Time to HIV rebound after infusion of long-acting broadly neutralising antibodies 3BNC117-LS and 10-1074-LS and analytical treatment interruption (the RIO trial): a double-blind, randomised, placebo-controlled trial

Ming J Lee, Louise-Rae Cherrill, Panagiota Zacharopoulou*, Simon Collins, Marcilio Fumagalli, Emanuela Falaschetti, Mohammed Altaf, Timothy Tipoe, Piyumika Godakandaarachi, Julie Fox, Alison Uriel, Amanda Clarke, Sabine Kinloch-de Loes, Sarah Pett, Marta Boffito, Gary Whitlock, Ole S Søgaard, Kyle Ring, Irvine Mangawa, Jesal Gohil, Tamara Elliott, Henrik Nielsen, Jesper Damsgaard Gunst, Chloe Orkin, Rebecca Sutherland, Lisa Hamzah, Paola Cicconi, Graham P Taylor, Jacquie Ujetz, Ishrat Jahan, Helen Brown, Nicola Robinson, Stephen Fletcher, Hanna Box, Kelly E Seaton, Georgia D Tomaras, Margaret E Ackerman, Joshua A Weiner, Anna Kaczynska, Cintia Bittar, Jill Horowitz, Michel C Nussenzweig†, Marina Caskey†, John Frater†, Sarah Fidler†, for the RIO Study Team*

Summary

Background HIV-specific broadly neutralising antibodies (bNAbs) can maintain viral control after interrupting antiretroviral therapy (ART). We investigated the duration and efficacy of Fc-engineered long-acting bNAbs (LS-bNAbs) in maintaining ART-free HIV control compared with placebo.

Methods RIO is a double-blind, randomised, placebo-controlled trial. Eligibile participants were adults age 18–60 years, initiated on ART in early-stage HIV infection, virally suppressed on ART, and had no evidence of viral insensitivity to 10-1074. Participants were randomly assigned (1:1) to receive two LS-bNAbs (3BNC117-LS and 10-1074-LS) in arm A or saline placebo in arm B; participants and study staff were masked to assignment. Eligible participants interrupted ART after receiving blinded intravenous infusions of either bNAbs or placebo. A second optional infusion was offered after 20 weeks for participants who remained virally suppressed without ART. The primary outcome was time to viral rebound 20 weeks after ART interruption, defined as either the first of six consecutive plasma HIV RNA measurements greater than 1000 copies per mL, or two measurements greater than 100 000 copies per mL. All randomly assigned participants were included in the analyses. This study is registered with ClinicalTrials.gov, NCT04319367.

Findings 68 participants were randomly assigned, 34 to each arm. By week 20, viral rebound had occurred in eight participants in arm A and 30 in arm B; 75% (95% CI 61–92) of participants in arm A did not have viral rebound, compared with 11% (4–29) of participants in arm B. Participants in arm A were 91% less likely to rebound than were those in arm B (hazard ratio 0·09; 95% CI 0·04–0·21, p<0·0001). There were 326 adverse events in arm A and 260 in arm B, including 19 treatment-related or procedure-related adverse events in arm A and 41 in arm B. Of nine serious adverse events, none were treatment-related. The most commonly reported treatment-related or procedure-related adverse events were fatigue, lethargy, or somnolence: 11 in arm A and nine in arm B. There were two severe adverse events (anal abscesses) possibly related to the study protocol, both in the placebo arm.

Interpretation Long-acting bNAbs can sustain extended ART-free viral control in people treated during early-stage HIV and represent a promising step towards achieving ART-free HIV remission.

Funding Gates Foundation.

Lancet HIV 2026; 13: e527–37

Published Online May 27, 2026 https://doi.org/10.1016/S2352-3018(26)00059-7

See Comment page e516

*Contributed equally

†Joint senior authors

Department of Infectious Disease, and Imperial Clinical Trials Unit, School of Public Health, Faculty of Medicine, Imperial College London, London, UK (M J Lee PhD, L-R Cherrill MSc, E Falaschetti MSc, J Gohil MBChB, T Elliott PhD, Prof G P Taylor DSc, J Ujetz BSc, I Jahan MSc, S Fletcher BSc, H Box MPH, Prof S Fidler PhD)**; Imperial College Healthcare NHS Trust, London, UK** (M J Lee, T Elliott, J Gohil, Prof S Fidler)**; National Institute for Health Research, Imperial Biomedical Research Centre, London, UK** (T Elliott, H Box, Prof S Fidler)**; Nuffield Department of Medicine, University of Oxford** (P Zacharopoulou DPhil, M Altaf PhD, T Tipoe DPhil, P Cicconi PhD, H Brown BSc, N Robinson MSc, Prof J Frater PhD)**; HIV i-Base, London, UK** (S Collins)**; The Rockefeller University, New York, NY, USA** (M Fumagalli PhD, A Kaczynska MPH, C Bittar PhD, J Horowitz PhD, Prof M C Nussenzweig PhD, Prof M Caskey MD)**; Department of Medicine and Therapeutics, Faculty of Medicine, The Chinese University of Hong Kong, Hong Kong** (T Tipoe)**; Guy's and St Thomas' Hospital NHS Foundation Trust, London, UK**

Introduction

Antiretroviral therapy (ART) has transformed survival for people living with HIV and prevents viral transmission,[1] but it cannot cure HIV due to persistence of reservoirs of latently infected cells. As a result, ART is a lifelong therapy, introducing challenges of sustaining global access, funding, stigma, drug-related side-effects, and treatment fatigue. There is an enduring drive and need for safe and effective long-lasting therapies aimed at achieving either cure or long-term ART-free remission.

ART blocks viral replication, maintaining plasma viral suppression below the limit of detection. ART interruption is usually followed by rapid viral rebound within 2–4 weeks.[2] The HIV reservoir is the source of the rebounding virus.[3] The absence of assays to accurately predict viral rebound means the only way to determine efficacy of novel interventions is to interrupt ART, a process called analytical treatment interruption (ATI).[4]

HIV-specific broadly neutralising antibodies (bNAbs) targeting conserved regions on the HIV envelope

(P Godakandaarachi MBBS, Prof J Fox MD); **Manchester University NHS Foundation Trust, Manchester, UK** (A Uriel MD, I Mangawa MBChB); **University Hospitals Sussex NHS Foundation Trust and Brighton & Sussex Medical School, Brighton, UK** (A Clarke BM); **Royal Free London NHS Foundation Trust, London, UK** (S Kinloch-de Loes MD); **University College London, London, UK** (S Kinloch-de Loes, Prof S Pett PhD); **Central and North West London NHS Foundation Trust, London, UK** (Prof S Pett); **Chelsea and Westminster Hospital, London, UK** (Prof M Boffito PhD, G Whitlock PhD); **Aarhus University and Aarhus University Hospital, Aarhus, Denmark** (Prof O S Søgaard PhD, J D Gunst PhD); **Queen Mary University of London and Barts Health NHS Trust, London, UK** (K Ring MBBS, Prof C Orkin MBBCh); **Aalborg University and Aalborg University Hospital, Aalborg, Denmark** (Prof H Nielsen DMSci); **Western General Hospital, NHS Lothian Trust, Edinburgh, UK** (R Sutherland MBChB); **St George's University Hospitals, NHS Foundation Trust, London, UK** (L Hamzah PhD); **Centre for Clinical Vaccinology and Tropical Medicine and the Oxford University Hospitals NHS Foundation Trust, Oxford, UK** (P Cicconi); **Duke University, Durham, NC, USA** (K E Seaton PhD, Prof G D Tomaras PhD); **Dartmouth College, Hanover, NH, USA** (Prof M E Ackerman PhD, J A Weiner PhD); **National Institute for Health Research, Oxford Biomedical Research Centre, Oxford, UK** (Prof J Frater); **Howard Hughes Medical Institute, Chevy Chase, MD, USA** (Prof M C Nussenzweig)

Correspondence to: Sarah Fidler, Department of Infectious Disease, Imperial College London, London W2 1NY, UK
s.fidler@imperial.ac.uk

See Online for appendix

Research in context

Evidence before this study

We systematically searched MEDLINE, Embase, and Web of Science databases from Jan 1, 2015, to April 30, 2024, with additional searches updated until Jan 31, 2026, limited to English language publications. Search terms included "HIV", "antiretroviral therapy", "analytical treatment interruptions", "broadly neutralising antibodies". Combination therapy of HIV-specific broadly neutralising antibodies (bNAbs) has demonstrated periods of viral control for people living with HIV who interrupt their antiretroviral treatment. The development of long-acting LS-bNAbs with Fc-receptor modifications can increase serum half-lives by up to four times. To date, the clinical efficacy and duration of antiretroviral therapy (ART)-free HIV control with LS-bNAbs has not been evaluated in a sufficiently powered human trial.

Added value of this study

The prospective double-blind, randomised, placebo-controlled RIO trial shows for the first time that a single dose of two bNAbs (10-1074-LS and 3BNC117-LS) was 91% more effective in maintaining ART-free viral control to 20 weeks than was placebo. Viral control beyond 96 weeks after treatment interruption was more common than expected for post-treatment control in an early treated cohort of people living with HIV. Extended ART-free viral control is probably a result of mechanisms induced after bNAb dosing as modelled concentrations of bNAbs were below presumed therapeutic concentrations.

Implications of all the available evidence

LS-bNAbs are a major advance towards ART-free HIV control and remission as an achievable goal. These findings will inform future combination strategies to enhance mechanisms of post-bNAb HIV control.

glycoprotein neutralise a broad range of HIV strains, maintaining viral control after ART is interrupted.[5] Studies of single bNAbs including ATI showed variable but delayed time to viral rebound when antibodies were dosed either while participants were established[6] or initiated on ART.[7,8] When used as monotherapies in viraemic people with HIV, after initial periods of decreased viraemia, the presence of bNAbs selects for bNAb-resistant strains.[6] However, when used in combination, bNAbs 3BNC117 (anti-CD4-binding site)[9] and 10-1074 (anti-V3 loop),[10] conferred much longer periods of viral control in the absence of ART.[11–13] Engineering the Fc portion of bNAbs extends their half-life through modification of the interactions with the neonatal Fc receptor (FcRn). Mutations such as M428L and N434S (LS) at the Fc–FcRn interaction enhance FcRn binding and intracellular recycling, increasing antibody half-life.[14] This so-called LS modification extends bNAb half-lives by three to four times (eg, from 24 to 81 days for 10-1074-LS).[14] To date, the clinical efficacy and duration of ART-free viral control with long-acting bNAbs has not been evaluated in a sufficiently powered human trial.

The RIO study is an ongoing, double-blind, randomised, placebo-controlled trial comparing the safety, duration and efficacy of two LS-bNAbs, 3BNC117-LS and 10-1074-LS, with placebo, on time to viral rebound following ART interruption in people with HIV treated with ART since early-stage infection.

Methods

Study design and participants

RIO is a two-stage, placebo-controlled, double-blind, two-arm, prospective, phase 2, randomised controlled trial. The RIO study protocol has been previously published.[15] The study was done in clinic or hospital centres providing HIV care across 12 sites in the UK and Denmark (appendix p2). Further details of risk mitigation steps, for monitoring of participants undertaking a treatment interruption study, COVID-19 pandemic prevention measures, and prevention of HIV transmission through ensuring access to HIV pre-exposure prophylaxis (PrEP) for partners are included in the published protocol.[15]

Adults age 18–60 years living with HIV were eligible if they initiated ART during confirmed primary (with nadir CD4 count >350 cells per µL) or early-stage HIV (defined as CD4 count >500 cells per µL) and were virally suppressed with ART regimens containing integrase strand transfer inhibitors or boosted protease inhibitors.[15] Participants were screened for predicted sensitivity to 10-1074 by use of proviral single-genome amplification of *env* genes and an in silico prediction algorithm, as previously described[13] (appendix pp 13–16). All participants provided written informed consent to participate in the trial.

RIO is led by the Trial Management Group, which includes a representative from the community of people living with HIV. The study protocol received ethical approval from the London–Westminster Research Ethics Committee (reference: 19/LO/1669) on Sept 11, 2019. The Imperial Clinical Trials Unit provides oversight for the operational and regulatory conduct of the study. Independent Data Monitoring and Trial Steering Committees convene biannually to review trial safety and overall conduct, respectively.

This study is registered with ClinicalTrials.gov, NCT04319367.

Randomisation and masking

Randomisation was done centrally with a web-based system. Block randomisation with variable block sizes of two or four was used, without stratification. Participants, care providers, and outcome assessors were masked to assignment.

Procedures

In stage 1 of the protocol, participants were assigned (1:1) to receive one infusion of either 10-1074-LS (10 mg/kg) and 3BNC117-LS (30 mg/kg) in arm A or saline placebo infusion in arm B. 2 days after infusion, ART was interrupted. After early data indicating that multiple doses of bNAbs were associated with relative changes in intact proviral reservoir over 6 months,[13] a second dose substudy (protocol amendment approved on June 22, 2022) was introduced to allow an optional second blinded infusion offered after 20 weeks if viral rebound had not occurred.

Participants were unblinded and resumed ART once they met the protocol-defined criteria for viral rebound. In response to feedback from clinicians, participants, and the community, a subsequent protocol amendment allowed participants to provide consent for unblinding after 48 weeks while remaining off ART, extending duration of follow-up data collection (appendix p 23). Participants who were unblinded to placebo were offered open-label LSbNAbs in the second stage of the protocol. Only data from the first stage are reported here; the second stage of RIO is ongoing.

During ATI, weekly clinical assessments, CD4 counts, and plasma HIV viral load measurements were done for 8 weeks. Assessments were then done every 2 weeks until week 20, and every 4 weeks thereafter until viral rebound. Once viral load became detectable, assessments returned to a weekly schedule. Viral loads were measured with validated assays at local clinical sites, with undetectable results defined as less than 50 copies per mL (appendix p7). Serial serum bNAb concentrations were measured by use of validated anti-idiotype ELISA.[11,16] Antidrug antibodies were assayed at timepoints before and after bNAb infusion with a three-tiered electrochemiluminescence approach,[17] up to 6 months after the last bNAb dose. Plasma concentrations of tenofovir disoproxil, lamivudine, and dolutegravir were measured at multiple timepoints in participants with viral loads less than 50 copies per mL using validated liquid chromatograph-mass spectrometry assays.

Outcomes

The primary outcome was viral control, defined as time from ART interruption to plasma viral rebound. The primary outcome, originally defined at 36 weeks, was reported at 20 weeks after treatment interruption in accordance with the protocol amendment, which offered participants a second dose after this timepoint. Rebound was defined as either two consecutive viral loads greater than 100 000 copies per mL, six consecutive weeks with viral loads greater than 1000 copies per mL, or other protocol-defined instances including participant preference to restart ART.[15] Dates of rebound were confirmed by an independent endpoint adjudication committee blinded to study arm.

Secondary outcomes include time to rebound beyond 20 weeks, adverse events and serious adverse events by study arm, time to viral rebound by different viral load thresholds, CD4 cell counts and CD4/CD8 ratios during ATI. We also reported time to viral resuppression after restarting ART, longitudinal serum bNAb concentrations, and baseline predicted bNAb resistance. A full list of secondary and exploratory outcomes is included in the protocol.[15] Secondary outcomes were initially designed to capture outcomes up to 48 weeks after ATI. However, the second-dose study extension enabled reporting of outcomes up to 96 weeks after ATI for participants still in follow-up at the time of database lock.

Statistical analysis

RIO is a parallel-group trial that uses a superiority framework. Median follow-up was calculated using the reverse Kaplan–Meier analysis method. Survival proportions were estimated using the Kaplan–Meier method. Time-to-event analyses for primary and secondary outcomes were done in the intention-to-treat population. Differences in the time-to-viral rebound were assessed with the log-rank test and the Cox proportional hazard model at 20 weeks and 96 weeks. Participants who restarted ART before reaching the primary endpoint or viral rebound were censored at the time of ART restart or last viral load measurement. All statistical results were two-tailed, with a 5% significance level. Safety outcomes were reported descriptively. Statistical analysis was done with R version 4.5.0.

The trial was designed to detect a reduction in the rebound rate at 36 weeks from 90% in arm B to 55% in arm A (hazard ratio [HR] 0·35). At 5% significance level and 90% power, 36 participants per arm were required, allowing for a 10% dropout rate. The primary outcome timepoint was reduced from 36 weeks to 20 weeks, due to the second-dose substudy extension (appendix p 23). Statistical power was not compromised, as viral rebound rates in the placebo arm were predicted to remain at 90%.

Plasma viral load natural log doubling time was analysed as an exploratory endpoint with measurements between and inclusive of the first detectable plasma HIV RNA measurement greater than 50 copies per mL after ATI, and the first peak plasma HIV RNA greater than 1000 copies per mL before ART restart. The slope of increase (r) was calculated by linear regression and viral doubling time (t) calculated with the equation:

$$t = \frac{\ln(2)}{r}$$

Participants who withdrew from the first ATI or those who did not experience viral rebound were excluded from this analysis.

Pharmacokinetic analyses

Serum bNAb titres were measured using a validated anti-idiotype ELISA[11,16] with available samples. Because of the well defined pharmacokinetics of these antibodies, these data were used to derive a two-compartment model with Monolix software with the Stochastic Approximation for Model Building Algorithm[18] to infer missing values. The following covariates were tested: age, log(weight), HIV-1 clade, predicted baseline bNAb resistance mutations, and number of doses. The model that best fit the data for both bNAbs was a two-compartment model with a central compartment (V), a peripheral compartment with rates of transfer to and from represented by the constants k_{12} and k_{21}, and a linear elimination with a rate constant k. Parameters were transformed into A, B, alpha and beta using pharmacokinetic equations listed below. 95% prediction intervals (PI) were calculated with RsmLx in R with 1000 bootstrap replicates.

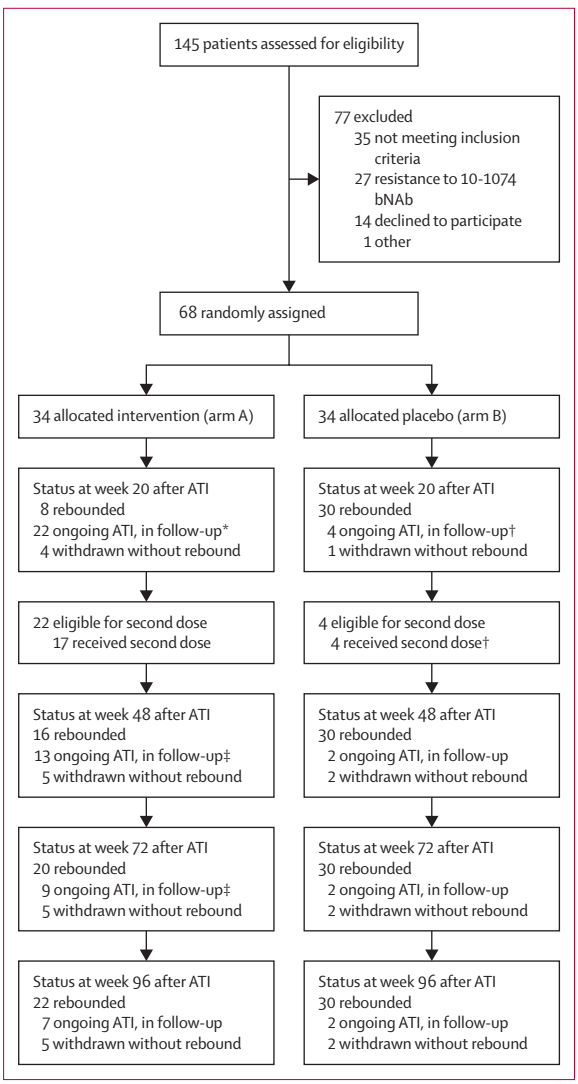


Figure 1: **Trial profile**
ATI=analytical treatment interruption. bNAb=broadly neutralising antibody. ART=antiretroviral therapy. *Includes one participant who temporarily restarted ART between weeks 12 and 20 of ATI due to concurrent illness, and rebounded at week 31. †Includes one participant who had two doses of placebo infusions and continued ATI until week 48. ‡Includes one participant who temporarily restarted ART between weeks 48 and 55 of ATI due to concurrent illness, and rebounded at week 97; time to rebound was retrospectively determined by the endpoint adjudication committee as 10 weeks, this particpant was included in both rebound and ongoing ATI numbers.

$$V = 1/(A+B)$$
$$k_{21} = \text{alpha} - A*V*(\text{alpha} - \text{beta})$$
$$k = (\text{alpha} * \text{beta})/k_{21}$$
$$k_{12} = \text{alpha} + \text{beta} - k_{21} - k$$

Pharmacokinetic simulations using Simulx were run with 100 replicates to estimate bNAb serum concentration estimates up to 1000 days after the first infusion. Estimated rebound concentrations at the time of viral rebound were reported; however, due to delays in receiving serum samples for bNAb ELISA assays, not all timepoints from all participants were available. In addition, because the timing of viral rebound was determined retrospectively, samples at the exact time of rebound may not have been collected. A bNAb concentration threshold of 10 µg/mL was selected because, in previous studies involving both bNAbs, viral rebound was not observed until at least one bNAb concentration had fallen below 10 µg/mL.[11,13] Additionally, animal studies have shown that serum concentrations required for in vivo protection (IC50) are typically one to two orders of magnitude higher than corresponding in vitro measurements.[19]

Role of the funding source

The funders of this study had no role in study design, data collection, analysis, or interpretation of data, the writing of this article, or the decision to submit it for publication.

Results

Of 145 people screened from May, 2021, to July, 2024 (figure 1), 77 were ineligible, including 27 (18·6%) with predicted insensitivity to 10-1074. 68 participants were enrolled across one Danish and nine UK sites. The cutoff date for the analysis presented in this publication was Sept 26, 2025. Median ATI follow-up time was 117 weeks (IQR 98–179, range 1–195 weeks). Baseline characteristics were balanced between study arms with most participants having started ART in primary HIV infection and received an integrase-inhibitor-based regimen at enrolment (table).

28 of 34 participants in arm A and 30 of 34 in arm B had less than 15% of proviral *env* sequences containing resistance-associated mutations to 10-1074, meeting the screening criteria;[15] Sequences from six participants in arm A and four in arm B were not possible to amplify at

	Arm A, bNAbs (n=34)	Arm B, placebo (n=34)	Total (n=68)
Age, years	36 (31–44)	42 (33–51)	40 (32–46)
Assigned male sex at birth	34 (100%)	34 (100%)	68 (100%)
Gender identity	34 (100%)	34 (100%)	34 (100%)
Weight, kg	73 (70–81)	78 (71–89)	77 (70–85)
BMI, kg/m²	23 (22–26)	25 (23–28)	24 (22–27)
Ethnicity			
Asian or Asian British	3 (9%)	0	3 (4%)
Black or Black British	1 (3%)	2 (6%)	3 (4%)
Other	2 (6%)	2 (6%)	4 (6%)
White	28 (82%)	30 (88%)	58 (85%)
Baseline CD4 count, cells per µL	742 (657–937)	810 (596–986)	776 (626–963)
HIV clade			
B clade	19 (76%)	21 (84%)	40 (80%)
Non-B clade	6 (24%)	4 (16%)	10 (20%)
Information not available	9	9	18
ART regimen at screening, n (%)			
NRTI	34 (100%)	33 (97%)	67 (99%)
INSTI	27 (79%)	31 (91%)	58 (85.3%)
bPI	3 (9%)	3 (9%)	6 (8.8%)
Time on ART before enrolment, years	5 (3–6)	5 (4–7)	5 (4–7)
Stage of HIV at time of diagnosis			
Primary HIV	32 (94%)	30 (88%)	62 (91%)
Early HIV*	2 (6%)	4 (12%)	6 (9%)

Data are median (IQR) or n (%) unless otherwise stated. bNAbs=broadly neutralising antibodies. ART=antiretroviral therapy. NRTI=nucleoside reverse transcriptase inhibitor. INSTI=integrase strand transfer inhibitor. bPI=boosted protease inhibitor. *Early HIV was defined as having been diagnosed and started ART while nadir CD4 count was above 500 cells per µL.

Table: **Participant characteristics**

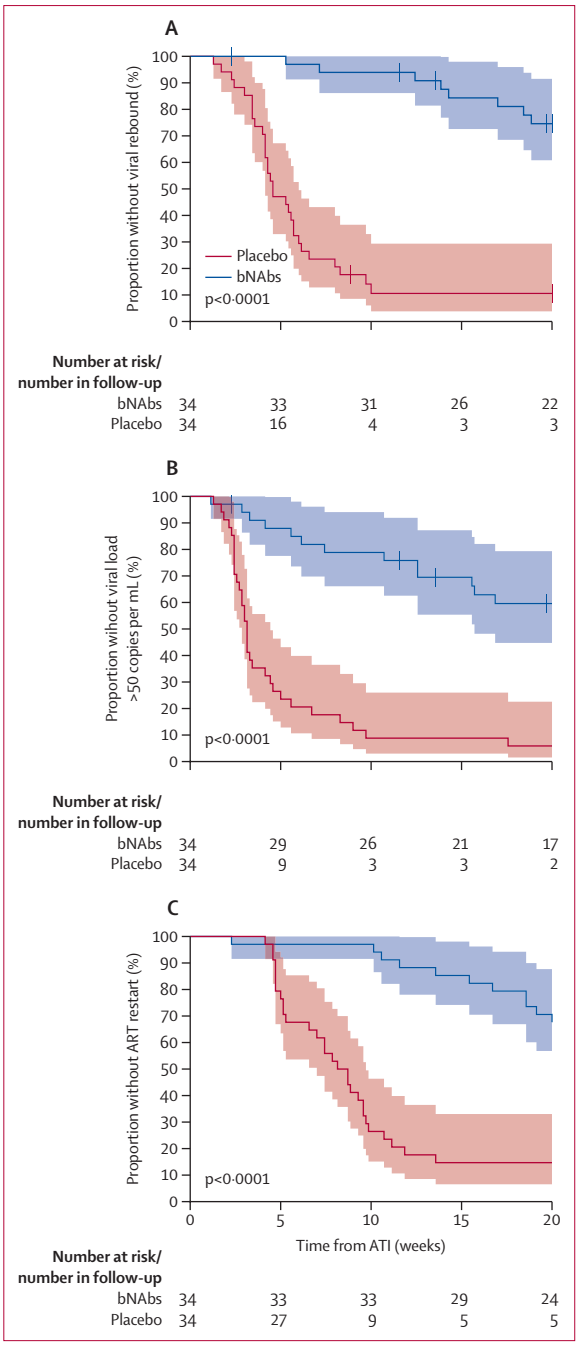


Figure 2: **Primary outcomes at week 20**

Kaplan–Meier survival curves. (A) Proportion of participants without viral rebound by the week 20 primary endpoint viral rebound criteria during the stage 1 ATI of the RIO study. (B) Proportion with undetectable viral loads during the ATI to 20 weeks. (C) Proportion who have not restarted ART during the ATI to week 20. Shaded areas show 95% CIs. ATI=analytical treatment interruption. ART=antiretroviral therapy.

baseline, and these participants were considered eligible. Two of these participants (one in each group) were subsequently found to harbour resistance-associated mutations to 10-1074 at post-hoc sequencing.

All participants received their assigned dosing. Four participants in arm A and one in arm B restarted ART before meeting the viral rebound criteria before week 20. One participant in arm-A died from a myocardial infarction before reaching week 20; this death was deemed unrelated to study drug or procedures. Of those maintaining viral control off ART beyond 20 weeks, two additional participants (one in each arm) chose to restart ART before viral rebound by 96 weeks. Of 26 eligible participants, 21 received a second infusion; the median time of the second blinded infusion was 27 weeks (IQR 24–42, range 21–50 weeks) after randomisation. Two participants in the bNAb arm temporarily resumed their ART during ATI due to concurrent illness and subsequently reinitiated treatment interruption and were included in the final analysis, in accordance with the protocol.

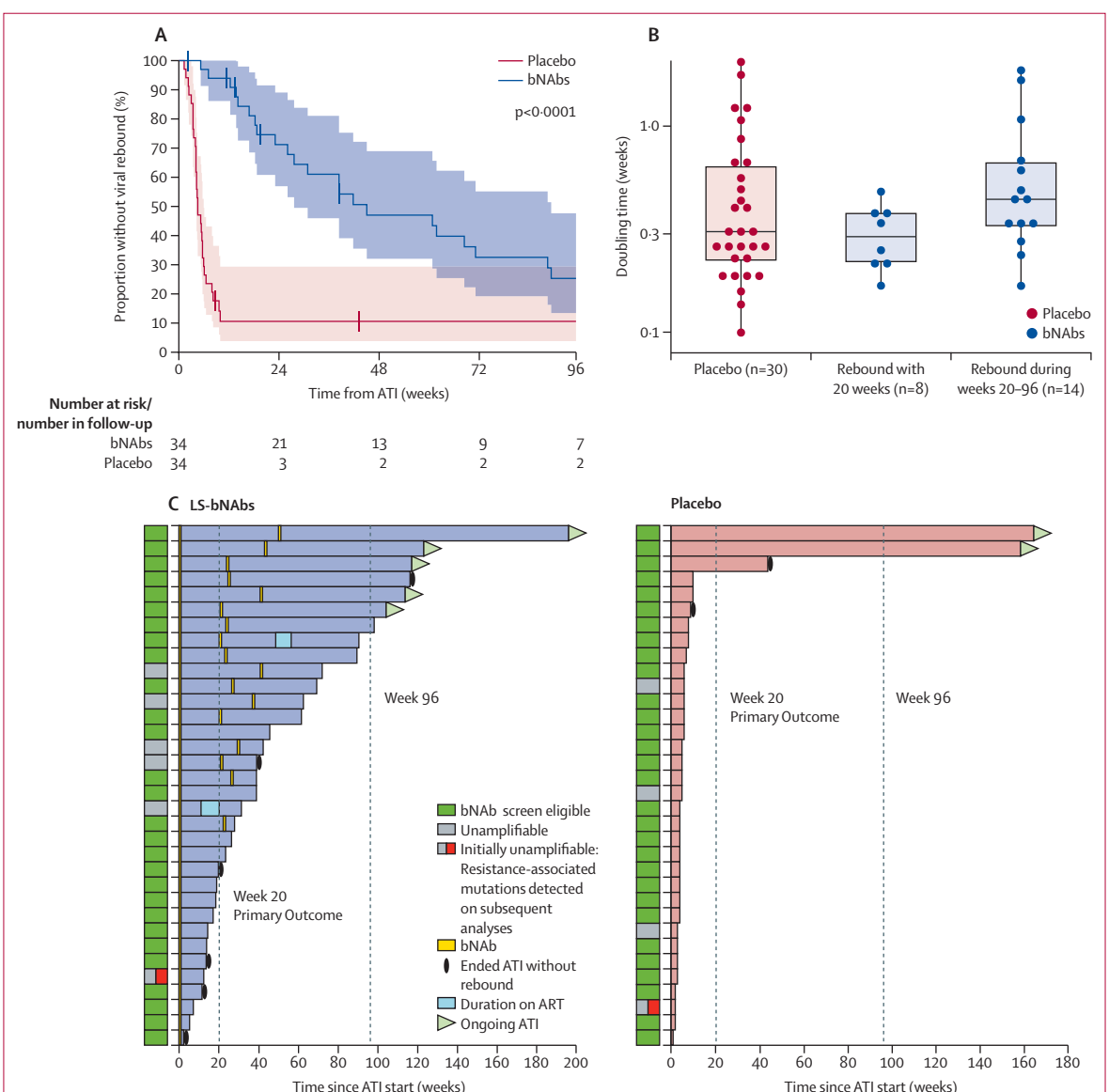
By week 20, viral rebound had occurred in eight participants in arm A and 30 in arm B. 75%

(95% CI 61–92) of arm A participants had not rebounded, compared with 11% (95% CI 4–29) of participants in arm B after censoring. In a Cox proportional-hazards regression, arm A participants were significantly less likely to rebound than were those in arm B (HR 0·09, 95% CI 0·04–0·21; p<0·0001; figure 2). The difference in restricted mean survival time was 11·9 weeks (95% CI 9·7–14·0). The results were consistent using different outcome thresholds at week 20. At week 20, the proportion of participants with undetectable viral loads (<50 copies per mL) was 60% (95% CI 45–79) in arm A and 6% (95% CI 2–23) in arm B (figure 2). By week 20, 68% (95% CI 54–85) of arm A participants remained ART-free and 15% (95% CI 7–33) in arm B (figure 2).

ART-free viral control at 96 weeks after ART interruption was evident in seven participants in arm A (25%, 95% CI 13–48), compared with two in arm B (11%, 4–29; figure 3).

Median time from randomisation to viral rebound was estimated as 4·6 weeks (95% CI 4·1–6·0) in arm B and 45·4 weeks (27·9–90·0) in arm A. In a Cox proportional-hazards regression, participants in arm A were less likely to rebound than were those in arm B (HR 0·22, 95% CI 0·12–0·40; p <0·001). Median time to rebound after last bNAb dose in arm A was 31·1 weeks (95% CI 23·3–68·0).

For participants in arm A, we observed three viral rebound patterns by time from ATI (figure 3). First, eight participants rebounded within 20 weeks. Second, 14 participants rebounded between 20 weeks and



(Figure 3 continues on next page)

96 weeks with predicted measured serum concentrations of bNAbs above the assumed therapeutic threshold of 10 µg/mL at the time of viral rebound. Third, seven participants remained off ART at and beyond 96 weeks, with predicted serum bNAb concentrations below 10 µg/mL. Five of these participants still remain off ART between 98 weeks and 195 weeks with their ATI ongoing. One participant chose to restart ART at week 113 without viral rebound, and one experienced viral rebound at week 116. These seven participants all had a second bNAb dose at a median time of 25 weeks after the first dose (IQR 23–38, range 21–50). Of note, no ART drugs were detectable in plasma samples from any participant with undetectable HIV RNA during the ATI.

To examine if LS-bNAbs treatment altered subsequent viral rebound kinetics, we compared viral rebound doubling times between study arms. Doubling times were evaluated across groups experiencing viral rebound by study arm. Participants who rebounded within 20 weeks after receiving LS-bNAbs in arm A had doubling times (median 0·29 weeks, IQR 0·22–0·38) comparable to those in arm B (0·31 weeks, IQR 0·22–0·64). Those who rebounded after 20 weeks had median doubling time of 0·44 (0·33–0·66) weeks (figure 3). These post-hoc analyses were exploratory in nature, so no formal statistical comparison was made. Participants who did not have amplifiable baseline sequences were not associated with different viral rebound outcomes to those with amplified sequences (figure 3).

Median peak HIV RNA viral load at rebound was also lower in 17 participants who received two doses of LS-bNAbs (6880 copies per mL, IQR 6129–17461, range 1280–58700) compared with placebo (9750 copies per mL, IQR 14543–480890, range 3236–10 million).

Serum LS-bNAbs were detected in available samples from 31 participants in arm A and fitted to a two-compartment model (figure 4). The estimated elimination half-lives of 10-1074-LS and 3BNC117-LS were 72·5 days (95% PI 66·0–78·8 days), and 64·7 days (95% PI 60·8–69·1), respectively (appendix p 8). 15 of 17 participants who had two LS-bNAb doses had measurements available after the second dose (figure 4). No antidrug antibodies were detected in post-infusion samples from 11 participants in arm A tested up to 6 months after bNAb infusion (appendix p 9). No ART drug concentrations were detected in plasma samples.

Median estimated concentration at rebound was 40·6 µg/mL for 10-1074-LS (IQR 11·5–80·7 µg/mL, range 0·6–149·0 µg/mL) and 52·4 µg/mL for 3BNC117-LS (14·8–95·4 µg/mL, 0·4–231·4 µg/mL; appendix pp 3, 8).

Simulations were used to estimate time for LS-bNAb concentrations to reach the previously assumed therapeutic threshold of 10 µg per mL after two doses given 21 weeks apart: for 10-1074-LS this was 47·6 weeks (95% PI 32·7–62·5) and for 3BNC117-LS this was 47·8 weeks (35·6–60·0) after the second dose

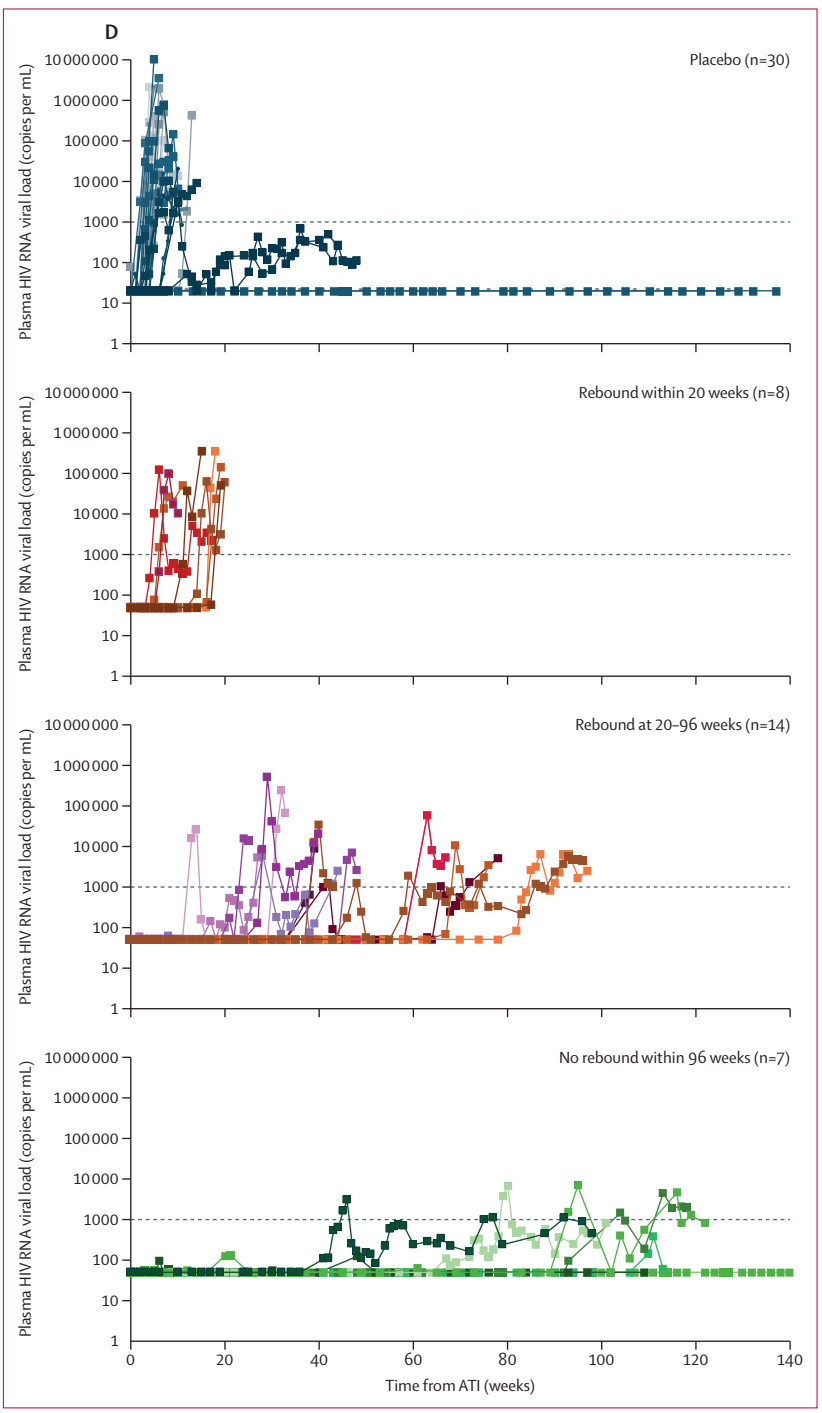


Figure 3: **Outcomes beyond week 20**
(A) Kaplan–Meier curves showing proportion of participants who had not experienced viral rebound; shaded areas represent the 95% CIs. (B) Comparison of initial natural log viral doubling time in plasma HIV RNA viral load, between participants who received placebo infusions and participants who received bNAbs. (C) Descriptive representation of relation between predicted baseline 10-1074 bNAb resistance and time from ATI start to viral rebound, each row is an individual participant; participants who remain off ART in an ongoing ATI are highlighted with green triangles. (D) Patterns of viral rebound of individual participants in both placebo and intervention arms; dashed lines show plasma HIV RNA viral load threshold of 1000 copies per mL. ATI=analytical treatment interruption. ART=antiretroviral therapy. bNAbs=broadly neutralising antibodies.

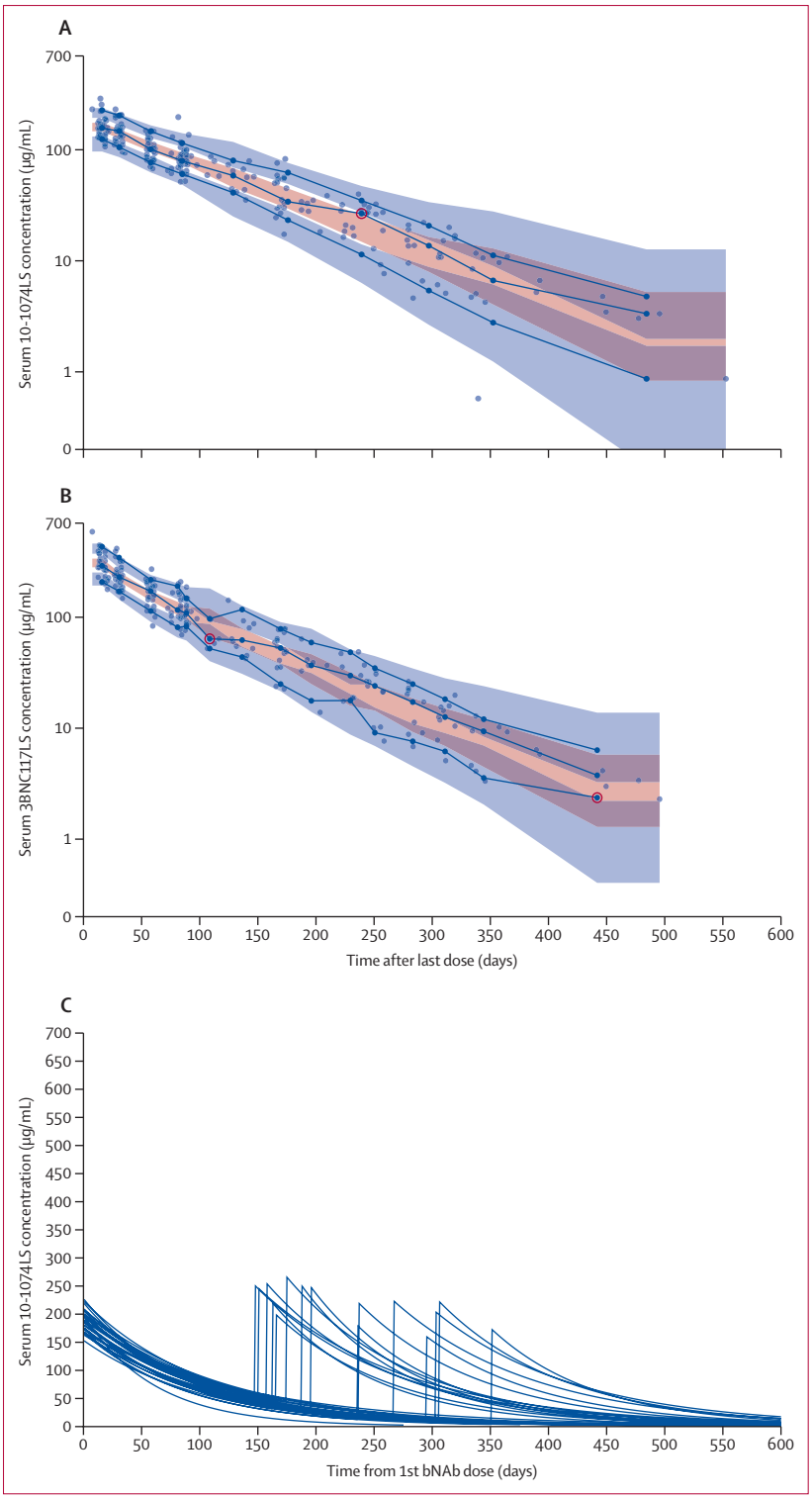


Figure 4: **bNAb pharmacokinetics**
Serum bNAb measurements fitted a two-compartment pharmacokinetic model in these visual predictive charts. (A) 10-1074-LS and (B) 3BNC117-LS. Each dot is a single bNAb measurement, and the lines show the 10th, 50th, and 90th percentiles. Shaded areas show 90% prediction intervals. (C) Serum 10-1074-LS concentrations modelled to 800 days after randomisation, to show the range of second dose times and peak serum concentrations after two doses.

In the first group who rebounded within 20 weeks, median 10-1074-LS concentration at time of rebound was 70·7 µg/mL (IQR 66·6–96·0); median rebound 3BNC117-LS concentration was 82·0 µg/mL (78·4–162·7) (appendix pp 3–6). Participants who rebounded during 20–96 weeks had median 10-1074-LS concentration at time of rebound of 21·9 µg/mL (9·2–47·5) and median rebound 3BNC117-LS concentration of 20·3 µg/mL (11·4–65·4; appendix pp 3–6). All six participants with available bNAb measurements who remained off ART at 96 weeks had bNAb rebound concentrations below 10 µg/mL (appendix pp 3–6). One participant did not have serum bNAb measurements available at the time of analysis, but remained off ART at 96 weeks where bNAb concentrations are expected to be below 10 µg/mL from population estimates (appendix pp 3–6).

60 adverse events were recorded as definitely, probably, or possibly related to treatment or protocol (appendix p 10). There were 326 adverse events in arm A and 261 in arm B, including 19 treatment-related or procedure-related adverse events in arm A and 41 in arm B. Nine serious adverse events were recorded, none of which were treatment-related; these included one death caused by myocardial infarction associated with pre-existing undiagnosed triple-vessel cardiovascular disease (appendix pp 11–14). The most commonly reported treatment-related or procedure-related adverse events were fatigue, lethargy, or somnolence: 11 in arm A and nine in arm B. Two serious adverse events (anal abscesses) were possibly related to the study protocol, both in the placebo arm.

94% of participants resuppressed HIV to undetectable plasma viral load within 12 weeks of restarting ART. There were no new antiretroviral drug resistance-associated mutations in arm A. All participants achieved viral resuppression eventually. Median time to viral suppression after restarting ART for arm A was 5 (IQR 2–8) weeks, and 3 (2–5) weeks for arm B (appendix p 1). Five participants in arm B rebounded with peak viral loads above 1 million copies per mL (all asymptomatic), taking a median of five weeks (IQR 5–8, range 2–24) weeks to achieve viral suppression, compared with none in arm A. There was no change in CD4 count or CD4/CD8 ratio during the period off ART in either study arm, and no HIV transmission events were recorded (appendix pp 15–16).

Discussion

In the absence of ART, two HIV-specific LS-bNAbs reduced the risk of viral rebound within 20 weeks by 91% compared with placebo. LS-bNAbs and ATI were not associated with adverse events. As well as confirming efficacy of Fc-engineered LS-bNAbs at likely therapeutic concentrations, we show for the first time extended viral control when serum bNAbs fall below this concentration. We report a significant increase in the frequency of participants who maintain viral control beyond 96 weeks,

compared with expected frequencies of post-treatment control from both previous reports in the literature,[2] as well as in comparison with the placebo arm. This is the first report of the extended duration and efficacy of two long-acting bNAbs on ART-free viral control among people starting ART in early-stage HIV compared to placebo.

Previous studies with multiple doses of shorter-acting bNAbs[11,13] showed sustained viral control without ART for up to 48 weeks and observed viral rebound when 3BNC117 fell below 10 µg/mL. The TITAN study[20] showed two doses of non-LS 10-1074 and 3BNC117, given 3 weeks apart with or without a TLR9 agonist, delayed viral rebound (median of 12·5 weeks after ATI), with no added benefit of the TLR9 agonist. Four (36%) of 11 TITAN participants who received non-LS bNAbs maintained virological control during the 25-week ATI, fewer than observed in RIO (75% by 20 weeks) after a single dose of the LS variants. A consideration for RIO is that 17 participants received one bNAb dose and 17 received two. Clearly two doses will extend the duration of likely viral control, and this has been incorporated into the analyses. However, with measured and modelled pharmacokinetic data, it is still possible to estimate when subtherapeutic bNAb concentrations are likely to have been achieved to allow analysis of potential post-bNAb control.

Studies with extended ATI periods highlight the importance of standardised strategies to guide the safe management of participants, including the frequency of clinic visits, ensuring access to HIV PrEP for partners, and considering the practical, quality-of-life and psychological aspects of participation. RIO includes an ongoing qualitative substudy to capture participant experiences as a key outcome, to inform the design of future ATI trials. The asymptomatic and unexpectedly high viral rebounds observed in some placebo recipients (>1 million HIV RNA copies per mL) should also be noted. Although ART-mediated viral resuppression was rapid and effective in all study participants, the increased potential risk of transmission associated with such high viral rebounds must be highlighted in participant information, with free access to PrEP provided to all partners during ATI studies.

Several mechanisms are postulated to explain bNAb-mediated ART-free viral control. Firstly, a direct antiviral effect of bNAbs associated with serum LS-bNAb above 10 µg/mL threshold has been reported.[11,13] The estimated therapeutic threshold of LS-bNAb antiviral activity remains uncertain with more recent studies[11,13] demonstrating a range of cutoff concentrations between 10–30 µg/mL. Our findings show LS-bNAb-mediated viral control in most participants in arm A. However, we observed a wide range of LS-bNAb concentrations at viral rebound, suggesting that the initial LS-bNAb mediated antiviral effect may vary depending on viral sensitivity to antibodies, and that the true threshold for therapeutic serum bNAb concentrations is likely higher for most individuals than the previously reported 10 µg/mL. Possible other host factors could include autologous antibodies, innate immunity, T-cell function, genetic, epigenetic, and HIV-specific cellular effector functions as well as characteristics of the HIV reservoir.

Despite prescreening for LS-bNAb sensitivity using genotypic methods, at least eight participants who received LS-bNAb in arm A experienced viral rebound by 20 weeks at levels of serum LS-bNAb much higher than 10 µg/mL, which raises the possibility of undetected or de novo LS-bNAb resistance. We report viral susceptibility to bNAbs of the rebound variants separately,[21] but there was evidence for emerging resistance, which might have been pre-existing or evolved after dosing. Current algorithms used to predict LS-bNAb sensitivity remain problematic; neither ex vivo phenotypic neutralisation[22] or viral envelope sequencing[23] can accurately predict clinical sensitivity.[11,13,24]

For most participants in arm A who eventually had HIV rebound despite prolonged viral suppression following ART interruption, viral rebound occurred as LS-bNAb plasma concentrations approached 10 µg/mL. Seven participants in arm A maintained viral control beyond 96 weeks compared with only two in arm B; at this time -point serum bNAb concentrations are expected to have washed out, although the actual concentration in blood or tissue where bNAbs are no longer effective has not yet been determined. These findings suggest the presence of a mechanism for viral control after bNAbs have been washed out. The mechanisms conferring sustained control are unknown and of great interest. bNAbs enhance pre-existing immune responses and induce and sustain novel HIV-specific CD4 and CD8 T-cell responses[25] in both non-human primate[26] and human studies,[27–29] suggesting that immune mediated mechanisms may underlie prolonged viral control after bNAb exposure. Altaf and colleagues[30] show a substantial impact of bNAbs and ATI on HIV-specific T-cell function and an association with T-cell function and the duration of post-bNAb control. Fumagalli and coauthors[21] report a significant correlation between baseline reservoir sensitivity to autologous antibodies to 10-1074 and time to rebound in RIO participants. In addition, a more rapid decay of intact proviral half-lives (0·65 years) compared with defective reservoir half-lifes (8·6 years) was observed following bNAbs administration.[21] Further work is ongoing to define the exact bNAb-induced immunological correlates of viral control. Finally, these findings are consistent with previously reported bNAb-mediated reductions in the intact HIV proviral reservoirs,[13] and may contribute to post-ART viral control observed in RIO (HIV-reservoir analysis is ongoing).

There are limitations to the generalisability of our findings. Study participation was restricted to individuals who initiated ART during early-stage HIV infection, a group characterised by smaller, more homogeneous HIV reservoirs and better preserved immune responses compared with those who started ART later. Most

participants were white cisgender men, with clade B virus; these characteristics reflect the demographics of people diagnosed during early-stage HIV at study sites. However, a study of CAP256V2-LS and VRC07-523LS with vesatolimod in African women, with primarily subtype C virus, reported similar results: six of 20 participants had delayed viral rebound within 48 weeks.[31]

Maintenance of viral load below the transmission threshold, with duration of remission greater than 2 years, has been proposed as a minimum target product profile for a cure or remission agent for HIV.[32] We observed seven participants with prolonged viral control past 96 weeks after receiving LS-bNAbs, with presumed subtherapeutic serum concentrations. This was higher than the expected frequency of post-treatment control beyond 96 weeks seen in arm B and frequencies of 6% in early treated people living with HIV reported in a meta-analysis.[2] Some participants had detectable viral loads above 200 copies per mL but less than 1000 copies per mL. Within routine clinical practice, a plasma HIV viral load greater than 200 copies per mL would prompt modification of ART. However, in this scenario, where we aimed to limit viral rebound, a more relaxed criteria of 1000 copies per mL was used. The ultimate goal is to identify interventions that maintain viral control below the recognised transmission threshold[32] in the absence of ART, as a step towards HIV remission. Future HIV cure trial strategies could include LS-bNAbs in combination with other small molecules or immunomodulatory agents to enhance HIV-specific cellular responses. These include therapeutic vaccinations and reversal of immune checkpoint blockade (eg, anti-PD1 and IL-15), with small proof-of-concept studies[33] supporting their use.

RIO shows the longest reported periods of ART-free viral remission after two LS-bNAbs or any other immunotherapeutic intervention in a prospective, double-blind, randomised controlled trial. Three-quarters of participants remained off ART for 20 weeks after a single dose of the LS-bNAbs, and ART-free viral control beyond 96 weeks was more common in participants who received bNAbs than in the placebo group, despite presumed subtherapeutic serum concentrations. LS-bNAbs represent a promising step towards achieving ART-free HIV control and remission, with sustained community engagement underscoring the importance of continued cure-focused research.

Contributors

SFi is chief investigator. JFr is the laboratory lead and co-chief investigator. MCN and MC are the co-investigators at Rockefeller University. MJL was the trial physician at Imperial College London and was responsible for preparation of the first draft of the manuscript. TE is the subsequent trial physician at Imperial College London. L-RC was responsible for the unblinded statistical analyses, as defined in the statistical analysis plan. PZ was responsible for the bNAb screening for study eligibility determination. L-RC and EF are the trial statisticians. Sthe community representative for people living with HIV. HBo and SFi are responsible for overall management, coordination, governance, and conduct of the study. HBr, NR, MA, TT, MF, CB, AK, KES, GDT, MEA, and JAW are responsible for HIV immunology, viral laboratory endpoints, bNAb, and antidrug-antibody assays. GPT, IJ, and JU are responsible for the central laboratory processing for the samples from UK participants. MJL, SFi, JFo, AU, AC, SK-dL, SP, MB, GW, OSS, JDG, KR, IM, JG, PG, HN, LH, RS, PC, and CO are clinical investigators responsible for recruitment and participant care. JH, MCN, and MC designed and developed the investigational medicinal products and contributed to the study design. All authors contributed to the writing and review of the manuscript. Authorship eligibility for this manuscript and all future manuscript output related to this study will be in accordance with the International Committee of Medical Journal Editors criteria for authorship (http://www.icmje.org/recommendations/browse/roles-and-responsibilities/defining-the-role-of-authors-and-contributors.html). No professional writers were involved in this work or are intended to be involved in future manuscripts. All authors had full access to all the underlying data. MJL, L-RC, PZ, EF, HBo, MCN, MC, JFr, and SFi had directly accessed and verified the underlying data reported in the manuscript and all authors had final responsibility for the decision to submit for publication. All staff involved in the study are listed in the supplementary appendix (pp 17–18).

Declaration of interests

MJL declares consulting fees from Randox Health, honoraria and conference support from Gilead Sciences and ViiV Healthcare, and participation in a *BMJ* STI editorial panel and BHIVA sub-committees. MEA declares grants from or contracts with CEPI, NIH, ARPA-H, Moderna, and BeBio made to institution, Elsevier royalties or licenses made to individual, consulting fees or honoraria from seromyx systems, NIH, academic institutions made to individual, and patents planned, issued, or pending from Dartmouth College. MB declares grants or contracts from Gilead, ViiV, and MSD to their institution, consulting fees and honoraria from and advisory board participation with Gilead, ViiV, and MSD. MC declares advisory board participation with Gilead, ViiV, Merck. AC declares grants or contacts from Gilead Sciences, ViiV, GSK, MSD, honoraria and conference registration from ViiV Healthcare. SFi declares participation on a data safety monitoring board or advisory board for Venetoclax study, Gilead sciences, ImmunoCore. MCN declares Gilead licensed 3BNC117 and 10-1074 from Rockefeller University, consulting fees from Celldex, patents issued for 3BNC117 and 10-1074, and stock or stock options from Celldex. CO declares grants or contracts from MSD, ViiVHealthcare, Gilead Sciences, consulting fees, honoraria, and meeting support from MSD, ViiV Healthcare, Gilead Sciences, Bavarian Nordic, and participation on an advisory board for MSD, ViiV healthcare, Gilead Science, and leadership role on the International AIDS Society Governing Council member, and WHO GPG Mpox group. KR declares grants from Barts Charity, honoraria from ViiV Healthcare, Gilead Sciences, support for meeting attendance from Janssen Pharmaceuticals, Gilead Sciences, ViiV Healthcare, and participation on an advisory boards for ViiV Healthcare, Gilead Sciences, and a leadership role as secretary for BASHH Gender and Sexual Minorities Specialist Interest Group. OSS declares consulting fees related to participation in scientific advisory boards for Merck, ViiV, Gilead, Immunocore, AbbVie. GPT declares grants from NIHR Imperial Biomedical Research Centre. GW declares speaker fees and support for attending meetings from Gilead and ViiV, and participation in advisory boards for ViiV and GSK. All other authors declare no competing interests.

Data sharing

Individual participant data underlying the results reported in this article (including de-identified participant data and data dictionaries) will be available after all protocol-defined endpoints have been published and the trial has formally closed from a regulatory perspective. Until that time, the data will remain under the custodianship of the Imperial Clinical Trials Unit. Following expected trial closure in 2029, data access will be granted by the Chief Investigator. Requests should be submitted by email to s.fidler@imperial.ac.uk, subject to approval by the Trial Steering Committee, and will require a signed data access agreement. The study protocol is publicly available, and the Statistical Analysis Plan will be made available on request.

Acknowledgments

The study team would like to acknowledge the extraordinary commitment of all RIO participants, their partners and families as well

as the clinical staff at each site involved in the RIO trial. The complete list of staff is available in the appendix (pp 21–22). The RIO trial was funded by the Gates Foundation (OPP1210792). SFi, HBo, and the Imperial Clinical Trials Unit acknowledge support from the NIHR Imperial Biomedical Research Centre (BRC). MCN and MC acknowledge support from the Stavros Niarkos Foundation and Robert Wennett. MCN is a Howard Hughes Medical Institute Investigator. Infrastructure support for this research was provided by the NIHR Imperial BRC and the NIHR Imperial Clinical Research Facility. MJL received funding from the Medical Research Council UK for a Clinical Research Training Fellowship (MR/W024454/1). JFr acknowledges support from the NIHR Oxford Biomedical Research Centre and the Martin Delaney REACH Collaboratory. KES and GDT acknowledge funding by the Gates Foundation (INV-036842) and the NIH Center for AIDS Research (P30AI064518). The remaining authors declare no competing interests.

References

1 Trickey A, Sabin CA, Burkholder G, et al. Life expectancy after 2015 of adults with HIV on long-term antiretroviral therapy in Europe and North America: a collaborative analysis of cohort studies. *Lancet HIV* 2023; **10:** e295–307.

2 Gunst JD, Gohil J, Li JZ, et al. Time to HIV viral rebound and frequency of post-treatment control after analytical interruption of antiretroviral therapy: an individual data-based meta-analysis of 24 prospective studies. *Nat Commun* 2025; **16:** 906.

3 De Scheerder MA, Vrancken B, Dellicour S, et al. HIV rebound is predominantly fueled by genetically identical viral expansions from diverse reservoirs. *Cell Host Microbe* 2019; **26:** 347–358.e7.

4 Julg B, Dee L, Ananworanich J, et al. Recommendations for analytical antiretroviral treatment interruptions in HIV research trials—report of a consensus meeting. *Lancet HIV* 2019; **6:** e259–68.

5 Schriek AI, Aldon YLT, van Gils MJ, de Taeye SW. Next-generation bNAbs for HIV-1 cure strategies. *Antiviral Res* 2024; **222:** 105788.

6 Bar KJ, Sneller MC, Harrison LJ, et al. Effect of HIV antibody VRC01 on viral rebound after treatment interruption. *N Engl J Med* 2016; **375:** 2037–50.

7 Caskey M, Klein F, Lorenzi JCC, et al. Viraemia suppressed in HIV-1-infected humans by broadly neutralizing antibody 3BNC117. *Nature* 2015; **522:** 487–91.

8 Caskey M, Schoofs T, Gruell H, et al. Antibody 10-1074 suppresses viremia in HIV-1-infected individuals. *Nat Med* 2017; **23:** 185–91.

9 Scheid JF, Mouquet H, Ueberheide B, et al. Sequence and structural convergence of broad and potent HIV antibodies that mimic CD4 binding. *Science* 2011; **333:** 1633–37.

10 Mouquet H, Scharf L, Euler Z, et al. Complex-type N-glycan recognition by potent broadly neutralizing HIV antibodies. *Proc Natl Acad Sci USA* 2012; **109:** E3268–77.

11 Mendoza P, Gruell H, Nogueira L, et al. Combination therapy with anti-HIV-1 antibodies maintains viral suppression. *Nature* 2018; **561:** 479–84.

12 Sneller MC, Blazkova J, Justement JS, et al. Combination anti-HIV antibodies provide sustained virological suppression. *Nature* 2022; **606:** 375–81.

13 Gaebler C, Nogueira L, Stoffel E, et al. Prolonged viral suppression with anti-HIV-1 antibody therapy. *Nature* 2022; **606:** 368–74.

14 Gautam R, Nishimura Y, Gaughan N, et al. A single injection of crystallizable fragment domain–modified antibodies elicits durable protection from SHIV infection. *Nat Med* 2018; **24:** 610–6.

15 Lee MJ, Collins S, Babalis D, et al. The RIO trial: rationale, design, and the role of community involvement in a randomised placebo-controlled trial of antiretroviral therapy plus dual long-acting HIV-specific broadly neutralising antibodies (bNAbs) in participants diagnosed with recent HIV infection—study protocol for a two-stage randomised phase II trial. *Trials* 2022; **23:** 1–26.

16 Bar-On Y, Gruell H, Schoofs T, et al. Safety and antiviral activity of combination HIV-1 broadly neutralizing antibodies in viremic individuals. *Nat Med* 2018; **24:** 1701–07.

17 Bharadwaj P, Riekofski C, Lin S, et al. Implementation of a three-tiered approach to identify and characterize anti-drug antibodies raised against HIV-specific broadly neutralizing antibodies. *J Immunol Methods* 2020; **479:** 112764.

18 Prague M, Lavielle M. SAMBA: a novel method for fast automatic model building in nonlinear mixed-effects models. *CPT Pharmacometrics Syst Pharmacol* 2022; **11:** 161–72.

19 Burton DR. Antiviral neutralizing antibodies: from in vitro to in vivo activity. *Nature Reviews Immunology* 2023; **23:** 720–34.

20 Gunst JD, Højen JF, Pahus MH, et al. Impact of a TLR9 agonist and broadly neutralizing antibodies on HIV-1 persistence: the randomized phase 2a TITAN trial. *Nat Med* 2023; **29:** 2547–58.

21 Fumagalli MJ, Kaczynska A, Allombert M, et al. Enhanced HIV-1 control after antibody therapy is associated with autologous antibodies and reservoir clearance in the RIO trial. *medRxiv* 2025; published onilne April 30, 2026. https://doi.org/10.1101/2025.11.03.25339415 (preprint).

22 Li M, Gao F, Mascola JR, et al. Human immunodeficiency virus type 1 env clones from acute and early subtype B infections for standardized assessments of vaccine-elicited neutralizing antibodies. *J Virol* 2005; **79:** 10108–25.

23 Salazar-Gonzalez JF, Bailes E, Pham KT, et al. Deciphering human immunodeficiency virus type 1 transmission and early envelope diversification by single-genome amplification and sequencing. *J Virol* 2008; **82:** 3952–70.

24 Scheid JF, Horwitz JA, Bar-On Y, et al. HIV-1 antibody 3BNC117 suppresses viral rebound in humans during treatment interruption. *Nature* 2016; **535:** 556–60.

25 Tipoe T, Fidler S, Frater J. An exploration of how broadly neutralizing antibodies might induce HIV remission: the 'vaccinal' effect. *Curr Opin HIV AIDS* 2022; **17:** 162–70.

26 Nishimura Y, Donau OK, Dias J, et al. Immunotherapy during the acute SHIV infection of macaques confers long-term suppression of viremia. *J Exp Med* 2021; **218:** e20201214.

27 Rosás-Umbert M, Gunst JD, Pahus MH, et al. Administration of broadly neutralizing anti-HIV-1 antibodies at ART initiation maintains long-term $CD8^+$ T cell immunity. *Nat Commun* 2022; **13:** 6473.

28 Kiani Z, Urbach JM, Wisner H, et al. CD8+ T cell stemness precedes post-intervention control of HIV viraemia. *Nature* 2025; **2025:** 1–9.

29 Peluso MJ, Sandel DA, Deitchman AN, et al. Correlates of HIV-1 control after combination immunotherapy. *Nature* 2025; **2025:** 1–9.

30 Altaf M, Nel C, Tipoe T, et al. T cell immunity predicts clinical outcomes on stopping antiretroviral treatment after HIV-specific broadly neutralising antibody therapy. *medRxiv* 2026; published online Feb 3. https://doi.org/10.64898/2026.02.02.26345374. (preprint).

31 Dong K, Asari V, Govender V, et al. Evaluation of 2 bNAbs plus vesatolimod in early-treated South African women with HIV-1 during ATI. https://www.croiconference.org/abstract/2240-2025/ (accessed April 15, 2025).

32 Lewin SR, Attoye T, Bansbach C, et al, and the Sunnylands 2019 Working Group. Multi-stakeholder consensus on a target product profile for an HIV cure. *Lancet HIV* 2021; **8:** e42–50.

33 Peluso MJ, Sandel DA, Deitchman AN, et al. Correlates of HIV-1 control after combination immunotherapy *Nature* 2026; **650:** 187–95.