the models that estimate the class probabilities.

Additionally, we performed an LRT at significance level a = 0.05 based on a parametric survival regression model adjusted for the discovered confounders. In this analysis the treatment group still significantly predicted the delay in rebound (Supplementary Table 7). For the analyses, the R (version 3.2.1) packages survival (version 2.38-3) and fitdistrplus (version 1.0-6) were used and Matlab (version R2015b) for implementation of the weighted log-rank test.

Sequence and phylogenetic analysis

Nucleotide alignments were generated using ClustalW $(v.2.11)^{43}$ and manually adjusted using Geneious R8 $(v.8.1.6)^{39}$ and MacClade $(v.4.08a)^{44}$. Sites that could not be unambiguously aligned were removed for all phylogenetic analyses. Optimal evolutionary model classes were determined using jModelTest $(v.2.1.4)^{45}$. Maximum likelihood phylogenetic trees were generated using PhyML $(v.3)^{46}$ with joint estimation of evolutionary model parameter values and phylogenies. The tree comparing all participants was midpoint rooted and each within-subject tree was rooted on the basal branch as determined by the between-subject tree. Sequences with premature stop codons and frameshift mutations that

fell in the gp120 surface glycoprotein region were excluded from all deduced protein analyses.

Sequences generated from the supernatants of viral outgrowth assays represented viruses that were present in the latent reservoir. Per assay, 4–8 million CD4⁺ T cells were activated. In an HIV-infected person who is completely suppressed on antiretroviral therapy, it has been determined that 1×10^{-6} resting CD4 cells are latently infected with replication competent virus⁴⁷. Thus, one would expect to identify up to eight distinct viral isolates per individual culture. Single genome sequencing of the culture supernatants revealed sets of clonally related sequences, which appear as 'rakes' in a phylogenetic tree (Extended Data Figs 7 and 8). The most recent common ancestor of these rakes represents the reactivated virus that was present in the host (similar to the inference of infectious molecular clones as described in ref. 48). As shown in Extended Data Figs 7 and 8, sequences from culture reactions fall in 1–3 rakes within a given individual. We inferred each rake's most recent common ancestor (MRCA) by building a majority-rule consensus and treated it as a single virus from the participant's latent pool. These MRCAs were used to build the phylogenetic trees shown in Fig. 3.

Because mixed culture isolates replicated for 14 or more days, *in vitro* recombinants were observed. *In vitro* recombinants from culture reactions were identified and removed from the data set if they: (i) had two identifiable parental sequences within the same culture reaction; and (ii) exhibited three consecutive informative sites relative to one parent followed by three consecutive informative sites relative to another. We independently verified that a subset of these sequences showed evidence of recombination using the Recco tool (v.0.93)⁴⁹.

Assessment of rebound virus clonality

The Poisson Fitter v2 tool⁵⁰ is designed to test if a set of homogeneous sequences exhibits random diversification. If such a set of sequences exhibits a star-like phylogeny and a Poisson distribution of pairwise differences (Hamming distances), it can be inferred that a single virus gave rise to those sequences. Poisson Fitter v2 tests these and other parameters using maximum likelihood methods and performs a χ^2 goodness of fit test to obtain a *P* value. A non-significant *P* value signifies that the observed Hamming distances adhere to a Poisson distribution and it can be inferred that a single virus gave rise to rebound. Single genome derived *env* sequences from the plasma at the earliest time point post-rebound from each participant were tested using Poisson Fitter (Supplementary Table 8).

ELISPOT T-cell response analysis

Interferon gamma Elispot assays were performed as described⁵¹. Briefly, 96-well polyvinylidene plates (Millipore, Bedford, Mass.) were precoated with 0.5 g/ml of anti-IFN γ monoclonal antibody, 1-DIK (Mabtech, Stockholm, Sweden) and previously frozen PBMCs were plated at a concentration of 50,000 to 100,000 cells per well in a volume of 100 µl of R10 medium (RPMI 1640 (Sigma), 10% fetal calf serum (Sigma), 10 mM HEPES buffer (Sigma)) with antibiotics (2 mM L-glutamine, 50 U of penicillin-streptomycin/ml). Plates were incubated overnight at 37°C, 5% CO₂, and developed as described⁵¹. Cells were tested against a panel of 410 B-clade overlapping 18-mer peptides (OLPs) spanning the

entire HIV-1 genome (consensus sequence from 2001). These peptides were used in a matrix system of 11–12 peptides per pool to screen study participants for HIV-specific T cell responses. Confirmation of recognized individual peptides within a peptide pool was undertaken in an additional Elispot assay, as described⁵². Wells containing PBMCs and R10 medium alone were used as negative controls and were run in duplicate on each plate. Wells containing PBMCs and phytohemagglutinin (PHA) served as positive controls. The numbers of spots per well were counted using an automated Elispot plate reader (ImmunoSpot Reader System; Cellular Technology Limited, Shaker Heights, OH). Responses were regarded as positive if they had at least three times the mean number of spot forming cells (SFC) in the two negative control wells and had to be >50 SFC/10⁶ PBMCs (ref. 51,52).

Extended Data

a



^{*}Participant 705 received only 1 dose due to VL > 1,000 at day 0. Some participants experienced viral rebound prior to completion of all 4 scheduled infusions: 709 – received 3 doses; 711 - 2 doses; 713 - 3 doses.



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Extended Data Figure 1. Study participant selection and neutralization of pre-infusion cultures by 3BNC117

a, Flow diagram showing the selection of study participants. **b**, Bar diagrams showing IC_{50} values (µg ml⁻¹) in TZM-bl assays for 3BNC117 against bulk virus outgrowth culture supernatants from the indicated time point pre-infusion for each participant (Supplementary Table 3). For some participants both screen and day 0 cultures were obtained and showed less than threefold variation in IC_{50} values. The red dotted line indicates an IC_{50} of 2 µg ml⁻¹ which was used as a threshold for inclusion in the study.



Extended Data Figure 2. CD4⁺ and CD8⁺ T cells during study period in participants a–d, Absolute T cell counts (**a**, **c**) and percentage of CD4⁺ and CD8⁺ T cells among CD3⁺T cells (**b**, **d**) for group A and B, respectively (Supplementary Table 4). 3BNC117 infusions are indicated with red arrows. **e**, Comparison of absolute CD4⁺ T cell counts and percentage of CD4⁺ T cells among CD3⁺T cells at screen, day 0, rebound and after re-suppression.

Shown is the data from participants 701, 702, 703, 704, 707, 708, 709, 711 and 713 for whom re-suppression CD4 counts were available (Supplementary Table 4). The last available time point was used as re-suppression time point. Red lines indicate the mean value and error bars indicate standard deviation. *P* values were obtained using a paired *t*-test comparing the indicated time points. **f**, Plasma viral loads and CD4 counts in all study participants. 3BNC117 infusions are indicated with red arrows. The left *y*-axis shows plasma viral loads in RNA copies per ml (black curves), and right *y*-axis shows absolute CD4 counts in cells per μ l (red curves). Grey areas indicate ART therapy.



Extended Data Figure 3. HIV-specific T-cell responses

Total breadth (open squares) and magnitude (bars) of T-cell responses against HIV-1 overlapping peptides (OLPs) at the designated time points following administration of 3BNC117 (yellow arrows indicate infusions of 3BNC117 at 30 mg kg⁻¹). For all study participants, antiretroviral therapy was discontinued on day 2 after the first 3BNC117

administration. Blue arrows indicate the time of viral rebound. For study participants 710, 712 and 715 rebound occurred at week 19, 16 and 11, respectively. Baseline samples for study participant 710 and week 12 samples for study participant 714 were not available for ELISpot analysis. Overall, breadth, magnitude and protein specificity were heterogeneous among the study participants.



Extended Data Figure 4. Viral rebound in ACTG control subjects and trial participants a, Kaplan–Meier plot summarizing viral rebound in 52 ACTG trial participants who underwent ATI without antibody treatment (black, Supplementary Table 6) and trial participants (Fig. 2a, b, Supplementary Table 4). Six group A participants are shown in red, seven Group B participants in blue and the combination in green as indicated. The *y*-axis indicates the percentage of participants with viral levels below 200 RNA copies per ml, *x*axis indicates weeks after ATI initiation. The survival curves of all considered partitions of

the trial participants (group A, group B and group A + B) differed significantly at significance level a = 0.05 from the survival curve of the ACTG trial participants. For the comparison of group A (group A + B) with the ACTG trial participants, we performed a weighted log-rank test adjusting for the clinical variables 'years on ART' and 'age' to correct for possible confounding factors (Supplementary Table 7 P < 0.00001). We identified those potential confounders by univariate parametric survival regression using a likelihood ratio test (Statistical Methods). Since we did not discover any confounders with the same analysis among all available clinical variables for the comparison between group B participants and the ACTG trial participants, we performed a standard log-rank test in that setting (P < 0.0001). **b–d**, In order to perform a survival regression, the distribution of the rebound times has to be determined. Therefore, we compared the empirical cumulative distribution function (CDF) of the rebound times (black, solid line) with the CDF of the rebound times to a fitted distribution (Weibull, exponential, normal, logistic, log-normal, and gamma) for each comparison group (combined trial participants, group A or group B with ACTG control patients). Since the Akaike information criterion (AIC) and the Bayesian information criterion (BIC) were smallest for the log-normal distribution (green), we have chosen to model the rebound times with the log-normal distribution. e, Dot plot indicating the relationship between cell associated HIV DNA in pre-infusion PBMCs (y-axis) and the week of rebound (x-axis). Group A and group B participants are coloured red and blue respectively. The P value was derived from calculating the Pearson correlation coefficient.



Extended Data Figure 5. *In vitro* neutralization of pre-infusion and rebound virus outgrowth cultures by 3BNC117 or 10-1074

a, **b**, TZM-bl assay neutralization by 3BNC117 (**a**) and 10-1074 (**b**) are shown for individual virus outgrowth cultures derived from pre-infusion (black lines/symbols) or rebound (red lines/symbols) time points for each participant. In some cases, multiple independent cultures were grown from a single time point and assayed for neutralization (Supplementary Table 3). 'Screen' refers to cultures of PBMC samples taken weeks before infusion during screening, while 'Day 0' refers to culture of PBMCs collected immediately before the first 3BNC117 infusion. Rebound culture time points are denoted by the week (W) at which the samples were collected. Symbols reflect the means of two technical replicates; error bars denote standard deviation.



Extended Data Figure 6. Phylogenetic tree of *env* nucleotide sequences from trial participants A maximum likelihood phylogenetic tree was constructed from single-genome-derived viral *env* sequences from outgrowth culture supernatants as well as plasma from participants 701 (olive), 702 (black), 703 (pink), 704 (yellow), 707 (light blue), 708 (green), 709 (dark blue) and 711 (brown). Hypervariable (as defined in http://www.hiv.lanl.gov/content/sequence/ VAR_REG_CHAR/) and other poorly aligned regions were excluded from the analysis. The tree was constructed using PhyML with a GTR+I+G substitution model and midpoint rooted. Asterisks indicate 100% bootstrap support (only values for major nodes are shown). The scale bar indicates 0.01 substitutions per site.



Extended Data Figure 7. Rebound virus clonality and neutralization sensitivity to 3BNC117 Maximum likelihood phylogenetic trees of plasma and culture-derived *env* sequences are shown for participants 701, 702, 703, 704. Sequences obtained at screening, on Day 0, and consecutive rebound time points (plasma and cultures) are colour coded as indicated. The trees were rooted based on the branch insertion identified in the between-subject tree (Extended Data Fig. 6). Bootstrap values $\ge 90\%$ are shown. Names of *env* sequences used to generate pseudoviruses for 3BNC117 neutralization analysis are indicated along with the respective IC₈₀ titres in µg ml⁻¹. Representative rebound viruses selected in Fig. 4b are marked with red stars (Fig. 4b, Supplementary Table 9). Zero branch length viruses in multi-rebounders 702 and 703 are marked with black stars.





Extended Data Figure 8. Rebound virus clonality and neutralization sensitivity to 3BNC117 Maximum likelihood phylogenetic trees of plasma- and culture-derived *env* sequences are shown for participants 707, 708, 709 and 711. Sequences obtained at screening, on day 0, and consecutive rebound time points (plasma and cultures) are colour coded as indicated. The trees were rooted based on the branch insertion identified in the between-subject tree (Extended Data Fig. 6). Bootstrap values 90% are shown. Names of *env* sequences used to generate pseudoviruses for 3BNC117 neutralization analysis are indicated along with the respective IC₈₀titres in µg ml⁻¹. Representative rebound viruses selected in Fig. 4b are marked with red stars (Fig. 4b, Supplementary Table 9). Zero branch length viruses in multi-rebounder 709 are marked with black stars.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Figure 1. 3BNC117 neutralization coverage, trial design and pharmacokinetics of 3BNC117 in HIV-1-infected individuals during ATI

a, **b**, Sensitivity of virus outgrowth cultures from 63 ART suppressed individuals to 3BNC117 and VRC01 (Supplementary Table 1). The *y*-axis shows the fraction of viral outgrowth culture supernatants neutralized by a given antibody concentration (*x*-axis) in Tzm-bl assays. Red line indicates cut-off IC₅₀ (2 µg ml⁻¹) for participation in the trial. **c**, **d**, Diagrammatic representation of study groups A and B respectively. 3BNC117 infusions indicated by the red arrows, and sampling for PK and virologic studies indicated below. Numbers indicate study weeks. **e**, **f**, 3BNC117 levels as determined by ELISA for group A (*n* = 6, left panel, red), group B (*n* = 7, right panel, red (*n* = 4), black (*n* = 2) and purple (*n* = 1)), HIV-1 negative (*n* = 3, blue) and viraemic individuals (*n* = 6, green)⁹. Curves indicate mean 3BNC117 levels, error bars the standard deviation. Arrows indicate 3BNC117 infusions.



Figure 2. Delay in viral rebound in the presence of 3BNC117

a, **b**, Plasma viral loads and 3BNC117 levels in group A and group B participants respectively. 3BNC117 infusions are indicated with red arrows. The left y-axis shows plasma viral loads in RNA copies per ml (black curves), and right y-axis shows antibody levels measured by ELISA (red curves). Average rebound time point (2.6 weeks, Supplementary Table 6) in 52 ACTG trial participants who underwent ATI without antibody treatment²⁹ is shown with dotted lines. Grey areas indicate ART therapy. c, Kaplan-Meier plot summarizing viral rebound in 52 ACTG trial participants who underwent ATI without antibody treatment (black, Supplementary Table 6), and the combination of all 13 participants (red) who underwent ATI with 3BNC117 infusions. The y-axis indicates the percentage of participants with viral levels below 200 RNA copies per ml, x-axis indicates weeks after ATI initiation. The P value is based on a bootstrap version of the weighted logrank test adjusting for the potential confounders 'years on ART', and 'age' (Supplementary Table 7, Methods Statistical Analyses). d, Dot plot indicating the relationship between 3BNC117 sensitivity of pre-infusion outgrowth cultures at screening (v-axis, IC₈₀ in μ g ml^{-1}) and the week of rebound (x-axis). Group A (n = 6) and group B (n = 7) participants are coloured red and blue respectively. The P value was derived from calculating the Pearson correlation coefficients. e, Dot plot indicating the relationship between 3BNC117 sensitivity of rebound outgrowth cultures (y-axis, IC_{80} in µg ml⁻¹) and the 3BNC117 serum concentration at rebound (x-axis, in $\mu g \text{ ml}^{-1}$). 704, 708, 709 and 713 did not reach IC₈₀ at the concentrations tested and were assigned a value of 22 μ g ml⁻¹. Group A (n = 6) and

group B (n = 7) participants are coloured red and blue, respectively. The *P* value was derived from calculating the Pearson correlation coefficients.

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Figure 3. Viral rebound during ATI and 3BNC117 treatment

a, **b**, Graph of 3BNC117 (**a**) or 10-1074 (**b**) IC_{80} titres against baseline and rebound outgrowth cultures. Blue and green bars represent average IC_{80} titres against screen and day 0 outgrowth cultures; red and purple bars represent IC_{80} titres against rebound outgrowth cultures from the indicated time points. Asterisks indicate cultures failing to reach an IC_{80} up to 20 µg ml⁻¹. **c**, **d**, Difference between rebound and pre-infusion culture IC_{80} titres (from **a**, **b**) for 3BNC117 (**c**) or 10-1074 (**d**). For cultures failing to reach an IC_{80} up to 20 µg ml⁻¹, a value of 20 µg ml⁻¹ was assigned, and such cultures are marked with an asterisk. **e**, **f**, Clonality of the rebound virus. Maximum likelihood phylogenetic trees comparing pre-ATI single genome derived *env* sequences (blue and orange) to rebound plasma *env* sequences (green and pink) are shown for participants whose rebound comprised single (**e**) versus multiple (**f**) viruses (Supplementary Table 8). Pre-ATI culture sequences were inferred as described in the Methods section 'Statistical analyses'.



Figure 4. 3BNC117 resistance in rebound viruses

a, Logogram shows *env* gp120 regions (amino acid positions; 270–285 and 455–467, according to HXBc2 numbering) indicating sequence changes from pre-infusion culture(s) (first row) to rebound sequences derived from plasma SGS at the indicated time points. The frequency of each amino acid is indicated by its height. Red residues represent mutations predicted to affect neutralization³⁰. **b**, 3BNC117 neutralization sensitivity of pseudoviruses derived from pre-infusion or rebound SGS. Black lines represent pre-infusion virus *envs*; red lines represent the major *env* at rebound for each participant (Extended Data Figs 7 and 8, Supplementary Tables 8 and 9 and Methods); grey lines represent minor rebound (Extended Data Figs 7 and 8, Supplementary Table 9). Symbols reflect the means of two technical replicates; error bars denote standard deviation.

Clade HIV-RNA level abs. CD4⁺T cell (copies/ml) cells/mm³)

Current ART regimen

Years since HIV Diagnosis

Study ID 3BNC117 dose Age

674

3,21043,650 5,3404,090 100

в В

ART naïve Off ART ART naïve Off ART

1

35 39 42 20 48 20

1 mg/kg 1 mg/kg 1 mg/kg

2A1 2A3 2A4 2B1

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3 mg/kg 3 mg/kg

520 607 264*

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DRV/r/TDF/FTC**

20

ART naïve

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3 mg/kg 10 mg/kg 10 mg/kg

2B3 2C2

2B2

706

777 728 805

30 820

QZ

ATV/r/3TC/ZDV**

 $\frac{12}{2}$ 23

51

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Off ART

54

2C4 2C5

38,190

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2D1 2C1

								Es)	30 mg/kg	9	0	ю
								(No. of A	10 mg/kg	0	0	1
								1-infected	3 mg/kg	0	2	0
								-VIH	1 mg/kg	1	1	-
								Es)	30 mg/kg	1	0	1
-								(No. of Al	10 mg/kg	0	2	0
1129	618	847	513	590	603	532		ninfected (3 mg/kg	1	-	0
0		0	0	0	0			IJ	1 mg/kg	1	-	0
47,65	640	15,78	6,99(22,03	32,22	3,61(No. Severe	0	0	0
в	ND	в	В	BF	ND	ND			No. Moderate	2	2	1
ART	naïve	naïve	naïve	naïve	naïve	naïve			No. Mild	8	5	5
Off ,	ART	ART	ART	ART	ART	ART			No. possibly related	3	5	ю
17	0.5	2	1.5	1.5	1	1			% of reported AEs	16.9	11.9	10.2
51	33	21	46	23	38	30			No. AEs	10	٢	9
30 mg/kg			erse Events	iea and/or cough	Malaise	Headache						
2C1	2D3	2E1	2E2	2E3	2E4	2E5	q		мр¥	Rhinorrh		Ŧ

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2

4

Sore throat

Myalgia/arthralgia (localized)

Diarrhea

3

8.5 6.8 6.8

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245*

9,260

В

ART naïve ART naïve

4

50 33

10 mg/kg 30 mg/kg

980

53,470 47,650

В в

2							Un	infected (No. of AE	(s)	HIV-	-1-infected	d (No. of /	vEs)
Adverse Events	No. AEs	% of reported AEs	No. possibly related	No. Mild	No. Moderate	No. Severe	1 mg/kg	3 mg/kg	10 mg/kg	30 mg/kg	1 mg/kg	3 mg/kg	10 mg/kg	30 mg/kg
Tenderness		5.1	-	ŝ	0	0	0	0	0	-	-	0	-	0
Increased Lacrimation	7	3.4	2	7	0	0	0	0	0	1	0	0	0	1
Myalgia	2	3.4	1	2	0	0	0	0	0	0	0	0	-	1
Chills	2	3.4	0	-	1	0	0	1	0	0	-	0	0	0
Conjunctival erythema	2	3.4	2	2	0	0	0	0		0	-	0	0	0
Fevershiness	2	3.4	0	-	1	0	0	0	0	0	-	-	0	0
Nausea	2	3.4	1	2	0	0	0	0	0	1	1	0	0	0
Pruritus	2	3.4	2	2	0	0	0	0	0	0	0	0	0	2
Blurry vision	1	1.7	1	-	0	0	0	0	0	0	0	0	-	0
Decreased appetite	1	1.7	0	-	0	0	0	0	0	0	1	0	0	0
Erythema	1	1.7	1	-	0	0	0	0	0	1	0	0	0	0
Paresthesia upper extremity	1	1.7	0	-	0	0	0	0	0	0	1	0	0	0
Shingles	1	1.7	0	0	1	0	0	0	0	0	0	0	0	1
Vomiting	1	1.7	1	1	0	0	0	0	0	0	1	0	0	0

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Table 2

а												
	2A1	HIV	-1 RNA	Level	2A3	HIV.	-1 RNA I	Level	2A4	-VIH	-1 RNA I	level
	Timepoint	c/ml	\log_{10}	$\Delta \log_{10}$	Timepoint	c/ml	\log_{10}	$\Delta \log_{10}$	Timepoint	c/ml	\log_{10}	$\Delta \log_{10}$
	Screen	1,340	3.13		Screen	41,670	4.62	-	Screen	5,350	3.73	
	Pre	1,100	3.04	1	Pre	48,100	4.68	-	Pre	6,490	3.81	
	Day 0	3,210	3.51	0.00	Day 0	43,560	4.64	0.00	Day 0	5,340	3.73	0.00
	Day 1	10,810	4.03	0.52	Day 1	50,180	4.70	0.06	Day 1	10,880	4.04	0.31
	Day 4	4,970	3.70	0.19	Day 4	24,050	4.38	-0.26	Day 4	8,430	3.93	0.20
1 mg/kg	Day 7	3,190	3.50	-0.01	Day 7	34,850	4.54	-0.10	Day 7	4,870	3.69	-0.04
	Day 14	2,600	3.41	-0.10	Day 14	31,770	4.50	-0.14	Day 14	11,000	4.04	0.31
	Day 21	3,820	3.58	0.07	Day 21	35,840	4.55	-0.09	Day 21	7,470	3.87	0.14
	Day 28	5,070	3.71	0.20	Day 28	38,500	4.59	-0.05	Day 28	7,880	3.90	0.17
	Day 42	3,570	3.55	0.04	Day 42	59,780	4.78	0.14	Day 42	12,150	4.08	0.35
	Day 56	6,370	3.80	0.29	Day 56	63,600	4.80	0.16	Day 56	14,020	4.15	0.42
	2B1	·ΛΙΗ	-1 RNA I	level	2B2	-VIH	-1 RNA I	level	2B3	-VIH	-1 RNA L	evel
	Timepoint	c/ml	\log_{10}	$\Delta \log_{10}$	Timepoint	c/ml	\log_{10}	$\Delta \log_{10}$	Timepoint	c/ml	\log_{10}	$\Delta \log_{10}$
	Screen	6,420	3.81	1	Screen	80*	1.90	-	Screen	53,660	4.73	
	Pre	4,950	3.69	T	Pre	30	1.48	-	Pre	28,810	4.46	
	Day 0	4,090	3.61	0.00	Day 0	100	2.00	0.00	Day 0	38,190	4.58	0.00
	Day 1	6,470	3.81	0.20	Day 1	140	2.15	0.15	Day 1	31,950	4.50	-0.08
	Day 4	2,690	3.43	-0.18	Day 4	190	2.28	0.28	Day 4	11,540	4.06	-0.52
3 mg/kg	Day 7	1,610	3.21	-0.40	Day 7	20	1.30	-0.70	Day 7	20,500	4.31	-0.27
	Day 14	4,880	3.69	0.08	Day 14	130	2.11	0.11	Day 14	35,830	4.55	-0.03
	Day 21	4,160	3.62	0.01	Day 21	90	1.95	-0.05	Day 21	41,570	4.62	0.04
	Day 28	3,800	3.58	-0.03	Day 28	70	1.85	-0.15	Day 28	30,810	4.49	-0.09
	Day 42	4,970	3.70	0.09	Day 42	90	1.95	-0.05	Day 42	29,020	4.46	-0.12
	Day 56	3,550	3.55	-0.06	Day 56	30	1.48	-0.52	Day 56	27,700	4.44	-0.14
	2C2	HIV	I RNA I	level	2C4	HIV.	-1 RNA I	level	2C5	-VIH	-1 RNA L	evel

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	2A1	HIV.	I RNA I	Level	2A3	-VIH	I RNA	Level	2A4	-VIH	I RNA I	evel
	Timepoint	c/ml	\log_{10}	$\Delta \log_{10}$	Timepoint	c/ml	\log_{10}	$\Delta \log_{10}$	Timepoint	c/ml	\log_{10}	$\Delta \log_{10}$
	Timepoint	c/ml	\log_{10}	$\Delta \log_{10}$	Timepoint	c/ml	\log_{10}	$\Delta \log_{10}$	Timepoint	c/ml	\log_{10}	$\Delta \log_{10}$
	Screen	20	1.30	-	Screen	2,510	3.41	-	Screen	19,970	4.30	-
	Pre	30	1.48	-	Pre	1,100	3.04		Pre	10,860	4.04	-
	Day 0	30	1.48	0.00	Day 0	820	2.91	0.00	Day 0	9,260	3.97	0.00
	Day 1	09	1.78	0.30	Day 1	069	2.84	-0.07	Day 1	5,300	3.72	-0.25
	Day 4	50	1.70	0.22	Day 4	980	2.99	0.08	Day 4	2,340	3.37	-0.60
10 mg/kg	Day 7	6	0.96	-0.52	Day 7	066	3.00	0.09	Day 7	410	2.61	-1.36
	Day 14	9	0.79	-0.69	Day 14	700	2.85	-0.06	Day 14	1,070	3.03	-0.94
	Day 21	20	1.30	-0.18	Day 21	1,420	3.15	0.24	Day 21	8,900	3.95	-0.02
	Day 28	2	0.23	-1.25	Day 28	630	2.80	-0.11	Day 28	8,550	3.93	-0.04
	Day 42	3	0.45	-1.03	Day 42	980	2.99	0.08	Day 42	12,410	4.09	0.12
	Day 56	21	1.32	-0.16	Day 56	940	2.97	0.06	Day 56	12,840	4.11	0.14
	2D1	-VIH	I RNA I	level	2C1	-VIH	I RNA I	Level	2D3	-VIH	-1 RNA I	level
	Timepoint	c/ml	\log_{10}	$\Delta \log_{10}$	Timepoint	c/ml	\log_{10}	$\Delta \log_{10}$	Timepoint	c/ml	\log_{10}	$\Delta \log_{10}$
	Screen	5,730	3.76		Screen	31,870	4.50		Screen	3,620	3.56	
	Pre	34,840	4.54	-	Pre	31,870	4.50	-	Pre	3,280	3.52	-
	Day 0	53,470	4.73	0.00	Day 0	47,650	4.68	0.00	Day 0	640	2.81	0.00
	Day 1	84,450	4.93	0.20	Day 1	46,040	4.66	-0.02	Day 1	450	2.65	-0.16
	Day 4	36,140	4.56	-0.17	Day 4	7,790	3.89	-0.79	Day 4	210	2.32	-0.49
30 mg/kg	Day 7	5,980	3.78	-0.95	Day 7	7,470	3.87	-0.81	Day 7	80	1.90	-0.91
	Day 14	4,830	3.68	-1.05	Day 14	19,360	4.29	-0.39	Day 14	50	1.70	-1.11
	Day 21	15,180	4.18	-0.55	Day 21	30,380	4.48	-0.20	Day 21	3	0.52	-1.77
	Day 28	10,960	4.04	-0.69	Day 28	25,610	4.41	-0.27	Day 28	40	1.60	-1.21
	Day 42	7,650	3.88	-0.85	Day 42	22,830	4.36	-0.32	Day 42	50	1.70	-1.11
	Day 56	9,820	3.99	-0.74	Day 56	32,310	4.51	-0.17	Day 56	11	1.04	-1.77
	2E1	-VIH	I RNA I	Level	2E2	-VIH	I RNA I	Level	2E3	-VIH	-1 RNA I	evel
	Timepoint	c/ml	log ₁₀	$\Delta \log_{10}$	Timepoint	c/ml	\log_{10}	$\Delta \log_{10}$	Timepoint	c/ml	\log_{10}	$\Delta \log_{10}$

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	2A1	НIV	-1 RNA	Level	2A3	HIV	-1 RNA	Level	2A4	-VIH	I RNA I	level
	Timepoint	c/ml	\log_{10}	Δlog_{10}	Timepoint	c/ml	\log_{10}	$\Delta \log_{10}$	Timepoint	c/ml	\log_{10}	$\Delta \log_{10}$
	Screen	8,742	3.94	-	Screen	3,394	3.53	-	Screen	23,168	4.36	
	Pre	12,031	4.08	-	Pre	1,802	3.26		Pre	30,570	4.49	
	Day 0	15,780	4.20	0.00	Day 0	6,990	3.84	0.00	Day 0	22,030	4.34	0.00
	Day 1	14,790	4.17	-0.03	Day 1	6,450	3.81	-0.03	Day 1	38,620	4.59	0.25
	Day 4	3,560	3.55	-0.65	Day 4	2,340	3.37	-0.47	Day 4	10,540	4.02	-0.32
30 mg/kg	Day 7	404	2.61	-1.59	Day 7	1,663	3.22	-0.62	Day 7	1,308	3.12	-1.22
	Day 14	468	2.67	-1.53	Day 14	253	2.40	-1.44	Day 14	3,901	3.59	-0.75
	Day 21	8,557	3.93	-0.27	Day 21	917	2.96	-0.88	Day 21	23,717	4.38	0.04
	Day 28	8,159	3.91	-0.29	Day 28	4,273	3.63	-0.21	Day 28	33,370	4.52	0.18
	Day 42	6,671	3.82	-0.38	Day 42	15,721	4.20	0.36	Day 42	22,699	4.36	0.01
	Day 56	13,486	4.13	-0.07	Day 56	3,465	3.54	-0.30	Day 56	27,998	4.45	0.10
	2E4	VIH	-1 RNA	Level	2E5	VIH	'-1 RNA	Level				
	Timepoint	c/ml	\log_{10}	$\Delta \log_{10}$	Timepoint	c/ml	\log_{10}	$\Delta \log_{10}$				
	Screen	45,311	4.66	1	Screen	4,720	3.67	1	_			
	Pre	66,889	4.83	-	Pre	4,244	3.63	-				
	Day 0	32220	4.51	0.00	Day 0	3610	3.56	0.00				
	Day 1	44980	4.65	0.14	Day 1	5300	3.72	0.16				
	Day 4	19,290	4.29	-0.22	Day 4	1,000	3.00	-0.56				
30 mg/kg	Day 7	3,642	3.56	-0.95	Day 7	181	2.26	-1.30				
	Day 14	683	2.99	-1.52	Day 14	LT	1.89	-1.67				
	Day 21	5,726	3.76	-0.75	Day 21	11	1.04	-2.52				
	Day 28	18,005	4.26	-0.25	Day 28	148	2.17	-1.39				
	Day 42	40,079	4.60	0.09	Day 42	1,064	3.03	-0.53				
	Day 56	22,100	4.34	-0.16	Day 56	589	2.77	-0.79				
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q		-	ľ		-							
	Contrast	<u> </u>	ose	Average	SE p.	value						

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0.607

0.258

-0.133

1mg/kg

Screen - Day 0

1 mg/kg

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	Contrast	Dose	Average	SE	p.value
	Day -7 - Day 0	1mg/kg	-0.112	0.200	0.573
	Day 1 - Day 0	1mg/kg	0.299	0.200	0.134
	Day 4 - Day 0	1mg/kg	0.043	0.258	0.866
	Day 7 - Day 0	1mg/kg	-0.047	0.290	0.873
	Day 14 - Day 0	1mg/kg	0.028	0.310	0.927
	Day 21 - Day 0	1mg/kg	0.046	0.323	0.888
	Day 28 - Day 0	1mg/kg	0.105	0.331	0.752
	Day 42 - Day 0	1mg/kg	0.180	0.337	0.592
	Day 56 - Day 0	1mg/kg	0.294	0.340	0.388
	Contrast	Dose	Average	SE	p.value
	Screen - Day 0	3mg/kg	0.172	0.316	0.587
	Day -7 - Day 0	3mg/kg	-0.020	0.244	0.936
	Day 1 - Day 0	3mg/kg	0.061	0.244	0.803
	Day 4 - Day 0	3mg/kg	-0.351	0.316	0.267
	Day 7 - Day 0	3mg/kg	-0.338	0.356	0.343
o mg/kg	Day 14 - Day 0	3mg/kg	0.024	0.380	0.949
	Day 21 - Day 0	3mg/kg	0.022	0.396	0.955
	Day 28 - Day 0	3mg/kg	-0.063	0.406	0.877
	Day 42 - Day 0	3mg/kg	-0.017	0.412	0.966
	Day 56 - Day 0	3mg/kg	-0.100	0.416	0.809
	Contrast	Dose	Average	SE	p.value
	Screen - Day 0	10mg/kg	0.415	0.316	0.189
	Day -7 - Day 0	10mg/kg	0.098	0.244	0.687
	Day 1 - Day 0	10mg/kg	-0.159	0.244	0.516
2	Day 4 - Day 0	10mg/kg	-0.260	0.316	0.410
10 mg/kg	Day 7 - Day 0	10mg/kg	-0.636	0.356	0.074
	Day 14 - Day 0	10mg/kg	-0.503	0.380	0.186
	Day 21 - Day 0	10mg/kg	0.111	0.396	0.780
	Dav 28 - Dav 0	10mo/kσ	-0.075	0.406	0.854

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Contrast	Dose	Average	SE	p.value
Day 42 - Day 0	10mg/kg	0.102	0.412	0.804
Day 56 - Day 0	10mg/kg	0.101	0.416	0.809
Contrast	\mathbf{D} ose	Average	SE	p.value
Screen - Day 0	30mg/kg	-0.084	0.158	0.593
Day -7 - Day 0	30mg/kg	0.022	0.122	0.860
Day 1 - Day 0	30mg/kg	0.065	0.122	0.593
Day 4 - Day 0	30mg/kg	-0.458	0.158	0.004
Day 7 - Day 0	30mg/kg	-1.043	0.178	< 0.001
Day 14 - Day 0	30mg/kg	-1.181	0.190	< 0.001
Day 21 - Day 0	30mg/kg	-0.866	0.198	< 0.001
Day 28 - Day 0	30mg/kg	-0.515	0.203	0.011
Day 42 - Day 0	30mg/kg	-0.339	0.206	0.099
Day 56 - Day 0	30mg/kg	-0.371	0.213	0.081

30 mg/kg

		Autologous	s virus isolates			H	V-1 envelopes cloned	from plasma	
Dose	Ð	Day post infusion	3BNC117 IC ₅ 0 (µg/ml)	3BNC117 IC ₅₀	Clone	Cloning procedure	Vector backbone	3BNC117 (IC ₅₀ ; µg/ml)	Average (geo. mean)
		Day 0	Ð	£					
	2A1	Day 28	0.00	QN			CIN .		
-		Day 0	0.11	, , ,			Ę		
1 mg/kg	CA2	Day 28	3.78	crec			UN		
		Day 0	0.07	1 C T			Ę		
	244	Day 28	0.94	c.tl			<u>UN</u>		
		Day 0	0.77				Ę		
	197	Day 28	>20	6:07			<u>UN</u>		
- <u>1</u> c	cac	Day 0	>20	L.			ι,		
3 mg/kg	782	Day 28	Q	AN			<u>UN</u>		
	çaç	Day 0	0.20				ģ		
	C87	Day 28	0.30	c.			UN		
	55	Day 0	0.49				ģ		
	777	Day 56	0.03	1.0			UN		
	555	Day 0	>20	No aboreo			ĊŅ		
10 mg/kg	+	Day 28	>20				<u>UN</u>		
					2C5_D0_12	gp120	IIIV2q	0.015	
	2C5	Day 0	0.09	167.0	2C5_D0_21 2C5_D0_27	gp120 gp120	IIIV2q	0.017 0.017	0.02
	_					-			

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Table 3

		Autologou	s virus isolates			HI	V-1 envelopes cloned	from plasma	
Dose	E I	Day post infusion	3BNC117 IC ₅ 0 (µg/ml)	3BNC117 IC₅₀	Clone	Cloning procedure	Vector backbone	3BNC117 (IC ₅₀ ; μg/ml)	Average (geo. mean)
					2C5_W4_59	gp120	IIIASq	11.543	
					2C5_W4_22	gp120	pSVIII	6.737	
		Day 28	15.36		2C5_W4_27	gp120	pSVIII	7.514	7.09
					2C5_W4_28	gp120	pSVIII	3.495	
					2C5_W4_34	gp120	pSVIII	8.758	
					2C1_D0_12	gp120	IIIASq	0.209	
		Day -7	0.54		2C1_D0_22	gp120	IIIV2q	0.158	0.06
	55			0	2C1_D0_32	gp120	IIIAg	0.006	
	701			Q'1	2C1_W4_12	gp120	IIIASq	0.043	
		Day 28	1.78		2C1_W4_18	gp120	pSVIII	0.225	0.14
					2C1_W4_31	gp120	pSVIII	0.262	
					2D1_D0_D5	gp160	pcDNA3.1	0.165	
		Day 0	0.68		2D1_D0_B3.1	gp160	pcDNA3.1	0.128	0.15
					2D1_D0_B10	gp160	pcDNA3.1	0.172	
	2D1			1.3	2D1_W4_37	gp120	IIIV2q	0.578	
30 mg/kg		90 YOU	000		2D1_W4_40	gp120	pSVIII	0.501	0.57
		Day 20	06.0		2D1_W4_69	gp120	IIIV2q	0.465	70.0
		_			2D1_W4_71	gp120	pSVIII	0.523	
	3D2	Day 0	0.13	L C					
	C17	Day 28	0.35	7.7					
					2E1_D0_12	gp160	pcDNA3.1	0.103	
		Screen	0.40		2E1_D0_20	gp160	pcDNA3.1	0.115	0.09
	2E1	_		ND	2E1_D0_34	gp160	pcDNA3.1	0.068	
					2E1_W4_23	gp160	pcDNA3.1	0.041	
		Day 28	ND		2E1_W4_E1	gp160	pcDNA3.1	0.590	0.23

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Dose

Screen 0.18 6.1 Day 28 1.10 6.1	2E1_W4_F6 2E1_W4_F6 2E2_D0_A10 2E2_D0_C3 2E2_D0_E9 2E2_W4_B9 2E2_W4_C11 2E2_W4_C11	Cloning procedure gp160 gp160 gp160 gp160 gp160 gp160	Vector backbone pcDNA3.1 pcDNA3.1 pcDNA3.1 pcDNA3.1 pcDNA3.1 pcDNA3.1 pcDNA3.1 pcDNA3.1 pcDNA3.1 pcDNA3.1	3BNC117 (IC₅₀; µg/ml) 0.496 0.017 0.018 0.018 0.017 0.020 0.020	Average (geo. me:
Day post infusion 3BNC117 IC ₅ 0 (µg/ml) 3BNC117 IC ₅ 0 C 2E1_ 2E1_ 2E2_ 2E2_ Screen 0.18 2E2_ 2E2_ Day 28 2.23 12.3 2E2_ Day 28 2.223 222_ 2E2_					
Day post infusion JBINCHT/LegU (Hg/ml) JBINCHT/Leg0 C 2E1_ 2E1_ 2E1_ 2E2_ Screen 0.18 2E2_ 2E2_ Day 28 2.23 12.3 2E2_ Day 28 2.23 2E2_ 2E2_	0110				
Bit <th>CIORE</th> <th>Cloning procedure</th> <th>Vector backbone</th> <th>3BNC117 (IC₅₀; μg/ml)</th> <th>Average (geo. me</th>	CIORE	Cloning procedure	Vector backbone	3BNC117 (IC ₅₀ ; μg/ml)	Average (geo. me
Screen 0.18 2E2_ Screen 0.18 2E2_ Day 28 2.23 12.3 Day 28 2.23 2E2_	2E1_W4_F6	gp160	pcDNA3.1	0.496	
Screen 0.18 2E22E2 Day 28 2.23 12.3 2E22E2	2E2 D0 A10	gp160	pcDNA3.1	0.017	
Day 28 2.23 12.3 2E22E2 Day 28 2.23 2E22E2 2E22E2	2E2_D0_C3	gp160	pcDNA3.1	0.010	0.01
Day 28 2.23 2E2_ 282_ 222_ 222_	2E2_D0_E9	gp160	pcDNA3.1	0.018	
Day 28 2.23 2.23 2.22 2.22	2E2_W4_B9	gp160	pcDNA3.1	0.017	
262_	2E2_W4_C11	gp160	pcDNA3.1	0.020	0.03
	2E2_W4_D5	gp160	pcDNA3.1	0.057	
Screen 0.18			Ę		
Day 28 1.10 0.1			UN		
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Day 28

Table 4

Ð	HIV-1/ART	3BNC117 (mg/kg)	Method	Cmax (µg/ml)	adjusted R-squared	Estimated T _{1/2} (days)	Lambda (lower)*	Lambda (upper)*	AUC (INF_pred)	Tlast*	Clast (pg/ml)	AUC_% Extrap_pred
		-	ELISA	27.4	n.d.	n.d.	ŗ	ı	n.d.		,	n.d.
IAI	Inegative	-	IZM.bl	27.4	0.936	21.32	14	42	184.0	42	1.2	19.2
	NT	Ŧ	ELISA	18.8	n.d.	n.d.		,	n.d.		,	n.d.
1A2	Negative	-	IZM.bl	27.8	0.893	12.89	7	42	181.7	42	1.0	9.0
(÷	ELISA	11.2	n.d.	n.d.	·	ı	n.d.	,	ı	n.d.
1A3	Inegative	-	IZM.bl	23.5	0.976	10.38	4	28	138.0	28	1.3	14.0
2A1	Positive/Off	1	ELISA	15.7	n.d.	n.d.	·	ı	n.d.	,	ı	n.d.
2A3	Positive/Off	1	ELISA	22.7	n.d.	n.d.	·	ı	n.d.		ı	n.d.
		÷	ELISA	33.8	n.d.	n.d.	ı	I	n.d.		ı	n.d.
2A4	Positive/OII	-	TZM.bl	15.6	n.d.	n.d.		ı	n.d.		·	n.d.
Ē	, in the second s	,	ELISA	6.68	0.985	19.64	7	56	685.2	56	3.1	12.1
181	Negative	'n	TZM.bl	70.9	0.881	24.30	7	56	483.7	56	2.7	17.9
		¢	ELISA	90.1	0.878	12.91	Ζ	42	523.5	42	2.2	8.8
182	Negative	n	IZM.bl	116.0	0.936	10.04	7	42	481.2	42	1.4	4.6
	N	ç	ELISA	243.4	0.954	21.54	14	56	1017.3	56	4.2	12.1
cqi	Inegauve	n	IZM.bl	74.5	0.954	21.70	Γ	56	706.6	56	3.9	15.6
		ç	ELISA	90.8	0.942	09.6	4	21	219.4	21	2.8	19.2
781	Positive/UII	Ś	IZM.bl	57.4	0.994	10.28	٢	28	245.9	28	1.9	12.1
2B2	Positive/On	С	ELISA	97.6	0.928	8.74	Γ	21	200.7	21	2.5	16.5
	20 	¢	ELISA	60.0	0.981	9.08	4	21	251.2	21	3.5	17.0
CB2	FOSIUVE/OII	n	TZM.bl	32.6	0.994	9.19	4	28	129.8	28	1.0	10.1
Ę		<u>,</u>	ELISA	347.8	0.942	16.33	7	56	1667.9	56	5.9	7.5
	Inegauve	10	IZM.bl	281.8	0.964	15.79	Γ	56	1598.9	56	5.6	7.3
ŝ	Mandree	5	ELISA	308.9	0.860	29.01	Γ	56	2529.4	56	15.8	23.5
2	Inegauve	10	IZM.bl	244.7	0.700	26.59	14	56	2228.5	56	13.1	19.3
Č	Monotino	0	ELISA	180.6	0.835	10.73	Г	42	859.1	42	4.0	5.5
5	Inegauve	10	TZM.bl	230.7	0660	10.56	14	56	1022.0	56	1.4	2.2
2C2	Positive/On	10	ELISA	326.8	0.866	10.87	7	42	904.5	42	2.7	5.6

A	HIV-1/ART	3BNC117 (mg/kg)	Method	Cmax (μg/ml)	adjusted R-squared	Estimated T _{1/2} (days)	Lambda (lower)*	Lambda (upper)*	AUC (INF_pred)	Tlast*	Clast (pg/ml)	AUC_% Extrap_pred
200	Doniting/Off	<u>-</u>	ELISA	178.2	0.944	6.92	4	28	550.2	28	2.8	5.1
2C4	Fositive/OII	10	TZM.bl	193.0	0.979	6.14	4	28	417.9	28	1.8	3.4
200	330/;+;E	0	ELISA	201.1	0.997	6.60	7	28	592.6	28	2.6	4.1
57	Positive/UII	10	TZM.bl	174.4	0.994	6.50	7	28	431.2	28	1.8	3.7
51	Montino	00	ELISA	360.8	0.930	14.48	7	56	4259.4	56	13.6	5.9
731	Inegalive	00	TZM.bl	1166.3	0.978	16.19	14	56	5901.2	56	16.1	6.2
163	Monotino	00	ELISA	361.8	066.0	16.26	٢	56	3177.5	56	11.7	8.2
150	Inegalive	00	TZM.bl	606.2	0.989	17.85	7	56	3422.2	56	12.3	9.3
105	Monotino	00	ELISA	765.0	0.992	14.15	4	56	5874.2	56	16.3	5.7
GI	Inegalitye	0¢	TZM.bl	939.6	0.959	15.22	14	56	6424.5	56	19.1	6.1
5	Docitive/Off	30	ELISA	410.2	0.991	5.80	7	28	1707.8	28	5.1	2.6
771	LOSINGOI	DC	TZM.bl	717.4	0.993	5.99	٢	42	2186.4	42	1.6	0.6
	Donition Off	00	ELISA	976.4	0.996	6.86	٢	42	2494.9	42	3.4	1.3
107	LOSINGOI	DC	TZM.bl	849.3	0660	8.83	7	56	1825.5	56	1.1	0.8
	Docition/Off	00	ELISA	571.0	0.962	13.39	٢	56	3616.5	56	9.9	4.8
CU12	LOSINGOI	0¢	TZM.bl	953.7	0.993	11.23	٢	42	4346.2	42	16.0	6.0
2E1	Positive/Off	30	ELISA	712.4	0.970	11.14	14	56	3028.5	56	4.6	2.3
2E2	Positive/Off	30	ELISA	789.4	0.920	11.14	٢	56	3596.1	56	6.7	2.4
2E3	Positive/Off	30	ELISA	559.6	0.821	8.54	7	28	2495.6	28	13.7	8.4

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Dose	HIV-1-status	Subjects	Method (subjects analyzed)		Cmax (нg/ml)		t _{1/2 (days}	(1)
				Mean	SD	Range	Mean	SD	Range
-		ç	ELISA (3)	19.1	8.1	11.2 - 27.4	n.d.	n.d.	n.d.
I mg	Iveg.	n	TZM.bl (3)	26.2	2.4	23.5 - 27.8	n.d.	n.d.	n.d.
-	Ë	,	ELISA (3)	24.1	9.1	15.7 - 33.8	n.d.	n.d.	n.d.
I IIIg	FOS.	n	TZM.bl (1)	23.5	n.d.	n.d.	n.d.	n.d.	n.d.
	Miss	ç	ELISA (3)	141.1	88.6	89.9 - 243.4	18.0	4.5	12.9 - 21.5
с gш с	INCG.	n	TZM.bl (3)	87.1	25.1	70.9 - 116.0	18.7	7.6	10.0 - 24.3
ç	ć	,	ELISA (3)	73.7	35.7	32.6 - 97.6	9.2	0.4	8.7 - 9.6
gm c	F0S.	n	TZM.bl (3)	50.6	15.7	32.6 - 61.7	11.2	2.2	9.5 - 13.73
01	N	,	ELISA (3)	279.1	87.5	180.6 - 347.8	18.7	9.4	10.7 - 29.0
gill UI	INCS.	n	TZM.bl (3)	252.4	26.4	230.7 - 281.8	17.7	8.1	10.7 - 26.6
010	Ĕ	ç	ELISA (3)	235.4	80.0	178.2 - 326.8	8.1	2.4	6.6 - 10.9
gill UI	ros.	n	TZM.bl (3)	213.6	52.6	174.4 - 273.4	8.8	4.3	6.5 - 13.7
20.02	Moo	ç	ELISA (3)	495.9	233.1	360.8 - 765.0	15.0	1.1	14.2 - 16.3
gill UC	INCS.	n	TZM.bl (3)	904.0	281.7	1166.3 - 606.2	16.4	1.3	15.2 -17.9
20 20	č	9	ELISA (6)	669.8	199.7	410.2 - 976.4	9.9	3.3	5.8 - 13.7
giii UC	FOS.	D	TZM.bl (3)	840.1	118.4	717.4 - 953.7	8.9	2.3	6.7 - 11.2

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10.7 - 29.0 10.0 - 26.6 5.7 - 13.7 6.1 - 13.7

5.5 5.7 2.6 2.9

17.2 17.6 9.3 9.6

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ELISA (9) TZM.bl (9) ELISA (12) TZM.bl (9)

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Neg.

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