ACTG

Advancing Clinical Therapeutics Globally for HIV/AIDS and Other Infections

A5416 / HVTN 806 / HPTN 108

A Phase I, Randomized, Placebo-Controlled Study of the Safety, Antiviral & Immunomodulatory Activity of Broadly Neutralizing Antibodies 3BNC117-LS-J and 10-1074-LS-J in Combination in ART-treated Adults in Sub-Saharan Africa Living with HIV during a Monitored Analytical Treatment Interruption

A Limited-Center Trial of Advancing Clinical Therapeutics Globally (ACTG)

NIAID CRMS # 39006

This file contains the current ACTG A5416 protocol, which includes the following document:

- Letter of Amendment #1, dated 20 Mar 2026
- Protocol Version 2.0, dated 14 Oct 2024

Letter of Amendment #1 for:

A5416

A Phase I, Randomized, Placebo-Controlled Study of the Safety, Antiviral & Immunomodulatory Activity of Broadly Neutralizing Antibodies 3BNC117-LS-J and 10-1074-LS-J in Combination in ART-treated Adults in Sub-Saharan Africa Living with HIV during a Monitored Analytical Treatment Interruption

A Limited-Center Trial of Advancing Clinical Therapeutics Globally (ACTG)

NIAID CRMS # 39006

ACTG NETWORK COORDINATING CENTER
DLH
6720B Rockledge Drive, Suite 777
Bethesda, MD 20817
Phone: 301-628-3000

LETTER OF AMENDMENT

DATE: March 20, 2026

TO: ACTG CTU Principal Investigators, CRS Leaders, and CTU/CRS Coordinators

FROM: A5416 Protocol Team

SUBJECT: Letter of Amendment #1 for Protocol A5416/HVTN 806/HPTN 108

The following information affects the A5416 study and must be forwarded to your institutional review board (IRB)/ethics committee (EC) as soon as possible for their information and review. This Letter of Amendment (LOA) must be approved by your IRB/EC before implementation.

The following information may also affect the Sample Informed Consent. Your IRB/EC is responsible for determining the process of informing participants of the contents of this LOA.

Upon receiving final IRB/EC and any other applicable regulatory entity approvals for this LOA, sites should implement the LOA immediately. Sites are still required to submit an LOA registration packet to the DAIDS Protocol Registration Office (PRO) at the Regulatory Support Center. Sites will receive a registration notification for the LOA once the DAIDS PRO verifies that all required LOA registration documents have been received and are complete. An LOA registration notification from the DAIDS PRO is not required prior to implementing the LOA. A copy of the LOA registration notification, along with this letter and any IRB/EC correspondence, should be retained in the site's regulatory file.

This LOA is being implemented for the following reasons:

- A sponsor request to remove the reference to the Source Document Guidelines on the DAIDS website. In response, the following section has been updated: 6.3, Instructions for Evaluations.
- A sponsor request to add language pertaining to Direct Data Entry (DDE) in compliance with International Council for Harmonisation (ICH) Guideline for Good Clinical Practice (GCP). In response, the following section has been updated: 6.3, Instructions for Evaluations.
- A team decision to record the data collected on the Decision-Making Aid tool, which was administered

to study candidates at the time informed consent was obtained. The data will be recorded on Medidata Rave, the same mechanism used to record all other study data, with no additional participant risk. In response, the following section has been updated: 6.3.4, Decision-Making Aid.

The following are changes (noted in bold and strikethrough) to A5416/HVTN 806/HPTN 108, Version 2.0, 14Oct2024, titled, "A Phase I, Randomized, Placebo-Controlled Study of the Safety, Antiviral & Immunomodulatory Activity of Broadly Neutralizing Antibodies 3BNC117-LS-J and 10-1074-LS-J in Combination in ART-treated Adults in Sub-Saharan Africa Living with HIV during a Monitored Analytical Treatment Interruption." These changes will be included in the next version of the A5416 protocol if it is amended at a future date.

1. A Protocol Signature Page (PSP) is appended for submission to the DAIDS Protocol Registration System (DPRS) as part of the LOA registration packet.

2. In section 6.3, the reference to the Source Document Guidelines on the DAIDS website has been removed from, and the language about direct data entry (DDE) has been added to, the second paragraph.

All clinical and laboratory information required by this protocol is to be present in the source documents. ~~Sites must refer to the Source Document Guidelines on the DAIDS website for information about what must be included in the source document: https://www.niaid.nih.gov/sites/default/files/score-source-documentation-requirements.pdf.~~
Direct data entry is not allowed for this study.

3. In section 6.3.4, the method for recording the decision-making aid data collected has been added.

6.3.4 Decision-Making Aid

The study staff will review and participate in the decision-making aid tool with participants as part of obtaining informed consent for participation (prior to enrollment). **Data collected on the decision-making aid tool will be recorded on the eCRF.**

A Phase I, Randomized, Placebo-Controlled Study of the Safety, Antiviral & Immunomodulatory Activity of Broadly Neutralizing Antibodies 3BNC117-LS-J and 10-1074-LS-J in Combination in ART-treated Adults in Sub-Saharan Africa Living with HIV during a Monitored Analytical Treatment Interruption

SIGNATURE PAGE

I will conduct the study in accordance with the provisions of this protocol and all applicable protocol-related documents. I agree to conduct this study in compliance with United States (U.S.) Health and Human Services regulations (45 CFR 46); applicable U.S. Food and Drug Administration regulations; standards of the International Council for Harmonisation Guideline for Good Clinical Practice (E6); Institutional Review Board/Ethics Committee determinations; all applicable in-country, state, and local laws and regulations; and other applicable requirements (e.g., U.S. National Institutes of Health, Division of AIDS) and institutional policies.

Principal Investigator: _____
Print/Type

Signed: _____Date: _____
Name/Title

A5416 / HVTN 806 / HPTN 108

A Phase I, Randomized, Placebo-Controlled Study of the Safety, Antiviral & Immunomodulatory Activity of Broadly Neutralizing Antibodies 3BNC117-LS-J and 10-1074-LS-J in Combination in ART-treated Adults in Sub-Saharan Africa Living with HIV during a Monitored Analytical Treatment Interruption

Short Title: Pausing Antiretroviral Treatment Under Structured Evaluation (PAUSE)

A Limited-Center Trial of the ACTG (Advancing Clinical Therapeutics Globally for HIV/AIDS and Other Infections))

Sponsored by:
National Institute of Allergy and Infectious Diseases

In Collaboration with:
HIV Vaccine Trials Network (HVTN)
HIV Prevention Trials Network (HPTN)
The Rockefeller University
Bill and Melinda Gates Foundation (Collaboration for AIDS Vaccine Discovery)

Non-US Protocol

Reservoirs Remission and Cure Transformative Science Group:	**Marina Caskey, MD, Chair**
Protocol Co-Chairs:	**Mina Hosseinipour, MD, MPH** **Rebone Maboa, MBChB, DOHM**
Protocol Co-Vice Chairs:	**Marina Caskey, MD** **William Hahn, MD**
DAIDS Representatives:	**Randall L. Tressler, MD** **Stella Latinovic, PhD** **Chris Duplessis, MD, MPH**
Clinical Trials Specialist:	**Parita Rathod, BS**

Final Version 2.0
October 14, 2024

A5416/HVTN 806/HPTN 108
Final Version 2.0
14Oct2024

A Phase I, Randomized, Placebo-Controlled Study of the Safety, Antiviral & Immunomodulatory Activity of Broadly Neutralizing Antibodies 3BNC117-LS-J and 10-1074-LS-J in Combination in ART-treated Adults in Sub-Saharan Africa Living with HIV during a Monitored Analytical Treatment Interruption

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Principal Investigator: _____
Print/Type

Signed: _____ Date: _____
Name/Title

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SITES PARTICIPATING IN THE STUDY

A5416/HVTN 806/HPTN 108 is a multicenter study open to selected ACTG, HVTN, and HPTN clinical research sites in sub-Saharan Africa.

Refer to the Site tab on the protocol's web page on the ACTG Member website for the list of eligible sites.

PROTOCOL TEAM ROSTER

Co-Chairs
Mina Hosseinipour, MD, MPH
University of North Carolina Global HIV Prevention and Treatment CTU
Kamuzu Central Hospital
Private Bag A-104, 100 Mzimba Road
Lilongwe
Malawi
Phone: +265 888-202-153
E-mail: mina_hosseinipour@med.unc.edu

Rebone Maboa, MBChB, DOHM
The Aurum Institute Pretoria CRS
Unit 3-7, The Enterprise Building
6 Mark Shuttleworth Street
Pretoria 0087
South Africa
Primary: +0799-555-446
E-mail: drmaboa@gmail.com

Co-Vice Chairs
Marina Caskey, MD
Weill Cornell Uptown CRS
1230 York Avenue
P.O. Box 176
New York, NY 10065
Phone: 212-327-7396
E-mail: mcaskey@rockefeller.edu

William Hahn, MD
Fred Hutch Cancer Research Center
1100 Fairview Avenue
Seattle, WA 19024
Phone: 216-667-3431
E-mail: whahn@fredhutch.org

DAIDS Clinical Representatives
Randall Tressler, MD
HIVRB/TRP/DAIDS/NIAID/NIH
5601 Fishers Lane, Room **Hoteling**
Rockville, MD 20852
Phone: **917-547-7279**
E-mail: randall.tressler@nih.gov

DAIDS Clinical Representatives (Cont'd)
Stella Latinovic, PhD, MBA, MSc
HIVRB/TRP/DAIDS/NIAID/NIH
5601 Fishers Lane, Room 9E40A, MSC 9810
Rockville, MD 20852
Phone: 301-761-6398
E-mail: stella.latinovic@nih.gov

VRP Medical Officers
Chris Duplessis, MD, MPH
VRP/DAIDS/NIAID/NIH
5601 Fishers Lane
MSC 9829 | Room 9C44
Rockville, MD 20852-9829
Phone: 240-292-0676
E-mail: chris.duplessis@nih.gov

Statisticians
Katherine Rodriguez, MS
Statistical and Data Analysis Center
Harvard School of Public Health
FXB Building, Room 533
651 Huntington Avenue
Boston, MA 02115
Phone: 617-432-5229
E-mail: krodrigu@sdac.harvard.edu

Clinical Trials Specialist
Parita Rathod, BS
ACTG Network Coordinating Center
DLH
6720B Rockledge Drive, Suite 777
Bethesda, MD 20817
Phone: 301-628-3378
E-mail: parita.rathod@dlhcorp.com

Data Managers
Autumn Rolack, BS, MPH
Frontier Science & Technology Research Foundation, Inc.
4033 Maple Road
Amherst, NY 14226-1056
Phone: 716-834-0900 Ext. 7406
E-mail: rolack@frontierscience.org

Data Managers (Cont'd)
James Blood, MSW
Frontier Science & Technology Research Foundation, Inc.
4033 Maple Road
Amherst, NY 14226-1056
Phone: 716-834-0900 Ext. 7263
E-mail: blood@frontierscience.org

Laboratory Data Managers
Philip Marzinek
Frontier Science & Technology Research Foundation, Inc.
4033 Maple Road
Amherst, NY 14226-1056
Phone: 716-834-0900 Ext. 7399
E-mail: marzinek@frontierscience.org

Sujith Valiyaparambil
Frontier Science & Technology Research Foundation, Inc.
4033 Maple Road
Amherst, NY 14226-1056
Phone: 716-834-0900 Ext. **7291**
E-mail: **valiyaparambil**@frontierscience.org

DAIDS Pharmacists
Justine Beck, PharmD, BCPS, RPh
Pharmaceutical Affairs Branch
DAIDS/NIAID/NIH
5601 Fishers Lane, **Room Hoteling**
Rockville, MD 20852
Phone: 301-761-5288
E-mail: justine.beck@nih.gov

Kelly Colsh, PharmD, BCPS, RPh
Pharmaceutical Affairs Branch
DAIDS, OCSO
5601 Fishers Lane, **Room Hoteling**
Rockville, MD 20852
Phone: 240-669-5721
E-mail: kelly.colsh@nih.gov

Investigators
Philip Andrew, RN
FHI360 359 Blackwell Street, Suite 200
Durham, NC 27701
Phone: 973-972-3118
E-mail: pandrew@fhi360.org

Shelly Karuna, MD, MPH
Fred Hutchinson Cancer Research Center
1100 Fairview Avenue N.
Seattle, WA 98109-1024
Phone: 206-667-4355
E-mail: skaruna@fredhutch.org

William Brumskine, MBChB
Rustenburg CRS
178 Beyers Naude Drive
Rustenburg 0300
South Africa
Phone: 278 713 515 75
E-mail: wbrumskine@auruminstitute.org

Ian Sanne, MBChB
University of the Witwatersrand Helen Joseph (WITS HJH) CRS
Johannesburg, Gauteng 2092
South Africa
Primary: 27-11-2768801
E-mail: isanne@witshealth.co.za

Virologists
Katharine Bar, MD
Penn Therapeutics CRS
502D Johnson Pavilion
3610 Hamilton Walk
Philadelphia, PA 19104-6073
Phone: 215-573-8497
E-mail: bark@upenn.edu

Sara Gianella Weibel, MD
University of California, San Diego
AntiViral Research Center CRS
9500 Gilman Drive
La Jolla, CA 92093-0679
Phone: 858-552-8585 Ext. 7193
E-mail: gianella@ucsd.edu

Pharmacologists
Qing Ma, PhD
University of Rochester Adult HIV
Therapeutic Strategies Network CRS
315 Kapoor Hall
Buffalo, NY 14214
Phone: 716-881-7500
E-mail: qingma@buffalo.edu

Joachim Lubbe Wiesner, PhD
University of Cape Town Pharmacology
Specialty Laboratory
Old Main Building, Groote Schuur Hospital
Observatory, 7925 Cape Town 7925
South Africa
Phone: 27-21-4066472
E-mail: lubbe.wiesner@uct.ac.za

Gary Maartens, MBChB, MMEd
Division of Clinical Pharmacology
University of Cape Town
Cape Town
South Africa
Phone: +27 214066286
E-mail: gary.maartens@uct.ac.za

Immunologist
Nilu Goonetilleke, PhD
University of North Carolina at Chapel Hill
120 Mason Farm Road
Office 2017 (Lab 2023A)
Genetic Medicine Building
P.O. Box CB#7042
Chapel Hill, NC 27599-7264
Phone: 919-962-3129
E-mail: nilu_goonetilleke@med.unc.edu

Socio-Behavioral Scientist
Karine Dubé, DrPH, MPhil
UCSD School of Medicine Division of
Infectious Diseases and Global Public Health
9500 Gillman Drive MC 0507
San Diego, CA 92093
Phone: 919-259-2489
E-mail: kdube@health.ucsd.edu

Laboratory Specialists
Faye Landsman
ACTG Laboratory Center at UCLA
10990 Wilshire Boulevard, Suite 260
Los Angeles, CA 90024
Phone: 310-825-4991
E-mail: flandsman@milabcentral.org

Orlinda Maforo, MAS
ACTG Laboratory Center at UCLA
10990 Wilshire Boulevard, Suite 260
Los Angeles, CA 90024
Phone: 310-889-4041
E-mail: omaforo@milabcentral.org

Laboratory Technologists
Michael Leonard, MS
Vanderbilt University Medical Center
One Hundred Oaks
719 Thompson Lane Suite 57180
Nashville, TN 37204
Phone: 615-875-1570
E-mail: michael.leonard@vumc.org

Africano Kamugisha
MU-JHU Research Collaboration
Infectious Diseases Institute (IDI) Core
Laboratory
Upper Mulago Hill, Kampala
Uganda
Phone: +256 777-396-200
E-mail: akamugisha@idi.co.ug

HVTN / HPTN Representatives
Julie Hunt, PhD
HIV Vaccine Trials Network (HVTN)
Fred Hutchinson Cancer Research Center
1100 Fairview Avenue N.
Seattle, WA 98109-1024
Phone: 206-667-4101
E-mail: jrhunt@fredhutch.org

HVTN / HPTN Representatives (Cont'd)
Gail Broder, MHS
HIV Vaccine Trials Network (HVTN)
Fred Hutchinson Cancer Research Center
1100 Fairview Avenue N.
Seattle, WA 98109-1024
Phone: 206-667-7348
E-mail: gbroder@fredhutch.org

Azwi Takalani, MBChB
HIV Vaccine Trials Network (HVTN)
Hutchinson Center Research Institute of South Africa
E-mail: atakalan@hcrisa.org.za

Estelle Piwowar-Manning
HPTN Lab Center
600 North Wolfe Street, Path 301
Baltimore, MD 21287
Phone: 410-614-6736
E-mail: epiwowa@jhmi.edu

Paul Richardson
HPTN Lab Center
600 North Wolfe Street, Path 306
Baltimore, MD 21287
E-mail: pricha18@jhmi.edu

Yaw Agyei
HPTN Lab Center
600 North Wolfe Street Path 306
Baltimore, MD 21287
E-mail: yagyei1@jhmi.edu

Matshidiso (Tshidi) Malefo
HIV Vaccine Trials Network (HVTN)
Hutchinson Center Research Institute of South Africa
South Africa
Phone: +27 76 800 7371
E-mail: mmalefo@hcrisa.org.za

HVTN / HPTN Representatives (Cont'd)
Jonathan Lucas
FHI360
359 Blackwell Street, Suite 200
Durham, NC 27701
Phone: 973-972-3118
E-mail: jlucas@fhi360.org

Smitha Sripathy, PhD
HIV Vaccine Trials Network (HVTN)
Fred Hutchinson Cancer Research Center
1100 Fairview Avenue N.
Seattle, WA 98109-1024
Phone: 206-747-7403
E-mail: ssripath@fredhutch.org

Meg Brandon
HIV Vaccine Trials Network (HVTN)
Fred Hutchinson Cancer Research Center
1100 Fairview Avenue N.
Seattle, WA 98109-1024
Phone: 206-631-9516
E-mail: mbrandon@fredhutch.org

Laurie Rinn
HIV Vaccine Trials Network (HVTN)
Fred Hutchinson Cancer Research Center
1100 Fairview Avenue N.
Seattle, WA 98109-1024
E-mail: lrinn@fredhutch.org

Maija Anderson
HIV Vaccine Trials Network (HVTN)
Fred Hutchinson Cancer Research Center
1100 Fairview Avenue N.
Seattle, WA 98109-1024
Phone: 206-667-7997
E-mail: maanders@fredhutch.org

Field Representatives
Romina Chinchay Collahua,
MSc, MBA
Houston AIDS Research Team CRS
6431 Fannin Street MSE R474
Houston, TX 77030
Phone: 713-500-5589
E-mail:
romina.chinchaycollahua@uth.tmc.edu

Jenny Orihuela Munive
Socios En Salud Sucursal Peru
Jr. Puno 279 Cercado de Lima
Lima 15001
Peru
E-mail: jorihuela_ses@pih.org

Site Specialist
Anshika Verma, BS
ACTG Network Coordinating Center
DLH
6720B Rockledge Drive, Suite 777
Bethesda, MD 20817
Phone: 301-628-3022
E-mail: anshika.verma@dlhcorp.com

Project Specialist
Jillian Laroche, MPH
ACTG Network Coordinating Center
DLH
6720B Rockledge Drive, Suite 777
Bethesda, MD 20817
Phone: 240-965-4992
E-mail: jillian.laroche@dlhcorp.com

Source Document Specialist
Josie Marshall, BS
ACTG Network Coordinating Center
DLH
6720B Rockledge Drive, Suite 777
Bethesda, MD 20817
Phone: 301-628-3000
E-mail: josie.marshall@dlhcorp.com

Community Representatives
Mandisa Jwara
University of the Witwatersrand Helen Joseph
(WITS HJH) CRS
Postnet Suite 176
P.O. Box 2600, Houghton 2041
Gauteng
South Africa
E-mail: mandi.jwara@gmail.com

Pearson Mmodzi
Lilongwe CRS
Private Bag A-104, 100 Mzimba Road
Lilongwe
Malawi
Phone: +265 999 560 187
E-mail: pmmodzi@unclilongwe.org

Maureen Phiri
Lilongwe CRS CAB
Private Bag A-104, 100 Mzimba Road
Lilongwe
Malawi
Phone: +265 993 706 577
E-mail: phirimaureen@gmail.com

Ernest Mosimanegape Moseki
Gaborone CRS
1836 Northring Road, Private Bag BO320
Gaborone
Botswana
E-mail: emoseki@bhp.org.bw

Ntando Yola
Desmond Tutu HIV Centre CRS
South Africa
E-mail: ntando.yola@hiv-research.org.za

STUDY MANAGEMENT

All general questions concerning this protocol should be sent to actg.teamA5416@fstrf.org via e-mail. The appropriate team member will respond generally within 1 business working day.

Protocol E-mail Group
Sites should contact the User Support Group at the Data Management Center (DMC) as soon as possible to have all relevant personnel at the site added to or removed from the actg.protA5416 e-mail group. Include the protocol number in the e-mail subject line. Send an e-mail message to actg.user.support@fstrf.org.

Clinical Management
For questions concerning entry criteria, toxicity management, concomitant medications, and co-enrollment, contact the Clinical Management Committee (CMC). Send an e-mail message to actg.cmcA5416@fstrf.org. Include the protocol number, patient identification number (PID), and a brief relevant history.

Laboratory
For questions specifically related to immunologic, virologic, or pharmacologic laboratory tests, send an e-mail message to actg.teamA5416@fstrf.org.

Data Management
- For nonclinical questions about transfers, inclusion/exclusion criteria, electronic case report forms (eCRFs), registration, and other data management issues, contact the protocol data manager. Completion guidelines for eCRFs and participant-completed CRFs can be downloaded from the FSTRF website at www.frontierscience.org.
- For transfers, reference the Study Participant Transfer SOP 119, and contact the protocol data manager directly.
- For other questions, send an e-mail message to actg.teamA5416@fstrf.org.
- Include the protocol number and “Data Management Question” in the subject line.

Participant Registration
For participant registration questions or problems and study identification number SID lists, contact the DMC Randomization Desk. Send an e-mail message to rando.support@fstrf.org or call at 716-834-0900, extension 7301.

DMC Portal and Medidata Rave Problems
For questions about the DMC portal or Medidata Rave, contact DMC User Support. Send an e-mail message to actg.user.support@fstrf.org or call 716-834-0900 x7302.

Copies of the Protocol
To request a hard copy of the protocol, send an e-mail message to ACTGNCC@dlhcorp.com. Electronic copies can be downloaded from the protocol-specific web page (PSWP) on the ACTG website at https://www.actgnetwork.org.

Product Package Inserts and/or Investigator Brochures
To request copies of product package inserts or investigator brochures, contact the DAIDS Regulatory Support Center (RSC) at RIC@tech-res.com or call 301-897-1708.

Protocol Registration
For protocol registration questions, send an e-mail message to protocol@tech-res.com or call 301-897-1707.

Protocol Activation
For questions related to protocol activation, contact the Clinical Trials Specialist and/or the ACTG Project Management Core (PMC) (actgpmc@dlhcorp.com). Send an e-mail message to actg.teamA5416@fstrf.org.

Study Product
For questions or problems regarding study product, dose, supplies, records, and returns, call the Protocol Pharmacists Justine Beck, at 301-761-5288, or Kelly Colsh, 240-669-5721.

Study Product Orders
Study product may be ordered through the Clinical Research Products Management Center (CRPMC) online ordering system. For any questions related study product ordering, call the Clinical Research Products Management Center (CRPMC) at 301-294-0741.

Expedited Adverse Event (EAE) Reporting/Questions
For any questions related to EAE reporting, contact DAIDS through the RSC Safety Office at DAIDSRSCSafetyOffice@tech-res.com or call 1-800-537-9979 or 301-897-1709; or fax 1-800-275-7619 or 301-897-1710.

Telephone Calls
Sites are responsible for documenting telephone calls made to A5416 team members. Send an e-mail message to actg.teamA5416@fstrf.org.

Protocol-Specific Web Page
Additional information about management of the protocol can be found on the PSWP.

GLOSSARY OF PROTOCOL-SPECIFIC TERMS

ACC	American College of Cardiology
ACTG	**Advancing Clinical Therapeutics Globally for HIV/AIDS and Other Infections**
ADA	anti-drug antibody
ADCC	antibody-dependent cellular cytotoxicity
AE	adverse event
AHA	American Heart Association
ALT	alanine transaminase
AMP	antibody-mediated prevention
ANC	absolute neutrophil count
AoU	assessment of understanding
ART	antiretroviral therapy
ASCVD	atherosclerotic cardiovascular disease
AST	aspartate transferase
ATI	analytical treatment interruption
bNAb	broadly neutralizing antibody
CD4bs	CD4 binding site
CDC	Centers for Disease Control and Prevention
CFR	Code of Federal Regulations
CI	Confidence Interval
CKD-EPI	Chronic Kidney Disease Epidemiology Collaboration
C_{min}	lowest concentration of a drug in the blood
C_{max}	highest concentration of a drug in the blood
cm	centimeter
CMC	Clinical Management Committee
COVID	coronavirus disease
CRMS	Clinical Research Management System
CRPMC	Clinical Research Products Management Center
CRS	Clinical Research Site
DAERS	DAIDS Adverse Experience Reporting System
DAIDS	Division of AIDS
dL	deciliter
DMC	data management center
DNA	deoxyribonucleic acid
DTG	dolutegravir
EC	ethics committee
E/CIA	enzyme or chemiluminescence immunoassay
eCRF	electronic case report form
eGFR	estimated glomerular filtration rate
ELISPOT	enzyme-linked immunospot

EMR	electronic medical record
EQA	external quality assessment
EUA	emergency use authorization
FDA	US Food and Drug Administration
g	gram
HCV	hepatitis C virus
HIPAA	Health Insurance Portability and Accountability Act
HIV	human immunodeficiency virus
HLA	human leukocyte antigen
HPTN	HIV Prevention Trials Network
HVTN	HIV Vaccine Trials Network
IATA	International Air Transport Association
IC_{50}	inhibitory concentration 50%
IC_{80}	inhibitory concentration 80%
IC_{90}	inhibitory concentration 90%
ICF	informed consent form
ICS	intracellular cytokine staining
IDI	**in-depth interviews**
ID_{80}	inhibitory dilution 80%
IP	investigational product
IPDA	Intact proviral DNA assay
IQA	immunology quality assurance
IRB	institutional review board
IV	intravenous
kg	kilogram
LLOQ	lowest level of quantification
LPC	lab processing chart
LTFU	lost to follow up
mAbs	monoclonal antibodies
mcg	microgram
µL	microgram
mg	milligram
mIU	milli-international units
mL	milliliter
mm	millimeter
MOPS	manual of procedures
NAAT	nucleic acid amplification test
NIAID	National Institute of Allergy and Infectious Diseases
ng	nanogram
NK	natural killer
NNRTI	non-nucleoside reverse transcriptase inhibitors
NWCS	new works concept sheet

OCSO	Office of Clinical Site Oversite
OHRP	Office for Human Research Protections
PBMC	peripheral blood mononuclear cells
PCR	polymerase chain reaction
PID	participant identification
PK	pharmacokinetics
PML	Progressive Multifocal Leukoencephalopathy
PrEP	pre-exposure prophylaxis
PRO	Protocol Registration Office
PWH	participants on study with HIV / people living with HIV
Q4PCR	quadruplex PCR with four probes
RBC	red blood cell
RNA	ribonucleic acid
RPR	rapid plasma reagent
RSC	Regulatory Support Center
SAE	serious adverse event
SCA	single copy assay
SDMC	statistics and data management center
SID	study identification
SOC	standard of care
SOE	schedule of evaluations
SOP	standard operating procedure
STI	sexually transmitted infection
SUSAR	suspected, unexpected severe adverse reaction
TAF	tenofovir alafenamide
TFV	tenofovir
VL	viral load
VQA	virology quality assurance
WBC	white blood cell

SCHEMA

A5416/HVTN 806/HPTN 108
A Phase I, Randomized, Placebo-Controlled Study of the Safety, Antiviral & Immunomodulatory Activity of Broadly Neutralizing Antibodies 3BNC117-LS-J and 10-1074-LS-J in Combination in ART-treated Adults in Sub-Saharan Africa Living with HIV during a Monitored Analytical Treatment Interruption

Short/Abbreviated Title: Pausing Antiretroviral Treatment Under Structured Evaluation (PAUSE)

DESIGN A5416/HVTN 806/HPTN 108 (also referred to as A5416) is a Phase I, double-blind, randomized, placebo-controlled multi-step study designed to evaluate the effects of the combination of long-acting broadly neutralizing antibodies (bNAbs) 3BNC117-LS-J and 10-1074-LS-J compared to placebo in adult people/participants living with HIV (PWH) who discontinue antiretroviral therapy (ART) during a monitored analytical treatment interruption (ATI).

DURATION Up to 96 weeks (24 weeks in Step 1 [ATI], then if they have not met ART restart criteria, 48 weeks (week 25 to 72) in Step 2 [extended ATI], followed by 24 weeks in Step 3 [follow-up on ART])

SAMPLE SIZE 48 participants will be enrolled into Step 1:

Arm A (3BNC117-LS-J + 10-1074-LS-J): 32 participants

Arm B (placebo): 16 participants

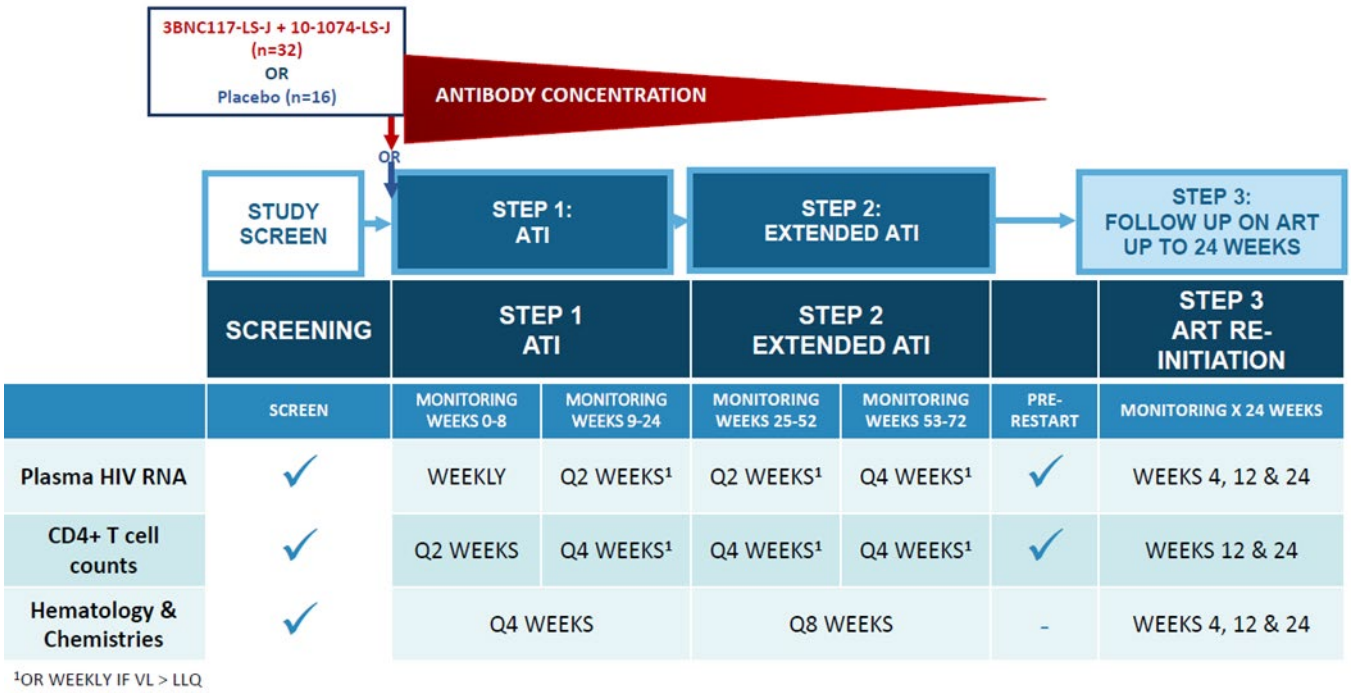
Up to 25 participants will participate in optional in-depth interviews (IDIs).

POPULATION Individuals living with HIV, age ≥18 to ≤70 years, on stable ART who have a CD4+ count of >450 cells/μL, plasma viral load [VL] <50 copies/mL for at least 96 weeks prior to Step 1 entry, no history of receipt of any therapeutic HIV vaccine or HIV monoclonal antibody therapy.

REGIMEN Participants will be randomized in a 2:1 ratio to receive either the study investigational product (Arm A) or placebo (Arm B) and will discontinue ART 2 days later.

Arm A: 32 participants will receive a single intravenous infusion of 3BNC117-LS-J (30 mg/kg) and a single intravenous infusion of 10 1074-LS-J (10 mg/kg).

Arm B: 16 participants will receive a single intravenous infusion of Placebo for 3BNC117-LS-J (0.9% Sodium Chloride Injection) and a single intravenous infusion of Placebo for 10-1074-LS-J (0.9% Sodium Chloride Injection).



	SCREENING	STEP 1 ATI		STEP 2 EXTENDED ATI			STEP 3 ART RE-INITIATION
	SCREEN	MONITORING WEEKS 0-8	MONITORING WEEKS 9-24	MONITORING WEEKS 25-52	MONITORING WEEKS 53-72	PRE-RESTART	MONITORING X 24 WEEKS
Plasma HIV RNA	✓	WEEKLY	Q2 WEEKS[1]	Q2 WEEKS[1]	Q4 WEEKS[1]	✓	WEEKS 4, 12 & 24
CD4+ T cell counts	✓	Q2 WEEKS	Q4 WEEKS[1]	Q4 WEEKS[1]	Q4 WEEKS[1]	✓	WEEKS 12 & 24
Hematology & Chemistries	✓	Q4 WEEKS		Q8 WEEKS		-	WEEKS 4, 12 & 24

[1]OR WEEKLY IF VL > LLQ

Figure Schema: Study design

1.0 HYPOTHESES AND STUDY OBJECTIVES

1.1 Hypotheses

1.1.1 Primary hypothesis: Intravenous infusions of the combination of long-acting broadly neutralizing antibodies (bNAbs) 3BNC117-LS-J and 10-1074-LS-J will be safe and well tolerated; and compared to placebo, will maintain durable viral suppression in the absence of ART while levels are therapeutic in people living with HIV in sub-Saharan Africa.

1.1.2 Secondary hypothesis: Intravenous infusions of the combination of 3BNC117-LS-J and 10-1074-LS-J will be associated with a decrease in the size of the latent HIV-1 reservoir, and will be associated with immunomodulatory effects, including but not limited to humoral and cellular anti-HIV responses.

1.2 Primary Objectives

1.2.1 To evaluate the safety and tolerability of intravenous infusions of 3BNC117-LS-J and 10-1074- LS-J in virally suppressed adults with HIV in sub-Saharan Africa.

1.2.2 To evaluate the efficacy of the combination of 3BNC117-LS-J and 10-1074-LS-J versus placebo in preventing the return of sustained HIV-1 viremia (confirmed HIV-1 viral load >200 copies/mL) for 24 weeks after ART discontinuation in adults with HIV who have maintained viral suppression prior to the analytical treatment interruption (ATI) in sub-Saharan Africa.

1.3 Secondary Objectives

1.3.1 To evaluate the efficacy of the combination of 3BNC117-LS-J and 10-1074-LS-J versus placebo in maintaining plasma HIV-1 RNA levels <50 copies/mL for 24 weeks after ART discontinuation in people/participants living with HIV (PWH) who have maintained viral suppression prior to the ATI.

1.3.2 To evaluate the efficacy of the combination of 3BNC117-LS-J and 10-1074-LS-J in preventing the return of sustained HIV-1 viremia (confirmed HIV-1 viral load >200 copies/mL) while serum concentration of each bNAb remains ≥10 mcg/mL after ART discontinuation in PWH who have maintained viral suppression prior to the ATI.

1.3.3 To evaluate the efficacy of the combination of 3BNC117-LS-J and 10-1074-LS-J in preventing the return of sustained HIV-1 viremia (confirmed HIV-1 viral load >200 copies/mL) for 24 weeks after serum concentration of each bNAb declines to <10 mcg/mL after ART discontinuation in PWH who have maintained viral suppression prior to the ATI.

1.3.4 To evaluate the pharmacokinetic (PK) parameters of the combination of 3BNC117 LS-J and 10-1074-LS-J during ATI in PWH in sub-Saharan Africa.

1.3.5 To estimate the minimum effective concentrations of bNAbs required to maintain viral suppression.

1.3.6 To evaluate evidence of anti-drug antibodies (ADA) against 3BNC117-LS-J and/or 10-1074-LS-J in samples collected at selected time points throughout the study.

1.3.7 To evaluate the effects of the combination of 3BNC117-LS-J and 10-1074-LS-J on CD4+ T-cell count after ART discontinuation in adults with HIV who have maintained viral suppression prior to the ATI.

1.4 Exploratory Objectives

1.4.1 To compare the frequency of control of HIV-1 viremia at weeks 12 and 24 between this study and previous trials of 3BNC117 in combination with 10-1074, trials of 3BNC117-LS and 10-1074-LS and treatment interruption studies conducted in the ACTG.

1.4.2 To evaluate the capacity for the combination of 3BNC117-LS-J and 10-1074-LS-J to induce post-bNAb virus control defined as: maintaining HIV-1 viral load <200 copies/mL in the absence of ART AND effective concentrations of circulating bNAbs (defined as a concentration <1 or 5 or 10 microgram/mL for both 3BNC117-LS-J and 101074-LS-J).

1.4.3 To correlate the predictive capacity of a range of assays, including Monogram PhenoSense assay, Monogram NGS V3 sequencing assay, bulk CD4+ viral outgrowth assay, and other appropriate assays, comparing neutralization sensitivity of entry samples and on-study samples (PBMCs and plasma) to duration of virus suppression.

1.4.4 To evaluate predictors (e.g., years from HIV diagnosis, time from HIV diagnosis to initiation of ART, reported time of continuous ART use, and reported CD4 nadir) of baseline sensitivity to 3BNC117-LS-J and/or 10-1074-LS-J and time to ART restart in PWH who have maintained viral suppression prior to the ATI.

1.4.5 To genotypically and phenotypically characterize the HIV-1 rebound virus populations arising during or after receipt of combination of 3BNC117-LS-J and 10-1074-LS-J, compared to the virus populations in pre-ART plasma samples (when available) and proviral DNA from PBMCs obtained on ART, with respect to genetic clonality, neutralization resistance, and other genotypic or phenotypic properties.

1.4.6 To evaluate the effect of the combination of 3BNC117-LS-J and 10-1074-LS-J on the size, composition, and activity of the HIV-1 reservoir compared to baseline measurements.

1.4.7 To evaluate effects of the combination of 3BNC117-LS-J and 10-1074-LS-J on immune responses, including, but not limited to, humoral and cellular anti-HIV responses, compared to baseline responses.

1.4.8 To evaluate the serum neutralizing activity against a panel of pseudoviruses.

1.4.9 To evaluate participant responses to social sciences questionnaires about understanding of the study and associated interventions, comfort level with ATI, partner protection measures, and experiences in the study.

2.0 INTRODUCTION

2.1 Background

In the last 40 years, great strides have been made towards HIV prevention, treatment and cure. Yet considerable gaps remain in each of these realms as evidenced by ongoing HIV incidence in the face of persistent challenges with ART initiation and adherence [1] and limited success with curative strategies [2-4]. Broadly neutralizing antibodies (bNAbs) have the potential to fill gaps in prevention, treatment, and cure, and analytical treatment interruption (ATI) trial designs facilitate simultaneous exploration of bNAbs' potential in all of these areas. Results from early phase clinical trials using different classes of bNAbs such as those targeting the CD4 binding site (VRC01 and 3BNC117) and the V3 loop (10-1074 and PGT121) have been encouraging, demonstrating the potential for and challenges of developing anti-HIV-1 bNAbs as preventive and therapeutic agents [5-9].

3BNC117 and 10-1074 are bNAbs that target distinct epitopes on HIV-1 gp120 envelope. 3BNC117 binds to the CD4 binding site (CD4bs) and 10-1074 to the base of the V3 loop in HIV-1 envelope gp-120, respectively [10, 11]. Both antibodies show exceptional breadth and potency in vitro, and they protect against or suppress active infection in animal models [12-15]. The combination of 3BNC117 and 10-1074 has shown favorable safety profile in phase 1 studies in approximately 400 people living with HIV (PWH) and without HIV. During viremia, one or three doses of 3BNC117 plus 10 1074 at 30 mg/kg of each mAb led to an average decline in viral load of 1.65 $\log_{10}$ copies/mL, and viremia remained significantly reduced for 12 weeks [16]. Repeated doses of 3BNC117 and 10-1074 over 6 to 20 weeks maintained viral suppression following ART discontinuation in participants harboring-bNAb sensitive viruses [17, 18]. In these studies, viral rebound did not occur until 3BNC117 reached serum concentrations below 10 µg/mL. In addition, the combination of 3BNC117 and 10-1074 led to changes in the size ($p=0.04$) and composition ($p=0.03$) of the intact proviral reservoir after 6 months of antibody therapy among participants who had been on suppressive ART for > 7 years prior to the study (n=12), and in contrast to no measurable decrease in the defective reservoir in the same individuals [18]. These data are consistent with the notion that bNAb administration impacts the HIV reservoir, but additional studies are needed to define the precise effects of bNAbs on the reservoir.

Most bNAb studies completed to date in PWH were conducted in the US or Europe, where clade B is the predominant circulating strain. However, the African continent carries the greatest burden of the pandemic where non-clade B viruses are in circulation. It is therefore imperative that promising new therapeutic and cure strategies also be evaluated in PWH in sub-Saharan Africa, where clade-specific virologic features and population-specific immunologic characteristics may be at play [19-24]. 3BNC117 and 10-1074 have not yet been tested clinically in non-clade B geographic areas, but as discussed above the combination maintained viral suppression in the absence of ART for a median of 28 weeks

in 76% participants chronically living with HIV (13 out of 17; 15 with clade B viruses) who were not pre-selected for bNAb sensitivity.

The in vitro neutralizing activity of this antibody combination against non-B clades PBMC derived primary African isolates was evaluated by the Nussenzweig group [25]. Of the 59 clade C isolates tested, 81% were sensitive to the 3BNC117-LS + 10-1074-LS combination and 59% were sensitive to VRC01 at IC_{80} concentrations <10 mcg/mL. The geometric mean IC_{80} of the 3BNC117-LS+10-1074-LS combination was 2.26 mcg/mL. In contrast, geometric mean IC_{80} of VRC01, which was evaluated in the antibody-mediated prevention (AMP) studies, was 24.02 mcg/mL. Notably, all bNAbs tested showed decreased potency and breadth against primary isolates in comparison to well-characterized pseudovirus panels and the related decrease in activity varied by bNAb specificity. For example, while the CD4bs antibodies 3BNC117 and VRC01 showed an average decrease in potency of 6.9- and 9 fold against clade C primary isolates, the V3 loop antibody 10-1074-LS showed a decrease of 3.9-fold. Two V2 loop bNAbs were also evaluated, and they were unusual in that they had very different relative potencies against primary and pseudotyped clade C viruses: CAP256-VRC25.26 showed no significant difference in activity but in contrast PGDM1400 was 42 fold less active against primary clade C viruses.

The AMP studies demonstrated that neutralization sensitivity of HIV-1 pseudoviruses to VRC01 measured in a TZM-bl assay was a biomarker of VRC01 prevention efficacy, and confirmed the predictive value of neutralization ID_{80} titer, as initially noted in a meta analysis of NHP challenge studies, for HIV-1 prevention efficacy [26]. Use of the ID_{80} neutralization titer as a predictive biomarker of efficacy may facilitate screening and down selection of potential bNAb combinations for HIV prevention, however, it is not yet known if the findings can be extended to other antibody combinations and how the AMP findings relate to antibody efficacy in maintaining viral suppression during infection. Overall, available data (summarized above) support the notion that the combination of 3BNC117 and 10-1074 provides greater coverage against clade C viruses than observed with VRC01 alone in the AMP study. The data also show that the estimated coverage and potency of bNAbs against primary isolates can often be significantly lower than what was predicted by Env pseudotyped viruses and that this decrease is related to the bNAb binding site class, which should be considered in the planning of future bNAb studies.

<u>The proposed study will evaluate the combination of 3BNC117-LS-J and 10-1074-LS-J during ATI in individuals who initiated ART during chronic infection</u>.

<u>Clinical experience with 3BNC117 and 10-1074 in combination</u>
Four clinical trials of the combination of 3BNC117 plus 10-1074, administered intravenously, have been completed. In one study (NCT02824536), individuals without HIV received 1-3 doses of the antibody combination at 3 or 10 mg/kg or placebo [7]. A total of 24 participants enrolled in the study, and 18 received the 3BNC117 and 10-1074 combination.

In the second study (NCT02825797), individuals with HIV on or off ART received 1 to 3 doses of 3BNC117 and 10-1074 at 10 or 30 mg/kg each or placebo [5, 6]. Fifteen study participants discontinued ART and received up to 3 infusions of the monoclonal antibodies (mAbs) at weeks 0, 3, and 6. A total of 34 individuals enrolled (30 received the antibody combination and 4 received placebo). Of those, 12 received 3 infusions of 30 mg/kg,

administered 3 weeks apart, and 3 received 3 infusions of 30 mg/kg, 2 weeks apart. When administered during viremia, the bNAb combination led to an average decline in viral load of 1.65 $\log_{10}$ copies/mL. Viremia decline was transient and followed by selection of resistant strains in most participants. In contrast to the results in viremic individuals, the combination of 3BNC117 and 10-1074 successfully maintained viral suppression in a group of ART-treated individuals harboring sensitive viruses. In the first study, participants with baseline sensitivity to 3BNC117 and 10-1074, defined as IC_{50} <2 µg/mL against viruses outgrown from PBMC, discontinued ART 2 days after the first infusions of 3BNC117 and 10-1074 (week 0) and received two additional combination antibody infusions at weeks 3 and 6. The median time to rebound (HIV-1 RNA >200 copies/mL) for 7 of the 9 antibody-sensitive participants who experienced viral rebound during the study period was 15 weeks after last mAb infusions. The 2 other participants continued to maintain viral suppression after the study follow up period. The average 3BNC117 serum concentration at the time of rebound in these participants with sensitive virus was 1.9 µg/mL and rebounding viruses remained sensitive to 3BNC117, suggesting lack of selective pressure by 3BNC117 at the time of viral rebound. In contrast, the average serum concentration of 10-1074 at rebound was 14.8 µg/mL.

Two additional studies evaluated the effects of repeated doses of 3BNC117 and 10-1074 over 20 to 24 weeks in individuals who initiated ART during chronic [24] or primary HIV infection [27]. In these two studies participants were not pre-screened for bNAb sensitivity. In one study, 13 out of 17 participants maintained viral suppression for 20 weeks or longer after ART interruption. In the second study, 5 of the 7 bNAb-recipients maintained viral suppression for at least 28 weeks during ATI. In these studies, viral rebound did not occur until 3BNC117 reached serum concentrations below 10 µg/mL. Importantly, analysis of baseline proviruses by PhenoSense assay was performed post hoc. In this small data set, results from this phenotypic sensitivity assay did not correlate with clinical outcome or time to viral rebound [26].

As bNAbs have the potential to directly eliminate HIV-infected cells [23], reservoir analysis was performed to evaluate the effects of 3BNC117 plus 10-1074 therapy over 6 months during ART interruption or suppressive ART [14]. Analysis of proviruses was performed by combined quantitative PCR and next-generation sequencing (Q4PCR) which distinguishes intact and defective proviruses and measures reservoir content in peripheral blood. These assessments revealed changes in the size ($p=0.04$) and composition ($p=0.03$) of the intact proviral reservoir after 6 months of antibody therapy among participants who had been on suppressive ART for >7 years prior to the study (n=12). The observed median reduction in the intact reservoir was 46%. In contrast, there was no measurable decrease in the defective reservoir in the same individuals. Subgroup analyses were performed on specimens from participants who interrupted ART during bNAb dosing and participants who remained on ART. Both subgroups showed similar reservoir alterations, but the limited sample size did not reach statistical significance for participants who remained on ART. These data are consistent with the notion that bNAb administration impacts the HIV-1 reservoir, but additional larger and longer studies are needed to define the precise effect of antibody immunotherapy on the reservoir.

Across all studies, no SAEs considered possibly related to the antibodies were reported. Most reported AEs were graded as mild, and the most commonly reported AEs were upper respiratory infection, headache, and malaise/fatigue (see Investigator's Brochures).

3BNC117's half-life when in combination with 10-1074 was 18.4 ±2.5 days versus 17.6±5.7 days when administered alone; 10-1074's half-life when in combination with 3BNC117 was 22.3 ±1.5 days versus 24 ±6.6 days when administered alone.

Clinical Experience with 3BNC117-LS and 10-1074-LS

The modified LS versions of 3BNC117 and 10-1074 contain two one-amino acid substitutions of methionine to leucine at Fc position 428 (M428L), and asparagine to serine at Fc position 434 (N434S). These substitutions enhance the antibody binding affinity to the neonatal Fc receptor (FcRn), prolonging its half-life in vivo. Affinity binding to other Fc receptors remains unchanged. These modifications do not alter the fragment antigen-binding domain (Fab) of the antibody and therefore do not alter its interaction with antigen [8, 9]. The LS variants of 3BNC117-LS and 10-1074-LS have shown similar safety profile to the unmodified variants with most reported adverse events being of Grade 1 severity (NCT04250636, NCT03254277, and NCT03554408) (see Investigator's Brochures). As expected, both LS antibodies have extended half-lives: 3BNC117-LS has a half-life of approximately 63 days and 10-1074-LS of approximately 75 days. Single infusions of 3BNC117-LS and 10-1074-LS, each antibody dosed at 30 mg/kg intravenously, led to median decline in viremia was 1.86 $\log_{10}$ copies/mL in a recently completed pilot study of 6 viremic participants. The observed magnitude of viremia decline was similar to what was observed following single infusions of the unmodified antibodies.

An ongoing study (RIO / NCT04319367) is being conducted in the United Kingdom and is evaluating single infusions of 3BNC117-LS and 10-1074-LS during ATI in individuals who initiated ART during primary HIV infection.

In summary, approximately 400 participants have received 3BNC117, 10-1074, 3BNC117-LS, and/or 10-1074-LS. Of these, approximately 300 were PLWH and 100 of these participated in studies that included a period of ATI.

Clinical Experience with 3BNC117-LS-J & 10-1074-LS-J

Just – Evotec Biologics has optimized the LS-modified 3BNC117 and 10-1074 antibodies in order to improve their manufacturability profile while preserving the reassuring parental safety profile and the antiviral and pharmacokinetic properties of the LS antibodies. The JustBio-modified LS antibodies ("LS-J") are manufactured in a newly derived cell line. 10 1074-LS-J contains not only the LS modification but also an additional light chain amino acid modification (Y2P) and three additional heavy chain amino acid mutations (V79T, L89F and T108R), which confer increased conformational stability while maintaining full neutralization activity (26). These antibodies are being evaluated singly and in combination via SC and IV routes in the C100 study (NCT04173819) conducted at US and sub-Saharan African sites. Approximately 150 participants without HIV enrolled and received the antibodies alone or in combination. Doses ranged from 300 to 600 mg SC and 30 mg/kg IV of each antibody alone or in combination. In total, 30 participants received the antibodies intravenously, 10 of these received the antibody combination.

Dosing has been completed but the study remains blinded. As of October 21, 2022, 43% of the participants across all sites reported a Grade 1 solicited AE, 29% reported a Grade 2 solicited AE, and 5s% reported a Grade 3 solicited AE. Grade 1, Grade 2, and Grade 3 unsolicited AEs were reported by 30%, 45%, and 4% of all participants enrolled, respectively. The most commonly reported local solicited AE was administration site tenderness (Grade 1: 41% of participants; Grade 2: 18% of participants), and the most commonly reported systemic solicited AE was headache (Grade 1: 30%; Grade 2: 17%; Grade 3: 2%). In addition, Grade 1 and Grade 2 ocular pruritus was reported by 14% and 6% participants and resolved without sequelae. Overall, the most commonly reported unsolicited AE was upper respiratory tract infection: Grade 1: 11% and Grade 2: 9%, and the most common unsolicited event(s) deemed at least possibly related to the IP was headache, reported by 5% of the participants (see Investigator's Brochure).

Two SAEs occurred during follow-up considered not related to IP or placebo administration: a motor vehicle accident leading to hospital admission, and gastritis also leading to hospitalization. One participant enrolled in Group 6 (IP combination by subcutaneous route, administered to abdominal area) discontinued IP early due to late occurring pruritus, edema, and erythema at injection site, with subsequent hyperpigmentation and dryness. Symptoms resolved without sequelae.

Pharmacokinetics: The parental 3BNC117 showed an average half-life of 17 days in individuals without HIV, and 10-1074 showed an average half-life of 24 days in the same study population.

Population PK models were developed for 3BNC117-LS and 10-1074-LS. Data from the first in-human studies of 3BNC117-LS and 10-1074-LS were used to construct models characterizing the preliminary population pharmacokinetics of 3BNC117-LS and 10-1074-LS in adults. For both 3BNC117-LS and 10-1074-LS, a linear two-compartment (2CM) model was used to describe the serum concentrations of these agents. The estimated serum half-life of 3BNC117-LS and 10-1074-LS in adults without HIV were 62 and 80 days, respectively. The other PK parameter estimates are summarized in Table 2.1-1.

Table 2.1-1: Pharmacokinetic Parameter Estimates for 3BNC117-LS and 10-1074-LS

Parameter	3BNC117-LS		10-1074-LS	
	Population Estimate (RSE%)	IIV as CV% (RSE%)	Population Estimate (RSE%)	IIV as CV% (RSE%)
CL, mL/day	55.2 (4.6%)	30.3% (11%)	28.5 (3.0%)	21.9% (10%)
Vc, liters	2.18 (4.5%)	26.4% (14%)	1.61 (3.0%)	19.3% (12%)
Vp, liters	2.38 (6.3%)	39.5% (13%)	1.62 (3.1%)	18.3% (13%)
Q, mL/day	181 (15%)	101% (11%)	302 (16%)	124% (10%)

CL, clearance; Vc, volume of distribution in the central compartment; Vp, volume of distribution in the peripheral compartment; Q, intercompartmental clearance; RSE, relative standard error; IIV, interindividual variability; CV, coefficient of variation

Clinical trial simulations were performed using these models to determine the number of days until 3BNC117-LS and 10-1074-LS serum concentrations decreased to less than 10 mcg/mL. Based on the clinical trial simulations, the dosing strategy was determined for the A5416/HVTN 806/HPTN 108 protocol, in which study participants will receive one intravenous infusion of 3BNC117-LS (30 mg/kg, 2100 mg dose for a 70 kg person) and one

intravenous infusion of 10-1074-LS (10 mg/kg, 700 mg dose for a 70 kg person). According to simulations of 2500 adults, the time it would take for median serum concentrations to be maintained above 10 mcg/mL was similar for both agents (~48 weeks from Day 0 of the study). Figure 2.1-1 displays the simulated 3BNC117-LS and 10-1074-LS serum concentration versus time curves.

In general, 10-1074-LS shows higher potency than 3BNC117-LS and it is therefore expected that lower concentrations of 10-1074-LS will maintain antiviral activity compared to 3BNC117 LS [12, 13]. In addition, previous studies have demonstrated a higher bar to selection of 3BNC117 escape variants compared to 10-1074. Therefore, based on currently available in vitro [12, 13], preclinical [14, 15], and clinical [1, 4, 6] data, the proposed dosing regimen has been adequately optimized to prevent inadvertent selection of bNAb resistance.

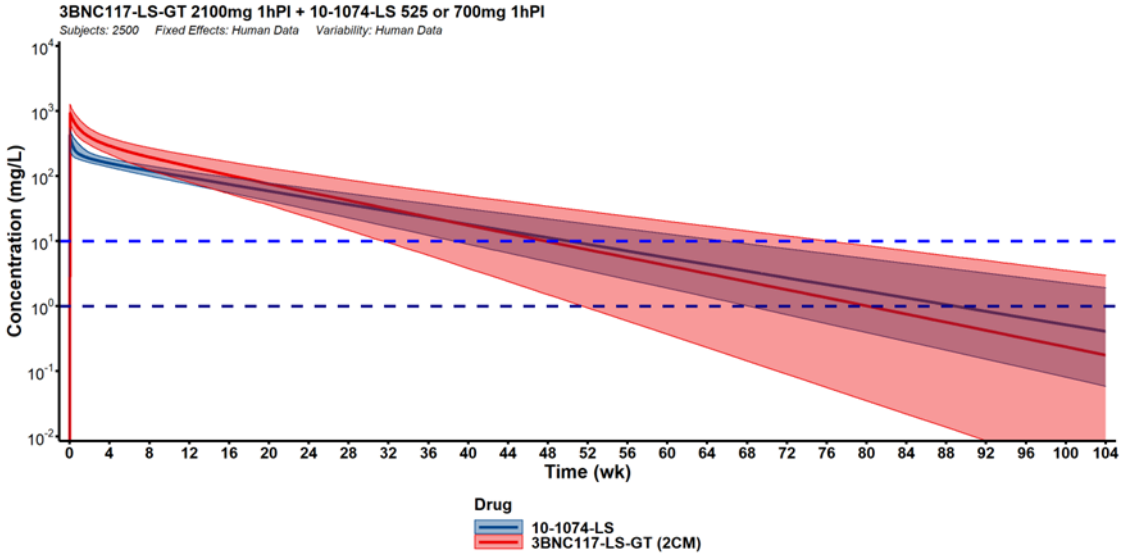


Figure 2.1-1: Simulated 3BNC117-LS and 10-1074 LS serum concentrations versus time in adults. The dashed line represents serum concentration equal to 1 and 10 mg/mL. The simulated concentration versus time data are displayed as median, 10th prediction interval, and 90th prediction interval.

Available preliminary PK data with 3BNC117-LS(-J) and 10-1074-LS(-J) was analyzed by Dr. Qing Ma, applying similar approaches to what had been done for 3BNC117-LS and 10-1074-LS (see above). Preliminary PK analysis showed that 3BNC117-LS-J has an estimated termination half-life of 69 days and 10-1074-LS-J of 72 days. Both have comparable PK parameters, e.g., terminal half-life, but slightly increased clearance, to 3BNC117-LS and 10-1074-LS (Tables 2.1-2 and 2.1-3). Therefore, we expect similar serum decay curves with the LS-J molecules as modeled for the LS variants, which to support the selected doses of 3BNC117-LS-J, 30 mg/kg and 10-1074-LS-J, 10 mg/kg. More accurate estimates are expected when long term follow-up samples become available from all study groups.

Table 2.1-2: Estimated 3BNC117-LS and 3BNC117-LS-J Median PK Parameters and Fold Differences

Antibody	3BNC117-LS	3BNC117-LS-J	Fold Difference
Terminal half-life (days)	72.5	69.1	0.953-1.02
Clearance (mL/day)	76.0	92.0	1.31-1.79

Table 2.1-3: Estimated 10-1074-LS and 10-1074-LS-J Median PK Parameters and Fold Differences

Antibody	10-1074-LS	10-1074-LS-J	Fold Difference
Terminal half-life (days)	74.7	72.4	0.919-0.976
Clearance (mL/day)	31.0	47.0	1.65-2.21

2.2 Rationale

Analytical Treatment Interruption & Biomarkers to Evaluate bNAbs' Therapeutic and Prevention Potential

ATIs provide a direct measure of the antiviral potential of a bNAb combination, which can be used as an in vivo biomarker not only of the therapeutic or curative potential of an intervention but also of its prophylactic potential. Administration of bNAbs during ATI also allows safety evaluation of this strategy and provides information about candidate antibodies in an efficient manner. For example, the combined AMP trials enrolled 4611 participants whereas the proposed trial involves a targeted population of only 48 participants. The first reports of the efficacy of VRC01 in the context of an ATI were published in 2016 [17] whereas results from the AMP trial were published in 2021.

Virologic rebound in an ATI is a corollary to HIV acquisition in an HIV-1 prevention efficacy trial. During viral rebound, the emergence of reservoir viruses in many ways mimic the viral swarm to which an individual at risk of HIV acquisition may be exposed. Unlike natural exposure, in an ATI both the time of this viral emergence and the concentration of the experimental intervention (e.g., bNAbs) at that time is known with some precision due to frequent monitoring of ATI participants. However, the diversity of viruses that might emerge from the reservoir across participants who undergo ATI and the variability in the time of reactivation of those viruses translates to a dynamic range of bNAb concentrations against which a given virus breaks through. Therefore, the expected intra- and inter-participant viral diversity provides an opportunity to evaluate in vivo breadth and potency of a given bNAb combination in a small number of participants.

The empiric demonstration of antiviral activity observed in an ATI acts as a biomarker—complementary to the neutralization titer biomarker demonstrated in the AMP studies [28] – to efficiently demonstrate bNAbs' potential and inform decision-making regarding optimal bNAb regimens for therapeutic, curative, and prophylaxis approaches. The proposed evaluation will supplement our understanding of the immunologic and virologic mechanisms underlying bNAb-mediated prophylaxis, virologic suppression and remission in Africans living with HIV.

Rationale for Not Prescreening for bNAb Sensitivity

The PhenoSense neutralizing antibody assay platform developed by Monogram BioSciences is currently the only method available for clinical use to screen proviral DNA or

plasma viruses for sensitivity to a bNAbs. This assay generates HIV-1 pseudovirions that express envelope proteins that are representative of the quasispecies of either the cell-associated HIV DNA, which enables the interrogation of combination bNAb susceptibility of PBMC-derived virus from aviremic individuals, or from circulating viruses [29].

The correlate of clinical activity in the bNAb treatment scenario evaluated in this study (i.e., during ATI) is not yet known, nor is the relationship between the PhenoSense assay results and other assays previously used in a 3BNC117 and 10-1074 combination ATI study [30].

Preliminary evidence suggests that this assay may not predict viral susceptibility to bNAbs during treatment interruption. The PhenoSense assay was used to measure neutralizing sensitivity on PBMC samples from individuals who participated in studies of 3BNC117 in combination with 10 1074 during ATI (Protocol MCA-906, Protocol MCA-965) [6, 26]. These studies were conducted in geographic areas where clade B variants are predominant. In these studies, antibody sensitivity was defined by IC_{90} <1 mcg/mL for both bNAbs. Of the tested samples, about 30% did not yield a result, possibly because of failure of the primer set used to amplify proviral DNA sequences. Of the 20 resulted samples from participants who underwent ATI (Table 2.2-1), 3 of 10 participants enrolled in Protocol MCA-906 who experienced early viral rebound had test results suggesting sensitivity to both antibodies. Conversely, 6 of 10 participants in Protocol MCA-965 who maintained viral suppression for >24 weeks after ART discontinuation had test results suggesting resistance to one or both antibodies.

Based upon these results, this study will not prescreen participants for bNAb sensitivity, as the ability of the Monogram PhenoSense assay to predict clinical responses to antibody infusions across different viral clades has not been formally evaluated during clinical studies and illustrated in Table 2.2-1. This study also aims to evaluate the antiviral activity of this bNAb combination in individuals harboring non-clade B viruses and to evaluate minimum serum concentrations of the bNAbs to prevent return of viremia, while exploring the relationship between antibody sensitivity (determined by different PhenoSense assay cutpoints (e.g., IC_{50}, IC_{80}, IC_{90}) and time to viral rebound. Enrolling participants with a wider range of PhenoSense cutpoints will enhance our ability to understand the clinical predictive value of the assay and to better define sensitivity cutpoints.

Table 2.2.-1: In Vitro Neutralizing Sensitivity of 3BNC117 and 10-1074 against Pseudoviruses Generated from PBMCs by Monogram's PhenoSense Assay

Study	Study ID	Rebound (weeks)	PhenoSense		Pheno Sense - Monogram							
					3BNC117				10-1074			
			3BNC117	10-1074	IC50	IC80	IC90	IC95	IC50	IC80	IC90	IC95
MCA-906 (Mendoza et al)	9245	5	Sens	Sens	0.034	0.109	0.218	0.413	0.008	0.028	0.059	0.125
	9250	6	Sens	Sens	0.037	0.151	0.344	0.734	0.020	0.095	0.237	0.553
	9251	7	Sens	Sens	0.035	0.118	0.240	0.467	0.008	0.021	0.038	0.065
	9242	15	Sens	Sens	0.043	0.183	0.430	0.944	0.015	0.055	0.119	0.243
	9246	19	Sens	Sens	0.017	0.073	0.170	0.368	0.006	0.020	0.044	0.090
	9243	20	Sens	Sens	0.088	0.309	0.644	1.266	0.028	0.099	0.209	0.417
	9244	21	Sens	Sens	0.052	0.178	0.368	0.723	0.006	0.019	0.037	0.068
	9241	21	Sens	Sens	0.027	0.135	0.343	0.801	0.026	0.098	0.218	0.460
	9252	22	Sens	Sens	0.051	0.179	0.373	0.733	0.024	0.094	0.208	0.433
	9247	26	Sens	Sens	0.032	0.123	0.270	0.557	0.006	0.030	0.075	0.174
MCA-965 (ongoing)	5105	7	Res	Res	0.374	1.452	3.308	7.500	0.567	4.362	>50	>50
	5112	10	Res	Sens	0.163	0.558	1.137	2.174	0.061	0.187	0.360	0.657
	5115	27	Sens	Res	0.013	0.044	0.092	0.181	0.157	0.845	2.225	5.251
	5118	27	Res	Res	>50	>50	>50	>50	0.424	1.321	2.568	4.716
	5111	30	Sens	Res	0.046	0.154	0.314	0.613	0.277	1.115	2.629	6.412
	5125	30	Res	Sens	0.151	0.783	2.007	4.688	0.044	0.151	0.310	0.603
	5114	32	Sens	Sens	0.037	0.130	0.540	0.022	0.032	0.069	0.167	0.031
	5128	36	Sens	Sens	0.054	0.200	0.429	0.868	0.023	0.075	0.149	0.281
	5106	>48	Res	Res	31.906	>50	>50	>50	>50	>50	>50	>50
	5120	>48	Sens	Res	0.032	0.152	0.376	0.859	>50	>50	>50	>50
	5122	no ATI	Sens	Sens	0.052	0.165	0.324	0.606	0.159	0.443	0.826	1.519
	5126	no ATI	Sens	Sens	0.071	0.288	0.645	1.344	0.008	0.025	0.048	0.088

MCA-906: 3BNC117 and 10-1074 in combination (dosed over 6 wks), participants selected by bulk PBMC cultures (IC_{50} <2 mcg/mL).
MCA-965: 3BNC117 and 10-1074 in combination (dosed over 20 wks), participants not pre-selected by sensitivity testing.

Rationale for Inclusion of a Placebo Control Group

It is known that people with virally-suppressed HIV who discontinue ART generally experience a return to detectable HIV in the peripheral blood within a few weeks [26, 27, 31]. However, most of these data come from studies conducted with outdated ART regimens, and in regions with HIV epidemics caused by different HIV-1 subtypes than those found in sub Saharan Africa.

Viral subtype has been associated with differences in disease pathogenesis, progression, and outcomes, so it cannot be assumed that people living with the HIV-1 subtypes that are common in sub-Saharan Africa will experience viral rebound at a similar pace as has been observed in populations with predominantly subtype B virus. For example, the presence and number of transcription factor binding sites vary depending on HIV-1 subtype, which in some cases may alter transcriptional activation [32, 33, 34, 35]. Several small studies have suggested that people with subtype B virus tend to have larger viral reservoirs than people with other subtypes [36, 37, 38]. Subtype C virus has been linked to rapid disease progression in South African women [39]. Subtype D virus has been associated with faster disease progression as compared to subtype A [40, 41, 42]. In recent treatment interruption studies conducted among participants in Thailand with predominantly subtype CRF01_AE virus, viral rebound occurred more rapidly than had been predicted based on data from studies of people with predominantly subtype B virus [43, 44, 45].

Importantly, studies involving African women (SPARTAC and PROMISE cohorts), in particular women treated during recent infection showed greater rate of post-treatment control than European/American men [22, 23, 24]. As discussed in the Statistical

Considerations section, the SPARTAC trial found a significant delay in time to viral rebound in African participants compared to non-African participants. In particular, 5 of the 22 African women (22.7%) who had initiated ART during primary infection maintained HIV-1 RNA <400 copies/mL over a median of 188 weeks following ART interruption [46]. In the larger PROMISE trial, including 1067 virally suppressed, postpartum women who underwent ATI (70% from Africa), 16.8% maintained HIV-1 RNA <400 copies/mL at week 12 following the ATI.

Given the known differences in host population, circulating viral strains and viral load targets, a placebo arm is included to strengthen our ability to interpret the safety and efficacy data with 3BNC117-LS-J/10-1074-LS-J in Africans living with HIV, as compared to the existing historical control data from ATI studies conducted in other regions. Moreover, data generated from this placebo group will contribute to building a historical control for future ATI studies conducted in Africa.

In terms of risk, the placebo per se (i.e., sodium chloride infusion) poses negligible risks, the risks to participants from interrupting ART during the ATI will be minimized through careful monitoring, and the risks to participants' sex partners will be minimized by a comprehensive mitigation plan (discussed in section 6.3.22) aimed at reducing the risk of unintended HIV transmission.

Rationale for Conducting This Study in Sub-Saharan Africa

As discussed above, most bNAb studies completed to date in PWH were conducted in the US or Europe, where subtype B is the predominant circulating strain. However, the African continent carries the greatest burden of the HIV pandemic where non-subtype B viruses are in circulation. It is therefore imperative that promising new therapeutic and cure strategies also be evaluated in PWH in sub-Saharan Africa, where subtype-specific virologic features and population-specific immunologic characteristics may be at play [38, 46, 47, 48, 49]. 3BNC117 and 10-1074 are the two bNAbs most studied in ATI studies to date. The proposed evaluation in a region where non-subtype B viruses are in circulation will supplement our understanding of their direct antiviral activity, as well as potential immunologic mechanisms underlying bNAb-mediated virologic suppression and remission in Africans living with HIV. In addition, the proposed study will help build local capacity to conduct future remission studies. Lastly, investigators and PWH in Africa have highlighted the importance to share potential additional tools against HIV for evaluation in the continent bearing the greatest burden of HIV, and to do so now to avoid unnecessary delays in implementation later.

Rationale for Social Science Questionnaires

The main objective of the A5416/HVTN 806/HPTN 108 social sciences questionnaires is to incorporate participant-centered outcomes. Participant-centered domains will include, but will not be limited to, motivations to participate, decision-making, understanding of the study (including interventions, ATIs, and possible risks and benefits), concerns about the study, quality of life during the study (including emotion/anxiety related to being off ART), and protection of sex partners. These assessments will occur at strategic time points during the study and in parallel to the clinical and other planned laboratory-based assessments.

HIV cure-related research provides an opportunity to improve the lives of PWH, but center on biomedical and clinical endpoints. There is limited knowledge of participant experiences during ATIs, for example, a nested decision-making study in Thailand with brief ATIs [50, 51], and the A5345 biomarker study involving a short-term viral rebound ATI. In A5345, data were limited by infrequent and uneven timing of survey administrations, limiting the ability to make robust generalizations. There is a strong rationale for incorporating socio-behavioral and psychosocial assessments as part of the HIV cure research process to ensure patient centricity. At the July 2018 ATI consensus workshop held at the Ragon Institute, there was consensus that the psychosocial and lived experiences of study participants should be strategically assessed, particularly during ATIs.

The A5416/HVTN 806/HPTN 108 protocol provides an opportunity to assess how participants experience the study intervention and ATIs. PWH enrolled in HIV cure studies may experience psychosocial benefits from participation [52, 53], but may also experience anxiety and other concerns. Further, there is strong community support for integrating socio-behavioral methodologies as part of protocols utilizing ATIs [54]. With the proposed socio-behavioral assessments, we seek to address the critical knowledge gap in the field in terms of how participants perceive and experience prolonged ATIs. We will also assess the partner protection measures put in place by each participant enrolled in this study.

HIV cure-related studies raise a number of ethical concerns, including how to conduct studies in the face of uncertain scientific utility coupled with potential risk [55, 56]. The study team will ensure decisions about participation are adequately informed [31, 53], including adequate understanding of the possible risks and benefits involved in research participation. An assessment of understanding (AoU) tool will be used to ensure participant understanding.

The AoU tool was adapted from the tool used in the AMP ATI trial (HVTN 805/HPTN 093) and will help re-review of any misunderstandings as part of the initial informed consent process. The tool addresses the fact that treatment interruptions are not recommended in clinical care, the risk of HIV transmission to sexual partners who do not have HIV, as well as the need for close monitoring of viral loads and CD4 counts as it is not known how long HIV-1 RNA will remain below quantifiable levels after ART is discontinued. In addition to the AoU tool, the team will develop additional tools to facilitate optimal informed consent and decision-making. Specifically, the team will develop decision aids, such as those developed for the AMP ATI study and will partner with participant advocates including, but not limited to study staff familiar with ATIs and this study specifically, who could work with the potential participant to further facilitate optimal decision-making regarding study participation. Study staff will also be in consultation with each participant's primary HIV care provider, as needed, to ensure their understanding and ability to support the participants. Any such materials developed for participants will be submitted for review and approval to the IRB/EC prior to using with participants.

Study participants will not receive any direct benefit from participation in social science questionnaires, including the optional IDIs. Future participants or others in the community may benefit later from what is learned from the social sciences questionnaires, as this information may help us improve the conduct of future studies.

The greatest risk related to participation in social sciences questionnaires may involve participants' privacy. To protect participants' privacy, social sciences questionnaires will be done in a private area that will allow participants to speak comfortably without being overheard. Possible risks or harms as a result of this study are small. One of the possible risks of the study is a breach in confidentiality; however, all reasonable and necessary precautions will be taken to maintain the confidentiality of all study participants at all times. There is a small possibility that study participants may feel stigma as a result of being asked questions about HIV, although this risk is minimal.

Feasibility of A5416 Enrollment

The study team has extensive prior experience conducting studies of broadly-neutralizing HIV-specific monoclonal antibodies, during ART interruption [6, 7, 16, 17, 57, 58]. Importantly, the members of the study team are conducting ongoing ATI studies in sub-Saharan Africa (HVTN 805/HPTN 093, A5390). In addition to the experience of the protocol team, this study includes African investigators representing three countries who have participated in past ACTG-, HVTN-, or HPTN-led interventional studies including intravenous administration of investigational products and/or ATI.

This study will include 48 individuals who initiated ART during chronic infection and have maintained suppression on ART for at least 96 weeks.

A stakeholder engagement meeting was held in Johannesburg with site investigators, coordinators, and representatives of regulatory entities to address different aspects of the study, including intravenous administration of two investigational products, inclusion of a placebo arm, the ATI period and planned partner protection measures, and identification of potential barriers to accrual. The protocol team will continue to work closely with site investigators to engage with community members and local clinicians throughout protocol development, implementation, and dissemination of study results. A second stakeholder engagement meeting will be held in Johannesburg for community stakeholders roughly three months prior to protocol opening to seek input about community education and recruitment efforts to support smooth study implementation and accrual.

3.0 STUDY DESIGN

A5416/HVTN 806/HPTN 108 is a Phase I, randomized, double-blind, placebo-controlled trial designed to evaluate the effects of the combination of long-acting bNAbs 3BNC117-LS-J and 10-1074-LS-J or placebo in ART suppressed PWH who discontinue ART during a monitored ATI.

The study will enroll 48 participants, and aims for at least 40% enrollment of cisgender women, with an ideal goal of reaching 50 to 60% cisgender women out of the total number of participants.

Step 1 (Day 0 – Week 24)
At the time of enrollment into Step 1 (Day 0), participants will receive the combination of 3BNC117-LS-J with 10-1074-LS-J (Arm A) or placebo (Arm B) and discontinue ART 2 days later.

Follow-up for participants who do not meet ART restart criteria will continue through week 24. Participants who meet ART restart criteria before week 24 will move to Step 3.

Step 2 (extended ATI, Week 25 – Week 72)
Participants who do not meet ART restart criteria in Step 1 will enter Step 2 25 weeks after Day 0.

Participants who enter Step 2 and who have not met ART restart criteria through week 72 may be invited to enroll in A5385 (An Observational Post-Intervention Cohort Destination Protocol), if available, for long term follow-up off ART. ART is not provided by the study.

Step 3 (ART restart through Week 24 post-ART restart)
Participants will restart ART and enter Step 3 at any time during Step 1 or Step 2 if any of the ART restart criteria listed in section 6.3.14 are met. Participants will be followed in Step 3 for 24 weeks.

After ART is resumed, participants will return for safety assessments and monitoring of viral load and CD4+ T-cell counts to ensure a return to viral suppression.

Refer to the study design figure in Schema.

4.0 SELECTION AND ENROLLMENT OF PARTICIPANTS

4.1 Step 1 Inclusion Criteria

4.1.1 Ability and willingness of participant to provide informed consent.

4.1.2 Individuals age ≥18 to ≤70 years.

4.1.3 HIV-1 infection, documented by:

- Any licensed rapid HIV test or HIV enzyme or chemiluminescence immunoassay (E/CIA) test kit at any time prior to study entry

  AND

- Confirmed by one of the following:
  - A second antibody test from different manufacturers or based on different principles and epitopes (combination antigen-antibody-based rapid tests may be used)
  - HIV-1 antigen, or
  - Plasma HIV-1 RNA viral load, or
  - A licensed Western blot

NOTE: The term “licensed” refers to a U.S. FDA-approved kit.

4.1.4 On stable suppressive ART for at least 96 weeks prior to study entry.

NOTE **A**: ART interruptions of up to 7 days occurring ≥90 days prior to study entry are acceptable. Within- and between-class changes in ART within the year prior to study entry are acceptable.

NOTE B: As noted in section 5.6.1, participants must be on an integrase inhibitor-based or protease inhibitor-based regimen at least 4 weeks prior to study entry.

4.1.5 Plasma HIV-1 RNA levels of <50 copies/mL for at least 96 weeks prior to study entry at any licensed local laboratory or Network-approved non-US laboratory that is VQA certified.

NOTE: Two “blips” (i.e., plasma HIV-1 RNA >50 and <400 copies/mL) are allowed if each blip is preceded and followed by values <50 copies/mL. At least one viral load measurement in greater than 56 days and within 48 weeks prior to the entry visit and another viral load within 56 days prior to the entry visit must be available for review.

4.1.6 CD4+ cell count >450 cells/μL obtained within 56 days prior to study entry at any Network-approved non-US laboratory that is IQA certified.

4.1.7 The following laboratory values obtained within 56 days prior to study entry by any Network-approved non-US laboratory that is EQA certified:

- Absolute neutrophil count (ANC) ≥750/mm^3
- Hemoglobin ≥10 g/dL for participants who were assigned female sex at birth, ≥11.0 g/dL for participants who were assigned male sex at birth
- Platelet count ≥100,000/mm^3
- Estimated glomerular filtration rate (eGFR) ≥60 mL/min/1.73m^2 as calculated using the Chronic Kidney Disease Epidemiology Collaboration (CKD-Epi) **2021** equation **[Refer to FSTRF portal]**
- ALT <2.5 times the institutional upper limit of normal
- Direct bilirubin within the institutional range of normal

4.1.8 For participants who can become pregnant (i.e., participants assigned female sex at birth who have not been post-menopausal for at least 24 consecutive months, who have had menses within the preceding 24 months, or who have not undergone surgical sterilization, specifically hysterectomy and/or bilateral oophorectomy or bilateral salpingectomy), negative serum or urine pregnancy test within 24 hours prior to Step 1 entry (Day 0) by a Network-approved non-US laboratory that is EQA certified.

NOTE: Participant-reported history is acceptable documentation of hysterectomy and bilateral oophorectomy, tubal ligation, tubal micro-inserts.

4.1.9 Participants who can become pregnant must agree to use two methods of contraception, one of which must be from the highly effective methods for contraception listed below. Barrier methods of contraception are permitted for the second method of contraception. Contraception must be used from 10 days prior to study entry and participants must agree to use contraception for 36 weeks after receiving study treatment, and until ART is reinitiated and viral suppression is achieved. Acceptable methods of contraception include:

- Contraceptive subdermal implant
- Intrauterine device or intrauterine system
- Combined estrogen and progestogen oral contraceptive
- Injectable progestogen
- Contraceptive vaginal ring
- Percutaneous contraceptive patches
- Partner sterilization with documentation of azoospermia prior to the participant's entry into the study, and this partner is the sole partner for that participant. The documentation of partner sterility can come from the site personnel's review of medical records, medical examination and/or semen analysis, or medical history interview provided by the participant or the partner. Self-reported documentation of reproductive potential should be entered in the source documents.

4.1.10 Participants who can impregnate (i.e., individuals assigned male sex at birth who have not undergone a sterilizing procedure) a partner and who are engaging in sexual activity that could lead to pregnancy must agree to use condoms from 10 days prior to study entry and for 36 weeks after receiving study treatment to avoid impregnating a partner.

4.1.11 Willingness to use barrier protection (i.e., external or internal) for all sexual activity during ATI and until viral suppression is achieved after re-starting ART.

4.1.12 Willingness to not participate in other research studies of investigational drugs while on this study.

4.1.13 Willingness to provide a specimen for a genetic test (HLA Typing).

4.2 Step 1 Exclusion Criteria

4.2.1 History of any AIDS-defining illness prior to study entry.

NOTE: History of treated and resolved pulmonary TB will not be exclusionary.

4.2.2 Known nadir CD4+ cell count <200 cells/μL.

NOTE: If laboratory reports or clinical notes are not available, then participant recall is acceptable for nadir CD4 T-cell count.

4.2.3 Any clinically significant acute or chronic medical condition (such as autoimmune diseases or active tuberculosis), other than HIV infection, that in the opinion of the investigator would preclude participation.

4.2.4 Any history of an HIV-associated malignancy, including Kaposi's sarcoma, or any type of lymphoma or virus-associated cancers.

4.2.5 History of Progressive Multifocal Leukoencephalopathy (PML).

4.2.6 Active or recent non-HIV-associated malignancy requiring systemic chemotherapy or surgery within 36 months prior to study entry or for whom such therapies are expected in the subsequent 12 months.

NOTE: Minor surgical removal of localized skin cancers (squamous cell carcinoma, basal cell carcinoma) is not exclusionary.

4.2.7 Receipt of an NNRTI within 30 days prior to study entry.

4.2.8 Receipt of cabotegravir-LA IM, rilpivirine-LA IM, or other long-acting ARVs within 24 months prior to study entry.

4.2.9 Receipt of any standard-of-care (SOC) vaccines within 7 days prior to study entry.

4.2.10 Known resistance to all drugs within two or more ARV drug classes.

NOTE: M184V/I is an exception and should not be considered when assessing this criterion. Prior HIV resistance testing is not required.

4.2.11 History of systemic corticosteroids (>14 days concurrent use), immunosuppressive anti-cancer or other immunosuppressive agents, interleukins, systemic interferons, systemic chemotherapy, or other medications considered significant by the investigator within the 24 weeks prior to study entry.

4.2.12 ART initiated during acute infection (defined as p24, HIV NAAT, or HIV RNA PCR positive, and negative or indeterminate HIV antibody testing).

4.2.13 Any history of receipt of therapeutic HIV vaccine or HIV monoclonal antibody therapy.

4.2.14 Participation in any clinical study of an investigational product within 12 weeks prior to study entry or expected participation in such a study while on A5416.

4.2.15 Known allergy/sensitivity or any hypersensitivity to components of either study agent or their formulation.

4.2.16 Breastfeeding.

4.2.17 Chronic hepatitis B or C infection as indicated by the presence of Hepatitis B surface antigen (HBsAg), hepatitis C antibody without documented history of prior treatment and clearance or virus RNA (HCV-RNA) or HCV antigen in blood at a Network-approved non-US laboratory that is EQA certified.

4.2.18 Current untreated or incompletely treated active tuberculosis disease or untreated latent tuberculosis infection.

NOTE: Individuals who are on treatment for latent TB with at least 4 weeks of treatment completed are not excluded.

4.2.19 History of or current clinical atherosclerotic cardiovascular disease (ASCVD), as defined by 2013 American College of Cardiology/American Heart Association (ACC/AHA) guidelines, including a previous diagnosis of any of the following:

- Acute myocardial infarction
- Acute coronary syndromes
- Stable or unstable angina
- Coronary or other arterial revascularization
- Stroke
- Transient ischemic attack
- Peripheral arterial disease presumed to be of atherosclerotic origin

4.2.20 Diagnosis of cirrhosis.

4.2.21 Diagnosis of untreated syphilis, gonorrhea, or chlamydia.

NOTE: Individuals who began treatment at least 3 days prior to study entry for any of the above are not excluded.

4.3 Step 2 Inclusion Criteria

4.3.1 Participant who has completed Step 1, including receipt of both bNAb infusions, and has not met ART restart criteria described in section 6.3.14 at any time during Step 1.

4.3.2 Willingness to continue ATI and be monitored.

4.4 Step 2 Exclusion Criteria

4.4.1 None.

4.5 Step 3 Inclusion Criteria

4.5.1 Meeting one or more ART restart criteria described in section 6.3.14.

OR

Despite completing 72 weeks of ATI without meeting one or more ART restart criteria, participant declines participation in A5385, or is unable to enter A5385.

4.6 Step 3 Exclusion Criteria

4.6.1 None.

4.7 Study Enrollment Procedures

4.7.1 Protocol Registration

Prior to implementation of this protocol, and any subsequent full version amendments, each site must have the protocol and the protocol consent form approved, as appropriate, by their local IRB or EC and any other applicable regulatory entity. Upon receiving final approval, sites will submit all required protocol registration documents to the DAIDS Protocol Registration Office (DAIDS PRO) at the Regulatory Support Center (RSC). The DAIDS PRO will review the submitted protocol registration packet to ensure that all of the required documents have been received.

Site-specific informed consent forms (ICFs) WILL be reviewed and approved by the DAIDS PRO, and sites will receive an Initial Registration Notification from the DAIDS PRO that indicates successful completion of the protocol registration process. A copy of the Initial Registration Notification should be retained in the site's regulatory files.

For any protocol amendments, upon receiving final IRB/EC and any other applicable RE approval(s) as well as meeting any additional study-specific requirements as determined by the protocol team, sites should implement the amendment immediately. Sites are required to submit an amendment registration packet to the DAIDS PRO at the RSC. The DAIDS PRO will review the submitted protocol registration packet to ensure that all required documents have been received. Site-specific ICF(s) WILL NOT be reviewed or approved by the DAIDS PRO. Sites will receive an Amendment Registration Notification when the DAIDS PRO receives a complete registration packet. A copy of the Amendment Registration Notification should be retained in the site's regulatory files.

For additional information on the protocol registration process and specific documents required for initial and amendment registrations, refer to the current version of the DAIDS Protocol Registration Manual.

Once a candidate for Step 1 study entry has been identified, details will be carefully discussed with the participant. The participant will be asked to read and sign the approved protocol consent form.

For participants from whom a signed informed consent has been obtained, an ACTG Screening Checklist must be entered through the Data Management Center (DMC) Study Enrollment System.

4.7.2 Protocol Activation

Prior to enrollment, sites must complete the Protocol Activation Checklist found on the ACTG Member website. This checklist must be approved prior to any screening of participants for enrollment.

4.7.3 Participant Registration

Participants who meet the enrollment criteria will be registered to the study according to standard ACTG DMC procedures.

For participants from whom informed consent has been obtained, but who are deemed ineligible or who do not enroll into Entry, an ACTG Screening Failure Results form must be completed and keyed into the database.

4.8 Co-enrollment Guidelines

- Participants cannot co-enroll in studies administering one or more immune modulating agents, or any investigational drug while enrolled in A5416.
- For specific questions and approval for co-enrollment in other studies, sites should first check the PSWP or contact the protocol team via e-mail as described in the Study Management section.

5.0 STUDY TREATMENT

Study treatment is defined as 3BNC117-LS-J, 10-1074-LS-J, placebo for 3BNC117-LS-J, and placebo for 10-1074-LS-J.

CRS pharmacists should consult the *Pharmacy Guidelines and Instructions for DAIDS Clinical Trials Networks* for standard pharmacy operations. Refer to the relevant Investigator's Brochures (IBs) for further information about the study products.

5.1 Regimen

Participants will be randomized 2:1 (study products:placebo) in a blinded fashion to receive one of the following two regimens:

Arm A:

3BNC117-LS-J 30 mg/kg to be administered IV at Step 1 entry (Day 0)
AND
10-1074-LS-J 10 mg/kg to be administered IV at Step 1 entry (Day 0)

Discontinue ART on Day 2

Arm B:

Placebo for 3BNC117-LS-J (0.9% Sodium Chloride Injection) to be administered IV at Step 1 entry (Day 0)
AND
Placebo for 10-1074-LS-J (0.9% Sodium Chloride Injection) to be administered IV at Step 1 entry (Day 0)

Discontinue ART on Day 2

5.2 Study Product Formulation and Storage

5.2.1 3BNC117-LS-J is a sterile solution that will be supplied in vials at a concentration of 150 mg/mL, in a buffered solution. Store vials between 2°C and 8°C protected from light.

5.2.2 10-1074-LS-J is a sterile solution that will be supplied in vials at a concentration of 150 mg/mL, in a buffered solution. Store vials between 2°C and 8°C protected from light.

5.2.3 Placebo for 3BNC117-LS-J and Placebo for 10-1074-LS-J will be 0.9% Sodium Chloride Injection. The product must be locally sourced and stored according to the manufacturer's recommendation.

5.3 Preparation

Prior to preparation, a new prescription will be sent to the pharmacy and must contain the participant's weight from the Step 1 entry visit (Day 0).

Pharmacists must follow appropriate aseptic technique and sterile preparation procedures/guidance as outlined by their country, institution, and pharmacy regulatory authority. The study products and placebo should be prepared in a sterile environment, utilizing a pharmacy biosafety cabinet/isolator.

Any unused portion of study product will not be used for another participant. Any empty vials, unused portion of entered vials, or unused prepared study product should be discarded in a biohazard container and disposed of in accordance with institutional or pharmacy policy.

5.3.1 3BNC117-LS-J: 30 mg/kg

1. Calculate the total dose (mg) and corresponding volume (mL) of 3BNC117-LS-J required based on the participant's weight (in kg).
2. Remove an appropriate number of 3BNC117-LS-J vials from the refrigerator. Additionally, remove an IV container with 100 mL 0.9% Sodium Chloride Injection from storage.
3. Withdraw an equal volume (mL) of 0.9% Sodium Chloride Injection from the container that matches the participant's calculated dose volume.
4. Add the calculated volume of 3BNC117-LS-J to the IV container with 0.9% Sodium Chloride Injection. Record this as the study product preparation time.

   The prepared 3BNC117-LS-J IV container may be stored at controlled room temperature for up to 4 hours from the preparation time. The infusion must be completed within 4 hours of the preparation time.

5.3.2 10-1074-LS-J: 10 mg/kg

1. Calculate the total dose (mg) and corresponding volume (mL) of 10-1074-LS-J required based on the participant's weight (in kg).
2. Remove an appropriate number of 10-1074-LS-J vials from the refrigerator. Additionally, remove an IV container with 100 mL 0.9% Sodium Chloride Injection from storage.
3. Withdraw an equal volume (mL) of 0.9% Sodium Chloride Injection from the container that matches the participant's calculated dose volume.
4. Add the calculated volume of 10-1074-LS-J to the IV container with 0.9% Sodium Chloride Injection. Record this as the study product preparation time.

The prepared 10-1074-LS-J IV container may be stored at controlled room temperature for up to 4 hours from the preparation time. The infusion must be completed within 4 hours of the preparation time.

5.3.3 Placebo for 3BNC117-LS-J and Placebo for 10-1074-LS-J

Remove an IV container containing 100 mL of 0.9% Sodium Chloride Injection from storage. Record this as the placebo preparation time. (NOTE: Keep in mind preparation time for active study product to maintain the blind.)

The prepared placebo container may be stored at controlled room temperature for up to 4 hours from the preparation time. The infusion must be completed within 4 hours of the preparation time.

5.3.4 Label the prepared study products with the following:

- Participant identifier(s)
- Protocol number
- Study product name
  - 3BNC117-LS-J 30mg/kg or Placebo
  - 10-1074-LS-J 10 mg/kg or Placebo
- Final volume (mL)
- Route of administration (IV)
- Infusion time
- Beyond use date and time
- Any additional information required by jurisdiction

5.4 Administration

Each prepared bNAb dilution will be administered as an intravenous infusion over 30 to 60 minutes. The total time needed to administer the dose may be longer, based on factors such as participant tolerance. At the Step 1 entry visit, 3BNC117-LS-J or Placebo for 3BNC117-LS-J will be administered first, followed by 10-1074-LS-J or Placebo for 10-1074-LS-J. A new 0.2 or 0.22 micron in-line filter must be used for each administration of 3BNC117-LS-J and 10-1074-LS-J, as well as placebo. The entire contents of the infusion bags must be administered. At the end of each infusion, the IV line will be flushed with normal saline to ensure all the study product has been delivered.

5.5 Pharmacy: Product Supply, Distribution, and Accountability

5.5.1 Study Product Acquisition/Distribution

3BNC117-LS-J and 10-1074-LS-J, manufactured by Just – Evotec Biologics, will be supplied by the Rockefeller University. Both 3BNC117-LS-J and 10-1074-LS-J will be available through the NIAID Clinical Research Products Management Center (CRPMC). The site pharmacist should obtain the study product(s) for this protocol by following the instructions in the *Pharmacy Guidelines and Instructions for DAIDS Clinical Trials Networks*.

Ancillary supplies such as syringes, needles, in-line filters, and 0.9% Sodium Chloride Injection must be obtained locally by the site.

ART will not be provided by the study.

5.5.2 Study Product Accountability

The site pharmacist is required to maintain complete records of all study products received from the NIAID CRPMC and subsequently dispensed. The site pharmacist at non-US CRSs must follow the instructions in the *Pharmacy Guidelines and Instructions for DAIDS Clinical Trials Networks* for the destruction of unused study products. The procedures to be followed are in the manual *Pharmacy Guidelines and Instructions for DAIDS Clinical Trials Networks*.

5.6 Concomitant Medications

Whenever a concomitant medication or study agent is initiated or a dose changed, investigators must review the concomitant medication's and study agent's most recent package insert, Investigator's Brochure, or updated information from DAIDS to obtain the most current information on drug interactions, contraindications, and precautions.

Additional drug information may be found on the ACTG Precautionary and Prohibited Medications Database located at https://www.ppmdb.org/PPMD.

5.6.1 Required Medications

Participants must be on an integrase inhibitor-based **or protease-inhibitor based** regimen at least 4 weeks prior to study entry.

NOTE: ART will not be provided by the study.

5.6.2 Prohibited Medications

We do not anticipate significant drug interactions with the study products at this time. Participants who enroll in the study agree to not participate in other studies of investigational drugs.

Long-acting ART will interfere with the ATI. Long-acting cabotegravir (CAB LA), long-acting rilpivirine (RPV LA) or other long-acting ARVs are prohibited. NNRTIs are prohibited during Step 1 and Step 2.

Participants should not receive any other anti-HIV antibody therapy, other investigational agents, or systemic immunomodulators.

NOTES:
- Topical and inhaled corticosteroids are not prohibited.
- Topical immune modulators are not prohibited.
- Systemic corticosteroids of ≤14 days' duration are not prohibited.

5.6.3 Precautionary Medications

We do not anticipate significant drug interactions with the study products at this time.

Where possible, standard-of-care (SOC) vaccines, including COVID vaccines with EUA and FDA or other regulatory approval, should be given a minimum of 2 weeks prior to bNAb infusions (Step 1 entry Participants should not receive SOC vaccines within 7 days prior or 7 days after to bNAb dosing. If vaccines are given during Step 1 and 2, they should be given at the end of the visit after the specimens have been collected. If a participant receives a vaccine during this time period, the Clinical Management Committee (CMC) should be informed and the vaccine recorded on the eCRF.

6.0 CLINICAL AND LABORATORY EVALUATIONS

6.1 Schedule of Evaluations (SOE)

Table 6.1-1: Screening and Step 1 (Entry to Week 12)

Screening and Step 1 Evaluations	Screening	Step 1															
				Week												Premature Study / Treatment Discontinuation	Confirmation of Viral Rebound
		Entry (Day 0)	Day 2**	1	2	3	4	5	6	7	8	9*	10	11*	12		
(Visit Window)	Within 56 days of Entry		(±1 day)	(±3 days)								(±3 days)					
Documentation/Confirmation of HIV-1	X																
Documentation of Pre-ART HIV-1 RNA, Nadir CD4+ Count, and Available HIV-1 RNA Levels	X																
Assessment of Understanding	X																
Decision-Making Aid	X																
Medical History	X	X															
Medication History	X	X															
Complete Physical Exam	X																
Targeted Physical Exam		X		X	X	X	X	X	X	X	X		X		X		
Weight	X	X															
Verification of ART Discontinuation			X														
STI Testing	X	X		if suspected			X	if suspected			X	if suspected			X		
Review of STI Testing Results	at the next visit after results are available																
Hepatitis Testing	X			as clinically indicated													
Hematology	X	X		X			X				X				X	X	

Screening and Step 1 Evaluations	Screening	Step 1														Premature Study / Treatment Discontinuation	Confirmation of Viral Rebound
		Entry (Day 0)	Day 2**	Week 1	2	3	4	5	6	7	8	9*	10	11*	12		
(Visit Window)	Within 56 days of Entry		(±1 day)	(±3 days)								(±3 days)					
Liver Function Tests	X	X		X			X				X				X	X	
Chemistry	X	X		X			X				X				X	X	
Urine Dipstick with Reflex Urinalysis	X	X		X	whenever indicated		X	whenever indicated								X	
Pregnancy Testing	X	X		whenever suspected			X	whenever suspected			X				X	X	
CD4+ [1]	X	X		C	X	C	X	C	X	C	X	X	C	X	X	X	
HIV-1 RNA [1]	X	X		X	X	X	X	X	X	X	X	X	X	X	X	X	
Monogram PhenoSense Assay		X															
HIV-1 ART Resistance Testing (Genotype) [3]																	C
Assessment of ART Restart Criteria				X	X	X	X	X	X	X	X	X	X	X	X		
Infusion bNAb PK		X															
Sparse bNAb PK [2]				C	C	C	X	C	C	C	X	C	C	C	X		X
ARV PK (Plasma) [4]							X				X				X		
Stored Plasma [2]		X		X	X	X	X	X	X	X	X	C	C	C	X		X
Stored Serum [2]		X		C	C	C	X	C	C	C	X	C	C	C	X		X
Stored PBMCs [2]		X		C	X	C	X	C	C	C	X	C	C	C	X		X
HLA Typing		X															
Large Blood Draw		X													X		
Infusion of 10-1074-LS-J and 3BNC117-LS-J OR placebo		X															

Screening and Step 1 Evaluations	Screening	Step 1													Premature Study / Treatment Discontinuation	Confirmation of Viral Rebound
				Week												
		Entry (Day 0)	Day 2**	1	2	3	4	5	6	7	8	9*	10	11*	12	
(Visit Window)	Within 56 days of Entry		(±1 day)	(±3 days)								(±3 days)				
Discontinuation of ART			X													
Pregnancy Avoidance and Risk Reduction Counseling		X		X	X	X	X	X	X	X	X	X	X	X	X	X	
Mitigation of HIV Transmission Risk		X		X	X	X	X	X	X	X	X	X	X	X	X	X	
Social Science Questionnaire		X														X	

Footnotes:

* Visit weeks shaded in gray are conditional visits and will be scheduled following HIV-1 RNA level >200 copies/mL.

** Day 2 is telephone and/or text message contact only.

[1] Visits marked X = Required evaluation and C = Conditional evaluation. Evaluation is required at visits marked with “X”. For visits marked with “C”, perform (the evaluation) if the HIV-1 RNA at the previous visit was >200 copies/mL. If the participant has HIV-1 RNA <200 copies/mL for 4 consecutive weeks, then the participant can stop the conditional visits.

[2] Visits marked X = Required evaluation and C = Conditional evaluation. Evaluation is required at visits marked with “X”. For visits marked with “C”, perform at the next visit following a participant’s first plasma HIV-1 RNA >200 copies/mL. **See section 6.2.3 for more info.**

[3] Conditional evaluation to be performed once for any participant with a plasma HIV-1 RNA ≥1000 copies/mL following ART discontinuation. **See section 6.2.3 for more info.**

[4] Samples collected and stored as scheduled until participants have Confirmed Viral Rebound.

Table 6.1-2: Step 1 (Week 13 to Week 24)

Step 1 Evaluations	Step 1													
	Week												Premature Study / Treatment Discontinuation	Confirmation of Viral Rebound
	13*	14	15*	16	17*	18	19*	20	21*	22	23*	24		
(Visit Window)	(±3 days)													
Targeted Physical Exam		X		X		X		X		X		X	X	
STI Testing	if suspected			X	if suspected			X	if suspected			X		
Review of STI Testing Results	at the next visit after results are available													
Hepatitis Testing	as clinically indicated													
Hematology				X				X				X	X	
Liver Function Tests				X				X				X	X	
Chemistry				X				X				X	X	
Urine Dipstick with Reflex Urinalysis	whenever indicated													
Pregnancy Testing	whenever suspected			X	whenever suspected			X	whenever suspected			X		
CD4+ [1]	X	C	X	X	X	C	X	X	X	C	X	X	X	
HIV-1 RNA [1]	X	X	X	X	X	X	X	X	X	X	X	X	X	
HIV-1 ART Resistance Testing (Genotype) [3]														C
Assessment of ART Restart Criteria [1]	X	X	X	X	X	X	X	X	X	X	X	X		
Sparse bNAb PK [2]	C	C	C	X	C	C	C	X	C	C	C	X		X
ARV PK (Plasma) [4]				X				X				X		
Stored Plasma [2]	C	C	C	X	C	C	C	X	C	C	C	X		X
Stored Serum [2]	C	C	C	X	C	C	C	X	C	C	C	X		X
Stored PBMCs [2]	C	C	C	X	C	C	C	X	C	C	C	X		X
Large Blood Draw												X		
Pregnancy Avoidance and Risk Reduction Counseling	X	X	X	X	X	X	X	X	X	X	X	X		

Step 1 Evaluations	Step 1													
	Week												Premature Study / Treatment Discontinuation	Confirmation of Viral Rebound
	13*	14	15*	16	17*	18	19*	20	21*	22	23*	24		
(Visit Window)	(±3 days)													
Mitigation of HIV Transmission Risk	X	X	X	X	X	X	X	X	X	X	X	X		
Social Science Questionnaire													X	

Footnotes:

* Visit weeks shaded in gray are conditional visits and will be scheduled following HIV-1 RNA level >200 copies/mL.

[1] Visits marked X = Required evaluation and C = Conditional evaluation. Evaluation is required at visits marked with “X”. For visits marked with “C”, perform (the evaluation) if the HIV-1 RNA at the previous visit was >200 copies/mL. If the participant has HIV 1 RNA <200 copies/mL for 4 consecutive weeks, then the participant can stop the conditional visits.

[2] Visits marked X = Required evaluation and C = Conditional evaluation. Evaluation is required at visits marked with “X”. For visits marked with “C”, perform at the next visit following a participant’s first plasma HIV-1 RNA >200 copies/mL. **See section 6.2.3.**

[3] Conditional evaluation to be performed once for any participant with a plasma HIV-1 RNA ≥1000 copies/mL following ART discontinuation. **See section 6.2.3.**

[4] Samples collected and stored as scheduled until participants have Confirmed Viral Rebound.

Table 6.1-3: Step 2 (Week 25 to Week 48)

Step 2 Evaluations	Step 2																								Premature Study Discontinuation	Confirmation of Viral Rebound
	Week																									
	25*	26	27*	28	29*	30	31*	32	33*	34	35*	36	37*	38	39*	40	41*	42	43*	44	45*	46	47*	48		
(Visit Window)	(±3 days)																									
Targeted Physical Exam		X		X		X		X		X		X		X		X		X		X		X		X	X	
STI Testing	if suspected			X	if suspected			X	if suspected			X	if suspected			X	if suspected			X	if suspected			X		
Review of STI Testing Results	at the next visit after results are available																									
Hepatitis Testing	as clinically indicated																									
Hematology				X				X				X				X				X				X	X	
Liver Function Tests				X				X				X				X				X				X	X	
Chemistry				X				X				X				X				X				X	X	
Urine Dipstick with Reflex Urinalysis	whenever indicated																								X	
Pregnancy Testing	whenever suspected			X	whenever suspected			X	whenever suspected			X	whenever suspected			X	whenever suspected			X	whenever suspected			X	X	
CD4+ [1]	X	C	X	X	X	C	X	X	X	C	X	X	X	C	X	X	X	C	X	X	X	C	X	X	X	
HIV-1 RNA [1]	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	
HIV-1 ART Resistance Testing (Genotype) [3]																										C
Assessment of ART Restart Criteria	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X		
Sparse bNAb PK [2]	C	C	C	X	C	C	C	X	C	C	C	X	C	C	C	X	C	C	C	X	C	C	C	X		X
ARV PK (Plasma) [4]				X				X				X				X				X				X		
Stored Plasma [2]	C	C	C	C	C	C	C	C	C	C	C	X	C	C	C	C	C	C	C	C	C	C	C	X		X
Stored Serum [2]	C	C	C	X	C	C	C	X	C	C	C	X	C	C	C	X	C	C	C	X	C	C	C	X		X
Stored PBMC [2]	C	C	C	C	C	C	C	C	C	C	C	X	C	C	C	C	C	C	C	C	C	C	C	X		X
Large Blood Draw																								X		

Step 2 Evaluations	Step 2																								
	Week																							Premature Study Discontinuation	Confirmation of Viral Rebound
	25*	26	27*	28	29*	30	31*	32	33*	34	35*	36	37*	38	39*	40	41*	42	43*	44	45*	46	47*	48	
(Visit Window)	(±3 days)																								
Pregnancy Avoidance and Risk Reduction Counseling	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	
Mitigation of HIV Transmission Risk	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	
Social Science Questionnaire																								X	

Footnotes:

* Visit weeks shaded in gray are conditional visits and will be scheduled following HIV-1 RNA level >200 copies/mL.

[1] Visits marked X = Required evaluation and C = Conditional evaluation. Evaluation is required at visits marked with “X”. For visits marked with “C”, perform (the evaluation) if the HIV-1 RNA at the previous visit was >200 copies/mL. If the participant has HIV-1 RNA <200 copies/mL for 4 consecutive weeks, then the participant can stop the conditional visits.

[2] Visits marked X = Required evaluation and C = Conditional evaluation. Evaluation is required at visits marked with “X”. For visits marked with “C”, perform at the next visit following a participant’s first plasma HIV-1 RNA >200 copies/mL. **See section 6.2.3 for more info.**

[3] Conditional evaluation to be performed once for any participant with a plasma HIV-1 RNA ≥1000 copies/mL following ART discontinuation. **See section 6.2.3.**

[4] Samples collected and stored as scheduled until participants have Confirmed Viral Rebound.

Table 6.1-4: Step 2 (Week 49 to Week 72)

Step 2 Evaluations	Step 2																								
	Week																							Premature Study Discontinuation	Confirmation of Viral Rebound
	49*	50*	51*	52	53*	54*	55*	56	57*	58*	59*	60	61*	62*	63*	64	65*	66*	67*	68	69*	70*	71*	72	
(Visit Window)	(±3 days)																								
Targeted Physical Exam				X				X				X				X				X				X	X	
STI Testing	if suspected			X	if suspected			X	if suspected			X	if suspected			X	if suspected			X	if suspected			X		
Review of STI Testing Results	at the next visit after results are available																								
Hepatitis Testing	as clinically indicated																								
Hematology				X				X				X				X				X				X	X	
Liver Function Tests				X				X				X				X				X				X	X	
Chemistry				X				X				X				X				X				X	X	
Urine Dipstick with Reflex Urinalysis	whenever indicated																								X	
Pregnancy Testing	whenever suspected			X	whenever suspected			X	whenever suspected			X	whenever suspected			X	whenever suspected			X	whenever suspected			X	X	
CD4+ [1]	X	C	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	
HIV-1 RNA [1]	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	
HIV-1 ART Resistance Testing (Genotype) [3]																										C
Assessment of ART Restart Criteria	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X		
Sparse bNAb PK [2]	C	C	C	X	C	C	C	X	C	C	C	X	C	C	C	X	C	C	C	X	C	C	C	X		X
ARV PK (Plasma) [4]				X				X				X				X				X				X		
Stored Plasma [2]	C	C	C	C	C	C	C	C	C	C	C	X	C	C	C	C	C	C	C	C	C	C	C	X		X

Step 2 Evaluations	Step 2																									
	Week																								Premature Study Discontinuation	Confirmation of Viral Rebound
	49*	50*	51*	52	53*	54*	55*	56	57*	58*	59*	60	61*	62*	63*	64	65*	66*	67*	68	69*	70*	71*	72		
(Visit Window)	(±3 days)																									
Stored Serum [2]	C	C	C	X	C	C	C	X	C	C	C	X	C	C	C	C	C	C	C	C	C	C	C	X		X
Stored PBMCs [2]	C	C	C	C	C	C	C	C	C	C	C	X	C	C	C	C	C	C	C	C	C	C	C	X		X
Large Blood Draw																								X		
Pregnancy Avoidance and Risk Reduction Counseling	C	X	C	X	C	X	C	X	C	X	C	X	C	X	C	X	C	X	C	X	C	X	C	X		
Mitigation of HIV Transmission Risk	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X		
Social Science Questionnaire																									X	

Footnotes:

* Visit weeks shaded in gray are conditional visits and will be scheduled following HIV-1 RNA level >200 copies/mL.

[1] Visits marked X = Required evaluation and C = Conditional evaluation. Evaluation is required at visits marked with "X". For visits marked with "C", perform (the evaluation) if the HIV-1 RNA at the previous visit was >200 copies/mL. If the participant has HIV-1 RNA <200 copies/mL for 4 consecutive weeks, then the participant can stop the conditional visits.

[2] Visits marked X = Required evaluation and C = Conditional evaluation. Evaluation is required at visits marked with "X". For visits marked with "C", perform at the next visit following a participant's first plasma HIV-1 RNA >200 copies/mL. **See section 6.2.3.**

[3] Conditional evaluation to be performed once for any participant with a plasma HIV-1 RNA ≥1000 copies/mL following ART discontinuation. **See section 6.2.3.**

[4] Samples collected and stored as scheduled until participants have Confirmed Viral Rebound.

Table 6.1-5: Schedule of Evaluations, Step 3

Step 3 Evaluations	Entry (R)	Step 3			Premature Study Discontinuation
		ART/Monitoring (Weeks)			
		R+4	R+12	R+24	
(Visit Windows)		(±7 days)			
Documentation of ART Restart Date	X				
ART Re-Adherence Counseling	X				
Clinical Assessment		X	X	X	X
Hematology [1]		C	C	C	X
Liver Function Tests [1]		C	C	C	X
Chemistry [1]		C	C	C	X
Urine Dipstick with Reflex Urinalysis [1]		C	C	C	
STI Testing [1]		C	C	C	
Review of STI Testing Results		as needed			
Pregnancy Testing	whenever suspected				
CD4+			X	X	X
HIV-1 RNA		X	X	X	X
Stored Plasma	X			X	
Stored Serum	X		X	X	
Stored PBMCs	X			X	
Pregnancy Avoidance and Risk Reduction Counseling		X	X	X	
Social Science Assessments	X			X	X

[1] C = Conditional evaluation, if clinically indicated per site investigator's discretion.

6.2 Timing of Evaluations

6.2.1 Screening Evaluations

Screening evaluations must occur prior to the participant starting any study medications, treatments, or interventions.

Screening evaluations to determine eligibility must be completed within 56 days prior to Step 1 entry unless otherwise specified.

In addition to data being collected on participants who enroll into the study, demographic, clinical, and laboratory data on screening failures will be captured in a Screening Failure Results form and entered into the ACTG database.

6.2.2 Step 1 Entry Evaluations

In this study, Step 1 entry (Day 0) is defined as the day of the bNAb or placebo infusions and will take place only after screening is completed and eligibility is confirmed. Randomization should occur on the same day as Step 1 entry (Day 0). Day 0 evaluations are the baseline for subsequent safety assessments.

6.2.3 Post-Entry Evaluations

<u>Step 1</u>
The Day 2 visit has a visit window of ±1 day. All other Step 1 visits have a visit window of ±3 days. Conditional evaluations are evaluations that are only conducted following an HIV-1 RNA >200 copies/mL.

If the participant has HIV-1 RNA <200 copies/mL for 4 consecutive weeks, then the participant can stop the conditional evaluations.

<u>Step 2</u>
Step 2 visits will have windows of ±3 days. Conditional evaluations are evaluations that are only conducted following an HIV-1 RNA >200 copies/mL.

If the participant has HIV-1 RNA <200 copies/mL for 4 consecutive weeks, then the participant can stop the conditional evaluations.

Confirmation of viral rebound
During Step 1 and Step 2, any participant with plasma HIV-1 RNA >200 copies/mL will have HIV-1 RNA confirmed at the next scheduled **or conditional** visit.

Study sites should contact the CMC for any confirmed viral rebound >200 copies/mL occurring in Step 1 and Step 2.

HIV-1 resistance testing should be performed at the next scheduled visit for any participant with a plasma HIV-1 RNA ≥1000 copies/mL.

NOTE: The confirmation of viral rebound is not an additional visit. The conditional visits following an HIV-1 RNA >200 copies/mL serves as the confirmation of viral rebound. The "confirmation of viral rebound" is to be followed in terms of the samples collected. Refer to SOE footnotes.

Step 3
All visits in Step 3 have a visit window of ±7 days.

Step 3 registration should occur as soon as possible after the participant has met an ART restart criterion. If possible, Step 3 registration should occur on the day that the participant restarts ART.

6.2.4 Discontinuation Evaluations

Premature Treatment Discontinuation Evaluations
Registered participants who do not receive any infusions of 3BNC117-LS-J and/or 10-1074-LS-J or placebo will have premature treatment discontinuation evaluations performed according to the SOE. No further evaluations or follow-up are required for these participants. Participants who receive partial infusions will remain on ART and transition to Step 3 and be followed per study.

Premature Study Discontinuation Evaluations
Participants who have received both study products and who prematurely discontinue study participation will undergo the premature study discontinuation evaluations according to the SOE as their final study visit.

6.3 Instructions for Evaluations

Each study site and laboratory involved in this study will comply with the DAIDS policy on Requirements for DAIDS Funded and/or Sponsored Laboratories in Clinical Trials Policy, which is available at: https://www.niaid.nih.gov/sites/default/files/laboratorypolicy1.pdf.

All clinical and laboratory information required by this protocol is to be present in the source documents. Sites must refer to the Source Document Guidelines on the DAIDS website for information about what must be included in the source document: https://www.niaid.nih.gov/sites/default/files/score-source-documentation-requirements.pdf.

All stated evaluations are to be recorded on the eCRF unless otherwise specified. Refer to section 7.0 for information on the Division of AIDS Table for Grading the Severity of Adult and Pediatric Adverse Events (DAIDS AE Grading Table) and AE reporting of adverse events requirements.

The protocol team and/or study oversight bodies (e.g., Study Monitoring Committee [SMC]) may determine that additional source data associated with procedures or evaluations performed per protocol should be entered into eCRFs so that the data can be used for analysis or to otherwise assist with interpretation of study findings. In such cases, sites will be officially instructed to enter the additional data into eCRFs from available source documentation.

6.3.1 Documentation/Confirmation of HIV-1

Section 4.1.3 specifies assay requirements for HIV-1 documentation. HIV-1 documentation is not recorded on the eCRF.

If results of past HIV-1 serology are not available, HIV-1 serology will be performed as part of the screening process, following the assay requirements in section 4.1.3.

6.3.2 Documentation of Pre-ART HIV-1 RNA, Nadir CD4+ Count, and Available HIV-1 RNA Levels

Laboratory records or clinical notes are preferred for pre-ART HIV-1 RNA and nadir CD4 T-cell counts. If laboratory reports or clinical notes are not available, then participant recall is acceptable for nadir CD4 T-cell count. If no pre-ART HIV-1 RNA laboratory report or clinical note is available, then the data should be considered missing.

HIV-1 RNA laboratory reports over 96 weeks prior to entry should be reviewed and results recorded in the source documents.

6.3.3 Assessment of Understanding

The study staff will participate in the informed consent process, which will include completion of the A5416-specific Assessment of Understanding (AoU) tool to evaluate participants' comprehension of the risks and lack of direct benefits of study participation. The AoU will be posted on the A5416 Protocol Specific Webpage (PSWP). Participant completion of the AoU will not be recorded on the eCRF.

6.3.4 Decision-Making Aid

The study staff will review and participate in the decision-making aid tool with participants as part of obtaining informed consent for participation (prior to enrollment).

6.3.5 Medical History

The medical history must include all signs and symptoms regardless of grade and all diagnoses identified by the ACTG criteria for clinical events and other diagnoses regardless of grade within the past 56 days prior to entry. In addition, the following diagnoses should be recorded regardless of when the diagnosis was made:

- AIDS-defining conditions
- Bone fractures (verbal history accepted)
- Coronary heart disease (exclusionary)
- Cancer (exclusive of basal/squamous cell skin cancer)
- Diabetes
- Latent Tuberculosis (exclusionary if not treated for at least 4 weeks prior to Step 1 entry)

- Active Tuberculosis (exclusionary if not treated for at least 4 weeks prior to Step 1 entry)
- Chronic hepatitis C (exclusionary, unless HCV cure or clearance documented)
- Chronic hepatitis B (exclusionary)
- Year of HIV Diagnosis
- Past history of syphilis

Any allergies to any medications and their formulations must be documented.

Details of any previous reaction to vaccination must be documented.

6.3.6 Medication History

A medication history must be present, including start and stop dates. The date of first ART initiation should be documented. The table below lists the medications that must be included in the history.

Table 6.3.6-1: Medication History

Medication Category	Complete History or Timeframe
Antiretroviral therapy (including prior use of PrEP)	Complete history
Immune-based therapy	Complete history
Latent and active tuberculosis therapy	Complete history
Blinded study treatment	Within past year
HIV-1-related vaccines	Complete history
Syphilis treatment	Complete history
Prescription drugs (other)	Within 90 days prior to entry
Sex-hormone medications or sex-hormone analogues or antagonists*	Last 12 months except as noted below

*Includes: hormone-releasing IUDs (e.g., Mirena inserted in the last 5 years); oral, injectable, implanted, or patch contraceptives; vaginal ring, creams, or inserts; estrogen, progesterone, or testosterone therapy; leuprolide or other synthetic gonadotropin-releasing hormone; tamoxifen, raloxifene, aromatase inhibitors or any other androgen, estrogen, or progesterone analogue or antagonist therapy.

6.3.7 Clinical Assessment

<u>Complete Physical Exam</u>
A complete physical exam will be performed at screening only and is to include, at a minimum:

- Examination of the skin, head, mouth, and neck
- Auscultation of the chest
- Cardiac exam; respiratory; abdominal exam
- Examination of the lower extremities for edema
- Signs and symptoms
- Diagnoses
- Height (in cm)
- Weight (in kg)

- Vital signs (temperature, pulse, respiration rate, and blood pressure)

Targeted Physical Exam
Targeted physical exam will be performed after Screening at visits per the SOE and is to be driven by any previously identified or new signs or symptoms including diagnoses or adverse events that the participant has experienced since the last visit. The exam must include:

- Vital signs (temperature, pulse, respiration rate, and blood pressure)
- Examination of the infusion site (after Step 1 entry)

Refer to section 7.2 for AE collection requirements.

Post-Step 1 entry, see section 8.3 for collection requirements for pregnancy.

Weight
Collect weight (in kg) at additional visits per the SOE.

Concomitant Medications
Post-entry, the following new and discontinued concomitant medications must be recorded on the eCRFs:

- Sex-hormone medications or sex-hormone analogues or antagonists (see section 6.3.6 for examples)
- Interruption (>3 days), reinitiation, or changes to ART regimen
- STI treatment

6.3.8 Verification of ART Discontinuation

Participants will discontinue ART 2 days after receiving the bNAb infusions. Site staff should call participants and confirm that ART was discontinued.

NOTE: Participants who do not discontinue ART prior to the week 1 visit in Step 1 will transition to Step 3 of the study for safety follow up. They will be excluded from virologic or immunologic analyses.

6.3.9 STI Testing and Review of STI Testing Results

Treponemal Antibody Test/Rapid Plasma Reagin (RPR) for Syphilis

NOTE: The order of testing will follow local standards.

Screening

- Candidates with a positive test for syphilis will be referred to their clinicians for evaluation of active syphilis. Candidates who are found by their clinicians to not have active syphilis (e.g., a prior history of treated syphilis) are eligible.
- Candidates diagnosed at screening with primary syphilis, secondary syphilis, latent syphilis, or syphilis of unknown duration without neurologic symptoms, should receive local SOC treatment from their clinicians.

- Candidates diagnosed at screening with neurosyphilis should receive local SOC treatment from their clinicians.
- Candidates who have initiated syphilis treatment are eligible for study entry, if they receive at least 3 days of treatment prior to Step 1 entry.

Post-Screening
Syphilis will be performed per protocol. In the event of a positive test of RPR, with or without confirmatory testing, the site must contact the participant and discuss safer sex practices and the use of barrier protection (external or internal) during sexual activity during the ATI. The study will facilitate PrEP access to participant's partners who are interested. The participant will be referred to a clinician for appropriate treatment.

Nucleic Acid Amplification Test for Gonorrhea and Chlamydia

Screening
Urine gonorrhea and chlamydia will be tested using a nucleic acid amplification test (e.g., Gen-Probe Aptima). Additional samples may be obtained with oral swabs and self-swabs of rectum, if participant agrees and depending on the site of possible exposure. Sites will arrange for testing to be done at a Network-approved certified non-US laboratory (i.e., testing will not be performed centrally for this study).

- If chlamydia and/or gonorrhea infection is found, the candidate will be referred to a clinician for appropriate treatment.
- Candidates who have initiated chlamydia and/or gonorrhea treatment are eligible for study entry, if they receive at least 3 days of treatment prior to Step 1 entry.

Post-Screening
Gonorrhea/chlamydia will be performed per protocol. In the event of a positive test, the site must contact the participant and discuss safer sex practices and the use of barrier protection (external or internal) during sexual activity during the ATI. The participant will be referred to a clinician for appropriate treatment.

6.3.10 Laboratory Evaluations

At Screening and Entry all laboratory values must be recorded on the eCRF.

In Step 1, all blood draws during the bNAb or placebo administration visit must occur before the infusions are administered, unless otherwise noted (see section 6.3.16).

For post-entry assessments, record on the eCRF abnormal laboratory findings as per section 7.2 (i.e., all Grade ≥2 AEs).

Hepatitis Testing
HBsAg testing will be done per the SOE.

HCV antibody testing will be done per the SOE. HCV RNA or HCV antigen testing is required if HCV antibody is positive.

Hematology
WBC and differential absolute count, hemoglobin/hematocrit, platelet count

Liver Function Tests
AST [SGOT], ALT [SGPT], alkaline phosphatase, total and direct bilirubin

Chemistry
Creatinine and eGFR

Urine Dipstick with Reflex Urinalysis
A urine dipstick with reflex urinalysis will be performed per the SOE and when clinically indicated. If dipstick results are abnormal, perform urinalysis for protein, WBCs, RBCs, and casts.

Clinical indications to perform a urine dipstick include, but are not limited to, symptoms suggestive of urinary tract infection, hematuria, worsening of kidney function by creatinine and eGFR measurements, or other urinary symptoms.

Pregnancy Testing
For individuals who can become pregnant: Serum or urine □-HCG (urine test must have a sensitivity of ≤25 mIU/mL). Record pregnancy and pregnancy outcome per section 8.3.

HLA Typing
HLA typing will be done per the SOE; however, if HLA type is available in the medical record, it does not need to be repeated. The result will be used for research purposes.

6.3.11 Immunologic Studies

CD4+ Counts
For screening, obtain absolute CD4+ count within 56 days prior to Step 1 entry from a laboratory that possesses IQA certification.

For Step 1 entry and post-entry evaluations, all laboratories must possess IQA certification. For sample collection, processing, and shipping instructions, refer to the lab processing chart (LPC).

NOTE: CD4+ T-cell counts are known to have diurnal variation; therefore, participants will be encouraged to return for appointments that include CD4+ count at approximately the same time (e.g., morning or afternoon), whenever possible.

6.3.12 Virologic Studies

Plasma HIV-1 RNA

Screening HIV-1 RNA by a clinically approved assay with lower limit of quantification <50 copies/mL must be performed within 56 days prior to study entry at a laboratory that possesses VQA certification. Samples must be processed and shipped to the designated laboratory. For sample collection, processing, and shipping instructions, refer to the A5416 LPC.

All HIV-1 RNA results should be entered on the eCRF within 3 business days.

Eligibility will be determined based on the screening value.

Plasma HIV-1 RNA at Step 1 entry and all post-entry evaluations in all steps will be measured in real time using an approved assay at a laboratory that possesses VQA certification. For entry and post-entry evaluations, samples must be processed and shipped to the designated testing laboratory.

See section 6.2.3 for instructions regarding confirmation of viral rebound and HIV-1 resistance testing. Sites should contact the CMC for any confirmed viral rebound >200 copies/mL occurring in Step 1 and Step 2.

6.3.13 Monogram PhenoSense Assay

A sample (PBMC) for Monogram PhenoSense for 3BNC117-LS-J and 10-1074-LS-J susceptibility will be collected at Entry.

6.3.14 Assessment of ART Restart Criteria

ART will be restarted and the participant will enter Step 3 if any of the following criteria are met:

- Viral load remains ≥1,000 copies/mL for ≥4 consecutive weeks AND viral load has not dropped 0.2 $\log_{10}$ from the previous week;
- CD4+ T-cell counts decrease to <350 cells/μL or CD4% <15% (if available) and this change is confirmed at the next visit;
- Participant becomes pregnant;
- Participant develops symptoms of severe acute retroviral syndrome;
- If requested by the participant or their clinician.

Refer to section 6.3.15 if ART restart criteria are met.

NOTE A: In the assessment of ≥4 consecutive weeks, a missed or unavailable HIV-1 RNA level before or after a viral load ≥1000 copies/mL will also be considered as being ≥1000 copies/mL.

NOTE B: Acute retroviral syndrome can be defined as any signs or symptoms attributable to HIV rebound other than mild fatigue (including, but not limited to, unintentional weight loss [>5% of pre-ATI body weight],

otherwise unexplained persistent fever [>38°C], persistent night sweats, persistent diarrhea, oral candidiasis, and generalized lymphadenopathy), at the discretion of site investigator.

Refer to section 6.3.9 for participant management following new STI diagnosis during ATI for guidance on assessment of HIV transmission risk and additional counseling of participants.

6.3.15 Documentation of ART Restart and ART Adherence Counseling

Site staff should contact participants who meet ART Restart Criteria and advise the participant to resume ART and schedule for the participant to return to the study clinic for Step 3 entry as soon as possible. During the Step 3 entry visit, study staff will confirm that ART has been restarted, document ART restart date, and also counsel about appropriate adherence to ART.

6.3.16 Infusion bNAb PK

Serum samples will be collected from all participants on the day of the infusion per the SOE. PK blood draws should be collected from the opposite arm as the location of the infusion. Samples will include a pre-dose blood sample before the infusion and a post-dose sample after completion of last infusion. Dose information (date/time of each infusion dose) will be captured on an eCRF.

6.3.17 Sparse bNAb PK

Serum samples for bNAb PK testing will be collected from all participants per the SOE.

6.3.18 ARV PK

Plasma will be collected and stored for determination of the presence or absence of ARV concentrations during ATI in Steps 1 and 2. See the LPC for sample processing, storage, and shipping instructions.

The participant's last dose of all ARVs taken (actual date) prior to ATI in Step 1 will be recorded at week 1.

6.3.19 Stored Samples

Samples will be collected and stored per the SOE. See the LPC for processing, storage, and shipping instructions.

Stored Plasma

Plasma will be collected and stored for virological assays, including but not limited to:

- HIV-1 single copy assay (SCA) of plasma RNA
- Characterization of rebound virus (env genotype and phenotype)

Plasma will be collected and stored for immunological assays, including but not limited to:

- Immune activation markers such as: IL-6, sCD14, and hsCRP

Stored Serum

Serum will be collected and stored for immunogenicity assays, including but not limited to:

- bNAb anti-drug antibodies (ADA)
- Autologous neutralizing antibody responses against rebound virus and/or panels of pseudoviruses to determine breadth of responses.

Stored PBMCs

PBMCs will be collected and stored for virological assays, including but not limited to:

- Intact proviral DNA assay (IPDA)
- Q4PCR
- Total Cell-associated HIV-1 RNA and DNA
- Other assays to recover autologous reservoir virus and characterize the virologic effects of study treatment may be performed.

PBMCs will be collected and stored for immunological assays, including but not limited to:

- HIV-1-specific T-cell responses – polyfunctional intracellular cytokine staining (ICS), activation and proliferation
- Epitope mapping (ELISPOT)
- Viral inhibition assay
- ADCC by ex vivo autologous NK cells

Other assays to characterize the immunologic effects of study treatment may be performed.

NOTE: Only sites certified by the IQA Cryopreservation PT Program at the Duke Human Vaccine Institute are required to collect PBMCs. HVTN and HPTN sites need to be in good standing per HVTN PBMC processing protocols.

6.3.20 Procedures

Large Blood Draw

Large blood draw will be performed for all study participants per the SOE. For sample collection, processing, and shipping instructions, refer to the LPC.

Infusion of 3BNC117-LS-J and 10-1074-LS-J or placebo

Before Infusion

- For participants who can become pregnant, infusion may not proceed unless a negative urine or serum pregnancy test has been obtained within 24 hours prior to infusion.
- Perform targeted physical exam before infusion (per section 6.3.7)

- Collect PK sample before infusion (per section 6.3.16)

Infusion
- The infusion must be administered as described in section 5.4.
- Record the infusion, including dose administered, whether administration was temporarily halted for any reason, duration of infusion, and whether the full dose was administered.

After Infusion
- Vital signs (pulse, respiratory rate, blood pressure, and temperature) will be monitored at the end of each infusion and at 1 hour (±5 min) after the end of the last infusion. These values should be recorded on the source document.
- Collect PK sample after infusion (as per section 6.3.16).
- Participants will be observed during each infusion and for one hour after the end of the last infusion. Presence or absence of adverse events will be assessed 1 hour post-infusion.

Discontinuation of ART
Participants will discontinue ART 2 days following the Day 0 infusion. Participants who do not discontinue ART before the week 1 visit in Step 1 will be registered to Step 3 and followed until R+12. The Premature Study/Treatment Discontinuation evaluations should be performed at the Step 3 R+12 visit.

6.3.21 Pregnancy Avoidance and Risk Reduction Counseling

At visits noted on the SOE, study personnel will review prior study STI testing results and counsel participants about the importance of prevention of pregnancies and the use of condoms, as well as other effective family planning methods.

Site staff will also counsel participants about the potential added protection from HIV transmission if their HIV-negative partners use pre-exposure prophylaxis (PrEP). The study will facilitate PrEP access to participant's partners who are interested.

6.3.22 Mitigation of HIV Transmission Risk

During Steps 1 and 2, participants will be at increased risk of transmitting HIV to their partners if they become viremic, and of HIV-1 superinfection from a partner with HIV-1. The protocol team and site staff will implement rigorous counseling for participants on reducing HIV transmission risk to their partners. The study will also facilitate PrEP access to participant's partners who are interested. Free barrier protection will be provided.

If, despite agreeing to comply with the use of barrier protection, the participant engages in a high-risk exposure to a partner without HIV-1 or of unknown HIV-1 status, the participant will be counseled of the importance to use barrier protection while off ART and until HIV-1 viral load is undetectable. In the event that a participant is unable to comply with this study requirement, ART will be re-initiated

and the participant will be registered to Step 3 and continue study follow up according to the Step 3 SOE.

In the event of a high-risk exposure to a partner with HIV-1 of unknown viral suppression status or with known viremia, the participant will be advised to seek evaluation by their primary care clinician to determine the need to reinitiate ART. Documentation of counseling is not recorded on an eCRF; sites should record this on the source document.

Access to Barrier Protection and PrEP for Partners at Risk to Acquire HIV
During the screening period, site staff will discuss with candidates the willingness to discuss their study participation, and the period of ART interruption with all partners that are without HIV or serostatus unknown, such as pros and cons related to disclosure.

Site staff will also counsel candidates that, in addition to the use of barrier protection, there is potential added protection from HIV transmission if their partners without HIV use PrEP.

Candidates who are unable or unwilling to use barrier protection during sex with partners without HIV or partners with unknown HIV status will not be enrolled in the study.

Site staff will facilitate access to PrEP for participants' partners who are at risk to acquire HIV and are interested in initiating PrEP:

- Study sites will develop a site-specific plan to facilitate access or provide PrEP to interested partners at risk to acquire HIV.
- Study sites will inform participants and interested partners about the availability of PrEP at the study site.
- Site staff will provide information and arrange for interested partners to be evaluated by a clinician to obtain PrEP at the site or another local clinic.
    - As part of PrEP services, participant's partners will be provided with information about HIV prevention tools and will have access to prompt testing in the event of a high risk exposure.
    - Additionally, the site staff and/or PrEP provider will assist participant's partners being promptly connected to care, in the unlikely event that they become infected with HIV during the participant's ATI.
- If PrEP is not available free of charge through existing clinical services at the site or another local clinic, PrEP will be locally sourced by the study site and interested partners will be linked to PrEP services locally.
- Site staff will also assess participant's risk of intimate partner violence following disclosure of study participation and HIV status, and provide counseling where possible, including mediating the discussion between the participant and partner if this is acceptable to both parties.
- Lastly, the study team and study sites plan to hold meetings with community members and prospective and enrolled study participants to raise awareness about the need for partner protections in ATI studies.

6.3.23 Social Science Questionnaire

Social science questionnaire regarding motivations, understanding of the study, and experiences with study participation – including antibodies, ATI, and partner protection measures, will be performed as per the SOE. There will be closed-ended surveys and open-ended questionnaires administered by site staff.

All participants will complete closed-ended surveys. Closed-ended surveys will be recorded on eCRFs.

Open-ended questionnaires, also referred to as in-depth interviews (IDIs), will be completed with only a subset of participants **and are optional. Up to 25 participants will participate in IDIs. Participants may withdraw from participating in IDIs at any time.**

Open-ended surveys will not be recorded on eCRFs. Special instructions will be provided for site staff conducting these assessments **in the Manual of Procedures (MOPS) (Section 8)**. **Per the participant's consent, IDIs will be audio recorded and transcribed.**

Study staff conducting in-depth interviews will familiarize themselves with the interview guide prior to conducting IDIs. IDIs should be conducted in a private room where the interviewer and participant cannot be overhead by others. If any of the questions make the participant feel uneasy or uncomfortable, the interviewer may stop the IDI at any time. If needed, the interviewer may provide contact and referral information to a study counsellor within or outside the study.

7.0 ADVERSE EVENTS AND STUDY MONITORING

7.1 Definition of Adverse Event

An adverse event (AE) is any unfavorable and unintended sign (including an abnormal laboratory finding), symptom, or diagnosis that occurs in a study participant during the conduct of the study REGARDLESS of the attribution (i.e., relationship of event to medical treatment/study product/device or procedure/intervention). This includes any occurrence that is new in onset or aggravated in severity or frequency from the baseline condition (Step 1 Entry).

7.2 Adverse Event Collection Requirements for This Protocol

AEs must be recorded on the eCRFs if the following criteria has been met:

- All AEs related to study procedures and study treatment (starting at Step 1 Entry)
- All Grade ≥2 AEs
- All local and systemic infusion reactions within 7 days of study product administration regardless of grade
- All AEs meeting serious adverse event (SAE) definition or expedited adverse event (EAE) reporting requirement

NOTE: SAEs or events meeting EAE reporting requirements should also be entered into the DAIDS Adverse Experience Reporting System (DAERS), an Internet-based reporting system.

All AEs that are reported must have their severity graded. To grade AEs, sites must refer to the DAIDS AE Grading Table, corrected Version 2.1, July 2017, which can be found on the DAIDS RSC website at https://rsc.niaid.nih.gov/clinical-research-sites/daids-adverse-event-grading-tables.

Serious Adverse Events (SAEs)
An SAE is defined as any untoward medical occurrence that:

- Results in death
- Is life-threatening
- Requires inpatient hospitalization or prolongation of existing hospitalization
- Results in persistent or significant disability/incapacity
- Is a congenital anomaly/birth defect
- Is an important medical event that may not be immediately life-threatening or result in death or hospitalization but may jeopardize the patient or may require intervention to prevent one of the other outcomes listed in the definition above).

7.3 Expedited Adverse Event (EAE) Reporting to DAIDS

7.3.1 Expedited Reporting of Adverse Events to DAIDS

Requirements, definitions and methods for expedited reporting of Adverse Events (AEs) are outlined in Version 2.0 of the DAIDS EAE Manual, which is available on the RSC website at https://rsc.niaid.nih.gov/clinical-research-sites/manual-expedited-reporting-adverse-events-daids.

The DAIDS Adverse Experience Reporting System (DAERS), an internet-based reporting system, must be used for EAE reporting to DAIDS. In the event of system outages or technical difficulties, EAEs may be submitted using the DAIDS EAE Form. This form is available on the DAIDS RSC website at https://rsc.niaid.nih.gov/clinical-research-sites/paper-eae-reporting.

For questions about DAERS, please contact NIAID CRMS Support at CRMSSupport@niaid.nih.gov. Please note that site queries may also be sent from within the DAERS application itself.

For questions about expedited reporting, please contact the DAIDS RSC Safety Office at (DAIDSRSCSafetyOffice@tech-res.com).

7.3.2 Reporting Requirements for this Study

- The SAE Reporting Category, as defined in Version 2.0 of the DAIDS EAE Manual, will be used for this study.
- The study agents for which expedited reporting are required are: 3BNC117-LS-J and 10-1074-LS-J.

7.3.3 Expedited AE Reporting Period

- The expedited AE reporting period for this study is for the duration of the study (beginning with Step 1 Entry).
- After the protocol-defined AE reporting period, unless otherwise noted, only suspected, unexpected serious adverse reactions (SUSARs), as defined in Version 2.0 of the DAIDS EAE Manual, will be reported to DAIDS if the study staff become aware of the events on a passive basis (from publicly available information).

7.4 Study Monitoring

Accrual, baseline characteristics, conduct of the study, and AEs will be monitored during the trial with reports sent to the CMC on a regular basis. The CMC will review the individual safety data frequently to assess the relationship of all reported AEs to the study treatment (blinded to active/placebo treatment), incorporating the site investigator's opinion in their relation to the treatment reported on the eCRFs.

The DAIDS clinical representative will review and assess select EAE reports for potential impact on study participant safety and protocol conduct as per DAIDS policies, guidance documents, and SOPs as applicable.

The study will undergo its first SMC review by an ACTG-appointed SMC approximately 6 months after the first enrollment or after the first six participants have entered Step 1, whichever is earlier. Subsequent reviews will take place approximately every 6 months after the prior review. If an ad hoc review (triggered by the criteria listed below) occurs within 6 weeks of a planned review, the planned review will be postponed until 6 months after the most recent ad hoc SMC review.

The SMC will review information, by unblinded treatment arm, on accrual, baseline characteristics, conduct of the study (including premature study discontinuations and, if any, premature treatment discontinuations), AEs, CD4+ T-cell counts, HIV-1 RNA levels, and completeness of follow-up.

An SMC review will be triggered if more than one participant reinitiates ART, triggered by the virologic criteria, but does not achieve viral resuppression (viral resuppression is defined as >2 $\log_{10}$ copies/mL reduction or <200 copies/mL) within 12 weeks of ART reinitiation. Enrollment and initiation of treatment and ATI will not be paused during this period of review.

New enrollments (and ATI for participants yet to initiate ATI) will be paused by the CMC if:
- One or more participants experience a Grade 4 AE that is assessed by the CMC as at least possibly related to study treatment (as judged by the CMC, blinded to active/placebo treatment), or
- Two or more participants experience a Grade 3 AE that is assessed by the CMC as at least possibly related to study treatment (as judged by the CMC, blinded to active/placebo treatment)

Pre-existing resistance is hypothesized to be the main cause of viral rebound among participants receiving active treatment during this study. In the study reported by Gaebler et al., which evaluated the effect of the combination of 3BNC117 and 10-1074 on maintaining viral suppression during ATI, four of the 17 participants (24%) experienced viral rebound by week 12 [57]. The other 13 participants maintained suppression until week 20 or beyond. To guard against the scenario where pre-existing resistance is higher than predicted, an SMC review will be convened when the first 16 participants (regardless of treatment arm) either reach the week 12 visit or enter Step 3 (ART restart). It is anticipated that approximately 10 of these 16 participants will have received active treatment. The SMC will review unblinded HIV-1 RNA and CD4+ T-cell data during ATI and after ART restart, with tabulations of confirmed viral rebound during ATI by treatment arm. At this review, the probability of observing viral rebound in more than 2/3 of active participants would be low (<0.05) if the true success rate of the active treatment is at least 60%. If the bNAbs are ineffective (e.g., a true success rate <10%), that probability of observing viral rebound in more than 2/3 of active participants is high (>90%). For this review, the team guidance to the SMC is that if more than 2/3 of active participants, who received a full dose of both bNAbs, have confirmed viral rebound by week 12 (confirmed HIV-1 RNA >200 copies/mL), the SMC would consider a recommendation to pause enrollment and to provide guidance on how the study should proceed, including considerations for additional SMC reviews.

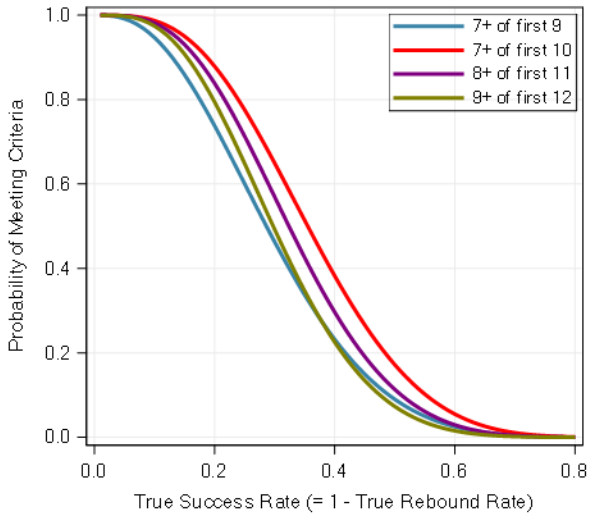


Figure 7.4-1: Probability of Meeting Review Criteria versus Study Treatment Success Rate

Detailed plans for study monitoring will be outlined in a Study Monitoring Plan developed by the Statistical and Data Management Center (SDMC) prior to enrollment of the first participant.

8.0 CLINICAL MANAGEMENT

8.1 Toxicity

Only toxicities related to study medications provided through the study will be considered.

The general guidelines presented in this section apply to toxicities that are not specifically addressed in section 8.2.

8.1.1 Grade 1 or 2 Toxicity

Participants who develop a Grade 1 or Grade 2 AE or toxicity or any clinically significant laboratory abnormality during Step 1 may complete study treatment at the discretion of the site investigator.

Grade 1 or 2 AEs that may be related to infusion should be handled according to standard clinical practice and documented.

If Grade 1 or 2 AEs occur during or shortly after the first infusion (3BNC117-LS-J or placebo) and prior to the start of the second infusion (10-1074-LS-J or placebo), the second infusion may be administered at the discretion of the site investigator.

8.1.2 Grade 3 or 4 Toxicity

If a participant develops a Grade 3 or Grade 4 AE or toxicity during or shortly after the first infusion and prior to the start of the second infusion, and is at least possibly related to study treatment, the second infusion should be withheld and the CMC must be notified.

Participants experiencing Grade 3 or Grade 4 AEs should be followed closely until the resolution of the AE to Grade ≤2.

8.2 Specific Management of Toxicities Related to Study-Provided Drugs

In case of AEs, the participant will be assessed and followed up by the clinical team. Supplemental visit(s) for further investigation may be planned at the discretion of the site investigator or designee. Supplemental visit(s) may be recommended if clinically indicated or to clarify observations.

Any AEs attributed to study drug, including laboratory abnormalities, should be subsequently followed until the event or its sequelae resolve or stabilize.

Cytokine Release Syndrome

Based on previous clinical experience with similar monoclonal antibodies and with 3BNC117 and 10-1074 and long-acting variants, it is unlikely that the administration of 3BNC117-LS-J and 10-1074-LS-J will lead to cytokine release syndrome as this syndrome has been described with mAbs targeting lymphocyte cell surface antigens. However, a potential side effect of a monoclonal antibody can be the stimulation of a massive release of cellular cytokines, which can have profound effects on blood pressure, vascular integrity, and myocardial, lung, liver, and kidney functions. If cytokine release syndrome occurs, the participant may need to be treated with intravenous fluids, vasopressors, and high-dose corticosteroids and may require ventilator support.

Study participants will be closely monitored for one hour after completion of the second antibody infusion.

Infusion Reaction
If a participant develops Grade ≥3 acute infusion reaction, an immediate hypersensitivity reaction, or a life-threatening event during study treatment administration, the infusion will be discontinued and will not be reinitiated. If the acute infusion reaction occurs during the first (3BNC117-LS-J or placebo) infusion on Day 0, the second infusion (10-1074-LS-J or placebo) will not occur.

Participants should be followed closely until resolution of the AE to Grade ≤2.

Acute Retroviral Syndrome
After ART is discontinued, participants may experience symptoms of acute retroviral syndrome. These include fever, rash, lymphadenopathy, headache, sore throat, nausea, and vomiting. In acute HIV-1 infection, the highest frequency of symptoms and signs are observed just before peak viremia, approximately 2 weeks after the initial detection of viral RNA. Most symptoms associated with acute HIV-1 infection are self-resolving; however, the severity and duration of symptoms vary widely from person to person.

If participants develop a constellation of symptoms that are judged by the study investigators to be consistent with acute retroviral syndrome, ART will be resumed, irrespective of the virologic and CD4+ T-cell count thresholds for ART reinitiation. In addition, participants will be managed symptomatically and will be advised to follow up with their primary care clinicians. Participants will be followed according to the Step 3 SOE.

Ophthalmic Toxicity
If symptoms of ocular disease develop after study infusions and persist for >48 hours, participants will be referred to an ophthalmologist for diagnosis and management.

8.3 Pregnancy

Pregnancy and pregnancy outcome will be recorded on the eCRFs. Pregnancies that occur on study should be reported prospectively to The Antiretroviral Pregnancy Registry. More information is available at www.apregistry.com. Telephone: 800-258-4263; Fax: 800-800-1052.

Pregnancy Outcomes and Reporting
Pregnant participants will be discontinued from the ATI period of the study, resume ART, and will be encouraged to continue on study and complete follow up under Step 3. Evaluations will be completed according to the Step 3 SOE, however, blood samples will only be collected for HIV-1 RNA, CD4+ T-cell count, hematology and chemistry. At the end of the pregnancy, outcome and adverse events for the participant and infant will be recorded on the outcome eCRF.

If a participant has completed the study or chooses to discontinue from the study before the end of the pregnancy, then site staff should request permission to contact them regarding pregnancy outcomes at the end of pregnancy. If the information is obtained, pregnancy outcomes will be submitted on an eCRF at the end of the pregnancy.

9.0 CRITERIA FOR DISCONTINUATION

9.1 Premature Treatment Discontinuation

Participants will be discontinued from receiving the planned second (10-1074-LS-J or placebo) infusion for any of the following reasons:

- Occurrence of Grade ≥3 acute infusion reactions that occur during the first (3BNC117-LS-J or placebo) infusion
- Occurrence of any immediate hypersensitivity reaction (such as urticarial rash; bronchospasm; laryngeal edema; anaphylaxis; syncope)

9.2 Premature Study Discontinuation

Participants will prematurely discontinue from the study for any of the following reasons:

- Request by the participant to withdraw from the study.
- Following an adverse event at the discretion of the investigator (or designee).
- Request of the primary care clinician if s/he thinks the study is no longer in the best interest of the participant.
- Participant judged by the investigator to be at significant risk of failing to comply with the protocol in a manner that might lead to harm to self or seriously interfere with the validity of the study results.
- At the discretion of the IRB/EC, NIAID, Office for Human Research Protections (OHRP), other local government agencies as part of their duties, investigator, or industry supporter.

NOTE: Participants who do not discontinue ART prior to the week 1 visit in Step 1 will not be discontinued and will transition to Step 3 of the study for safety follow up. They will be excluded from virologic or immunologic analyses.

A subset of participants will participate in IDIs. Participation in IDI may be ended early at the request by the participant to withdraw from the IDI and/or without the participant's consent if:

- **The research study or the IDI portion of the study is stopped or cancelled.**
- **Request from the investigator or study staff if they feel that taking part in the IDIs is no longer in the best interest of the participant.**

10.0 STATISTICAL CONSIDERATIONS

10.1 General Design Issues

A5416 is a Phase I, randomized, double-blind, placebo-controlled trial designed to evaluate the safety, pharmacokinetic, and virologic effects of 3BNC117-LS-J and 10-1074-LS-J in combination in adult participants in sub-Saharan Africa living with HIV on suppressive ART. Forty-eight participants will be randomized 2:1 to receive either the bNAb combination (n=32) or placebo (n=16) at Step 1 entry and discontinue ART 2 days later. Participants will be followed for up to 72 weeks. Accrual is anticipated to take 9 months. **Up to 25**

participants will participate in IDIs (an optional study evaluation).

10.2 Outcome Measures

Primary and secondary outcome measures listed below will be addressed in the study's primary Statistical Analysis Plan, which will define the content of the Primary Analysis Report. This report will form the basis for the primary study manuscript and results reporting to https://ClinicalTrials.gov. Outcomes of interest for exploratory objectives intended for subsequent publications are listed under "Other Outcome Measures."

10.2.1 Primary Outcome Measures

10.2.1.1 Occurrence of a Grade ≥3 systemic (i.e., not a local reaction) AE or any AE (regardless of grade) leading to premature study or treatment discontinuation at least possibly related (as judged by the CMC, blinded to active/placebo treatment) to the combination of 3BNC117-LS-J and 10-1074-LS-J.

10.2.1.2 Viral suppression, defined as no confirmed HIV-1 RNA >200 copies/mL, at or prior to week 24 of ART discontinuation.

10.2.2 Secondary Outcome Measures

10.2.2.1 Viral rebound, defined as confirmed HIV-1 RNA >200 copies/mL at or prior to week 24 of ART discontinuation.

10.2.2.2 HIV-1 RNA levels ≥50 copies/mL at or prior to week 24 of ART discontinuation.

10.2.2.3 Frequency of participants who do not meet the virologic or immunologic components of the ART resumption criteria (e.g., viral load, CD4 cell, or development of severe acute retroviral syndrome) while serum bNAb concentrations are ≥10 mcg/mL.

10.2.2.4 Frequency of participants who do not meet the virologic or immunologic components of the ART resumption criteria for 24 weeks after serum bNAb concentrations fall below 10 mcg/mL.

10.2.2.5 Frequency of participants who remain off ART and do not meet ART resumption criteria by study week in Step 1 and 2.

10.2.2.6 Time to meeting the virologic or immunologic components of the ART resumption criteria.

10.2.2.7 Pharmacokinetic parameters of the combination of 3BNC117-LS-J with 10-1074-LS-J.

10.2.2.8 Concentration of 3BNC117-LS-J and 10-1074-LS-J at the time of viral

rebound.

10.2.2.9 Proportion of participants who develop anti-3BNC117-LS-J and/or anti-10-1074-LS-J antibodies (ADA).

10.2.2.10 CD4+ T-cell counts (cells/mm^3) through entire study follow-up.

10.2.3 Other Outcome Measures

10.2.3.1 Proportion of viral suppression in this study and previous treatment interruption studies involving 3BNC117, 10-1074 and their long-acting variants, as well as other ACTG conducted ATI studies.

10.2.3.2 Proportion of participants who maintain suppression (<200 copies/mL) among those participants off ART AND with non-effective concentrations of circulating bNAbs (defined as a concentration less than 1 or 5 or 10 microgram/mL for both 3BNC117-LS and 10-1074-LS) by study week.

10.2.3.3 Time to viral rebound (confirmed HIV-1 RNA >200 copies/mL across 3BNC117-LS-J and 10-1074-LS-J IC_{50} and IC_{80} cut points determined by PhenoSense assay or other assay (e.g., bulk PBMC cultures).

10.2.3.4 Relationship between antibody sensitivity (determined by PhenoSense assay cut points [e.g., IC_{50}, IC_{80}, IC_{90}]) and different clinical characteristics (e.g., years from HIV diagnosis, time from HIV diagnosis to initiation of ART, reported time of continuous ART use, reported CD4 nadir).

10.2.3.5 Characterization of the genotype and phenotype of rebound virus populations arising after receipt of combination of 3BNC117-LS-J and 10-1074-LS-J and/or placebo, in terms of sensitivity to innate or adaptive immune responses or other phenotypic properties, in comparison to the virus populations in pre-ART plasma samples (if available) and proviral DNA from PBMCs obtained on ART.

10.2.3.6 Size and composition of the latent HIV-1 reservoir before and after receipt of combination of 3BNC117-LS-J and 10-1074-LS-J and/or placebo evaluated by IPDA, Q4PCR, single-copy assay of plasma RNA, or other appropriate assays that may become available before and after receipt of combination of 3BNC117-LS-J and 10-1074-LS-J and/or placebo.

10.2.3.7 Change from baseline to after receipt of combination of 3BNC117-LS-J and 10-1074-LS-J and/or placebo in the quality, breadth, and magnitude of HIV-specific T-cell responses by intracellular cytokine staining before and after receipt of combination of 3BNC117-LS-J and 10-1074-LS-J and/or placebo.

10.2.3.8 Change from baseline to after receipt of combination of 3BNC117-LS-J and 10-1074-LS-J and/or placebo in innate immune responses, autologous neutralization titers, HIV-specific T-cell responses before and after receipt of combination of 3BNC117-LS-J and 10-1074-LS-J and/or placebo.

10.2.3.9 Measurements of virologic (e.g., total cell-associated HIV-1 DNA and RNA, intact HIV-1 proviruses, low level plasma HIV-1 RNA, HIV-1 proviral integration sites), soluble (e.g., autologous anti-HIV-1 antibodies, cytokines, chemokines, complement proteins, metabolites, lipids, glycans), and cellular markers for association with virologic control or virologic rebound prior to and during the ATI period.

10.2.3.10 Participants' responses to social sciences assessments about understanding of the study and interventions, comfort level with ATI, partner protection measures, and experiences in the study.

10.3 Randomization and Stratification

Participants will be randomized (2:1) at Step 1 entry to receive an infusion of either 3BNC117-LS-J and 10-1074-LS-J or placebos, using the permuted block method without institutional balancing or stratification. The 2:1 randomization scheme will provide a larger sample size (compared to a 1:1) for the assessment of the primary safety outcome, which is only among participants in the active treatment group.

Participants who do not complete study treatment will be replaced. Additionally, participants may be enrolled to replace those who do not discontinue ART by the Step 1, week 1 visit in the efficacy analysis population.

10.4 Sample Size and Accrual

The study plans to enroll 48 participants with a 2:1 randomization ratio (32 to the 3BNC-117-LS-J and 10-1074-LS-J arm and 16 to the placebo arm). Accrual is estimated to take 9 months. This protocol aims for at least 40% enrollment of cisgender women but with an ideal goal of reaching 50 to 60% of participants enrolling into Step 1.

The primary safety outcome will be the occurrence of any adverse event Grade ≥3 or any AE (regardless of grade) leading to premature study or treatment discontinuation judged by the CMC to be at least possibly related to the combination of 3BNC117-LS-J and 10-1074-LS-J. The primary safety analysis will include all participants who receive active study treatment. The sample size of 32 treated participants will provide a 97% probability of observing at least one 3BNC117-LS-J and/or 10-1074-LS-J related AE that occurs in at least 10% of treated participants.

The primary efficacy outcome is viral suppression, defined as no confirmed HIV-1 RNA >200 copies/mL at or prior to week 24 of ART discontinuation. The proportion of participants with viral suppression at week 24 of ATI between the active 3BNC-117-LS-J and 10-1074-LS-J arm versus the placebo arm will be compared using a one-sided Fisher's exact test

with a type I error rate of 5%. This efficacy analysis will be limited to participants who are fully suppressed (defined as no HIV-1 RNA blip ≥50 copies/mL) on the day of the infusion, receive the infusion of both antibodies (active or placebo), and undergo an ATI according to the protocol.

We assume 20% (n=6) of active participants will not be evaluable for the primary efficacy outcome (due to blips on the infusion day or LTFU). We assume fewer placebo participants, only 10% (n = 2), will not be evaluable as they are expected to rebound sooner and thus, have less loss-to-follow up. The table below shows the power to detect a difference in proportion of participants with virologic rebound considering various underlying rates with 26 evaluable participants in the active arm and 14 in the placebo arm.

Table 10.4-1: Power for Various Underlying Rates of Virologic Suppression

N of evaluable Participants in Two Arms (active arm: placebo arm)	Proportion in Placebo Arm	Proportion in Active Arm	Power
26:14	10%	60%	90%
		65%	95%
		70%	97%
	20%	60%	70%
		65%	80%
		70%	88%
	30%	60%	44%
		65%	57%
		70%	69%

A sample size of 26 evaluable participants in the active arm and 14 in the placebo arm will provide at least 80% power to detect a difference in virologic suppression of 65% in the active arm compared to either 10% or 20% in the placebo arm.

In a pooled analysis (NWCS 371) of six ACTG clinical trials that utilized ATIs, time of viral rebound was estimated for 235 study participants who were on suppressive ART, received no immunologic interventions, and were suppressed (HIV-1 RNA <50 copies/mL) at the time of ATI [26]. At weeks 4, 8, and 12 the proportion of participants with HIV-1 RNA <200 copies/mL was 31%, 9%, and 6%, respectively. The participants included in this analysis were predominantly male (91%) and White, non-Hispanic (71%). Additionally, the large SMART trial [25], which measured HIV-1 RNA at 2 months after treatment interruption, reported 6% of the participants had HIV-1 RNA ≤400 copies/mL. Again, these participants were predominately male (74%) and White (56%).

Recognizing the participants enrolling into A5416 will differ demographically from those in the ATI studies discussed above and are expected to harbor clade C viruses, we also considered the results from the SPARTAC [48] and PROMISE [27] trials, who have participant populations that, although different, more closely resemble those we intended to enroll. In the SPARTAC trial, they found a significant delay in time to viral rebound in African participants compared to non-African participants. In particular, 5 of the 22 African women (22.7%) who had initiated ART during primary infection maintained HIV-1 RNA <400 copies/mL over a median of 188 weeks following ART interruption [48]. In the larger PROMISE trial, including 1067 virally suppressed, postpartum women who underwent ATI (70% from Africa), 16.8% maintained HIV-1 RNA <400 copies/mL at week 12 following the

ATI.

These differences may be related to different cohort characteristics, including time of ART initiation, sex, and viral subtypes [23].

Additionally, repeated doses of 3BNC117 and 10-1074 over a period of 20 weeks in a study conduct in the US (most clade B viruses) delayed viral rebound with only 23.5% (4/17) of participants with HIV-1 RNA >200 copies/mL at or prior to week 20 (last antibody infusion).

Considering these various estimates of virologic rebound in the absence of an intervention and the promising data suggesting the combination of 3BNC117 and 10-1074 is able to delay viral rebound, the suggested sample size (and associated power) shown in Table 10.4-1 are sufficient to detect a difference.

10.5 Data and Safety Monitoring

10.5.1 Interim Monitoring Guidelines

See section 7.4 for monitoring guidelines.

10.6 Analyses

10.6.1 Primary Analyses

The primary safety analysis will summarize events per section 10.2.1.1. All participants who have been exposed to active study treatment will be included in the analysis, and summaries will include the number and percentage of participants experiencing an event per section 10.2.1.1 with an exact binomial two-sided 95% CI.

For the primary efficacy analysis, the proportion of participants experiencing viral suppression (defined as no confirmed HIV-1 RNA > 200 copies/mL) at week 24 will be calculated and bounded with a two-sided exact 95% confidence interval separately for the active and placebo arms. These proportions will be compared using a one-sided Fisher's exact test with a type I error rate of 0.05. Participants who restart ART for reasons other than confirmed viral rebound or are lost to follow up will be considered as not achieving viral suppression.

All primary efficacy analyses will be per-protocol, limited to participants who are fully suppressed before the infusion (defined as no HIV RNA blip ≥50 copies/mL), receive the infusion of both antibodies (active or placebo) and undergo an ATI according to the protocol.

10.6.2 Secondary Analyses

The cumulative probability of participants experiencing viral rebound at or prior to week 24 (10.2.2.1), will be estimated using Kaplan-Meier methods, separately in each treatment arm. A standard two-sided 95% CI around the true viral rebound

probability by 24 weeks will be calculated using the adaption of Greenwood's variance estimate with a log (-log) transformation [59]. Participants who restart ART due to low CD4 count or acute retroviral syndrome will be considered as having viral rebound; otherwise they will be censored at last HIV-1 RNA before restart.

Other secondary efficacy outcomes (10.2.2.2, 10.2.2.6) will be analyzed using a similar Kaplan-Meier approach.

In the active arm, the frequency of participants who do not meet the virologic or immunologic components of the ART resumption criteria described in section 6.3.14 will be tabulated by serum bNAb concentration (10.2.2.3, 10.2.2.4). Proportion of participants who remain off ART and do not meet ART resumption criteria will be summarized by study week, separately in each arm (10.2.2.5).

In the active arm, descriptive summaries, will be presented for the estimated PK parameters (10.2.2.7 and section 11.0). Graphical approaches will display concentration and HIV-1 viral load over time (10.2.2.8).

In the active arm, the attribution of induced anti-3BNC117-LS-J and/or anti-10-1074-LS-J antibodies (10.2.2.9) will be summarized. Graphical displays and summary descriptions will be presented for the longitudinal CD4 (10.2.2.10) and HIV-1 RNA measures, separately for each arm.

10.7 Unblinding

For unblinding requests, including emergency unblinding, refer to ACTG Standard Operating Procedure (SOP)-123, Unblinding Participants, for details. In the event that emergency disclosure of treatment assignment is thought to be required, the site investigator must follow ACTG SOP-123.

Planned Unblinding
Participants will be unblinded at completion of the study. Refer to ACTG SOP-123 Unblinding Participants for details.

Sudden/Unplanned Unblinding
(1) Sudden (or unplanned) unblinding of one or more arms due to interim analysis results or results of another trial: The decision to unblind one or more arms of an ongoing study is made by the team in conjunction with the relevant Scientific Committee and the Executive Committee. This can occur based on a recommendation from the DSMB or an SMC or the results of another trial (also see the DAIDS SOP "Termination of a Trial or a Single Treatment Arm").

(2) Participant contact: If the decision is made to unblind, participants should be unblinded as soon as possible. Unblinding is conducted through the DMC, which sends treatment assignments to the sites soon after the unblinding decision. Every effort should be made by the sites to contact participants who have completed follow-up in order to explain the study results.

(3) Implications of unblinding on study data: When a treatment comparison is unblinded based on an interim analysis, the results of that interim analysis must be reported in publications. Data from visits that occurred before the interim review but that were not in the database at the data cutoff date have little potential for bias and may be reported with a comment. Data from visits that occurred after unblinding are potentially biased and must not be used if the intent is to claim that all the data are from a blinded study. In unblinding due to both “interim analysis” and the “other trial results” situations, if analyses are reported on clinical data or samples taken after the unblinding date, the conditions under which these data were gathered must be made clear in any publication.

11.0 PHARMACOLOGY PLAN

ARV Pharmacology Testing During ATI

An ATI is included in ACTG protocols as a mechanism to evaluate novel interventions in participants living with HIV who are virologically suppressed with combination ART. If an intervention is evaluated and viral suppression is maintained after the removal of combination ART, the protocol objectives are able to be investigated without any contributions related to ARV effects. Therefore, sustained periods of undetectable viral loads are considered to reflect beneficial virologic effects of the intervention under investigation. An increase in viral load is judged to represent loss of virologic suppression and would indicate the need for reinitiation of combination ART. To appropriately evaluate long-term virologic suppression using novel interventions, it is imperative that there is no continued use of ARVs during an ATI. Since ATI-containing protocols often have a long duration of follow-up during an intervention, repeated sampling for ARV pharmacology testing provides an approach that will identify participants who continue to take ARVs during an ATI.

ARV Plasma Concentration Decline During ATI

The plasma concentration profiles of tenofovir (TFV) after a single-dose administration of tenofovir alafenamide (TAF) are presented in Figure 11-1. The TFV concentrations range between 1 to 10 ng/mL 96 hours post-administration, at least two-fold above the lower limit of quantification (0.5 ng/mL). The current liquid chromatography–mass spectrometry assays will be able to adequately identify incident TAF taken 96 hours (4 days) post-administration.

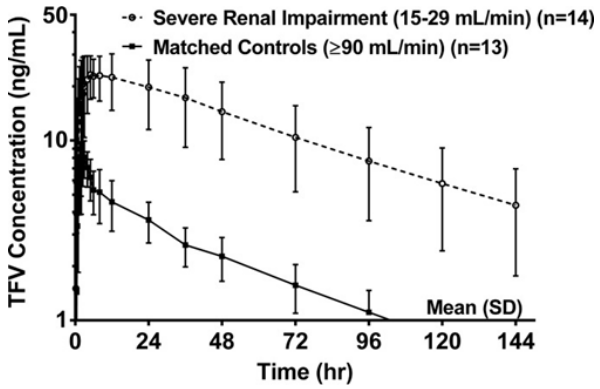


Figure 11-1: TFV plasma concentration-time profile following a single dose of TAF 25 mg [60].

The plasma concentration profiles of dolutegravir (DTG) under fed and fasted states, and

with and without calcium carbonate administration after single-dose administration of DTG are presented in Figure 11-2. The DTG concentrations range between 0.25 to 2 mcg/mL 48 hours post-administration, at least 25-fold above the lower limit of quantification (10 ng/mL). Based on the DTG elimination rate constant (ke=0.045/hr), the current assays will be able to adequately identify incident DTG taken 120 hours (5 days) post-administration.

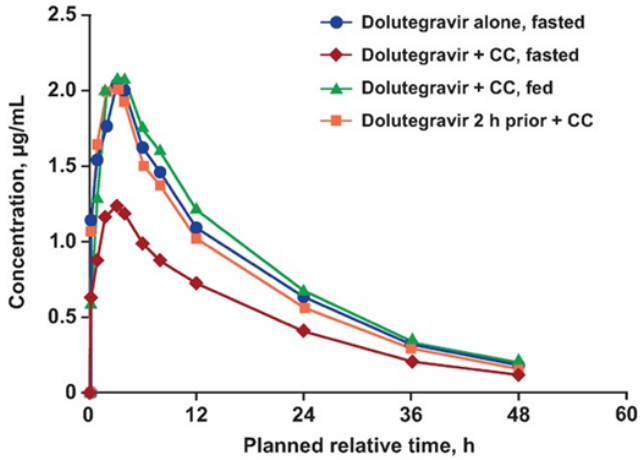


Figure 11-2: Mean plasma concentration-time profiles of dolutegravir (50 mg, single dose) administered with and without calcium carbonate (CC) (1200 mg, single dose) [61].

This pharmacology evidence, that is, ARV plasma concentration decline, indicates the utility of ARV plasma concentration measurement as a screening tool to identify participants who incidentally take ARV during ATI.

11.1 Pharmacology Objectives

11.1.1 Determine the serum concentration versus time profiles for 3BNC117-LS-J and 10-1074-LS-J.

11.1.2 Determine the PK parameters (e.g., AUC, $t_{1/2}$, C_{max}, C_{min}, clearance and volume of distribution) of 3BNC117-LS-J and 10-1074-LS-J.

11.1.3 Compare the PK parameters of 3BNC117-LS-J and 10-1074-LS-J to historic data for each agent when administered alone.

11.1.4 To determine the proportion of protocol participants with quantifiable ARVs in blood samples during an ATI that would suggest a protocol violation of the planned ATI period.

11.2 Pharmacology Study Design

11.2.1 Samples will be collected per the SOE on the day of infusion to perform an abbreviated PK study of 3BNC117-LS-J and/or 10-1074-LS-J. These samples will include a pre-dose blood sample at time 0, and then a sampling at the end of the antibody infusions. Dose information (date/time of each infusion dose) will be captured on an eCRF.

11.2.2 ARVs being taken prior to ATI will be identified by the protocol pharmacologist utilizing data provided by the DMC. The decision to assay specific same time points for ARV concentrations will be determined by the protocol team, based on participants with prolonged viral suppression during the ATI. Blood samples (5 mL) will be collected during the study visit and plasma samples will be analyzed for TFV. In participants not on a TFV-containing regimen, the protocol pharmacologist will identify the ARV to be assayed. This will most likely be DTG but may be other ARVs in certain situations.

11.3 Primary and Secondary Data, Modeling, and Data Analysis

11.3.1 The serum samples will be required and used to calculate key PK parameters of 3BNC117-LS-J and 10-1074-LS-J, including exposure indicated by AUC, half-life, clearance (Cl/F) and volume of distribution. Population PK analysis of serum concentrations will be performed.

11.3.2 Pharmacodynamics/responses. The PK estimates of bNAbs will then be used in analyses to correlate with the virologic and immunologic measures during ATI and for comparison of exposure between participants with and without treatment-related AEs.

11.4 Anticipated Outcomes

Anticipated outcomes will include an understanding of the 3BNC117-LS-J and 10-1074-LS-J PK and the relationship of the PK to the duration of viral suppression during ATI and emergence of resistance during viral rebound. The monitoring of ARVs will provide information regarding the completeness of the ATI.

12.0 DATA COLLECTION AND MONITORING

12.1 Records to Be Kept

Electronic case report form (eCRF) screens will be made available to sites for data entry. Participants must not be identified by name on any data submitted to the DMC. Participants will be identified by the patient identification number (PID) and study identification number (SID) provided by the ACTG DMC upon registration.

12.2 Role of Data Management

12.2.1 Instructions concerning entering study data on eCRFs will be provided by the ACTG DMC. Each CRS is responsible for keying the data in a timely fashion.

12.2.2 It is the responsibility of the ACTG DMC to ensure the quality of computerized data for each ACTG study. This role extends from protocol development to generation of the final study databases.

12.3 Clinical Site Monitoring and Record Availability

Site monitors under contract to the NIAID will visit participating clinical research sites to review the individual participant records, including consent forms, eCRFs, supporting data, laboratory specimen records, and medical records (physicians' progress notes, nurses' notes, individuals' hospital charts), to ensure protection of study participants, compliance with the protocol, and accuracy and completeness of records. The monitors also will inspect sites' regulatory files to ensure that regulatory requirements are being followed and sites' pharmacies to review product storage and management.

Monitoring visits may be conducted on-site or remotely. Remote visits may include remote source document verification using methods specified for this purpose by NIAID. Remote monitoring visits may be performed in place of, or in addition to, onsite visits to ensure the safety of study participants and data integrity [62]. The site must make available study documents for site monitors to review utilizing a secure platform that is HIPAA and 21 CFR Part 11 compliant. The DMC will configure Medidata Remote Source Review (RSR) and make it available to all sites. We encourage sites to use the DMC-provided Medidata RSR platform but other potential platform options include: Veeva SiteVault, site-controlled SharePoint or cloud-based portal, and direct access to Electronic Medical Record (EMR). Other secure platforms that are 21 CFR Part 11 compliant may be utilized, as allowed by the DAIDS Office of Clinical Site Oversight (OCSO).

The site investigator will make study documents (e.g., consent forms, drug distribution forms, eCRFs) and pertinent hospital or clinic records readily available for inspection by the local IRB, site monitors, NIAID, OHRP, the industry supporter or designee, other local, US and international regulatory entities for confirmation of the study data.

13.0 PARTICIPANTS

13.1 Institutional Review Board (IRB)/Ethics Committees (ECs) Review and Informed Consent

This protocol and the informed consent document and any subsequent modifications will be reviewed and approved by the IRB or EC responsible for oversight of the study. A signed consent form will be obtained from the participant. The consent form will describe the purpose of the study, the procedures to be followed, and the risks and benefits of participation. A copy of the consent form will be given to the participant and this fact will be documented in the participant's record.

13.2 Participant Confidentiality

All laboratory specimens, evaluation forms, reports, and other records that leave the site will be identified by coded number only to maintain participant confidentiality. All records will be kept locked. All computer entry and networking programs will be done with coded numbers only. Clinical information will not be released without written permission of the participant, except as necessary for monitoring by the ACTG, HVTN, HPTN, IRB/EC, NIAID, OHRP, drug companies supporting this study, and other local, US, and international regulatory entities as part of their duties.

Data storage and retention related to IDIs will follow the study, national/in-country, local, and/or site requirements.

13.3 Study Discontinuation

The study may be discontinued at any time by the ACTG, IRB/EC, NIAID, OHRP, and other government agencies as part of their duties to ensure that research participants are protected.

14.0 PUBLICATION OF RESEARCH FINDINGS

Publication of the results of this trial will be governed by ACTG, HVTN, and HPTN policies.

15.0 BIOHAZARD CONTAINMENT

As the transmission of HIV and other blood-borne pathogens can occur through contact with contaminated needles, blood, and blood products, appropriate blood and secretion precautions will be employed by all personnel in the drawing of blood and shipping and handling of all specimens for this study, as currently recommended by the CDC and the National Institutes of Health.

All dangerous goods and materials, including diagnostic specimens and infectious substances, must be transported using packaging mandated by CFR 42 Part 72. Please refer to instructions detailed in the International Air Transport Association (IATA) Dangerous Goods Regulations.

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APPENDIX I: SAMPLE INFORMED CONSENT

DIVISION OF AIDS
Advancing Clinical Therapeutics Globally for HIV/AIDS and Other Infections (ACTG)
HIV Vaccine Trials Network (HVTN)
HIV Prevention Trials Network (HPTN)
For protocol: A5416/HVTN 806/HPTN 108

A Phase I, Randomized, Placebo-Controlled Study of the Safety, Antiviral & Immunomodulatory Activity of Broadly Neutralizing Antibodies 3BNC117-LS-J and 10-1074-LS-J in Combination in ART-treated Adults in Sub-Saharan Africa Living with HIV during a Monitored Analytical Treatment Interruption

ABBREVIATED TITLE: Pausing Antiretroviral Treatment Under Structured Evaluation (PAUSE)

SUMMARY

PURPOSE

This research study will test two new investigational antibodies: 3BNC117-LS-J and 10-1074-LS-J, compared to a placebo. An investigational product is one that has not been approved by the United States Food and Drug Administration (FDA) or another regulatory agency. Your participation in this research study is voluntary.

Both 3BNC117-LS-J and 10-1074-LS-J are antibodies against the Human Immunodeficiency Virus (HIV), and we will call them the study antibodies. The study antibodies or placebo will be given by intravenous (IV) infusion. IV infusions are also known as “getting a drip.” Some people will get infusions of a placebo. The placebo will be sterile salt water. It does not have any of the study antibodies in it.

The main purpose of this study is to see if it is safe to give the study antibodies (3BNC117-LS-J and 10-1074-LS-J) by IV infusion to people living with HIV (PWH), and to see if they cause any side effects. We also want to see how they affect the level of HIV in your blood when you are not taking your regular HIV treatment for an extended period of time. This extended period of time when you are not taking your regular HIV treatment is called an analytical treatment interruption (ATI).

Stopping your HIV treatment is not recommended as part of standard care. It poses risks to you and your sex partner(s), as described in more detail later in this form. However, during this study we will monitor you closely while you are not taking HIV treatment. You will restart taking your HIV treatment again if blood tests show that it is necessary. You may need to switch to a different treatment regimen if your current treatment is no longer effective.

STUDY TREATMENT

Some participants will receive the study antibodies (3BNC117-LS-J and 10-1074-LS-J) and some participants will receive placebo (sterile salt water). You will be in one of these two groups. You have a 2 to 1 chance of receiving antibodies or placebo. You will not know which group you are in. The study is double-blinded. Double-blinding procedures means participants and study doctors will not know which group participants are in.

NUMBER OF PARTICIPANTS

48 people will participate in this study.

LENGTH OF STUDY

The longest time that you are expected to be in the study is 96 weeks (about 2 years). The actual length of time you are in this study will mainly depend on how long you remain off HIV treatment.

REQUIRED ACTIVITIES

This section provides a summary of study activities. A detailed description of all study activities is provided below.

- Receiving the study antibodies or placebo through an IV drip
- Stopping your HIV treatment
- Physical exams which will be guided by symptoms you may have
- Blood samples will be collected from a vein in your arm at most visits
- Urine samples will be collected at a few visits
- Larger blood samples will be collected at up to five times (at entry, week 12, 24, 48, and 72)
- Questionnaires about your experience as a study participant during three study visits. Participants enrolled at pre-selected 3-5 sites will be requested to participate in interviews as well.

RISKS

This section describes the risks of the IV infusions and stopping HIV treatment. A detailed description of all study-related risks is provided below.

- IV infusions can cause pain, redness, and swelling at the site on your arm where the infusion is given. The most common side effects of the study antibodies are headache, generally feeling uncomfortable, nausea, and feeling tired. The placebo is not known to have any significant risks.
- When you stop taking your HIV treatment, the amount of HIV in your blood (known as viral load) could increase and become detectable. If this happens, you could have some of the same “flu-like” symptoms you may have had after you first got HIV.
- Your CD4 count (a measure of your immune system, the system that helps your body fight infections) could drop and put you at risk for HIV-related illnesses including pneumonia, other opportunistic infections, and certain types of cancer.
- If your sex partner(s) do not have HIV, it is possible that you could

transmit HIV to them during the time when your viral load is detectable. Participants must be willing to use condoms for all sexual activity to protect their partners. Your partners should also get regular HIV testing during this time, and they may want to use PrEP (medicines that can prevent HIV). The study team will offer information and resources to help participants and their partners.
- If you fall pregnant while you are not taking HIV treatment and have a detectable viral load, you could transmit HIV to the developing baby.
- Participation in this study may prevent you from being in another study for a period of time.

BENEFITS — Because this is a research study, no direct benefits should be expected from participating in this study. It is not known if the study antibodies will help you maintain an undetectable viral load.

OTHER CHOICES — Instead of being in this study, you can continue using your current HIV treatment or starting a new treatment under the care of your regular health care provider.

STUDY CONTACT INFORMATION — If you have a question or concern about the study, you may contact the study doctor or another study staff member at [enter phone number].

INTRODUCTION

You are being asked to join this research study because you are between ages 18 and 70, are living with HIV (the virus that causes AIDS), and because you are taking HIV treatment (antiretrovirals, ARVs) to control HIV and have an undetectable viral load, which means that the amount of virus in your blood is so small that it does not show up on regular blood tests.

This study is sponsored by the US National Institutes of Health (NIH). The name and contact info for the study doctor in charge of this study at this site is provided in this consent form.

This is an informed consent form. It gives you information about this study. The study staff will talk with you about this information. You are free to ask questions about this study at any time. If you agree to join this study, you will be asked to sign and date this informed consent form. You will get a copy to keep.

It is completely up to you whether or not to join the study. Take your time in deciding. If it helps, talk to people you trust, such as your primary HIV healthcare provider, friends, or family. We will be happy to help you explain this study to anyone you wish. If you decide not to join this study, or if you leave the study after you have joined, your other care at this clinic and the benefits or rights you would normally have will not be affected.

You cannot be in this study while you are in another study where you get a study product. Being in more than one study may not be safe. If you choose not to join this study, you may be able to join another study.

If you would like to join this research study, you will be asked to sign and date this consent form and schedule a screening visit to see if you are eligible to join.

WHY IS THIS STUDY BEING DONE?

For people living with HIV, HIV treatment helps to stop the virus from multiplying in your body. The goal of HIV treatment is to have undetectable viral load. HIV also hides in cells throughout the body, and can start multiplying when HIV treatment is stopped. Interrupting HIV treatment is an experimental procedure that is only used in carefully monitored research. It is not recommended as part of routine healthcare for people living with HIV. Study participants will interrupt use of HIV treatment in this study and will be carefully monitored.

We are doing this study to answer several questions.

- Is it safe to give the study antibodies to people living with HIV, and do they cause any side effects?
- Are people who get the study antibodies more likely to control HIV (undetectable viral loads) for a longer period of time without taking HIV treatment than people who get the placebo?
- Do the study antibodies affect the level of HIV in your blood when you are not taking HIV treatment for an extended period of time?

To answer these questions, you will stop taking your HIV treatment during this study. We will monitor you closely, with study visits every 1 to 4 weeks. We will check your health and the amount of HIV in your blood frequently to reduce the chance of harm to you.

An antibody is a protein that the body makes in response to an infection. Researchers can also make antibodies in laboratories and give them to people by infusions into a vein. Antibodies attach to HIV and can block HIV from attacking cells in the body and from spreading to other parts of the body. These study antibodies are being developed to potentially treat and prevent HIV. The study antibodies are not made from actual HIV. It is impossible for them to give you HIV. Also, they cannot cause you to give HIV to someone else.

WHAT DO I HAVE TO DO IF I AM IN THIS STUDY?

To be eligible for this study, you need to be using HIV treatment known as an integrase inhibitor-based **or protease inhibitor-based** regimen before you have your Study Entry visit. Your HIV treatment will not be provided in this study, and you will not get routine care for HIV or any other medical conditions as part of being in the study.

You will have an entry visit when you get the IV drip, and frequent study visits. The longest time that you are expected to be in the study is about 2 years. The actual length of time you are in this study will depend on how long you do not use HIV treatment and on other factors (e.g., pregnancy status). The schedule of visits and study procedures is explained below.

Screening Visit

We will do some tests to see if you are eligible to be in the study. The screening visit will take about 1.5 hours. At this visit:

- We will confirm your HIV status. If there is no record available, we will do another HIV test. You may have to sign and date another consent form before having this test.
- We will ask questions about your health and medicines you have taken in the past or are taking now.
- We will do a physical exam and ask about your health history. A physical exam may include, but is not limited to:
  - Checking your weight, temperature and blood pressure
  - Looking in your mouth and throat
  - Listening to your heart and lungs
  - Feeling your abdomen (stomach and liver)
- If you are able to become pregnant (i.e., participants assigned female at birth who have not been post-menopausal for at least 24 consecutive months, who have had menses within the preceding 24 months, or who have not undergone surgical sterilization), we will collect a urine or blood sample to see if you are pregnant. You will not be able to enroll in this study if you are pregnant or breastfeeding.
- We will collect a blood sample for the following tests:
  - CD4+ count
  - HIV-1 viral load
  - Checking the health of your kidneys and liver
  - Hepatitis and syphilis screening. If the test results are positive, you will be referred to your regular healthcare provider for evaluation and treatment.
- We will ask you about conditions that put you at risk for heart disease.
- You will provide a urine sample for:
  - Tests of how well your kidneys are working
  - Screening for chlamydia and gonorrhea. If the tests are positive, you will be referred to your regular healthcare provider for evaluation and treatment.
- We will ask for permission to communicate with your primary healthcare provider to coordinate your care during this study. We will check to make sure your HIV is well controlled by your HIV treatment and has been for at least 2 years.
- We will ask if you are willing to use condoms every time you have sex for the extended period of time when you are not taking HIV treatment, until you restart your HIV treatment and your viral load returns to undetectable. This is to protect your partner(s) and prevent transmission of HIV.

We will review the screening results with you. The screening results may show you are not eligible to join the study, even if you want to.

Information Collected at Screening

There is some information that we collect on everyone who is screened. As part of your screening visit, we will ask you about whether you currently use intravenous drugs, or have used them in the past.

We will collect this information even if you do not join this study. This information is collected so that researchers can look for patterns or common reasons why people do not join studies.

Vaccinations
We ask that you do not get any approved vaccinations, including COVID vaccines or any other locally approved vaccines, within 2 weeks before the Entry visit. We also ask that you do not receive these vaccines within 7 days before or 7 days after you receive the infusions. If you decide to join, the study staff will work with you to schedule your entry visit where the infusion is given, and manage the timing of vaccines you need while you are participating in this study.

Avoiding Pregnancy
If you can become pregnant, you must agree to use effective contraception in addition to condoms to join this study. At the screening visit, we will review the approved methods of contraception with you and confirm that you are willing to use contraception during the time that you are not taking HIV treatment, until you restart HIV treatment, and your viral load returns to undetectable.

Current HIV treatment guidelines recommend using HIV treatment during pregnancy to prevent transmission to the baby. Since you will interrupt your HIV treatment in this study, you should not become pregnant. In addition to using condoms every time you have sex to prevent HIV transmission to your partner, we will ask you to use contraception as well. We will talk to you about the effective methods of contraception that are approved for this study.

If you become pregnant or start breastfeeding after you stop taking your HIV treatment, you will immediately restart taking your HIV treatment, and can remain in the study. If you become pregnant or start breastfeeding after you have restarted your HIV treatment, you will continue taking it. In both of these situations, we would like you to come for clinic visits for up to 6 months so we can continue to follow you for safety.

If you were assigned male sex at birth and have a sexual partner(s) who could become pregnant, we will talk with you about the requirement to use condoms and for your partner to use an approved method of contraception during the time when you are not using treatment, until you have restarted treatment, and your viral load has returned to undetectable.

Study Steps
The study is divided into 3 steps.

In Step 1 [entry visit through week 24 (6 months)], you will get 1 IV drip (through a vein in your arm) of the study antibodies or placebo on the study entry day. Two days later you will stop taking your HIV treatment. After you stop HIV treatment, for the first 2 months you will visit the clinic every week (8 visits). For the next 4 months, you will visit the clinic every 2 weeks (8 visits).

Step 2 (week 25 through week 72): you will enter this step if you do not meet any of the conditions to restart HIV treatment while in Step 1. In Step 2, you will continue to stay off your HIV treatment. For these 12 months you will visit the clinic about every 2 to 4 weeks (18 visits).

Step 3 (restarting HIV treatment and follow-up for 6 months): you will enter this step if you have completed Step 2 or have to restart your HIV treatment for any reason while in Step 1 or Step 2, In Step 3, you will restart taking HIV treatment. For the next 6 months, you will visit the clinic about 3 times.

ART Restart: Moving to Step 3

We do not know if the study antibodies might help people to control HIV, or how long control could last. Some people will get the placebo, which does not control HIV. For this reason, people could skip Step 2 entirely, or could be in Step 1 or Step 2 for a shorter or longer amount of time. You will restart taking your HIV treatment and move to Step 3 if one of these things happen while you are in Step 1 or Step 2:

- Your viral load increases to 1,000 copies/mL or higher, and stays at that level or higher for 4 weeks in a row
- If your CD4+ count drops to less than 350 cells/μL
- If you become pregnant
- If you develop “flu-like” symptoms that look like acute retroviral syndrome, similar to what you might have had when you were first diagnosed with HIV
- If you are not willing to use condoms for all sexual activity while you are in study Steps 1 or 2
- If you want to restart HIV treatment
- If your primary HIV healthcare provider thinks you should restart HIV treatment

The study staff can answer any questions you have about individual study visits, and how long they will last, or about the tests that will occur. The tables below can be used as a quick reference for you, along with the explanations that follow.

Step 1 Study Schedule

Evaluation or Procedure	Screening	Step 1					Confirmation of Viral Rebound
		Entry (Day 0)	Day 2 (±1 day)	Study Visits Every Week from Week 1 to Week 8	Study Visits Every 2 Weeks from Week 9 to Week 24	Visits As Needed Based on Testing for ART Restart Criteria	
				Weeks 1, 2, 3, 4, 5, 6, 7, 8	Weeks 10, 12, 14, 16, 18, 20, 22, 24	Weeks 9 through 24	
(Visit Window)				(±3 days)	(±3 days)	(±3 days)	
Informed consent	X						
Assess understanding and complete the decision-making aid	X						
Medical and medication history	X	X					
Complete physical exam	X						
Weight	X	X					
Blood sample for tests on overall health	X	X		week 1, and then every 4 weeks	every 4 weeks		
Blood sample for tests on hepatitis testing	X			as needed	as needed		
Blood and urine sample for STI testing	X	X		every 4 weeks; otherwise, as needed	every 4 weeks; otherwise, as needed		
Urine samples for tests on overall health	X	X		weeks 1 and 4; otherwise, as needed	as needed		

Evaluation or Procedure	Screening	Step 1					Confirmation of Viral Rebound
		Entry (Day 0)	Day 2 (±1 day)	Study Visits Every Week from Week 1 to Week 8	Study Visits Every 2 Weeks from Week 9 to Week 24	Visits As Needed Based on Testing for ART Restart Criteria	
				Weeks 1, 2, 3, 4, 5, 6, 7, 8	Weeks 10, 12, 14, 16, 18, 20, 22, 24	Weeks 9 through 24	
(Visit Window)				(±3 days)	(±3 days)	(±3 days)	
Blood or urine sample for pregnancy test (if applicable)	X	X		every 4 weeks; otherwise, as needed	every 4 weeks; otherwise, as needed		
Blood sample for HIV viral load	X	X		X	X	X	
Blood sample for CD4 count	X	X		every 2 weeks; otherwise, as needed	every 4 weeks	X	
Targeted physical exam		X		X	X		
IV infusion (drip)		X					
Discontinuation of ART			X				
Verify HIV treatment stopped			X				
Blood draw for other testing and storage	X	X		X	every 4 weeks		X
Large Blood Draw		X			at week 12 and 24		
Blood sample stored to test for study antibody sensitivity		X					
Blood sample stored to test for sensitivity to ARVs (HIV medications)							X
Blood sample stored to measure study antibody levels		X		every 4 weeks	every 4 weeks		X
Blood sample stored to measure ARV levels				every 4 weeks	every 4 weeks		
Blood sample stored to test for how your immune system respond to infections		X					
Assess if restarting HIV treatment is needed				X	X	X	
Contraception counseling		X		X	X	X	
Transmission reduction counseling		X		X	X	X	
Questionnaire/interview		X					

Step 2 Study Schedule

Evaluation or Procedure	Step 2		
	Study Visits Every Two or Four Weeks	Conditional Visits As Needed Based on Testing for ART Restart Criteria	Confirmation of Viral Rebound
	Weeks 25 to Week 72	Week 25 through 72	
(Visit Window)	(±3 days)	(±3 days)	
Targeted physical exam	X		
Blood sample for tests on overall health	every 4 weeks		
Urine sample for tests on overall health	as needed		
Blood and urine sample for STI testing	every 4 weeks; otherwise, as needed		
Blood or urine sample for pregnancy test (if applicable)	every 4 weeks; otherwise, as needed		
Blood sample for CD4 count	every 4 weeks; otherwise as needed for ART restart criteria	X	X
Blood sample for HIV viral load	every 2 weeks until week 48, and then every 4 weeks until week 72	X	X
Blood draw for other testing, including storage	every 4 weeks from weeks 28 through 60, and week 72	if needed	X
Large blood draw	at weeks 48 and 72		
Blood sample stored to test for sensitivity to ARVs (HIV medications)			X
Blood sample stored to measure study antibody levels			X
Blood sample stored to measure ARV levels			X
Assess if restarting HIV treatment is needed	X	X	
Contraception counseling	X	X	
Transmission reduction counseling	X	X	

Step 3 Study Schedule

Evaluations or Procedure	Entry (R)	Step 3			Premature Study Discontinuation
		ART/Monitoring (Weeks)			
		R+4	R+12	R+24	
(Visit Windows)		(±7 days)			
Verify HIV treatment restarted	X				
ART re-adherence counseling	X				
Targeted physical exam		X	X	X	X
Blood sample for tests on overall health		if needed	if needed	if needed	X
Urine sample for tests on overall health		if needed	if needed	if needed	
Blood and urine sample for STI testing		if needed	if needed	if needed	
Blood or urine sample for pregnancy test (if applicable)		as needed	as needed	as needed	

Evaluations or Procedure	Entry (R)	Step 3			Premature Study Discontinuation
		ART/Monitoring (Weeks)			
		R+4	R+12	R+24	
(Visit Windows)		(±7 days)			
Blood sample for HIV viral load		X	X	X	X
Blood sample for CD4 count			X	X	X
Blood draw for sample storage	X		X	X	
Contraception counseling		X	X	X	
Transmission reduction counseling		X	X	X	
Questionnaire/interview	X			X	X

Explanation of Visits

Screening Visit: After you have read and signed the consent form, you will have several tests done to see if you are eligible to join the study.

Entry Visit: If you are eligible and decide to join the study, you will enter the study in Step 1. You will be randomly assigned (by chance, like flipping a coin) in a 2 to 1 ratio to get either an IV drip (through a vein in your arm) of the study antibodies or the placebo. This means for every three people in this study, two will receive the study antibodies and one will receive the placebo.

This is a blinded study which means that neither you nor the study doctor will know whether you are receiving the study antibodies or the placebo. The study antibodies and the placebo will be given through a small plastic tube that will be placed into a vein in your arm. The infusions of the two study antibodies or the placebo are given separately and will take about 1 hour. You will be observed in the clinic for 1 hour after the two infusions.

Day 2: You will stop taking your ART 2 days after the IV drip. A site staff member will contact you to confirm you have stopped taking HIV treatment.

Study Visits: You will have study visits as explained in the consent form and shown in the tables above.

Visits if needed: Assessing whether it is time to restart HIV treatment may require additional visits. This assessment will include, but is not limited to, viral load values, CD4+ count, pregnancy status, any “flu-like” symptom that look like acute retroviral syndrome, willingness to continue using condoms until viral load returns to undetectable, and whether you or your primary healthcare provider want you to restart HIV treatment.

Leaving the Study Early: If you leave the study early, we will ask you to come in for a Premature Study Discontinuation visit. If you do not get the full infusion during the Entry Visit, you will also have this visit.

Explanation of Evaluations

Below are descriptions of the evaluations.

Documentation of HIV-1
We will confirm your HIV status. If there is no record available, we will do another HIV test. You may have to sign and date another consent form before having this test.

Assessment of Understanding
A study staff member will ask you questions to make sure they have completely explained the study and that you understand the study requirements. You will answer the questions to show your understanding of the study, and any information that is unclear will be reviewed.

Decision-Making Aid
A study staff member will help you to review and complete the decision-making aid. This will help you to think about whether joining the study and completing the study requirements aligns with your values, and if you want to consult with anyone else before deciding to join the study.

Complete Physical Exam, Medical History, Medication History
We will do a physical exam and ask about your health history. We will ask questions about your health and medicines you have taken in the past or are taking now.

We will do routine blood tests to check your overall health and collect a urine sample to confirm that your kidneys are working well.

HIV Viral Load and CD4+ Count
These tests show how much HIV is in your blood and how many infection-fighting cells are in your blood.

Pregnancy Test
If you are able to become pregnant, we will collect a urine or blood sample to see if you are pregnant.

Hepatitis Testing
We will use some of your blood samples for Hepatitis B and C tests. Hepatitis is inflammation of the liver. If the test results are positive, you will be referred to your regular healthcare provider for evaluation and treatment.

STI Testing, Contraception Counseling, and Transmission Reduction Counseling
We will test you for sexually transmitted infections (STIs) such as syphilis, chlamydia, and gonorrhea using urine, vaginal swabs, or blood samples. We will counsel you about the results of your STI tests. We will counsel you on the importance of avoiding pregnancy (for yourself or your sex partners) and the approved methods of contraception, and how you and your partner(s) can have safer sex while you are not taking HIV treatment including the use of condoms for all sexual activity. We will counsel you about the added protection from HIV transmission if your HIV-negative partners use pre-exposure prophylaxis (PrEP) and can provide information about how to access PrEP if they are interested.

Urinalysis or Urinalysis Dipstick
This is a test to see how well your kidneys are working.

IV Drip of Study Antibodies OR Placebo
At the Entry Visit, the infusions of the two study antibodies or their placebo are given separately, one after the other and will take about 1 hour. You will be observed in the clinic for 1 hour afterward to watch for any side effects.

HLA Typing
HLA typing is a genetic test used to identify certain individual variations in a person's immune system. People with certain HLA types might be more or less likely to develop certain diseases. Simply having those HLA types does not mean they will develop those diseases. HLA typing can reveal family relationships. It is our policy not to discuss your HLA results unless they have direct medical or reproductive implications for you or your family. Genetic information about you will not be revealed to others, including your relatives, without your permission. We will not release any information about you or your family to any insurance company or employer.

Discontinuation of ART
You will stop taking your ART 2 days after the infusions at the Entry Visit. A site staff member will contact you to confirm you have stopped taking HIV treatment.

ART Restart Criteria
You will restart HIV treatment and move to Step 3 if one of these things happens:
- Your viral load increases to 1,000 copies/mL or higher and stays at that level or higher for 4 weeks in a row,
- If your CD4+ count drops to less than 350 cells/μL
- If you become pregnant
- If you develop "flu-like" symptoms that look like acute retroviral syndrome, similar to what you might have had when you first were diagnosed with HIV
- If you are not willing to use condoms for all sexual activity until your viral load returns to undetectable
- If you want to restart HIV treatment
- If your primary HIV healthcare provider thinks you should restart HIV treatment

Large Blood Draw
We will collect a large blood sample up to five times during the study to be stored for future study-required testing.

Social Science Questionnaires
You will be asked questions about your experience in the study at 3 specific study visits: Entry visit; when you restart taking HIV treatment; at the end of the study, or if you leave the study early. You will be asked about your perceptions of risks and benefits of the study, your emotional state, your quality of life, your experience with the partner protection measures, and other questions about your experiences in the study. **You will also be asked to take part in optional in-depth interviews (IDIs) as explained in Attachment B.**

WILL I RECEIVE THE RESULTS OF ANY TESTS?

You will receive the results of routine safety lab tests that are done at study visits (for example, blood counts, liver and kidney tests, pregnancy tests, urine tests, viral load, CD4 count, tests for STIs).

You will not receive the results from tests that are only used for research, and do not provide information that can be used for your medical care.

We will tell you any new information we learn during the study that might cause you to change your mind about participating. If we find out important information that may affect your medical care, we will tell you. At the end of the study, we will tell you the study results.

HOW MANY PEOPLE WILL TAKE PART IN THIS STUDY?

About 48 people will take part in this study.

WILL THE STUDY DOCTOR TAKE ME OUT OF THIS STUDY EARLY?

The study doctor may need to take you out of the study early, without your permission, if:
- You do not get the infusion at the entry visit;
- You do not stop taking HIV treatment as required;
- Your study doctor or your regular healthcare provider thinks the study is no longer in your best interests;
- The study is stopped or cancelled;
- You are not able to attend the study visits or meet other study requirements;
- Continuing in the study might be harmful to you;
- You need a treatment that you may not take while in the study;
- You become pregnant.

If you choose to leave the study early, the study doctor may ask you to continue to be part of the study and return for some study visits and procedures, and/or complete some tests for your safety. The study staff will work with you to ensure that you have restarted your HIV treatment and returned to an undetectable viral load.

Because the study antibodies are only approved for use in research, they will not be made available to anyone outside of the study.

WHAT ARE THE RISKS OF THE STUDY?

It is not known if the study antibodies will control HIV. Because they have only been tested in a small number of people without HIV, we do not know all of the risks.

There is a risk of serious and/or life-threatening side effects when non-study medications are taken with the study antibodies. Since we do not know which participants will be getting the study antibodies or the placebo, for your safety you must tell the study doctor or nurse about all medications you are taking before you start the study, and also before starting any new medications during the study. Also, you must tell the study doctor or nurse before enrolling in any other research studies while you are participating in this study.

Risks of the Study Antibodies:
The two study antibodies have been given to approximately 150 people without HIV, in a study that involved participants in the United States and in African countries. They have been given together as an IV drip to approximately 10 people without HIV. In addition, earlier versions of these study antibodies called 3BNC117 or 3BNC117-LS and 10-1074 or 10-1074-LS were tested in about 400 people in studies that occurred in the United States or in Europe. About 300 of them were people living with HIV and, of these, 100 participated in studies that included stopping their HIV treatment for a period of time. The antibodies did not cause any serious side effects when given at a similar dose.

The commonly reported side effects with the study products were generally mild, resolved in a couple of days, did not require treatment, and did not interfere with people going to work or school. The most commonly reported side effects were:
- Tenderness at the site where the antibodies were given
- Headache
- Cold-like illnesses
- Some participants also reported itching in their eyes.

In studies with the earlier versions of the study antibodies, the mostly commonly reported side effects were:
- Headache
- Generally feeling uncomfortable
- Nausea
- Feeling tired

Additional side effects that have been seen with the study antibodies as well as with other study antibodies used in other studies are:
- Allergic reactions. This means that the body is very sensitive to something. These reactions usually happen shortly after getting the IV infusion, which is why we observe you for one hour after the infusion is complete. Very rarely, allergic reactions can be severe and can even cause death. This severe reaction is called “anaphylaxis”. An allergic reaction could include:
  - A rash on your skin
  - Fever
  - Chills
  - Trouble breathing

Antibodies activate your immune system, helping it “wake up” to fight against infections. This may cause:
- Body aches
- Sore muscles
- Fever
- Chills
- Feeling shaky or trembling
- Pain in the stomach
- Pain in the back

Another possible side effect of the study antibodies is the release of chemicals in the body called cytokines. They can cause allergic reactions like those noted above, as well as:

- Swelling of the face or other soft tissues
- Low blood pressure
- Rapid heart rate
- Throat irritation or tightness
- Tightening of the muscles that line the airways
- Shortness of breath

The earlier versions of these study antibodies, 3BNC117 and 10-1074, were found to attach to the tissues of the human eye in laboratory tests. This might lead to inflammation of the eyes and can cause eye redness, swelling, itching, or pain. Some participants who got 3BNC117 complained of itching, watering, or redness of the eyes. These symptoms went away within a few days. One participant who got 10-1074 had mild dryness in his eyes that was temporary. It remains unclear if the antibodies caused these symptoms, or if there could be another cause. We do not know if the current versions of the study antibodies used in this study will have the same effects. Please tell the study staff if you have any symptoms like these in your eyes.

Strains of HIV in your body that are resistant to (not blocked by) the study antibodies could become detectable in your blood after you get the study infusions and stop using HIV treatment. However, restarting HIV treatment will likely control these viruses. If resistance to the study antibodies develops, this may limit your ability to use the study antibodies if they are ever approved for clinical use and sold in the future.

With any new study antibody, there is a possibility of unexpected side effects. Because there may be side effects that we do not yet know about, participants with certain medical problems will not be able to participate in the study. Examples include a history of heart attack and other heart problems, and autoimmune diseases like lupus, rheumatoid arthritis, and Crohn's disease.

Risks of Placebo
The risks of the sterile salt water that will be used as the placebo in this study are minimal.

Risks of Stopping HIV Treatment (Analytical Treatment Interruption (ATI))

High Viral Load
When you stop taking HIV treatment, your viral load may rise and become detectable again. If your viral load becomes high, it means that HIV is in more cells in your body, and that the size of the HIV reservoir (where HIV hides) in your body could increase, at least temporarily. This could mean that your HIV becomes worse.

In this study, we will closely monitor you for changes in your viral load. There is a small chance that the rise in viral load could cause fever, headache, and swollen glands. These symptoms are expected to go away or become less severe once you restart HIV treatment.

Acute Retroviral Syndrome
As described in Step 3 above, you could have symptoms of acute retroviral syndrome. These symptoms can include:
- Fever
- Sore throat

- Swollen lymph nodes
- Headache
- Body or joint aches
- Tiredness
- Diarrhea
- Rash
- Nausea
- Vomiting

If you have any of these symptoms, you should tell the study staff right away.

Risk of limitations to research participation
As a result of being in this study, you may not be eligible to participate in other HIV treatment or cure studies that require you to have an undetectable viral load for a period of time. After you restart taking your HIV treatment and your viral load becomes undetectable again, this limitation will go away over time.

Inflammation
If your viral load increases, you could have inflammation. High levels of inflammation are linked with heart disease (such as a heart attack) and other conditions. Restarting HIV treatment should reduce inflammation.

Low CD4 Count
It is possible that your CD4 count could drop. This could increase your risk for other HIV-related illnesses. It is also possible that your CD4 count might not return to its highest level even after you restart HIV treatment. Your CD4 count will be monitored closely while you are not taking HIV treatment, and you will restart ART if the count drops to less than 350 cells/mL.

Risk of Transmitting HIV to Your Sex Partner(s)
While your viral load is undetectable, the risk that you could transmit HIV to a sex partner is very low, often described as U=U (Undetectable = Untransmittable). However, since your viral load may rise and become detectable again while you are in this study, you must agree to use barrier protection like internal and external condoms for all sexual activity until you start taking your HIV treatment again and your viral load returns to undetectable.

If your sex partner(s) is not living with HIV, they should be tested regularly for HIV while you are in this study. We are not able to provide testing or PrEP to your partners as part of this study, but we will refer you to where these services are available.

Using condoms will also protect you from other sexually transmitted infections. If you test positive for any STI while you are not taking HIV treatment, you will be counseled about the use of condoms, and we will refer you for care and treatment of the STI.

If you are unable or unwilling to use barrier protection during the study as directed, you will restart taking HIV treatment.

Developing HIV Drug Resistance
When you stop taking HIV treatment, the HIV in your body might mutate (change itself). This mutation could lead to HIV drug resistance, which means that some of the treatment that you were taking before will not control HIV when you start taking it again. We do not think that this is very likely, but because it is an important possible complication, we will do frequent viral load tests after you stop taking HIV treatment. By testing your viral load frequently, we can make sure you are taking a treatment regimen that works for you, and reduce the chance of developing drug resistance.

Risks of Blood Draw
Having blood drawn may cause discomfort, bleeding, bruising, swelling where the needle enters the body, and in rare cases it may cause fainting. There is a small risk of infection at the place where the needle goes into your arm.

Risks of IV Infusions
Getting an IV drip may cause stinging, discomfort, pain, soreness, redness, bruising, itching, rash, and swelling where the needle goes into the skin. There is a small risk of infection at the place where the needle goes into the arm.

Risks of Loss of Confidentiality or Other Personal Problems
Although the study site will make every effort to protect your privacy and confidentiality, it is possible that your involvement in the study could become known to others and that others learn your HIV status. You could be treated unfairly or discriminated against by family members, friends, and/or the community. Rarely, a person loses a job because the study took too much time away from work, or because their employer learned they had HIV. We have comprehensive precautions in place to maintain confidentiality of all study participants and their data at all times. The risk of a breach of confidentiality is very small.

Risk to Future Study Participation
If you participate in this study, you may be excluded from participating in future research studies that include immune-based therapies.

Risk of Anxiety or Embarrassment
Some of the questions asked, such as those about HIV, mental health, and sexual behavior, may cause anxiety or discomfort. Also, waiting for test results could make you feel anxious. You could feel worried if your test results show that your viral load has become detectable, or if it rises. Trained study staff will be able to address any concerns you might have. If you feel embarrassed or anxious, please tell us and we will try to help you.

ARE THERE RISKS RELATED TO PREGNANCY?

Because we don’t know how these study antibodies could affect a baby or an unborn child, and because we will not know who is getting the study antibodies or the placebo, if you can become pregnant you will need to use condoms plus an effective form of contraception for 10 days before receiving the infusion, and until you have restarted HIV treatment and your viral load returns to undetectable. In addition, if you become pregnant while you are not taking HIV treatment and have a detectable viral load, you could transmit HIV to the developing baby. If you are the sexual partner of someone who could become pregnant and you have not had a vasectomy, you must also use

condoms from 10 days prior to study entry and for 36 weeks after receiving study treatment. If you think that you or your partner are pregnant, tell your study doctor or study nurse at once.

Effective forms of contraception include:
- Contraceptive subdermal implant
- Intrauterine device that uses hormones or intrauterine system
- Hormonal contraception [birth control pills, injections, or implants]
- Injectable progestogen
- Contraceptive vaginal ring
- Percutaneous contraceptive patches
- Tubal ligation (tubes tied)
- Diaphragm or cervical cap with spermicide

If you need to start using contraception, please talk with study staff about how you can obtain your desired contraception method.

If you are taking HIV treatment when you become pregnant, your pregnancy will be reported to an international database that collects information about pregnancies in people using HIV treatment. This report will not use your name or other information that could be used to identify you.

Breastfeeding
It is unknown whether the study antibodies could pass to the baby through breastmilk, and whether this may cause harm to your baby. People who are breastfeeding will not be allowed to participate in this study.

ARE THERE BENEFITS TO TAKING PART IN THIS STUDY?

Because this is a research study, we do not expect the study to benefit you directly. However, information learned from this study may help others who have HIV. Being in the study might still help you in some ways. The lab tests and physical exams that you get while in this study might detect health problems you don't yet know about. This study may help in the search for a treatment or other ways to prevent HIV.

WHAT ABOUT CONFIDENTIALITY?

Efforts will be made to keep your personal information confidential. We cannot guarantee absolute confidentiality. Your personal information may be disclosed if required by law. Any publication of this study will not use your name or identify you personally.

Your records may be reviewed by the ACTG, the HVTN, the HPTN, the U.S. Office for Human Research Protections, or other local, US, and international regulatory entities as part of their duties, the local Ethics Committee (a committee that protects the rights and safety of participants in research), National Institutes of Health (NIH), study staff, study monitors, drug companies supporting this study, and their designees.

All information collected about you as part of the study will be sent securely to the ACTG Statistical and Data Management Center in the United States for combining with information from other study participants and statistical analysis of study results. Your name and other personal identifiers will

not be sent. Your research site is responsible for sending your information in accordance with the laws, regulations and policies of your country and research site.

Some of your samples collected as part of this study will be stored and used for study-required testing. Some of your samples will also be shipped to and/or stored in another country. Identifiers will be removed from your samples and from any private information that is collected during the study.

A description of this clinical trial will be available on https://ClinicalTrials.gov. This Web site will not include information that can identify you. At most, the Web site will include a summary of the results. You can search this Web site at any time.

Remainder of section for South African sites: The study has been structured in accordance with the Declaration of Helsinki (last updated October 2013) which deals with the recommendations guiding doctors in biomedical research involving human participants, the Ethics in Health Research: Principles, Structures and Processes Second Edition 2015, and Guidelines for Good Practice in the Conduct of Clinical Trials in Human Participants in South Africa. We can provide you with copies of these guidelines if you wish to review them. In addition, the recent Protection of Personal Information Act (POPIA) ensures that all South African institutions conduct themselves in a responsible manner when collecting, processing, storing and sharing another entity's personal information by holding them accountable should they abuse or compromise your personal information in any way. If you want to leave this study, contact [name or title and telephone number of the investigator or other study staff].

You may also contact the [name of local IRB/EC] at [insert contact information].

If you want to leave this study, contact [name or title and telephone number of the investigator or other study staff].

You can reach a study staff member 24 hours a day at [telephone number].

If you have questions about this trial, you should first discuss them with your doctor or the EC (contact details as provided on this form). After you have consulted your doctor or the EC, and if they have not provided you with answers to your satisfaction, you should write to the South African Healthcare Products Regulatory Authority (SAHPRA) at:

The Chief Executive Officer
South African Health Products Regulatory Authority
Loftus Park, Building A
402 Kirkness Street
Arcadia, Pretoria 0083
E-mail: Boitumelo.Semete@sahpra.org.za
Tel: 012 501 0413

WHAT ARE THE COSTS TO ME?

The study will pay for all study tests. Taking part in this study may lead to added costs to you and/or your insurance company. In some cases, it is possible that your insurance company will not

pay for these costs because you are taking part in a research study. The cost of contraception will not be provided by the study.

WILL I RECEIVE ANY PAYMENT?

You will be compensated up to a total of $xx.xx for time and effort in participating in this study. You will receive compensation for the visits you complete according to the following schedule:

- $xx.xx for Visits xxx.
- $xx.xx for Visits xxx.
- $xx.xx for Visits xxx.

If you do not complete the study, for any reason, you will be compensated for each study visit you do complete.

You will be compensated _____ ["after each visit," "annually," "bi-weekly," etc.]

If you have any questions regarding your compensation for participation, please contact the study staff.

If the study antibodies later become approved and sold, there are no plans to share any money with you.

WHAT HAPPENS IF I AM INJURED?

If you are injured as a result of being in this study, you will be given immediate treatment for your injuries. Tell your study doctor or study staff by contacting them at the telephone number provided in the consent form, and they will help you get the care that you need. The U.S. National Institutes of Health (NIH) does not have a way to provide direct compensation for research related injury.

[Sites: Please modify (if necessary) and insert one of these two statements, as appropriate to your site. If your site is required to carry clinical trials insurance (CTI), this must be indicated in the informed consent.]

- *This site has clinical trials insurance. This insurance will allow the site to provide you with monetary compensation if you suffer harm as a result of participating in this research study.*
- *The cost for this treatment will be charged to you or your insurance company. There is no program for compensation either through this institution or the NIH.*

WHAT ARE MY RIGHTS AS A RESEARCH PARTICIPANT?

Taking part in this study is completely voluntary. You may choose not to take part in this study and can leave this study at any time. Your decision will not have any impact on your participation in other studies and will not result in any penalty or loss of benefits to which you are otherwise entitled.

You will not be giving up any of your legal rights by signing and dating this consent form.

WHAT DO I DO IF I HAVE QUESTIONS OR PROBLEMS?

For questions about this study or a research-related injury, contact:

- Name of the investigator or other study staff
- Telephone number of above

For questions about your rights as a research participant, contact:

- Name or title of person on the Ethics Committee or other organization appropriate for the site
- Telephone number of above

SIGNATURE PAGE

If you have read this consent form (or had it explained to you), all your questions have been answered and you agree to take part in this study, please sign your name and date below.

Participant's Name (print)	Participant's Signature and Date
Study Staff Conducting Consent Discussion (print)	Study Staff's Signature and Date
Witness's Name (print) (As appropriate)	Witness's Signature and Date

ATTACHMENT A: CONSENT FOR USE OF SAMPLES IN OTHER STUDIES

When samples are no longer needed for this study, the ACTG may want to use them in other studies and share them with other researchers. These samples are called “extra samples”. The ACTG will only allow your extra samples to be used in other studies if you agree to this. If you have any questions, please ask.

Identifiers will be removed from your samples and from any private information that has been collected about you. This means that no one looking at the labels or at other information will be able to know that the samples or information came from you.

Extra samples are stored in a secure central place called a repository. Your samples will be stored in ACTG repositories located in the United States or in South Africa.

There is no limit on how long your extra samples will be stored.
[Sites: Revise the previous sentence to insert limits if your regulatory authority imposes them.]

When a researcher wants to use your samples and information, their research plan must be approved by the ACTG. Also, the researcher’s institutional review board (IRB) or ethics committee (EC) will review their plan. *[Sites: If review by your institution’s IRB/EC/RE is also required, insert a sentence stating this.]* IRBs/ECs protect the rights and well-being of people in research. If the research plan is approved, the ACTG will send your samples to the researcher’s location. This means that researchers who are not part of the study team may use your samples without asking you again for your consent.

You will not be paid for your samples. Also, a researcher may make a new scientific discovery or product based on the use of your samples. If this happens, there is no plan to share any money with you. The researcher will likely not have a way of finding you.

You may withdraw your consent for research on your extra samples at any time, and the specimens will be discarded.

Please choose the response that matches what you want by putting your initials in the space provided. Please ask the study staff any questions that you have before you indicate your selection.

<u>Research without Human Genetic Testing</u>
If you agree, your extra samples may be stored (with the usual protection of your identity) and used for ACTG/HVTN/HPTN-approved HIV-related research that does not include human genetic testing.

____ (initials) I understand and I agree to this storage and possible use of my samples

OR

____ (initials) I understand but I do not agree to this storage and possible use of my samples

ATTACHMENT B: SAMPLE INFORMED CONSENT FOR IN-DEPTH INTERVIEWS

SUMMARY

PURPOSE: The purpose of doing in-depth interviews (IDIs) during this study is to learn more about your experiences as a participant in this study.

NUMBER OF PARTICIPANTS: Interviews will be done with up to 25 participants.

RISKS: There may be a risk to your privacy. The study staff will take measures to protect your privacy, such as conducting the IDI in a private area that will allow you to speak comfortably without you or the interviewer being overheard.

BENEFITS: You will not receive any direct benefits. The information learned in the IDIs may help improve the conduct of future studies.

INVITATION TO JOIN IN-DEPTH INTERVIEWS

You are invited to take part in the IDI portion of the A5416/HVTN 806/HPTN 108 (PAUSE) study.

Before you learn more about the IDI portion of the study, it is important for you to know that:
- You do not have to take part in the IDI, if you do not want to – it is optional.
- If you join the IDI but later decide you want to stop, you can stop your participation at any time.
- Whether or not you take part in the IDI, you can still take part in the main study. Your decision not to take part in the IDI will not affect your medical care.

WHAT IS THE PURPOSE OF THE INTERVIEWS?

The purpose of the IDI is to learn how you feel about topics related to this study. We want to learn about your thoughts, opinions, and experiences as a participant in the study. We particularly want to know your thoughts about:
- The risks and benefits of taking part in the study,
- The ways you are protecting your sex partner(s) when you are not using HIV treatment.

What we learn from this study will help us to better understand the experiences participants with HIV have during studies that include stopping HIV treatment.

WHO WILL BE INTERVIEWED?

The IDI will enroll participants from study clinics in South Africa, Botswana, and Malawi that are taking part in the PAUSE study. IDIs will be done with up to 25 participants at up to 5 study clinics.

If you decide to join, you will take part in interviews at 3 study visits:
1. At entry/before stopping HIV treatment
2. At the time of restarting HIV treatment
3. At the end of the study or when you stop being in the study (if you decide to leave early)

WHAT WILL HAPPEN DURING THE INTERVIEW?

The IDIs will be led by a trained member of the study staff that you have not worked with during the main study.

At entry, the IDI asks questions about:
- Your overall feelings about being in the study
- Your reasons for joining and what you expect as a study participant
- Your thoughts about the PAUSE study
- Social support (help from family and friends) you have during the study
- Challenges that you think might come up during the study and how you might handle them
- Your plan for telling your sex partner(s) about being in the study
- Your plans to lower the chances of passing HIV to your partner(s) when you are not using HIV treatment.

At HIV treatment restart, the IDI asks these same questions and some follow-up questions.

At the end of the study, the IDI asks questions about:
- Your overall thoughts and feelings about being in the PAUSE study
- Social support you have access to during the study
- The steps you have taken to protect your sex partner(s) while you were not using HIV treatment until your viral load returned to undetectable after you resumed HIV treatment
- Follow-up questions
- End of study questions

If any of the questions make you feel uneasy or uncomfortable, you or the interviewer may stop the IDI at any time. If any of the questions brings up issues that you would like to talk about later, you can speak to a study counsellor, or we can provide contact and referral information to a counsellor outside the study.

The interviews will take place in a location agreed to by you and the study staff. The location will be private. Each IDI should take about 1 – 1½ hours.

WHAT ARE THE BENEFITS OF BEING IN THE IDI?

You will not receive any direct benefits. The findings and information learned from the IDI may help improve the conduct of future studies.

WHAT ARE THE POTENTIAL RISKS OR DISCOMFORTS WITH THE IDI?

The questions we will ask you may make you feel uneasy or uncomfortable. Your sex partner(s) or others may not like for you to talk about the study and how it affects your home life. The greatest risk may involve your privacy. To protect your privacy, the IDI will be done in a private area that will allow you to speak comfortably without you or the interviewer being overheard.

HOW WILL MY PRIVACY BE PROTECTED?

Every effort will be made to keep your personal information confidential. As we described in the consent form for the main study, your personal information (name, address, phone number) will be protected by the research clinic. Your name and anything else that might identify you will not be used in any publication about this study. A description of this clinical trial will be available on https://www.ClinicalTrials.gov. This Web site will not include information that can identify you. At most, the Web site will include a summary of the results. You can search this Web site at any time.

The entire IDI will be audio recorded. After the interview is finished, the audio recording will be typed (called a transcript). Only the researchers at the site will have access to the audio recording. All information that could identify you will be removed from the transcript, including your name. Data storage and retention related to interviews will follow study, local and/or site requirements. The study team will provide more information to sites regarding retention when appropriate.

Study staff and study monitors can see your study records. Your records may also be reviewed by groups that watch over this study to see that we are protecting your rights, keeping you safe, and following the study plan. These groups include:

- The US National Institutes of Health/Division of AIDS and its study monitors
- The ACTG, the HVTN, and the HPTN
- The US Office for Human Research Protections (OHRP)
- Any regulatory agency that reviews clinical trials
- Other local, US, and international regulatory entities as part of their duties
- Drug companies supporting this study, and their designees

All reviewers will keep your records private and confidential to the extent allowed by law. We cannot guarantee complete privacy.

South African sites: Include the following paragraph(s):
In addition, the recent Protection of Personal Information Act (POPIA) ensures that all South African institutions conduct themselves in a responsible manner when collecting, processing, storing and sharing another entity's personal information by holding them accountable should they abuse or compromise your personal information in any way.

REASONS WHY YOU MAY BE TAKEN OUT OF THE IDI WITHOUT YOUR CONSENT

Your participation in IDI may be ended early without your consent if:

- The main research study or the IDI portion of the study is stopped or cancelled.
- The study staff feels that taking part in the IDIs would be harmful to you.

Tell us if you decide to leave the IDI evaluation of the main study. You are free to leave the study at any time and for any reason. This will not affect your care at this clinic or your legal rights.

ARE THERE COSTS TO PARTICIPATE?

There will be no cost to you for taking part in these IDIs. You will not receive extra payment for being interviewed. You will receive reimbursement for your time, effort, and travel expenses associated with the 3 study visits when the interviews take place.

WHO CAN YOU CONTACT IF YOU HAVE ANY QUESTIONS?

If you have any questions about the main study or the IDI portion of the study or a research-related injury, contact:

- *[Sites, please add name and contact info of investigator or study staff]*

For questions about your rights as a research participant, contact:

- Name or title of person on the Ethics Committee or other organization appropriate for the site
- Telephone number of above

IN-DEPTH INTERVIEW (IDI) SIGNATURE PAGE

A5416 / HVTN 806 / HPTN 108

Short Title: Pausing Antiretroviral Treatment Under Structured Evaluation (PAUSE)

If you have read this consent form (or had it explained to you), all your questions have been answered, and you agree to take part in the IDI, please sign your name and date below.

_____	_____
Participant's Name (print)	Participant's Signature and Date
_____	_____
Study Staff Conducting Consent Discussion (print)	Study Staff's Signature and Date
_____	_____
Witness's Name (print) (As appropriate)	Witness's Signature and Date

We would like to audio record these interviews. If you do not want to be recorded, the interviewer will take notes during your interview. Mark the box with your answer.

_____ (initials) Yes, I consent to being recorded.

_____ (initials) No, I do not want to be recorded.