LETTER

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Viraemia suppressed in HIV-1-infected humans by broadly neutralizing antibody 3BNC117

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HIV-1 immunotherapy with a combination of first generation monoclonal antibodies was largely ineffective in pre-clinical and clinical settings and was therefore abandoned[1–3]. However, recently developed single-cell-based antibody cloning methods have uncovered a new generation of far more potent broadly neutralizing antibodies to HIV-1 (refs 4, 5). These antibodies can prevent infection and suppress viraemia in humanized mice and nonhuman primates, but their potential for human HIV-1 immunotherapy has not been evaluated[6–10]. Here we report the results of a first-in-man dose escalation phase 1 clinical trial of 3BNC117, a potent human CD4 binding site antibody[11], in uninfected and HIV-1-infected individuals. 3BNC117 infusion was well tolerated and demonstrated favourable pharmacokinetics. A single 30 mg kg^{-1} infusion of 3BNC117 reduced the viral load in HIV-1-infected individuals by 0.8–2.5 log$_{10}$ and viraemia remained significantly reduced for 28 days. Emergence of resistant viral strains was variable, with some individuals remaining sensitive to 3BNC117 for a period of 28 days. We conclude that, as a single agent, 3BNC117 is safe and effective in reducing HIV-1 viraemia, and that immunotherapy should be explored as a new modality for HIV-1 prevention, therapy and cure.

A fraction of HIV-1-infected individuals develop potent neutralizing serologic activity against diverse viral isolates[4,5]. Single-cell cloning methods to isolate antibodies from these individuals[12] revealed that broad and potent neutralization can be achieved by antibodies targeting many sites on the viral envelope[5,13,14]. Many of these antibodies can prevent infection, and some can suppress active infection in humanized mice (hu-mice) or macaques[6–10]. Therefore, it is generally accepted that a vaccine eliciting such antibodies is likely to be protective against HIV-1. However, potent anti-HIV-1 broadly neutralizing antibodies (bNAbs) are highly somatically mutated and many carry other uncommon features such as insertions, deletions, or long complementary determining regions[4,5,11,12,15], which may account for the difficulty in eliciting such antibodies by immunization. In view of the efficacy of passive bNAb administration in hu-mice and macaques[6–9,16], it has been suggested that bNAbs should be administered passively, or by viral vectors for prevention and immunotherapy[4,9,16]. However, their safety and efficacy has not been tested in humans.

To determine whether the new generation of more potent bNAbs are safe and active against HIV-1 in humans, we initiated an open label phase 1 study (Fig. 1a) with 3BNC117, an anti-CD4 binding site antibody cloned from a viraemic controller[11]. 3BNC117 neutralizes 195 out of 237 HIV-1 strains comprising 6 different clades with an average half-maximal inhibitory concentration (IC_{50}) of 0.08 μg ml^{-1} (Extended Data Fig. 1)[11]. 12 uninfected and 17 HIV-1-infected individuals (Table 1) were administered a single intravenous dose of 1, 3, 10 or 30 mg kg^{-1} of 3BNC117 (Extended Data Table 1a). 3BNC117 serum concentrations, plasma HIV-1 viral loads (VL), $CD4^+$ and $CD8^+$ T-cell counts, and safety were monitored closely (Fig. 1a, Extended Data Figs 2, 3, and Extended Data Tables 1b, 2). The two groups were comparable for gender, race and age (Table 1).

3BNC117 was generally safe and well tolerated at all doses tested in both uninfected and HIV-1-infected individuals. No grade 3, 4 or serious adverse events and no treatment-related laboratory changes were observed during 56 days of follow up (Extended Data Table 1b). $CD4^+$ or $CD8^+$ T-cell counts did not change after 3BNC117 infusion in the HIV-1-infected group, possibly because initial $CD4^+$ T-cell counts were near normal in most participants (mean absolute $CD4^+$ T-cell count was 655 cells per μl, Extended Data Fig. 2).

Two different assays were used to measure 3BNC117 levels in serum: TZM.bl neutralization assay to measure activity, and anti-idiotype-specific ELISA to measure antibody protein levels (Fig. 1b, Extended Data Fig. 3 and Extended Data Tables 4, 5). With few exceptions the two assays were generally in agreement in both groups (Fig. 1b and Extended Data Fig. 3). However, elimination of 3BNC117 activity was more rapid in the HIV-1-infected group, resulting in an estimated average $t_{1/2}$ of around 9 days as opposed to around 17 days in uninfected individuals (Fig. 1b and Extended Data Tables 4, 5). We conclude that 3BNC117 has pharmacokinetic properties consistent with a typical human IgG1 in uninfected individuals and a somewhat faster decay rate in HIV-1-viraemic individuals. Similar antigen-dependent enhanced clearance has been reported with anti-cancer antibodies[17]. Although there may be other explanations, we speculate that the increased rate of antibody elimination in the presence of HIV-1 is due to accelerated clearance of antigen–antibody complexes.

Viral loads were measured by standard assays or by single-copy assays. Baseline VLs in HIV-1-infected individuals not on anti-retroviral therapy (ART) varied from 640 to 53,470 copies ml^{-1} (mean 9,420 copies ml^{-1}). Two participants were on ART at the time of antibody infusion but had detectable baseline VLs (30 and 100 copies ml^{-1}). (Table 1, Extended Data Table 2a).

Virologic responses correlated with antibody dose. Infected individuals receiving 1 or 3 mg kg^{-1} 3BNC117 doses showed only small and transient changes in viraemia consisting of increases of up to threefold 1 day after infusion, followed by a short temporary decrease, and rapid return to baseline (Fig. 2, Extended Data Fig. 4, and Extended Data

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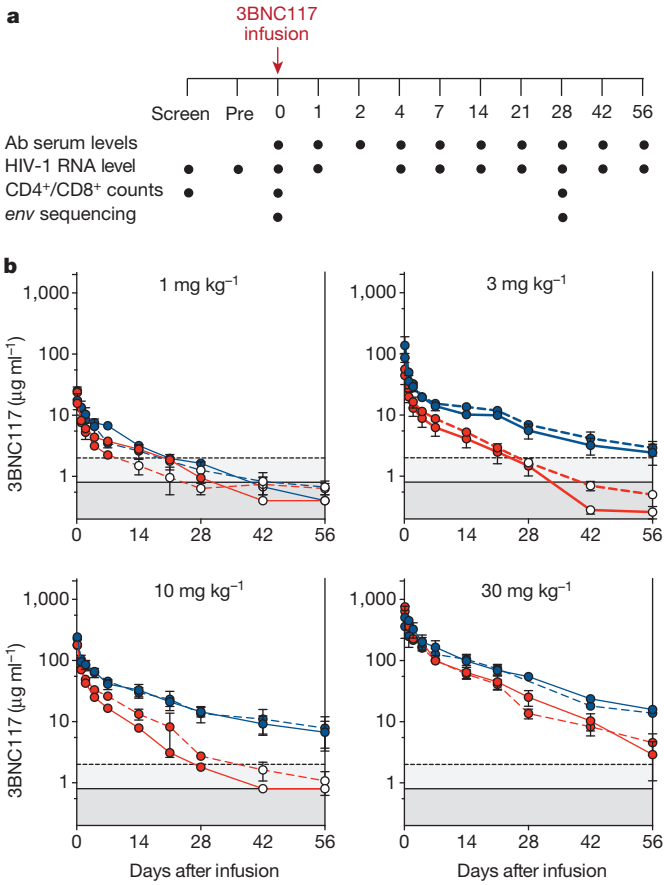

Figure 1 | Pharmacokinetics of 3BNC117 in uninfected and HIV-1-infected individuals. **a**, Diagrammatic representation of the study. Time of 3BNC117 infusion indicated by the red arrow, and sampling for 3BNC117 serum levels, HIV-1 viral load, $CD4^+/CD8^+$ T cell counts and *env* sequencing as indicated below. **b**, Antibody decay measured in TZM.bl assays (solid lines) and ELISA (dotted lines). Mean values and s.e.m. for uninfected individuals (3 per group) are shown in blue and for HIV-1-infected individuals (2–5 per group) in red. Light grey indicates lower level of accuracy by the ELISA assay and dark grey by the TZM.bl assay. Open circles indicate levels lower than the accuracy threshold.

Table 2a). The magnitude and kinetics of the initial increase in viraemia were consistent with those seen with viral entry inhibitors[18].

In contrast, 10 out of 11 individuals receiving 10 or 30 mg kg^{-1} infusions responded by dropping their VLs by up to 2.5 $\log_{10}$ (Fig. 2, Extended Data Fig. 4 and Extended Data Table 2a). Two individuals off ART received the 10 mg kg^{-1} dose, of whom 1 responded with 1.36 $\log_{10}$ decline in viraemia and the other did not (Fig. 2 and Extended Data Table 2a). The individual that did not respond was infected with a virus that was completely resistant to 3BNC117 (2C4; $IC_{50} > 20$ μg ml^{-1}; Fig. 3 and Extended Data Table 3). All 8 individuals that received the 30 mg kg^{-1} dose of 3BNC117 showed highly significant and rapid decreases in their viral loads that varied between −0.8 and −2.5 $\log_{10}$ (Figs 2 and 3 and Extended Data Table 2a, b). The magnitude of the decline was related to the starting VL and the sensitivity of the subjects' autologous virus to 3BNC117 (Figs 2 and 3, Extended Data Fig. 5). The median time to reach the lowest level in viraemia was 7 days, and the mean drop in VL was 1.48 $\log_{10}$ at lowest level. When compared to all available pre-treatment measurements, the drop in viraemia was highly significant from days 4 through 28 (Fig. 2 and Extended Data Table 2b). Although the limited data set does not allow us to determine viral set point, 4 of the 8 individuals receiving a single 30 mg kg^{-1} infusion did not entirely return to day 0 pre-infusion levels during the observation period of 56 days (Figs 2 and 3, Extended Data Table 2a).

Table 1 | Study participants demographics

	Uninfected (n = 12)	HIV-1-infected (n = 17)
Gender (% male)	83%	76%
Mean age (range)	43 (22–58)	37 (20–54)
Race/ethnicity		
White	42%	29%
Black or African American	50%	53%
Hispanic	8%	18%
ART status		
On ART n (%)	–	2 (12%)
Off ART n (%)	–	15 (88%)
Mean absolute $CD4^+$ count (cells μl^{-1}; day 0)	–	655 (245–1,129)
Mean % $CD4^+$ count (day 0)	–	29% (20–42%)
Mean HIV-1 RNA level - (copies ml^{-1}; day 0)*	–	9,420 (640–53,470)

*Mean HIV-1 RNA levels in HIV-1-infected participants off ART.

To further examine the virologic effects of 3BNC117 immunotherapy, autologous viral isolates were obtained from cultured PBMCs before (day 0, day −7) and after (day 28) antibody infusion. Paired samples from 12 of the 17 HIV-1-infected individuals were tested for 3BNC117 sensitivity (Fig. 3 and Extended Data Table 3). Samples obtained from individuals infused with 1 mg kg^{-1} showed 35- and 13.5-fold decreases in 3BNC117 sensitivity, indicating that the antibody exerts selective pressure on HIV-1 even at the lowest dose (2A3, 2A4; Fig. 3). Similar changes in sensitivity were seen for some (2B1, 2C5) individuals treated with 3 and 10 mg kg^{-1}, but others remained 3BNC117-sensitive throughout (2B3) (Fig. 3, Extended Data Table 3). Similarly, at 30 mg kg^{-1}, only 2 out of 5 individuals tested showed greater than fivefold reduction in 3BNC117 sensitivity on day 28 (Extended Data Table 3). In contrast, 2C1, 2D1, 2D3 showed only 3.2-, 1.3- and 2.7-fold changes in sensitivity and these individuals did not rebound to baseline viraemia levels at day 28 (Figs 2 and 3). We conclude that, in some individuals, HIV-1 develops high-level resistance to 3BNC117 by 28 days after a single dose, while in others it does not.

To examine the molecular nature of the changes in HIV-1 in response to 3BNC117, we cloned and sequenced HIV-1 envelopes from paired plasma samples from 10 individuals before and 28 days after infusion. Evidence for antibody-induced selection was seen in some but not all samples analysed (Fig. 4, Supplementary Fig. 1). For example, 2C5, who received a 10 mg kg^{-1} infusion, selected for a G459D mutation in 15 out of 23 *env* sequences, while the remainder showed a longer V5 loop. The G459D mutation alters the CD4 binding site and can result in resistance to 3BNC117 (ref. 9). Changes in the V5 loop can alter sensitivity to anti-CD4 binding site antibodies by steric clashing with the heavy or light chains of 3BNC117-type antibodies. Similarly, 10 or 30 mg kg^{-1} infusions selected single mutations at Q363H (2E1), S461D (2E2), and S274Y (2E2) (Fig. 4, Supplementary Fig. 1). These changes may alter sensitivity to 3BNC117 by interfering with binding[5]. Selection in these 3 individuals is also indicated by the emergence of a distinct group of closely related sequences in phylogenetic trees (Fig. 4, Supplementary Fig. 1). Consistent with the molecular analysis, and the viral culture data (Fig. 3), pseudoviruses produced from serum of 2C5 from days 0 and 28 showed high level 3BNC117 resistance, whereas the changes in pseudoviruses produced from 2C1, 2D1, 2E1 and 2E2 were modest (Fig. 4 and Extended Data Table 3). In contrast, autologous viral isolates from individuals who did not become resistant, or had only small changes in sensitivity, such as 2B3, showed little if any evidence of selection. We conclude that a single infusion of 3BNC117 leads to selection for high-level resistance in some but not all individuals.

Although immunotherapy was initially used to treat infectious diseases, the great majority of therapeutic monoclonal antibodies are currently used to treat cancer and autoimmune diseases. This form of therapy has been shown to be highly effective, well tolerated, and to function in large part by engaging the host immune system through Fc receptors[19].

In contrast, a role for antibodies in controlling HIV-1 infection has been difficult to establish. For example, the overall course of infection is

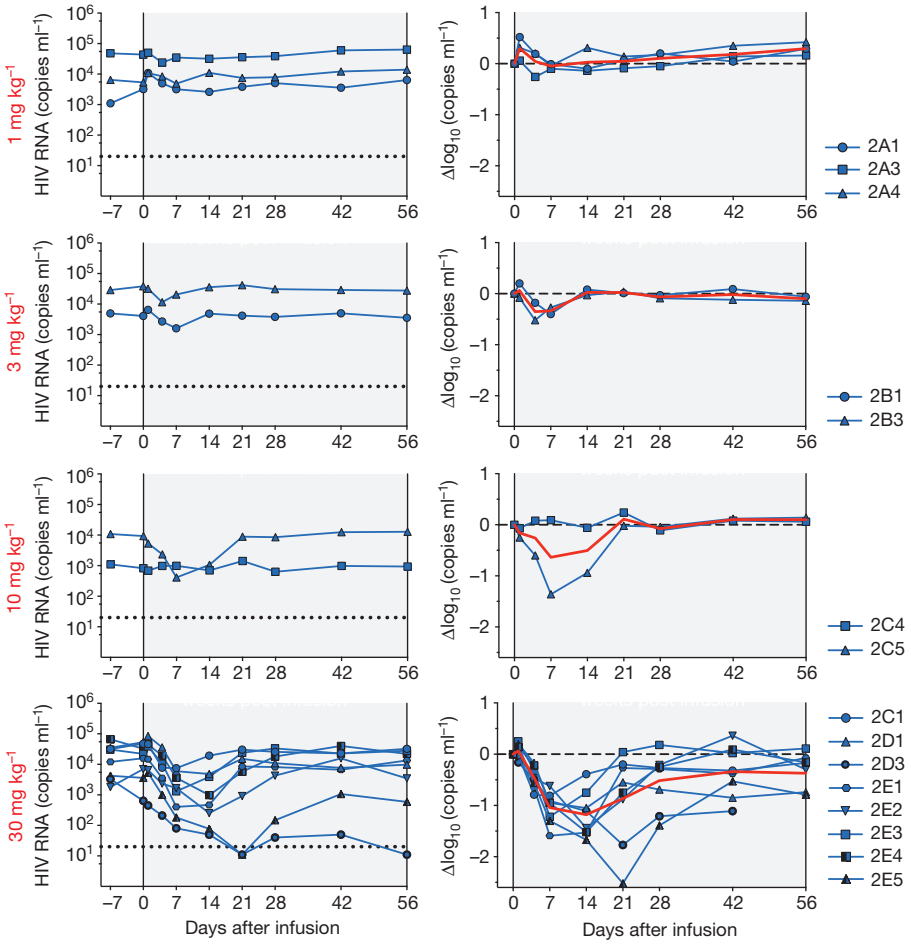

Figure 2 | HIV-1 viral load measurements. 3BNC117 dose indicated in red. Plots (left column) show absolute VLs in HIV-1 RNA copies ml^{-1} (*y* axis) versus time in days after infusion (*x* axis). Right column shows log_{10} changes in VL from day 0. Red line illustrates the average (least-squares means, by mixed-effect linear model). Individual subjects are indicated on the right. Subjects 2E1 to 2E5 were pre-screened for 3BNC117 sensitivity. At 30 mg kg^{-1} dose level, the change in viraemia was significant ($P = 0.004$, $P < 0.001$, $P < 0.001$, $P < 0.001$, $P < 0.011$ at days 4, 7, 14, 21, and 28, respectively) when compared to all available pretreatment values (Extended Data Table 2b).

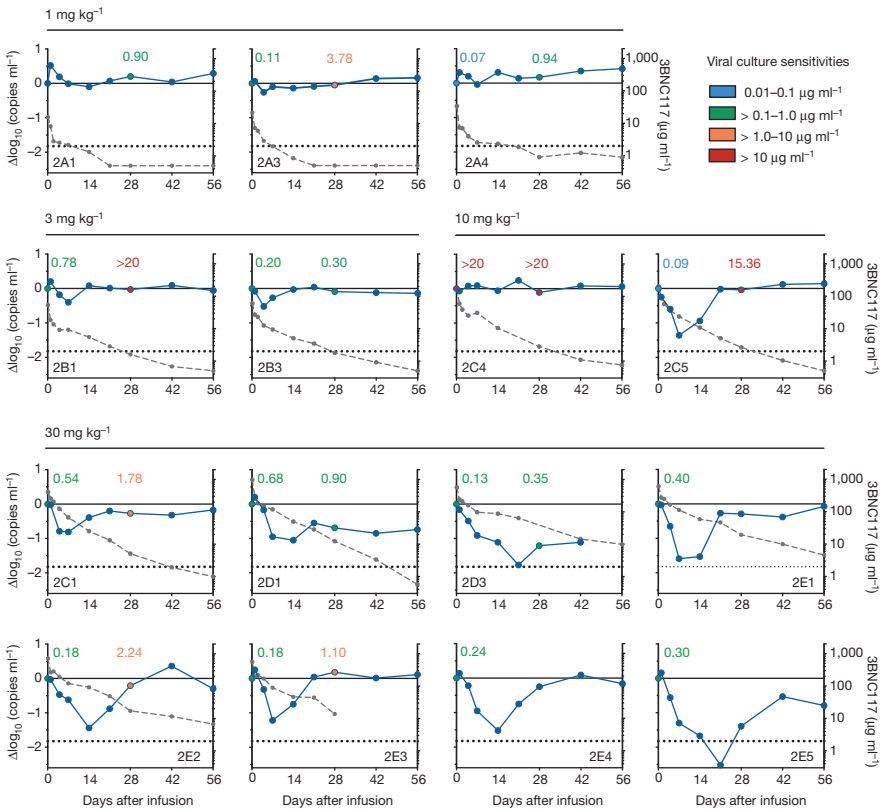

Figure 3 | 3BNC117 sensitivity, changes in viraemia, and 3BNC117 levels. 3BNC117 dose is indicated at the top of the graphs. The left *y* axis shows log_{10} change in viraemia from day 0, and right *y* axis shows antibody level measured by ELISA. Blue line reflects change in VL and dotted grey line antibody level. Numbers indicate IC_{50} values for 3BNC117 of autologous viral isolates measured by TZM.bl assay, colour-coded as indicated in the key. Dotted line indicates lower level of accuracy.

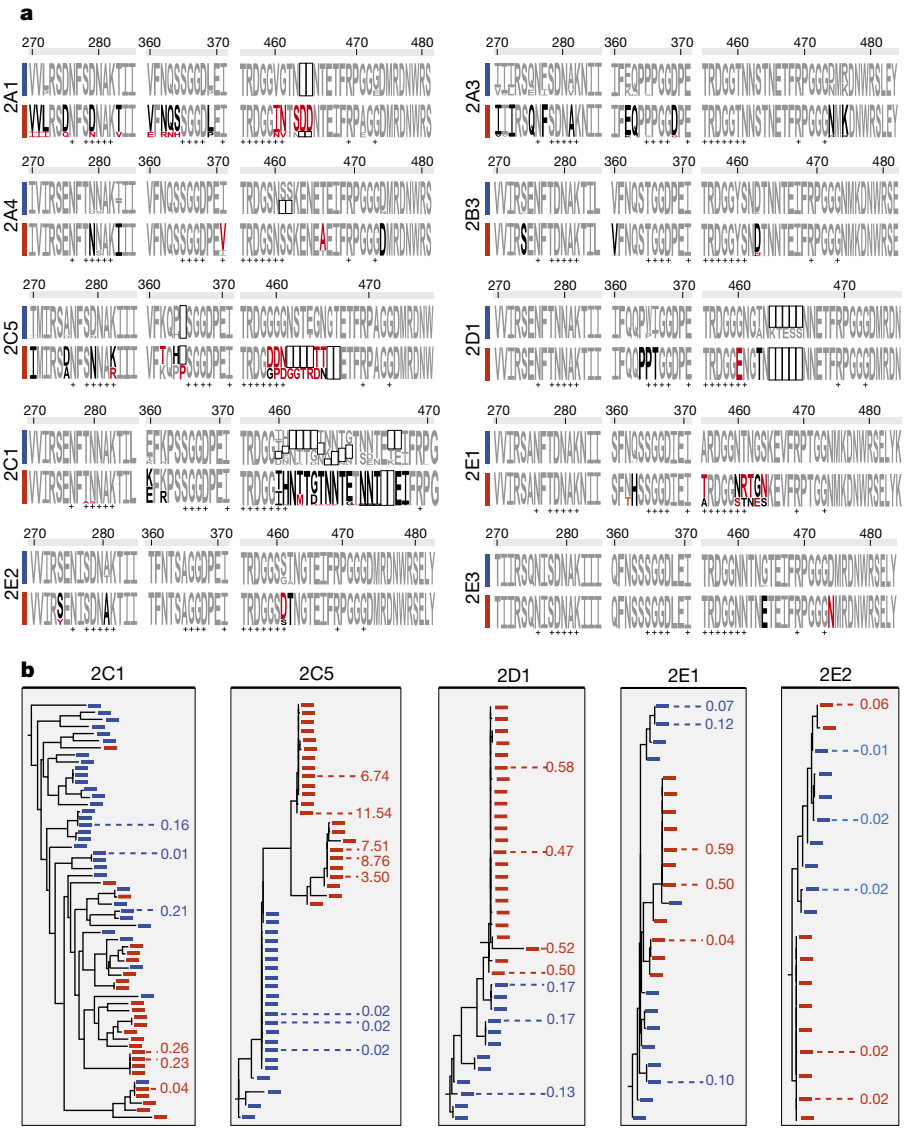

Figure 4 | HIV-1 envelope sequence analysis after 3BNC117 infusion. **a**, HIV-1 envelopes were cloned from plasma samples. Logogram showing *env* gp120 regions (amino acid positions; 270–285, 360–371, and 455 to 471–485, according to HXBc2 numbering) indicating sequence changes from day 0 (blue bar) to day 28 (red bar). The frequency of each amino acid is indicated by its height. Red residues represent mutations that were only found after treatment, black residues represent amino acids that changed in frequency after treatment, empty boxes represent gaps, and + symbols represent 3BNC117 contact sites on gp120 (ref. 30). **b**, Phylogenetic trees show gp120 evolution from day 0 to 28 after treatment for 2C1, 2C5, 2D1, 2E1 and 2E2. Blue and red bars represent sequences obtained on days 0 and 28, respectively (Supplementary Fig. 1). Illustrated values represent the IC_{50} of 3BNC117 in μg ml^{-1} against the cloned HIV-1 pseudoviruses from the analysed sequences (Extended Data Table 3). The geometric means of the pseudoviruses' IC_{50} values on days 0 and 28, respectively are for 2C1: 0.06 and 0.14 μg ml^{-1}; 2C5: 0.02 and 7.09 μg ml^{-1}; 2D1: 0.15 and 0.52 μg ml^{-1}; 2E1: 0.09 and 0.23 μg ml^{-1}; 2E2: 0.01 and 0.03 μg ml^{-1}.

not thought to be altered in individuals that develop bNAbs[20]. Moreover, first generation anti-HIV-1 bNAbs with limited breadth and activity produced little if any measurable effects in hu-mice or viraemic individuals[3,4,21]. However, antibodies can put strong selective pressure on the virus in individuals that develop anti-HIV-1 antibody responses[22–24]. In addition, recent studies in hu-mice showed that, when administered as monotherapy, new generation bNAbs can transiently reduce VLs, and in combination they control viraemia for as long as concentrations remain in the therapeutic range[6,9]. In contrast, single antibodies led to control of viraemia in SHIV-infected macaques for as long as antibody levels remained therapeutic, and immune escape was rarely observed[7,8]. The surprising difference between hu-mice and macaques might be attributed in part to an intact host immune system in the macaque, including endogenous antibodies[25], or differences between SHIV and HIV-1 infection. Our data establish that passive infusion of single bNAbs can have profound effects on HIV-1 viraemia in humans.

Combinations of antiretroviral drugs are the standard of care for HIV-1 infection because resistance develops to single agents[26]. Similarly, monotherapy with 3BNC117 alone is insufficient to control infection, and we expect that antibody-drug or antibody-antibody combinations will be required for complete viraemic control. Although the current generation of drugs is less expensive than antibodies, the latter have very long half-lives and have the potential to kill infected cells and to enhance host immunity by engaging Fc receptors[19,27]. Moreover, anti-HIV-1 antibodies can be made 100-fold more potent by molecular engineering[28]. Finally, the combination of antibodies with agents that activate latent viruses can interfere with the HIV-1 reservoir in hu-mice[29] and may be critical to HIV-1 eradication strategies.

Given the difficulties in developing an HIV-1 vaccine and in eradicating established infection, passive transfer of monoclonal antibodies is being considered for HIV-1 prevention, therapy, and cure. Our data establish the principle that monoclonal antibodies can be both safe and

effective against HIV-1 in humans. Antibody-mediated immunotherapy differs from currently available drugs in that it has the potential to affect the course of HIV-1 infection by engaging host immunity directly.

Online Content Methods, along with any additional Extended Data display items and Source Data, are available in the online version of the paper; references unique to these sections appear only in the online paper.

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Supplementary Information is available in the online version of the paper.

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Author Contributions M.C. and F.K. planned and implemented the study, analysed the data, and wrote the manuscript; J.C.C.L. performed sequence analyses, and contributed to writing the manuscript; M.S.S. performed TZM.bl neutralization assays; A.P.W. assisted with sequence analyses; N.B., G.K., S.B.-A., M.W.-P., M.P., L.A.B. implemented the study; L.N. and M.B. performed cloning and sequencing; I.S., C.L. coordinated sample processing; T.H. performed ELISA assays; and R.J.G. performed single copy assays. T.K. was responsible for 3BNC117 manufacture and provided regulatory guidance; J.F.S., B.D.W., J.A.H. contributed to study design and helped with the manuscript; R.M.G. contributed to study design; and G.F. and S.J.S. contributed to study design and implementation. M.C.N. planned and implemented the study, analysed the data and wrote the manuscript. All authors discussed the results and commented on the manuscript.

Author Information Reprints and permissions information is available at www.nature.com/reprints. The authors declare no competing financial interests. Readers are welcome to comment on the online version of the paper. Correspondence and requests for materials should be addressed to M.C.N. (nussen@rockefeller.edu).

METHODS

Study design. An open-label, dose-escalation phase 1 study was conducted in uninfected (Group 1) and HIV-1-infected subjects (Group 2; http://www.clinicaltrials.gov; NCT02018510). Study participants were enrolled sequentially according to eligibility criteria. A standard "3+3" phase I trial design was used in the dose-escalation phase of the study. 3BNC117 was administered as a single intravenous infusion at four dose levels: 1 mg kg^{-1} (subjects 1A1, 1A2, 1A3, 2A1, 2A3, 2A4), 3 mg kg^{-1} (subjects 1B1, 1B2, 1B3, 2B1, 2B2, 2B3), 10 mg kg^{-1} (subjects 1C1, 1C3, 1C4, 2C2, 2C4, 2C5) or 30 mg kg^{-1} (subjects 1E2, 1E3, 1E5, 2D1, 2C1, 2D3, 2E1, 2E2, 2E3, 2E4, 2E5), at a rate of 100 or 250 ml h^{-1}. 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, the Paul Ehrlich Institute in Germany and the Institutional Review Boards at the Rockefeller University and the University of Cologne.

Study participants. All study participants were recruited at the Rockefeller University Hospital, New York, USA and at the University Hospital Cologne, Cologne, Germany. Eligible subjects were adults aged 18–65 years, HIV-1-infected or uninfected, and without concomitant hepatitis B or C infections. HIV-1-infected subjects enrolled in study groups 2A through 2E were ART-experienced or naive. In groups 2A through 2D, subjects were either off standard ART for at least 8 weeks before study participation and had plasma HIV-1 RNA levels between 2,000 and 100,000 copies ml^{-1}, or they were on standard ART but had plasma HIV-1 RNA levels >20 copies ml^{-1}, measured on two separate occasions at least 1 week apart. Subjects recruited into group 2E were HIV-1-infected, off ART (2,000–100,000 copies ml^{-1}), and differed from the other groups in that they were pre-screened for sensitivity to 3BNC117 as described below. Subjects with CD4$^+$ T-cell counts <300 cells μl^{-1}, clinically relevant deviations from normal physical findings, abnormal electrocardiogram (ECG), and/or laboratory examinations were excluded. Women of childbearing potential were required to have a negative result of a serum pregnancy test on the day of 3BNC117 infusion. HIV-1-infected individuals, who were not on standard ART at enrolment, were given the option to initiate ART 6 weeks after 3BNC117 infusion.

Study procedures. The appropriate volume of 3BNC117 was calculated according to study dose group, diluted in sterile normal saline to a total volume of 100 or 250 ml, and administered intravenously over 60 min. Study participants received 3BNC117 on day 0 and remained under close monitoring in the inpatient unit of the Rockefeller University Hospital for 24 h. Participants returned for frequent follow up visits for safety assessments that included physical examination, measurement of clinical laboratory parameters such as haematology, chemistries, urinalysis, coagulation times, pregnancy tests (for women) as well as HIV-1 viral loads and CD4$^+$ and CD8$^+$ T-cell counts (Fig. 1a). Adverse events were graded according to the DAIDS AE Grading Table (HIV-1-infected groups) or the Toxicity Grading Scale for Healthy Adult and Adolescent Volunteers Enrolled in Preventive Vaccine Clinical Trials (uninfected groups). Blood samples (30 to 120 ml) were collected before and at multiple times after 3BNC117 infusion. 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.

Plasma HIV-1 RNA levels. Plasma was collected for measuring HIV-1 RNA levels at screening (from day −49 to day −14), the day −7 pre infusion visit (from day −42 to day −2), day 0 (before infusion), and on days 1, 4, 7, 14, 21, 28, 42 and 56. HIV-1 RNA levels were determined using the Roche COBAS AmpliPrep/COBAS TaqMan HIV-1 Assay, Version 2.0, which detects 20 to 10×10^6 copies ml^{-1}, or by the ABBOTT RealTime Assay, which detects 40 to 10×10^6 copies ml^{-1}. In samples with HIV-1 RNA <20 copies ml^{-1}, viraemia was measured by a quantitative real-time, reverse transcriptase (RT)-initiated PCR (RT–PCR) assay that can quantify HIV-1 RNA down to 1 copy ml^{-1} as previously described[31].

CD4$^+$ and CD8$^+$ T cells. CD4$^+$ and CD8$^+$ T-cell counts were determined at screening, on day 0 (before infusion), and day 28 by a clinical flow cytometry assay, performed at LabCorp or at the University Hospital Cologne. 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 envelope[11]. The antibody was cloned from an HIV-1-infected viraemic controller in the International HIV Controller Study[11,32], 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^{-1} 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 using two separate methods (ELISA and TZM.bl). 3BNC117 serum concentrations were measured by a validated sandwich ELISA. Plates (Sigma-Aldrich PN: CLS3590 96-well, High Bind, polystyrene) were coated with 4 μg ml^{-1} 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 horseradish peroxidase (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 4 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. The capture anti-idiotypic antibody was produced by immunizing BALB/c mice with a Fab′ fragment of 3BNC117 and plasma was tested for the presence of neutralizing antibodies in an ELISA. Briefly, the HIV-1 antigen (2CC core protein) was coated to a plate and blocked. Plasma dilutions were pre-incubated with a sub-saturating concentration of 3BNC117 then added to the plate. Binding to the antigen was detected with an HRP-conjugated goat anti-mouse IgG-Fc specific antibody. Plasma was considered neutralizing if it was able to block the binding of 3BNC117 to the antigen coated plate. Two mice were selected for fusion. Those hybridomas that showed high specificity when comparing binding to 3BNC117 versus binding to the irrelevant human IgG1 antibody were selected to expand, screened in the neutralization assay as described above, subcloned and purified for use in the anti-idiotype-specific ELISA.

In addition, the concentration of active 3BNC117 was determined by TZM.bl neutralization assay[7,8]. Serum samples were heat-inactivated for 1 h at 56 °C and measured for neutralizing activity against an HIV-1 strain that was highly sensitive to 3BNC117 but resistant to any autologous HIV-1 neutralizing serum activity. In all uninfected subjects serum samples were tested against Q769.d22 and ID_{50} values were derived by using a 5-parameter curve fitting, considering accurate within the pre-established limits (threefold variation with a 20% error rate). The serum concentration of active 3BNC117 was calculated by taking into account the sera ID_{50} titres multiplied by the known IC_{50} of 3BNC117 for Q769.d22. In HIV-1-infected subjects pre-infusion samples were first tested against a panel of 3BNC117-sensitive HIV-1 strains that included Q769.d22 (Clade A1, Tier 2), YU2.DG (Clade B, Tier 2), Q259.d2.17 (Clade C, Tier 1B), Q842.d12 (Clade A1, Tier 2), ZM135M.PL10a (Clade C, Tier 2), and TRO.11 (Clade B, Tier 2). A single strain per subject was selected that showed no or only minimal background activity and 3BNC117 serum levels were determined in the same way as described for Q769.d22.

Pharmacokinetic analysis. Blood samples were collected immediately before, at the end, 0.5, 3, 6, 9, 12 and 24 h after completion of the 3BNC117 infusion, and on days 2, 4, 7, 14, 21, 28, 42 and 56. 3BNC117 serum levels were obtained from ELISA (Celldex Therapeutics) and TZM.bl neutralization assay, and PK-parameters were estimated by performing a non-compartmental analysis (NCA) using WinNonlin 6.3.

Neutralization assay. Serum samples, viral supernatants, and control antibodies were tested against HIV-1 envelope pseudoviruses as previously described[33,34].

Virus cultures. Autologous virus was retrieved from HIV-1 infected individuals as previously described[35]. Briefly, healthy donor peripheral blood mononuclear cells (PBMCs) were obtained by leukapheresis from a single donor. Cells were cultured at a concentration of 5×10^6 ml^{-1} 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^{-1} phytohaemagglutinin (Life Technologies) at 37 °C and 5% CO_2. After 2–3 days, 5×10^6 cells were transferred into IMDM supplemented with 10% FBS, 1% penicillin/streptomycin, 5 μg ml^{-1} polybrene (Sigma), and 10 U ml^{-1} of IL-2, and co-incubated with 2–3 $\times 10^6$ PBMCs from the study participants obtained before and 28 days or later after 3BNC117 infusion (Extended Data Table 3). Media was replaced on a weekly basis and culture supernatants quantified using the Alliance HIV-1 p24 Antigen ELISA kit (PerkinElmer) according to the manufacturer's instructions. Tissue culture infectious dose for 50% of cells ($TCID_{50}$) values were determined for all HIV-1 containing supernatants[33,34] and then tested for sensitivity against 3BNC117 in a TZM.bl neutralization assay. Outgrowth of autologous virus isolates from subjects with low level viraemia was performed as previously described[36]. Briefly, 2–5 million CD4$^+$ T cells were cultured in the presence of 10 million irradiated healthy donor PBMCs and 3 million healthy donor PHA stimulated CD8$^+$ depleted lymphoblasts. Lymphoblasts were replenished weekly by adding 3

million healthy donor PHA stimulated $CD8^+$ depleted lymphoblasts. Blood samples and leukopheresis were collected under separate IRB-approved protocols and after study participants provided informed consent.

Sequence analysis. 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′[37] or 5′-GGTGTGTAGTTCTGCCAATCAGGGAAGWAGCCTTGTG-3′[6]. 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′-CACCTTAGGCATCTCCTATG-GCAGGAAGAAG-3′ and envB3in 5′-GTCTCGAGATACTGCTCCCACCC-3′. First round PCR was 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 2 µl of 1. PCR product as template and Phusion Hot Start Polymerase at 98 °C, 30 s; (98 °C, 8 s; 55 °C, 20 s; 72 °C, 1 min) × 35; 72 °C, 6 min. gp120 *env* was amplified using first round primers and conditions as described, but second round was performed by using second round nested primers 5′-TAGAAAGAGCAGAAGACAGTGGCAATGA-3′ and 5′-TCATCAATGGTGGTGATGATGATGTTTTTCTCTCTGCACCACTCTTCT-3′. Second round PCR was performed with 1 µl of 1. PCR product as template and High Fidelity Platinum Taq (Invitrogen) at cycling conditions, 94 °C, 2 min; (94 °C, 15 s; 58 °C, 35 s; 68 °C, 2 min and 30 s) × 35; 68 °C, 10 min. Following the second-round PCR amplification, 0.5 µl Taq polymerase was added to each 50 µl reaction and an additional 72 °C extension for 15 min was performed to add 3′dA overhangs for cloning inserts into pCR4-TOPO. PCR amplicons were gel-purified and ligated into pCR4-TOPO (Invitrogen) or pcDNA3.1 (Invitrogen), followed by transfection into MAX Efficiency Stbl2 Competent Cells (Life Technologies). Individual colonies were analysed for insert length by PCR, and successfully cloned envelopes sequenced by a set of *env* specific primers. Sequence alignments and mutation analysis of gp120 and gp160 was performed by using Geneious Pro software, version 5.6.7 (Biomatters Ltd), and residues were numbered according to HXBc2. Phylogenetic trees were generated using the PhyML tool at the Los Alamos HIV website[38], and sequence analysis was performed using Antibody database by Anthony West[39]. Logograms were generated using the Weblogo 3.0 tool[40]. Selected sequences were used to generate pseudoviruses and tested for 3BNC117 sensitivity in a TZM.bl assay[37].

Statistical analyses. The sample size to detect >1 $\log_{10}$ decline in viraemia with 80% power at 5% of significance was determined to be 5 HIV-1-infected individuals, not on ART, infected with 3BNC117-sensitive viruses assuming that the standard deviation would be similar to 3BNC117 effects in hu-mice[9]. Adverse events were summarized by the number of subjects who experienced the event, by severity grade and by relationship to 3BNC117 according to the DAIDS AE Grading Table (HIV-1-infected groups) or the Toxicity Grading Scale for Healthy Adult and Adolescent Volunteers Enrolled in Preventive Vaccine Clinical Trials (uninfected groups). PK-parameters were estimated by performing a non-compartmental analysis (NCA) using WinNonlin 6.3. $CD4^+$ and $CD8^+$ T-cell counts before and after 3BNC117 were analysed by one-way ANOVA. To assess the changes in HIV-1 viral loads, we used a mixed-effect linear model where dose and time were fixed effects and random intercepts for each participant. These models take full advantage of the repeated measure structure of the data while estimating parameters for each dose simultaneously, hence improving the power of small study groups. The final model was fitted assuming an AR(1) correlation structure over time, which was the best in terms of AIC/BIC criteria. The significance of the effect of 3BNC117 on viral load, defined as change between each time point and day 0, was assessed using least-squares means within each dose group (Extended Data Table 2b). Sensitivity analysis was also carried out with variations of these models and the same conclusions were achieved. Pearson and nonparametric Spearman coefficients were calculated to assess the correlation between maximum drop in viraemia after 3BNC117 infusion and baseline HIV-1 viral load or baseline sensitivity of autologous viruses to 3BNC117.

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a

3BNC117

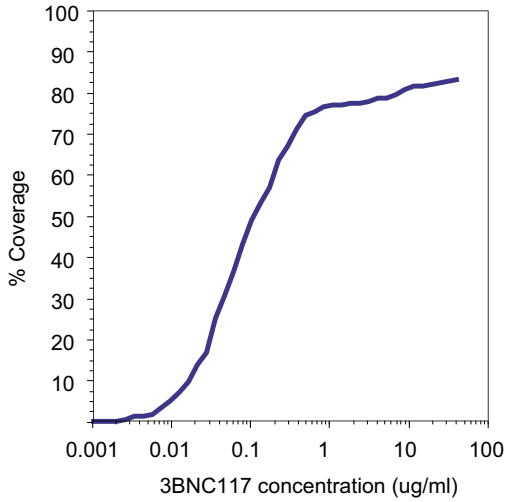
Clade	number of tested strains	Mean IC_{50}*	Coverage (%) (IC_{50} <10 µg/ml)
A	57	**0.04**	86.0
AE	22	**0.08**	90.9
B	49	**0.08**	91.8
C	84	**0.14**	71.4
D	17	**0.11**	88.2
G	7	**0.16**	71.4
All clades	237**	**0.08**	**82.3**

Data retrieved from AntibodyDatabase (West *et al*., PNAS, 2013)

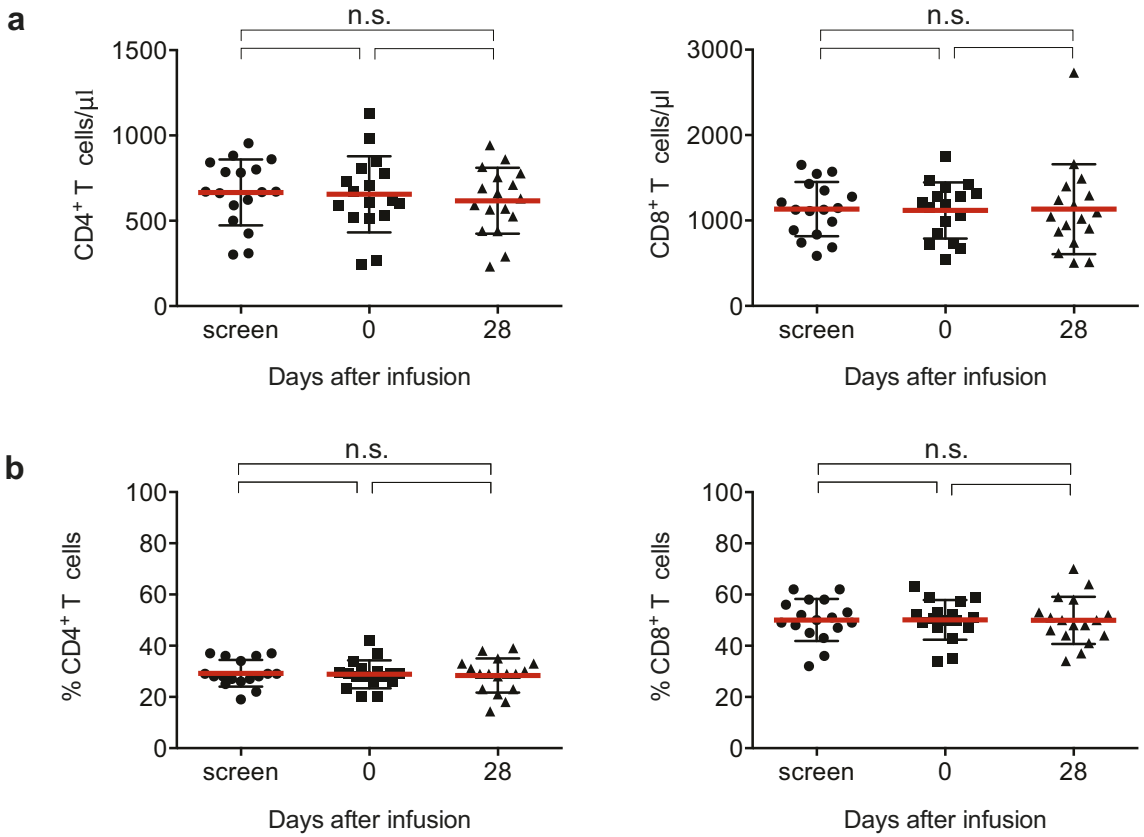
* Geometric Mean

* * Includes 1 strain, of which no clade was determined

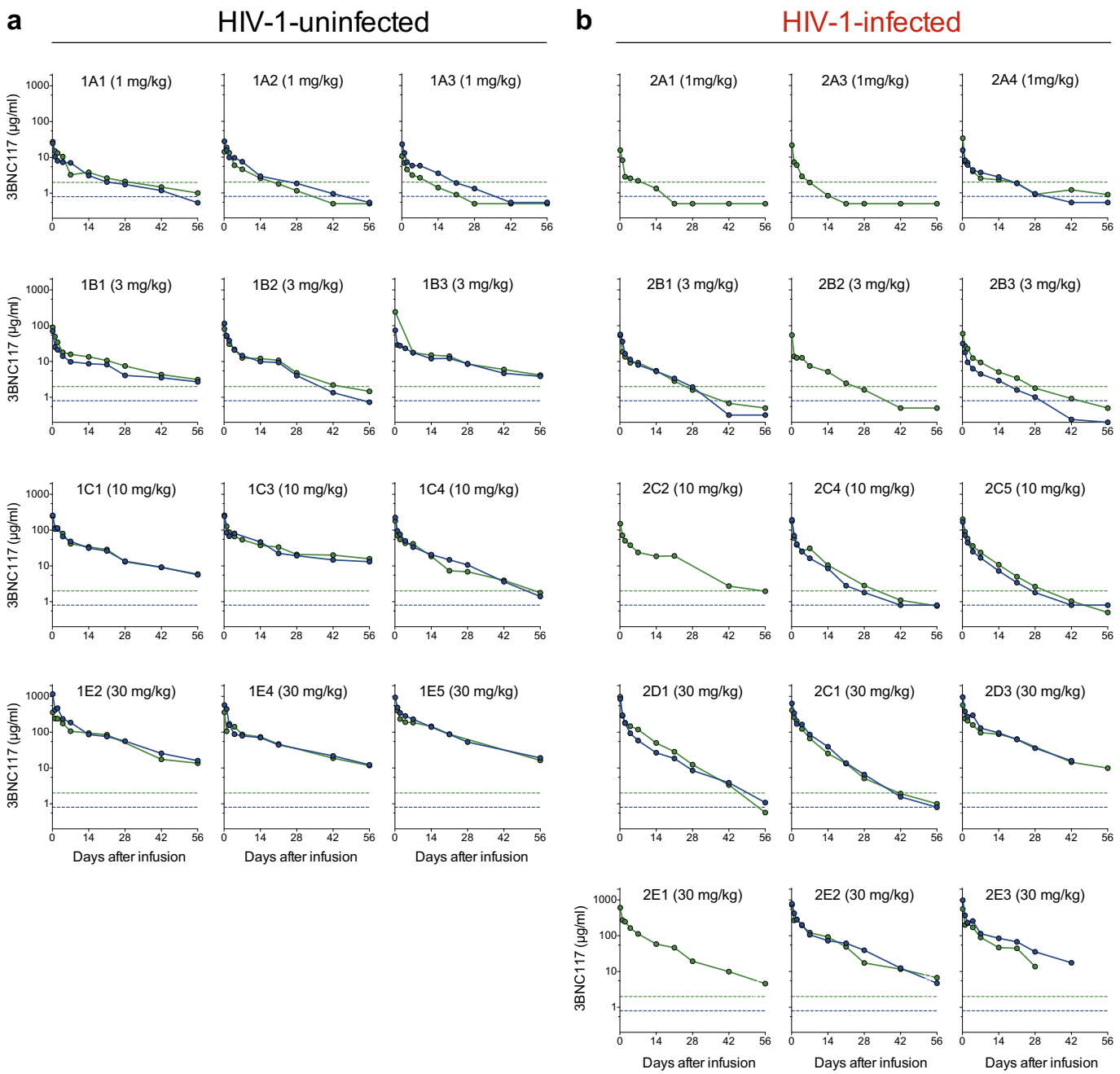
b



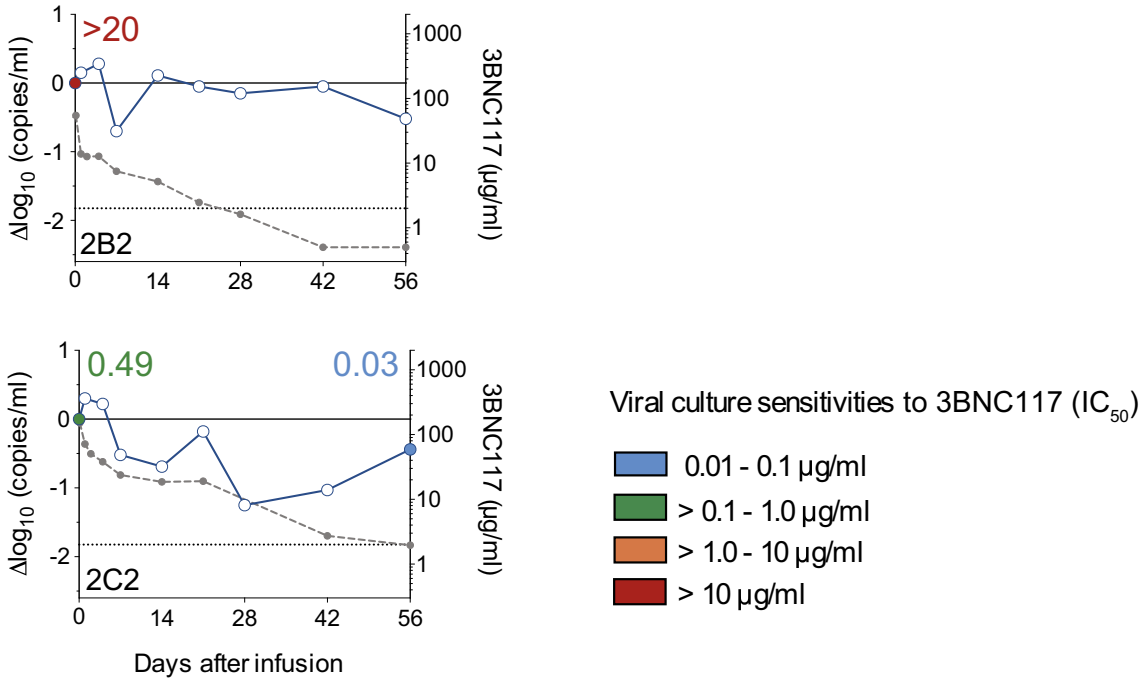
Extended Data Figure 1 | HIV-1 neutralizing activity of 3BNC117. **a**, Summary of 3BNC117 neutralizing *in vitro* activity based on 237 HIV-1 isolates comprising 6 different clades. Data were retrieved from the 'AntibodyDatabase' by A.P.W. (ref. 39). **b**, Illustration of the fraction (that is, % coverage; *y* axis) of HIV-1 isolates that are neutralized at a given IC_{50} (µg ml^{-1}; *x* axis) using the same data set.



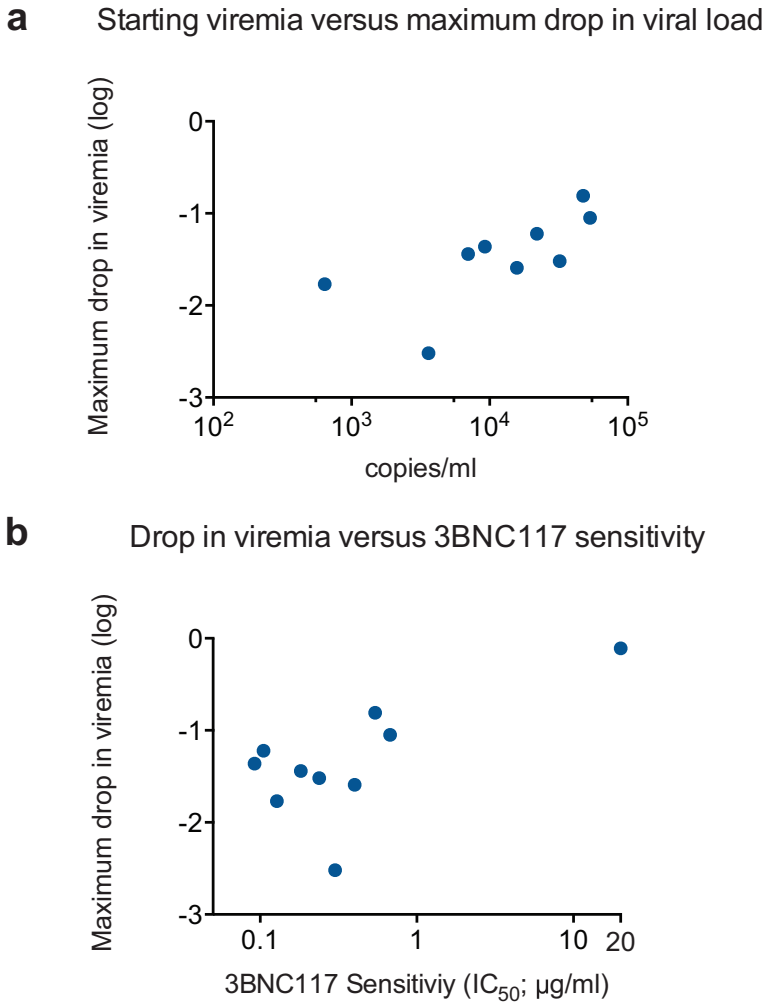
Extended Data Figure 2 | CD4$^+$ and CD8$^+$ T-cell counts before and after 3BNC117 infusion. **a**, Absolute numbers (cells µl^{-1}) of CD4$^+$ and CD8$^+$ T-cell counts of all enrolled HIV-1-infected participants at screen, on the day of 3BNC117 infusion (day 0), and at day 28 after infusion. **b**, Percentage of CD4$^+$ and CD8$^+$ T cells for the same subjects and time points. Mean and standard deviation are indicated in red and black, respectively. No significant differences between pre-infusion and post infusion levels were detected by using one-way ANOVA.



Extended Data Figure 3 | 3BNC117 serum concentration and activity in single subjects. **a**, **b**, Serum levels of 3BNC117 in all uninfected (**a**) and HIV-1-infected (**b**) individuals that received 1, 3, 10, or 30 mg kg^{-1} 3BNC117 at day 0. Antibody levels were measured by a sandwich ELISA using an anti-3BNC117 specific antibody (green) or by measuring the 3BNC117 serum activity in a TZM.bl neutralization assay (blue).



Extended Data Figure 4 | 3BNC117 sensitivity and changes in viraemia in 2 ART-treated subjects. Both subjects were on ART when enrolled in the study and received a single dose (2B2, 3 mg kg^{-1}; 2C2, 10 mg kg^{-1}) of 3BNC117 at day 0. The left *y* axis shows $\log_{10}$ change in viraemia from baseline, and right *y* axis shows antibody level measured in ELISA. Blue line reflects change in VL and dotted grey line antibody level. Numbers indicate IC_{50} values for 3BNC117 of autologous viral isolates measured by TZM.bl assay, colour-coded as indicated on the right.



Extended Data Figure 5 | Correlating viral decay with 3BNC117 sensitivity and starting viral load. **a**, Maximum decline in viral load in ART-untreated HIV-1-infected participants with baseline 3BNC117-sensitive viruses ($IC_{50} < 1\ \mu g\ ml^{-1}$) versus pre-treatment (day 0) viral load (Pearson coefficient $r = 0.72$ $P = 0.03$; Spearman coefficient rho = 0.78, $P = 0.02$). **b**, Maximum drop in viral load in HIV-1-infected and viremic individuals receiving a 10 or 30 $mg\ kg^{-1}$ dose of 3BNC117 (y axis) versus baseline autologous virus sensitivity to 3BNC117 (x axis; Pearson coefficient $r = 0.69$ $P = 0.03$; Spearman coefficient rho = 0.41, $P = 0.23$).

Extended Data Table 1 | Baseline characteristics of HIV-1-infected individuals and 3BNC117 safety data

a

Study ID	3BNC117 dose	Age	Years since HIV Diagnosis	Current ART regimen	Clade	HIV-RNA level (copies/ml)	abs. $CD4^+$ T cell count (day 0; cells/mm^3)
2A1	1 mg/kg	35	11	ART naïve	B	3,210	674
2A3	1 mg/kg	39	14	Off ART	B	43,650	520
2A4	1 mg/kg	42	8	ART naïve	B	5,340	607
2B1	3 mg/kg	20	1	Off ART	ND	4,090	264*
2B2	3 mg/kg	48	20	DRV/r/TDF/FTC**	ND	100	706
2B3	3 mg/kg	20	1	ART naïve	B	38,190	777
2C2	10 mg/kg	51	12	ATV/r/3TC/ZDV**	ND	30	728
2C4	10 mg/kg	54	23	Off ART	ND	820	805
2C5	10 mg/kg	50	4	ART naïve	B	9,260	245*
2D1	30 mg/kg	33	3	ART naïve	B	53,470	980
2C1	30 mg/kg	51	17	Off ART	B	47,650	1129
2D3	30 mg/kg	33	0.5	ART naïve	ND	640	618
2E1	30 mg/kg	21	2	ART naïve	B	15,780	847
2E2	30 mg/kg	46	1.5	ART naïve	B	6,990	513
2E3	30 mg/kg	23	1.5	ART naïve	BF	22,030	590
2E4	30 mg/kg	38	1	ART naïve	ND	32,220	603
2E5	30 mg/kg	30	1	ART naïve	ND	3,610	532

b

Adverse Events	No. AEs	% of reported AEs	No. possibly related	No. Mild	No. Moderate	No. Severe	Uninfected (No. of AEs)				HIV-1-infected (No. of AEs)			
							1 mg/kg	3 mg/kg	10 mg/kg	30 mg/kg	1 mg/kg	3 mg/kg	10 mg/kg	30 mg/kg
Rhinorrhea and/or cough	10	16.9	3	8	2	0	1	1	0	1	1	0	0	6
Malaise	7	11.9	5	5	2	0	1	1	2	0	1	2	0	0
Headache	6	10.2	3	5	1	0	0	0	0	1	1	0	1	3
Diarrhea	5	8.5	1	2	1	0	1	1	0	0	1	0	1	1
Myalgia/arthralgia (localized)	4	6.8	1	3	1	0	0	0	0	0	1	0	3	0
Sore throat	4	6.8	2	4	0	0	1	1	0	0	0	1	1	0
Tenderness	3	5.1	1	3	0	0	0	0	0	1	1	0	1	0
Increased Lacrimation	2	3.4	2	2	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	1
Chills	2	3.4	0	1	1	0	0	1	0	0	1	0	0	0
Conjunctival erythema	2	3.4	2	2	0	0	0	0	1	0	1	0	0	0
Fevershiness	2	3.4	0	1	1	0	0	0	0	0	1	1	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	1	0	0	0	0	0	0	0	0	1	0
Decreased appetite	1	1.7	0	1	0	0	0	0	0	0	1	0	0	0
Erythema	1	1.7	1	1	0	0	0	0	0	1	0	0	0	0
Paresthesia upper extremity	1	1.7	0	1	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

a, Baseline characteristics of HIV-1-infected individuals. *Absolute CD4 T-cell count was 309 and 302 cells μl^{-1} at screening. **DRV/r/TDF/FTC, darunavir, ritonavir tenofovir, emtricitabine; ATV/r/3TC/ZDV, atazanavir, ritonavir, lamividune, zidovudine. ND, not determined. **b**, 3BNC117 safety data. AE, adverse events. Subject 2D3 developed herpes zoster involving a lumbar dermatome 35 days after infusion. The event was graded as moderate and considered not related to 3BNC117.

Extended Data Table 2 | HIV-1 RNA levels and viral decay mixed-effect linear model

a

1 mg/kg

2A1	HIV-1 RNA Level		
Timepoint	**c/ml**	**log_{10}**	**Δ log_{10}**
Screen	1,340	3.13	-
Pre	1,100	3.04	-
Day 0	3,210	3.51	0.00
Day 1	10,810	4.03	0.52
Day 4	4,970	3.70	0.19
Day 7	3,190	3.50	-0.01
Day 14	2,600	3.41	-0.10
Day 21	3,820	3.58	0.07
Day 28	5,070	3.71	0.20
Day 42	3,570	3.55	0.04
Day 56	6,370	3.80	0.29

2A3	HIV-1 RNA Level		
Timepoint	**c/ml**	**log_{10}**	**Δ log_{10}**
Screen	41,670	4.62	-
Pre	48,100	4.68	-
Day 0	43,560	4.64	0.00
Day 1	50,180	4.70	0.06
Day 4	24,050	4.38	-0.26
Day 7	34,850	4.54	-0.10
Day 14	31,770	4.50	-0.14
Day 21	35,840	4.55	-0.09
Day 28	38,500	4.59	-0.05
Day 42	59,780	4.78	0.14
Day 56	63,600	4.80	0.16

2A4	HIV-1 RNA Level		
Timepoint	**c/ml**	**log_{10}**	**Δ log_{10}**
Screen	5,350	3.73	-
Pre	6,490	3.81	-
Day 0	5,340	3.73	0.00
Day 1	10,880	4.04	0.31
Day 4	8,430	3.93	0.20
Day 7	4,870	3.69	-0.04
Day 14	11,000	4.04	0.31
Day 21	7,470	3.87	0.14
Day 28	7,880	3.90	0.17
Day 42	12,150	4.08	0.35
Day 56	14,020	4.15	0.42

3 mg/kg

2B1	HIV-1 RNA Level		
Timepoint	**c/ml**	**log_{10}**	**Δ log_{10}**
Screen	6,420	3.81	-
Pre	4,950	3.69	-
Day 0	4,090	3.61	0.00
Day 1	6,470	3.81	0.20
Day 4	2,690	3.43	-0.18
Day 7	1,610	3.21	-0.40
Day 14	4,880	3.69	0.08
Day 21	4,160	3.62	0.01
Day 28	3,800	3.58	-0.03
Day 42	4,970	3.70	0.09
Day 56	3,550	3.55	-0.06

2B2	HIV-1 RNA Level		
Timepoint	**c/ml**	**log_{10}**	**Δ log_{10}**
Screen	80*	1.90	-
Pre	30	1.48	-
Day 0	100	2.00	0.00
Day 1	140	2.15	0.15
Day 4	190	2.28	0.28
Day 7	20	1.30	-0.70
Day 14	130	2.11	0.11
Day 21	90	1.95	-0.05
Day 28	70	1.85	-0.15
Day 42	90	1.95	-0.05
Day 56	30	1.48	-0.52

2B3	HIV-1 RNA Level		
Timepoint	**c/ml**	**log_{10}**	**Δ log_{10}**
Screen	53,660	4.73	-
Pre	28,810	4.46	-
Day 0	38,190	4.58	0.00
Day 1	31,950	4.50	-0.08
Day 4	11,540	4.06	-0.52
Day 7	20,500	4.31	-0.27
Day 14	35,830	4.55	-0.03
Day 21	41,570	4.62	0.04
Day 28	30,810	4.49	-0.09
Day 42	29,020	4.46	-0.12
Day 56	27,700	4.44	-0.14

10 mg/kg

2C2	HIV-1 RNA Level		
Timepoint	**c/ml**	**log_{10}**	**Δ log_{10}**
Screen	20	1.30	-
Pre	30	1.48	-
Day 0	30	1.48	0.00
Day 1	60	1.78	0.30
Day 4	50	1.70	0.22
Day 7	9	0.96	-0.52
Day 14	6	0.79	-0.69
Day 21	20	1.30	-0.18
Day 28	2	0.23	-1.25
Day 42	3	0.45	-1.03
Day 56	21	1.32	-0.16

2C4	HIV-1 RNA Level		
Timepoint	**c/ml**	**log_{10}**	**Δ log_{10}**
Screen	2,510	3.41	-
Pre	1,100	3.04	-
Day 0	820	2.91	0.00
Day 1	690	2.84	-0.07
Day 4	980	2.99	0.08
Day 7	990	3.00	0.09
Day 14	700	2.85	-0.06
Day 21	1,420	3.15	0.24
Day 28	630	2.80	-0.11
Day 42	980	2.99	0.08
Day 56	940	2.97	0.06

2C5	HIV-1 RNA Level		
Timepoint	**c/ml**	**log_{10}**	**Δ log_{10}**
Screen	19,970	4.30	-
Pre	10,860	4.04	-
Day 0	9,260	3.97	0.00
Day 1	5,300	3.72	-0.25
Day 4	2,340	3.37	-0.60
Day 7	410	2.61	-1.36
Day 14	1,070	3.03	-0.94
Day 21	8,900	3.95	-0.02
Day 28	8,550	3.93	-0.04
Day 42	12,410	4.09	0.12
Day 56	12,840	4.11	0.14

30 mg/kg

2D1	HIV-1 RNA Level		
Timepoint	**c/ml**	**log_{10}**	**Δ log_{10}**
Screen	5,730	3.76	-
Pre	34,840	4.54	-
Day 0	53,470	4.73	0.00
Day 1	84,450	4.93	0.20
Day 4	36,140	4.56	-0.17
Day 7	5,980	3.78	-0.95
Day 14	4,830	3.68	-1.05
Day 21	15,180	4.18	-0.55
Day 28	10,960	4.04	-0.69
Day 42	7,650	3.88	-0.85
Day 56	9,820	3.99	-0.74

2C1	HIV-1 RNA Level		
Timepoint	**c/ml**	**log_{10}**	**Δ log_{10}**
Screen	31,870	4.50	-
Pre	31,870	4.50	-
Day 0	47,650	4.68	0.00
Day 1	46,040	4.66	-0.02
Day 4	7,790	3.89	-0.79
Day 7	7,470	3.87	-0.81
Day 14	19,360	4.29	-0.39
Day 21	30,380	4.48	-0.20
Day 28	25,610	4.41	-0.27
Day 42	22,830	4.36	-0.32
Day 56	32,310	4.51	-0.17

2D3	HIV-1 RNA Level		
Timepoint	**c/ml**	**log_{10}**	**Δ log_{10}**
Screen	3,620	3.56	-
Pre	3,280	3.52	-
Day 0	640	2.81	0.00
Day 1	450	2.65	-0.16
Day 4	210	2.32	-0.49
Day 7	80	1.90	-0.91
Day 14	50	1.70	-1.11
Day 21	3	0.52	-1.77
Day 28	40	1.60	-1.21
Day 42	50	1.70	-1.11
Day 56	11	1.04	-1.77

30 mg/kg

2E1	HIV-1 RNA Level		
Timepoint	**c/ml**	**log_{10}**	**Δ log_{10}**
Screen	8,742	3.94	-
Pre	12,031	4.08	-
Day 0	15,780	4.20	0.00
Day 1	14,790	4.17	-0.03
Day 4	3,560	3.55	-0.65
Day 7	404	2.61	-1.59
Day 14	468	2.67	-1.53
Day 21	8,557	3.93	-0.27
Day 28	8,159	3.91	-0.29
Day 42	6,671	3.82	-0.38
Day 56	13,486	4.13	-0.07

2E2	HIV-1 RNA Level		
Timepoint	**c/ml**	**log_{10}**	**Δ log_{10}**
Screen	3,394	3.53	-
Pre	1,802	3.26	-
Day 0	6,990	3.84	0.00
Day 1	6,450	3.81	-0.03
Day 4	2,340	3.37	-0.47
Day 7	1,663	3.22	-0.62
Day 14	253	2.40	-1.44
Day 21	917	2.96	-0.88
Day 28	4,273	3.63	-0.21
Day 42	15,721	4.20	0.36
Day 56	3,465	3.54	-0.30

2E3	HIV-1 RNA Level		
Timepoint	**c/ml**	**log_{10}**	**Δ log_{10}**
Screen	23,168	4.36	-
Pre	30,570	4.49	-
Day 0	22,030	4.34	0.00
Day 1	38,620	4.59	0.25
Day 4	10,540	4.02	-0.32
Day 7	1,308	3.12	-1.22
Day 14	3,901	3.59	-0.75
Day 21	23,717	4.38	0.04
Day 28	33,370	4.52	0.18
Day 42	22,699	4.36	0.01
Day 56	27,998	4.45	0.10

30 mg/kg

2E4	HIV-1 RNA Level		
Timepoint	**c/ml**	**log_{10}**	**Δ log_{10}**
Screen	45,311	4.66	-
Pre	66,889	4.83	-
Day 0	32220	4.51	0.00
Day 1	44980	4.65	0.14
Day 4	19,290	4.29	-0.22
Day 7	3,642	3.56	-0.95
Day 14	983	2.99	-1.52
Day 21	5,726	3.76	-0.75
Day 28	18,005	4.26	-0.25
Day 42	40,079	4.60	0.09
Day 56	22,100	4.34	-0.16

2E5	HIV-1 RNA Level		
Timepoint	**c/ml**	**log_{10}**	**Δ log_{10}**
Screen	4,720	3.67	-
Pre	4,244	3.63	-
Day 0	3610	3.56	0.00
Day 1	5300	3.72	0.16
Day 4	1,000	3.00	-0.56
Day 7	181	2.26	-1.30
Day 14	77	1.89	-1.67
Day 21	11	1.04	-2.52
Day 28	148	2.17	-1.39
Day 42	1,064	3.03	-0.53
Day 56	589	2.77	-0.79

b

1 mg/kg

Contrast	Dose	Average	SE	p.value
Screen - Day 0	1mg/kg	-0.133	0.258	0.607
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

3 mg/kg

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
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

10 mg/kg

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
Day 4 - Day 0	10mg/kg	-0.260	0.316	0.410
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
Day 28 - Day 0	10mg/kg	-0.075	0.406	0.854
Day 42 - Day 0	10mg/kg	0.102	0.412	0.804
Day 56 - Day 0	10mg/kg	0.101	0.416	0.809

30 mg/kg

Contrast	Dose	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

a, HIV-1 RNA levels. Subjects 2B2 and 2C2 were on ART. Subject 2D3 started ART after day 42. Screen was performed between day −49 and day −14. Viraemia measurements at "Pre" were performed between day −42 and day −2. **b**, Viral decay mixed-effect linear model.

Extended Data Table 3 | Sensitivity of autologous virus isolates and cloned HIV-1 envelopes to 3BNC117

Autologous virus isolates					HIV-1 envelopes cloned from plasma				
Dose	ID	Day post infusion	3BNC117 IC_{50} (μg/ml)	3BNC117 IC_{50}	Clone	Cloning procedure	Vector backbone	3BNC117 (IC_{50}; μg/ml)	Average (geo. mean)
1 mg/kg	2A1	Day 0	ND	ND	ND				
		Day 28	**0.90**						
	2A3	Day 0	**0.11**	**35.3**	ND				
		Day 28	**3.78**						
	2A4	Day 0	**0.07**	**13.5**	ND				
		Day 28	**0.94**						
3 mg/kg	2B1	Day 0	**0.77**	**25.9**	ND				
		Day 28	>20						
	2B2	Day 0	>20	ND	ND				
		Day 28	ND						
	2B3	Day 0	**0.20**	**1.5**	ND				
		Day 28	**0.30**						
10 mg/kg	2C2	Day 0	**0.49**	**0.1**	ND				
		Day 56	**0.03**						
	2C4	Day 0	>20	**No change**	ND				
		Day 28	>20						
	2C5	Day 0	**0.09**	**167.0**	2C5_D0_12	gp120	pSVIII	0.015	**0.02**
					2C5_D0_21	gp120	pSVIII	0.017	
					2C5_D0_27	gp120	pSVIII	0.017	
		Day 28	**15.36**		2C5_W4_59	gp120	pSVIII	11.543	**7.09**
					2C5_W4_22	gp120	pSVIII	6.737	
					2C5_W4_27	gp120	pSVIII	7.514	
					2C5_W4_28	gp120	pSVIII	3.495	
					2C5_W4_34	gp120	pSVIII	8.758	
30 mg/kg	2C1	Day -7	**0.54**	**1.8**	2C1_D0_12	gp120	pSVIII	0.209	**0.06**
					2C1_D0_22	gp120	pSVIII	0.158	
					2C1_D0_32	gp120	pSVIII	0.006	
		Day 28	**1.78**		2C1_W4_12	gp120	pSVIII	0.043	**0.14**
					2C1_W4_18	gp120	pSVIII	0.225	
					2C1_W4_31	gp120	pSVIII	0.262	
	2D1	Day 0	**0.68**	**1.3**	2D1_D0_D5	gp160	pcDNA3.1	0.165	**0.15**
					2D1_D0_B3.1	gp160	pcDNA3.1	0.128	
					2D1_D0_B10	gp160	pcDNA3.1	0.172	
		Day 28	**0.90**		2D1_W4_37	gp120	pSVIII	0.578	**0.52**
					2D1_W4_40	gp120	pSVIII	0.501	
					2D1_W4_69	gp120	pSVIII	0.465	
					2D1_W4_71	gp120	pSVIII	0.523	
	2D3	Day 0	**0.13**	**2.7**	ND				
		Day 28	**0.35**						
	2E1	Screen	**0.40**	ND	2E1_D0_12	gp160	pcDNA3.1	0.103	**0.09**
					2E1_D0_20	gp160	pcDNA3.1	0.115	
					2E1_D0_34	gp160	pcDNA3.1	0.068	
		Day 28	ND		2E1_W4_23	gp160	pcDNA3.1	0.041	**0.23**
					2E1_W4_E1	gp160	pcDNA3.1	0.590	
					2E1_W4_F6	gp160	pcDNA3.1	0.496	
	2E2	Screen	**0.18**	**12.3**	2E2_D0_A10	gp160	pcDNA3.1	0.017	**0.01**
					2E2_D0_C3	gp160	pcDNA3.1	0.010	
					2E2_D0_E9	gp160	pcDNA3.1	0.018	
		Day 28	**2.23**		2E2_W4_B9	gp160	pcDNA3.1	0.017	**0.03**
					2E2_W4_C11	gp160	pcDNA3.1	0.020	
					2E2_W4_D5	gp160	pcDNA3.1	0.057	
	2E3	Screen	**0.18**	**6.1**	ND				
		Day 28	**1.10**						
	2E4	Screen	**0.24**	ND	ND				
		Day 28	ND						
	2E5	Screen	**0.30**	ND	ND				
		Day 28	ND						

ND, not determined.

Extended Data Table 4 | Pharmacokinetics of 3BNC117 based on a 56-day period post infusion

ID	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 (µg/ml)	AUC_% Extrap_pred
1A1	Negative	1	ELISA	27.4	n.d.	n.d.	-	-	n.d.	-	-	n.d.
			TZM.bl	27.4	0.936	21.32	14	42	184.0	42	1.2	19.2
1A2	Negative	1	ELISA	18.8	n.d.	n.d.	-	-	n.d.	-	-	n.d.
			TZM.bl	27.8	0.893	12.89	7	42	181.7	42	1.0	9.0
1A3	Negative	1	ELISA	11.2	n.d.	n.d.	-	-	n.d.	-	-	n.d.
			TZM.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.	-	-	n.d.	-	-	n.d.
2A3	Positive/Off	1	ELISA	22.7	n.d.	n.d.	-	-	n.d.	-	-	n.d.
2A4	Positive/Off	1	ELISA	33.8	n.d.	n.d.	-	-	n.d.	-	-	n.d.
			TZM.bl	15.6	n.d.	n.d.	-	-	n.d.	-	-	n.d.
1B1	Negative	3	ELISA	89.9	0.985	19.64	7	56	685.2	56	3.1	12.1
			TZM.bl	70.9	0.881	24.30	7	56	483.7	56	2.7	17.9
1B2	Negative	3	ELISA	90.1	0.878	12.91	7	42	523.5	42	2.2	8.8
			TZM.bl	116.0	0.936	10.04	7	42	481.2	42	1.4	4.6
1B3	Negative	3	ELISA	243.4	0.954	21.54	14	56	1017.3	56	4.2	12.1
			TZM.bl	74.5	0.954	21.70	7	56	706.6	56	3.9	15.6
2B1	Positive/Off	3	ELISA	90.8	0.942	9.60	4	21	219.4	21	2.8	19.2
			TZM.bl	57.4	0.994	10.28	7	28	245.9	28	1.9	12.1
2B2	Positive/On	3	ELISA	97.6	0.928	8.74	7	21	200.7	21	2.5	16.5
2B3	Positive/Off	3	ELISA	60.0	0.981	9.08	4	21	251.2	21	3.5	17.0
			TZM.bl	32.6	0.994	9.19	4	28	129.8	28	1.0	10.1
1C1	Negative	10	ELISA	347.8	0.942	16.33	7	56	1667.9	56	5.9	7.5
			TZM.bl	281.8	0.964	15.79	7	56	1598.9	56	5.6	7.3
1C3	Negative	10	ELISA	308.9	0.860	29.01	7	56	2529.4	56	15.8	23.5
			TZM.bl	244.7	0.700	26.59	14	56	2228.5	56	13.1	19.3
1C4	Negative	10	ELISA	180.6	0.835	10.73	7	42	859.1	42	4.0	5.5
			TZM.bl	230.7	0.990	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
2C4	Positive/Off	10	ELISA	178.2	0.944	6.92	4	28	550.2	28	2.8	5.1
			TZM.bl	193.0	0.979	6.14	4	28	417.9	28	1.8	3.4
2C5	Positive/Off	10	ELISA	201.1	0.997	6.60	7	28	592.6	28	2.6	4.1
			TZM.bl	174.4	0.994	6.50	7	28	431.2	28	1.8	3.7
1E2	Negative	30	ELISA	360.8	0.930	14.48	7	56	4259.4	56	13.6	5.9
			TZM.bl	1166.3	0.978	16.19	14	56	5901.2	56	16.1	6.2
1E3	Negative	30	ELISA	361.8	0.990	16.26	7	56	3177.5	56	11.7	8.2
			TZM.bl	606.2	0.989	17.85	7	56	3422.2	56	12.3	9.3
1E5	Negative	30	ELISA	765.0	0.992	14.15	4	56	5874.2	56	16.3	5.7
			TZM.bl	939.6	0.959	15.22	14	56	6424.5	56	19.1	6.1
2C1	Positive/Off	30	ELISA	410.2	0.991	5.80	7	28	1707.8	28	5.1	2.6
			TZM.bl	717.4	0.993	5.99	7	42	2186.4	42	1.6	0.6
2D1	Positive/Off	30	ELISA	976.4	0.996	6.86	7	42	2494.9	42	3.4	1.3
			TZM.bl	849.3	0.990	8.83	7	56	1825.5	56	1.1	0.8
2D3	Positive/Off	30	ELISA	571.0	0.962	13.39	7	56	3616.5	56	9.9	4.8
			TZM.bl	953.7	0.993	11.23	7	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	7	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

Estimation of PK parameters retrieved from study participants (ID) up to 8 weeks post 3BNC117 infusion. 3BNC117 was administered at 1, 3, 10, and 30 mg kg^{-1} in uninfected (Negative) and HIV-1-infected (Positive) individuals. 3BNC117 serum concentrations were determined by ELISA or TZM.bl assay (see Methods). PK-parameters were obtained by performing a non-compartmental analysis (NCA) using WinNonlin 6.3. $T_{1/2}$ was estimated using values between Lambda upper/lower. n.d., PK parameters were not determined because of insufficient data or an extrapolated AUC_inf that exceeded 25%. Values in red indicate extrapolated AUC_inf >10%. *Days post infusion of 3BNC117.

Extended Data Table 5 | Summary of 3BNC117 pharmacokinetics based on a 56-day period post infusion

Dose	HIV-1-status	Subjects	Method (subjects analyzed)	Cmax (µg/ml)			$t_{1/2\ (days)}$ (1)		
				Mean	SD	Range	**Mean**	SD	Range
1 mg	Neg.	3	ELISA (3)	**19.1**	8.1	11.2 - 27.4	**n.d.**	n.d.	n.d.
			TZM.bl (3)	**26.2**	2.4	23.5 - 27.8	**n.d.**	n.d.	n.d.
1 mg	Pos.	3	ELISA (3)	**24.1**	9.1	15.7 - 33.8	**n.d.**	n.d.	n.d.
			TZM.bl (1)	**23.5**	n.d.	n.d.	**n.d.**	n.d.	n.d.
3 mg	Neg.	3	ELISA (3)	**141.1**	88.6	89.9 - 243.4	**18.0**	4.5	12.9 - 21.5
			TZM.bl (3)	**87.1**	25.1	70.9 - 116.0	**18.7**	7.6	10.0 - 24.3
3 mg	Pos.	3	ELISA (3)	**73.7**	35.7	32.6 - 97.6	**9.2**	0.4	8.7 - 9.6
			TZM.bl (3)	**50.6**	15.7	32.6 - 61.7	**11.2**	2.2	9.5 - 13.73
10 mg	Neg.	3	ELISA (3)	**279.1**	87.5	180.6 - 347.8	**18.7**	9.4	10.7 - 29.0
			TZM.bl (3)	**252.4**	26.4	230.7 - 281.8	**17.7**	8.1	10.7 - 26.6
10 mg	Pos.	3	ELISA (3)	**235.4**	80.0	178.2 - 326.8	**8.1**	2.4	6.6 - 10.9
			TZM.bl (3)	**213.6**	52.6	174.4 - 273.4	**8.8**	4.3	6.5 - 13.7
30 mg	Neg.	3	ELISA (3)	**495.9**	233.1	360.8 - 765.0	**15.0**	1.1	14.2 - 16.3
			TZM.bl (3)	**904.0**	281.7	1166.3 - 606.2	**16.4**	1.3	15.2 -17.9
30 mg	Pos.	6	ELISA (6)	**669.8**	199.7	410.2 - 976.4	**9.9**	3.3	5.8 - 13.7
			TZM.bl (3)	**840.1**	118.4	717.4 - 953.7	**8.9**	2.3	6.7 - 11.2
All	Neg.	12	ELISA (9)	-	-	-	**17.2**	5.5	10.7 - 29.0
			TZM.bl (9)	-	-	-	**17.6**	5.7	10.0 - 26.6
All	Pos.	15	ELISA (12)	-	-	-	**9.3**	2.6	5.7 - 13.7
			TZM.bl (9)	-	-	-	**9.6**	2.9	6.1 - 13.7

(1) Estimation of half-lives; SD, standard deviation.