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Reporting Summary

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Statistical parameters

When statistical analyses are reported, confirm that the following items are present in the relevant location (e.g. figure legend, table legend, main text, or Methods section).

n/a	Confirmed	
☐	☒	The exact sample size (n) for each experimental group/condition, given as a discrete number and unit of measurement
☐	☒	An indication of whether measurements were taken from distinct samples or whether the same sample was measured repeatedly
☐	☒	The statistical test(s) used AND whether they are one- or two-sided *Only common tests should be described solely by name; describe more complex techniques in the Methods section.*
☐	☒	A description of all covariates tested
☐	☒	A description of any assumptions or corrections, such as tests of normality and adjustment for multiple comparisons
☐	☒	A full description of the statistics including central tendency (e.g. means) or other basic estimates (e.g. regression coefficient) AND variation (e.g. standard deviation) or associated estimates of uncertainty (e.g. confidence intervals)
☐	☒	For null hypothesis testing, the test statistic (e.g. F, t, r) with confidence intervals, effect sizes, degrees of freedom and P value noted *Give P values as exact values whenever suitable.*
☒	☐	For Bayesian analysis, information on the choice of priors and Markov chain Monte Carlo settings
☒	☐	For hierarchical and complex designs, identification of the appropriate level for tests and full reporting of outcomes
☐	☒	Estimates of effect sizes (e.g. Cohen's d, Pearson's r), indicating how they were calculated
☐	☒	Clearly defined error bars *State explicitly what error bars represent (e.g. SD, SE, CI)*

Our web collection on statistics for biologists may be useful.

Software and code

Policy information about availability of computer code

Data collection	Software for obtaining the sequencing data was MiSeq Control Software 2.6 2.1. Software for tracking the clinical samples was IRIS by iMedRIS.
Data analysis	- Pharmacokinetics analysis was performed with Phoenix WinNonlin Build 8 (Certara). - To measure the effect of the combination treatment on viral load (VL), we estimated simultaneous confidence bands (SCBs) for the delta log10 VLs. . We computed SCBs with the R package locfit (version 1.5-9.1) using the Gaussian family for the local likelihood function. To estimate whether there is a significant difference between 3BNC117 + 10-1074 combination therapy and 3BNC117 or 10-1074 monotherapy in viremic individuals off antiretroviral therapy, we fit a linear mixed effects model to the data, using time and treatment as fixed effects and a random intercept for each participant. Data for 3BNC117 and 10-1074 monotherapy have been published previously and only time points from viral load measurements off antiretroviral therapy were included. We compared it to a model without treatment as predictor using a likelihood ratio test. The time point of VL measurement was modeled as an ordered factor and correlation structure between measurements from the same individual was modeled based on the order of measurements using different options available in nlme (exponential, linear, rational quadratic, and spherical correlation structure, as well as different combinations of autocorrelation and moving average). The models were fit maximizing the log-likelihood with the lme function of the R package nlme (version 3.1-131). Time points were restricted to {day0, week1, week2, week3, week4, week6, week8, week12, week16, week20, week24} to have a sufficient number of measurements per time point. CD4+ T cell counts before and after 3BNC117 plus 10-1074 infusions were compared by one-way ANOVA using GraphPad Prism. Logo plots were generated using the longitudinal antigenic sequences and sites from intra-host evolution tool (LASSIE) - Analysis of HIV-1 envelope sequences was performed before infusion of the antibodies (day 0) and at viral rebound. Multiple alignment

of nucleotide sequences guided by amino acid translations of env sequences was performed by TranslatorX (http://translatorx.co.uk/). Sequences were analyzed for the presence of recombination using the 3SEQ recombination algorithm (http://mol.ax/software/3seq/).

For manuscripts utilizing custom algorithms or software that are central to the research but not yet described in published literature, software must be made available to editors/reviewers upon request. We strongly encourage code deposition in a community repository (e.g. GitHub). See the Nature Research guidelines for submitting code & software for further information.

Data

Policy information about availability of data

All manuscripts must include a data availability statement. This statement should provide the following information, where applicable:

- Accession codes, unique identifiers, or web links for publicly available datasets
- A list of figures that have associated raw data
- A description of any restrictions on data availability

Sequences from all isolated viruses will be made available in GenBank.

Field-specific reporting

Please select the best fit for your research. If you are not sure, read the appropriate sections before making your selection.

☒ Life sciences ☐ Behavioural & social sciences ☐ Ecological, evolutionary & environmental sciences

For a reference copy of the document with all sections, see nature.com/authors/policies/ReportingSummary-flat.pdf

Life sciences study design

All studies must disclose on these points even when the disclosure is negative.

Sample size

A single infusion of 3BNC117 at 30 mg/kg in 10 viremic participants led to an average decline in plasma HIV-1 RNA levels of 1.48 log10 copies/ml (SD = 0.6 log10 copies/ml). When administered at 30 mg/kg, 10-1074 led to similar decline in plasma HIV-1 RNA (average decline of 1.48 log10 copies/ml, SD = 0.62 log10 copies/ml). When the combination of 3BNC117 and 10-1074 was administered to SHIV-infected non-human primates average decline in plasma viremia was 2 log10 copies/ml. (SD = 0.75 log10 copies/ml).

The table below shows the minimum average decline in plasma HIV-1 RNA levels (log10) that can be detected with 80% power and a one-sided 0.05 test, assuming a standard deviation of 0.6 (log10 copies/ml) from the 3BNC117 single infusion data and 10-1074 at 30 mg/kg data in humans, and 0.75 (log10 copies/ml) from the 3BNC117 plus 10-1074 data in non-human primates. The calculations were performed for n=4 to 6 subjects off ART in Groups 1C and 3.

Table 1. Minimum average decline in plasma HIV-1 RNA levels

N	standard deviation (Log10)	Minimum average decline in plasma HIV-1 RNA (Log10)
4	0.6	0.99
4	0.75	1.24
5	0.6	0.82
5	0.75	1.02
6	0.6	0.71
6	0.75	0.89

Data exclusions

No data were excluded.

Replication

This study was a clinical trial and the analyses were performed on individual trial participants. Experiments did not include replicates as all participants and data points are unique. All available data is included in the manuscript.

Randomization

Two groups of the study, Groups 1A and 1B of ART-treated individuals were randomized 3:1 to receive the antibodies or placebo (sterile saline).

Blinding

Enrollment in all study groups was sequential. Enrollment in the ART-treated groups was double-blinded and placebo-controlled. Enrollment in the viremic groups was open label and not placebo-controlled. Upon careful consideration of risk-benefit and in view of current recommendations to start HIV-infected participants on ART at diagnosis or as soon as possible, we concluded that the information to be gained by including placebo comparators in the viremic groups did appropriately justify delaying initiation of standard of care in participants who might be randomized to receive sterile saline, at this early stage of clinical development.

Reporting for specific materials, systems and methods

Materials & experimental systems

n/a	Involved in the study
☐	☒ Unique biological materials
☐	☒ Antibodies
☐	☒ Eukaryotic cell lines
☒	☐ Palaeontology
☒	☐ Animals and other organisms
☐	☒ Human research participants

Methods

n/a	Involved in the study
☒	☐ ChIP-seq
☒	☐ Flow cytometry
☒	☐ MRI-based neuroimaging

Unique biological materials

Policy information about availability of materials

Obtaining unique materials	The study included the analyses of blood samples collected from enrolled HIV-infected trial participants. These samples were obtained under an IRB approved protocol for the purposes of this study and associated analytical plan.

Antibodies

Antibodies used

3BNC117 and 10-1074 are investigational anti-HIV-1 neutralizing antibodies manufactured for clinical use. They are being investigated under US FDA INDs 118225 and 123713, respectively.
Antibodies for the Ab detection in serum by ELISA included:
- Anti-ID 3BNC117: DHVI Protein Production Facility
  Lot #: 3BNC 29Nov2017
  Dilution: 4 ug/ml coating concentration
  Clone name: anti-ID 1F1-2E3 mAb
- Anti-ID 10-1074: DHVI Protein Production Facility
  Lot #: 3Aug2016
  Dilution: 2 ug/ml coating concentration
  Clone name: anti-ID 3A1-4E11 mAb
- (HRP)-conjugated mouse anti-human IgG kappa-chain-specific antibody (Abcam), Catalog #: ab79115
  Dilution: 1:15,000
  Clone name: SB81a

Validation

3BNC117 and 10-1074 that were administered to the participants were manufactured by Celldex Therapeutics under Good Manufacturing Practice and have been fully characterized in terms of biophysical properties and potency (INDs 118225 and 123713). Both drug products are under long term stability monitoring.
Anti-idiotypic antibodies from the Duke Human Vaccine Institute (DHVI) Protein Production facility have been validated for their use in ELISA against human antibodies.
HRP-mouse monoclonal anti-human IgG kappa-chain-specific antibody has been validated for its use in ELISA and ICC/IF, reactivity against Human Kappa Chain. This product has been referenced in Scheid JF et al. Nature 535:556-60 (2016).

Eukaryotic cell lines

Policy information about cell lines

Cell line source(s)	The 293T cell line was obtained from ATCC
Authentication	The cell line was not authenticated
Mycoplasma contamination	The cell line was not tested for mycoplasma
Commonly misidentified lines (See ICLAC register)	None

Human research participants

Policy information about studies involving human research participants

Population characteristics	HIV-infected participants, male and female, aged 18-65 enrolled in the study. Participants were either off ART, with HIV viral loads < 100,000 copies/ml, or were fully suppressed on ART with viral loads < 20 copies/ml. CD4 counts at screening was > 300 cells/ml in all study groups.
Recruitment	Participants were pre-screened for sensitivity of circulating viruses against 3BNC117 and 10-1074 antibodies by bulk PBMC viral outgrowth. Sensitivity was defined as an IC50 <2 µg/ml for both 3BNC117 and 10-1074 against outgrowth virus. Participants

harboring sensitive viruses were invited for screening and were enrolled in the study sequentially. Participants were enrolled at two clinical sites at the Rockefeller University (New York, US) and Cologne University Hospital (Germany).