A5357

A Study of Long-Acting Cabotegravir Plus VRC-HIVMAB075-00-AB (VRC07-523LS) to Maintain Viral Suppression in Adults Living with HIV-1

A Multicenter Trial of the AIDS Clinical Trials Group (ACTG)

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The ACTG Antiretroviral Therapy Strategies Transformative Science Group:	**Timothy Wilkin, MD, Chair**
Protocol Co-Chairs:	**Babafemi Taiwo, MBBS** **Pablo Tebas, MD**
Protocol Vice Chair:	**Leah Burke, MD**
DAIDS Clinical Representative:	**Pablo Francisco Belaunzaran Zamudio, MD, DTM&H, MSc**
Clinical Trials Specialist:	**Jennifer Tiu, MPH**

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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 (US) Health and Human Service regulations (45 CFR 46); applicable U.S. Food and Drug Administration regulations; standards of the International Conference on Harmonization 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., US National Institutes of Health, Division of AIDS) and institutional policies.

Principal Investigator: _____
Print/Type

Signed: _____ Date: _____
Name/Title

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SITES PARTICIPATING IN THE STUDY

This study is a multicenter study that will be implemented at ACTG US clinical research sites (CRSs).

PROTOCOL TEAM ROSTER

Co-Chairs
Babafemi Taiwo, MBBS
Northwestern University CRS
Feinberg School of Medicine
Division of Infectious Diseases
645 North Michigan Avenue, Suite 900
Chicago, IL 60611
Phone: 312-695-4994
Cell Phone: 312-404-0745
Assistant's Phone: 312-926-9877
Fax: 312-695-5088
E-mail: b-taiwo@northwestern.edu

Pablo Tebas, MD
Hospital of the University of Pennsylvania CRS
Division of Infectious Diseases
536 Johnson Pavilion
36th Street and Hamilton Walk
Philadelphia, PA 19104-6073
Phone: 215-615-4321
Phone: 215-349-8092
Fax: 215-615-4360
E-mail: pablo.tebas@uphs.upenn.edu

Vice Chair
Leah Burke, MD
Weill Cornell Chelsea CRS
Weill Cornell Medical College
1300 York Avenue, Box 125
New York, NY 10065
Office Phone: 212-746-4177
Office Fax: 212-746-8852
Work Cell: 203-361-7913
E-mail: leah.burke@ynhh.org

DAIDS Clinical Representative
Pablo Francisco Belaunzaran Zamudio, MD, DTM&H, MSc
DAIDS/NIAID/NIH/HIVRB
Therapeutics Research Program
5601 Fishers Lane
Room 9E40**B**
Rockville, MD 208**5**2
Phone: **240-292-4423**
E-mail: **belaunzaranzapabf@niaid.nih.gov**

Clinical Trials Specialist
Jennifer Tiu, MPH
ACTG Network Coordinating Center
Social & Scientific Systems**, Inc.,**
A DLH Holdings Company
8757 Georgia Avenue, 12th Floor
Silver Spring, MD 20910-3714
Phone: 301-628-3**000**
E-mail: **jennifer.tiu@dlhcorp**.com

Statisticiens
Katherine Rodriguez, MS
Statistical and Data Analysis Center
Harvard T.H. Chan School of Public Health
FXB Building, Room **643A**
Boston, MA 02115
Phone: **617-432-5229**
Fax: **617-432-2843**
E-mail: **krodrigu@sdac.harvard.edu**

Yu (Evelyn) Zheng, PhD
Statistical and Data Analysis Center
Harvard T.H. Chan School of Public Health
FXB Building, Room 615
Boston, MA 02115
Phone: 617-432-2480
Fax: 617-432-2843
E-mail: ezheng@sdac.harvard.edu

Data Managers
Scott Anderson, MS
Frontier Science & Technology Research Foundation, Inc.
4033 Maple Road
Amherst, NY 14226-1056
Phone: 716-834-0900
E-mail: **sanders@frontierscience.org**

Sheldon Tetewsky
Frontier Science & Technology Research Foundation, Inc.
4033 Maple Road
Amherst, NY 14226-1056
Phone: 716-834-0900
E-mail: tetewsky@frontierscience.org

DAIDS Pharmacists
Katherine Shin, PharmD
DAIDS/NIAID/NIH
Pharmaceutical Affairs Branch
5601 Fishers Lane
Room 9D30
Rockville, MD 20852
Phone: 240-627-3047
Fax: 301-402-1506
E-mail: kashin@niaid.nih.gov

Cynthia Parker, PharmD
DAIDS/NIAID/NIH
Pharmaceutical Affairs Branch
5601 Fishers Lane
Room 9D37
Rockville, MD 20852
Phone: 301-761-7199
Fax: 301-402-1506
E-mail: cindy.parker@nih.gov

Pharmacologist
Jennifer Kiser, PharmD, PhD
University of Colorado Hospital CRS Pharmaceutical Sciences
12850 E Montview Boulevard, C238
Aurora, CO 80045
Phone: 303-724-6131
Fax: 303-724-6135
E-mail: jennifer.kiser@cuanschutz.edu

Investigator
Katharine Bar, MD
University of Pennsylvania
502D Johnson Pavilion
3610 Hamilton Walk
Philadelphia, PA 19104-6073
Phone: 215-573-8497
Fax: 215-349-5111
E-mail: bark@upenn.edu

VRC Scientific Advisors
Lucio Gama, PhD
National Institutes of Health
Vaccine Research Center
Building 40, Room 5502
40 Convent Drive
Bethesda, MD 20814
Phone: 301-761-7580
E-mail: lucio.gama@nih.gov

Richard Koup, MD
National Institutes of Health
Vaccine Research Center
Building 40, Room 3502
40 Convent Drive
Bethesda, MD 20814
Phone: 301-594-8585
Fax: 301-480-2779
E-mail: richard.koup@nih.gov

Field Representative
Jenifer Baer, RN
Infectious Diseases Center
Cincinnati CRS
Holmes Division
231 Albert Sabin Way
Cincinnati, OH 45267-0405
Phone: 513-584-8022
Fax: 513-584-8454
E-mail: baerjk@uc.edu

Laboratory Technologist
Sikhulile Moyo, MSc, MPH, PhD
Gaborone CRS
Botswana Harvard Partnership
Bag BO 320
Gaborone 0000
Botswana
South Africa
Phone: 267-3902671 Ext. 2207
Fax: 267-3901284
E-mail: smoyo@bhp.org.bw

Community Scientific Subcommittee (CSS) Representative
Michael Dorosh, MA
University of Colorado Hospital CRS
38 W Maple Avenue
Denver, CO 80223
Phone: 303-777-5737
E-mail: michael@ontheten.org

Industry Representatives
Mark Baker, PhD
ViiV Healthcare
5 Moore Drive
Research Triangle Park, NC 27709
E-mail: mark.x.baker@viivhealthcare.com

Industry Representatives (Cont'd)
David Margolis, MD
ViiV Healthcare
5 Moore Drive
Research Triangle Park, NC 27709
E-mail: david.a.margolis@viivhealthcare.com

Christos Petropoulos, PhD
Monogram Biosciences, Inc.
345 Oyster Point Boulevard
South San Francisco, CA 94080
Phone: 650-866-7439
E-mail: petropc@labcorp.com

Kimberly Smith, MD, MPH
ViiV Healthcare
5 Moore Drive
P.O. Box 13398
Research Triangle Park, NC 27709
Phone: 919-491-2167
E-mail: kimberly.y.smith@viivhealthcare.com

Paul Wannamaker
ViiV Healthcare
5 Moore Drive
Mail Stop 5.3C
Research Triangle Park, NC 27703
E-mail: paul.g.wannamaker@viivhealthcare.com

Laboratory Data Manager**s**
Laura Hovind, **BS, MS**
Frontier Science & Technology Research Foundation
4033 Maple Road
Amherst, NY 14226
Phone: 716-834-0900 Ext. **7468**
Fax: 716-833-0655
E-mail: **hovind**@frontierscience.org

Laboratory Data Managers (Cont'd)

Sarah Wojcinski, BS
Frontier Science & Technology Research Foundation
4033 Maple Road
Amherst, NY 14226
Phone: 716-834-0900 Ext. 7267
E-mail: wojcinski@frontierscience.org

Laboratory Specialists

Deborah Anisman-Posner, BA, CPT
ACTG Laboratory Center at UCLA
11075 Santa Monica Boulevard
Suite 200
Los Angeles, CA 90025
Phone: 310-825-5382
E-mail: danisman@milabcentral.org

Emma Duffy
ACTG Laboratory Center at UCLA
11075 Santa Monica Boulevard
Suite 200
Los Angeles, CA 90025
Phone: 617-407-8713
E-mail: eduffy@milabcentral.org

STUDY MANAGEMENT

All general questions concerning this protocol should be sent to actg.teamA5357@fstrf.org via email. The appropriate team member will respond with a "cc" to actg.teamA5357@fstrf.org. A response should generally be received within 24 hours (Monday-Friday).

Protocol Email Group
Sites should contact the User Support Group at the Data Management Center (DMC) as soon as possible to have the relevant personnel at the site added to the actg.protA5357 email group. Include the protocol number in the email participant line.

- Send an email message to actg.user.support@fstrf.org

Clinical Management
For questions concerning entry criteria, toxicity management, concomitant medications, and coenrollment, contact the Clinical Management Committee (CMC).

- Send an email message to actg.cmcA5357@fstrf.org. Include the protocol number, patient identification number (PID), and a brief relevant history.

Laboratory
For questions specifically related to pharmacologic laboratory tests, contact the protocol team pharmacologist.

- Send an email message to actg.teamA5357@fstrf.org (ATTENTION: **Jennifer Kiser**).

Data Management

- For nonclinical questions about transfers, inclusion/exclusion criteria, electronic case report forms (eCRFs), registration, and other data management issues, contact the data manager. Completion guidelines for eCRFs and participant-completed eCRFs can be downloaded from the FSTRF website at www.frontierscience.org.
- For transfers, reference the Study Participant Transfer SOP 119, and contact **Scott Anderson and Sheldon Tetewsky** directly.
- For other questions, send an email message to actg.teamA5357@fstrf.org (ATTENTION: **Scott Anderson and Sheldon Tetewsky**).
- Include the protocol number, PID, and a detailed question.

Participant Registration
For participant registration questions or problems and study identification number SID lists.

- Send an email message to rando.support@fstrf.org or call the DMC Randomization Desk at 716-834-0900, extension 7301.

DMC Portal and Medidata Rave Problems
Contact DMC User Support:

- Send an email message to actg.user.support@fstrf.org or call 716-834-0900 x7302.

Protocol Document Questions
For questions concerning the protocol document, contact the clinical trials specialist. Send an email message to actg.teamA5357@fstrf.org (ATTENTION: Jennifer Tiu).

Copies of the Protocol
To request a hard copy of the protocol, send an email message to ACTGNCC**@dlhcorp.com**. Electronic copies can be downloaded from 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 email message to Protocol@tech-res.com or call 301-897-1707.

Protocol Activation
For questions related to protocol activation, contact the clinical trials specialist.
- Send an email message to actg.teamA5357@fstrf.org (ATTENTION: Jennifer Tiu).

Study Product
For questions or problems regarding study product, dose, supplies, records, and returns, call Katherine Shin and Cynthia Parker, protocol pharmacists, at 240-627-3047.

Orders for Study-Provided Drugs
Call the Clinical Research Products Management Center (CRPMC) at 301-294-0741.

IND (Investigational New Drug) Number or Questions
The IND number **is** available on the PSWP. For any questions related to the IND submission, contact the DAIDS RSC at Regulatory@tech-res.com or call 301-897-1706.

Expedited Adverse Event (EAE) Reporting/Questions
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.

Phone Calls
Sites are responsible for documenting any phone calls made to A5357 team members.
- Send an email to actg.teamA5357@fstrf.org.

Protocol-Specific Web Page
Additional information about management of the protocol can be found on the protocol-specific web page (PSWP).

GLOSSARY OF PROTOCOL-SPECIFIC TERMS

AE	adverse event
ART	antiretroviral therapy
ARV	antiretroviral
bNAb	broadly neutralizing antibody
CAB	cabotegravir
CAB LA	long-acting cabotegravir
CI	confidence interval
CLIA	Clinical Laboratory Improvement Amendment
eCRF	electronic case report form
IRC	infusion report card
IM	intramuscular
ISR	injection site reaction
LA	long-acting
NNRTI	nonnucleoside reverse transcriptase inhibitor
NRTI	nucleos(t)ide reverse transcriptase inhibitor
PK	pharmacokinetics
PR/RT	protease/reverse transcriptase
PT/INR	prothrombin time/international normalized ratio
RPV	rilpivirine
SAEs	serious adverse events
SDMC	Statistical and Data Management Center
SMC	Study Monitoring Committee
SOC	standard of care
SOE	schedule of **evaluations**
Study drugs	oral CAB for Step 1
	CAB LA and VRC-HIVMAB075-00-AB (VRC07- 523LS) for Step 2
Study treatment	Step 1: oral CAB (oral cabotegravir) and two NRTIs
	Step 2: CAB LA (injectable CAB) and VRC-HIVMAB075-00-AB (VRC07-523LS) via infusions
	Step 3: SOC ART regimen
Viral rebound	confirmed HIV-1 RNA ≥200 copies/mL
Virologic failure	two consecutive HIV-1 RNAs ≥200 copies/mL or last ≥200 copies/mL
VRC	Vaccine Research Center
VRC07-523LS	VRC-HIVMAB075-00-AB, a human monoclonal antibody

SCHEMA

A5357

A Study of Long-Acting Cabotegravir Plus VRC-HIVMAB075-00-AB (VRC07-523LS) to Maintain Viral Suppression in Adults Living with HIV-1

DESIGN

Phase II, single arm, open-label switch study to assess the safety, tolerability, pharmacokinetics, and antiviral activity of long-acting cabotegravir (CAB LA) plus the broadly neutralizing monoclonal antibody, VRC-HIVMAB075-00-AB (VRC07-523LS) in adults living with HIV-1 with suppressed plasma viremia.

At Step 1 entry, all participants will discontinue their current ART regimen except for nucleoside reverse transcriptase inhibitors (NRTIs), and initiate oral CAB. Viral load monitoring will occur at entry and week 4 (and also at week 5 if HIV-1 RNA is 50-199 copies/mL at week 4).

During Step 1, participants tolerating oral CAB plus their current two NRTIs with HIV-1 RNA <50 copies/mL at week 4, or HIV-1 RNA of 50-199 copies/mL at week 4 followed by HIV-1 RNA <50 copies/mL at week 5, will register to Step 2 and receive CAB LA every 4 weeks through week R2+44 plus VRC07-523LS every 8 weeks through week R2+40. Participants in Step 1 who are not eligible for Step 2 entry will be switched to a standard of care (SOC) regimen and followed on study every 2 weeks for a total of 4 weeks and then be taken off study.

Viral load monitoring in Step 2 will occur every 2 weeks until week R2+8 and then every 4 weeks until week R2+48. All participants who enter Step 2 will complete the week R2+48 visit; this visit will be used to confirm virologic rebound in those with HIV-1 RNA ≥50 copies/mL at week R2+44.

For participants who have a confirmed HIV-1 RNA ≥200 copies/mL during Step 2, or confirmed HIV-1 RNA ≥50 copies/mL at week R2+44 and ≥200 copies/mL at week R2+48, genotypic testing will be performed for protease/reverse transcriptase (PR/RT) and integrase resistance. In addition, samples from the failure confirmation visit and pre-ART or entry (if available) will be tested for viral clonality, integrase resistance, and VRC07-523LS neutralization resistance.

All participants who received any dose of CAB LA or VRC07-523LS in Step 2 will register to Step 3 (the 48-week follow up on SOC regimen) at the final study visit in Step 2 or at premature treatment discontinuation.

DURATION

Up to 101 weeks (approximately 5 weeks in Step 1, then 48 weeks in Step 2, followed by 48 weeks in Step 3)

SAMPLE SIZE

74 participants

POPULATION

Individuals living with HIV-1 ≥18 years of age who have current CD4+ T-cell count ≥350 cells/mm^3 and have maintained viral suppression (<50 copies/mL) on a conventional ART regimen (i.e., a boosted protease inhibitor, an NNRTI, or an integrase inhibitor, plus two NRTIs) for at least 2 years prior to entry and have been clinically stable on their current three-drug regimen for at least 8 weeks prior to study entry with no history of a switch due to virologic failure. Eligibility requires documentation of susceptibility to VRC07-523LS.

REGIMEN

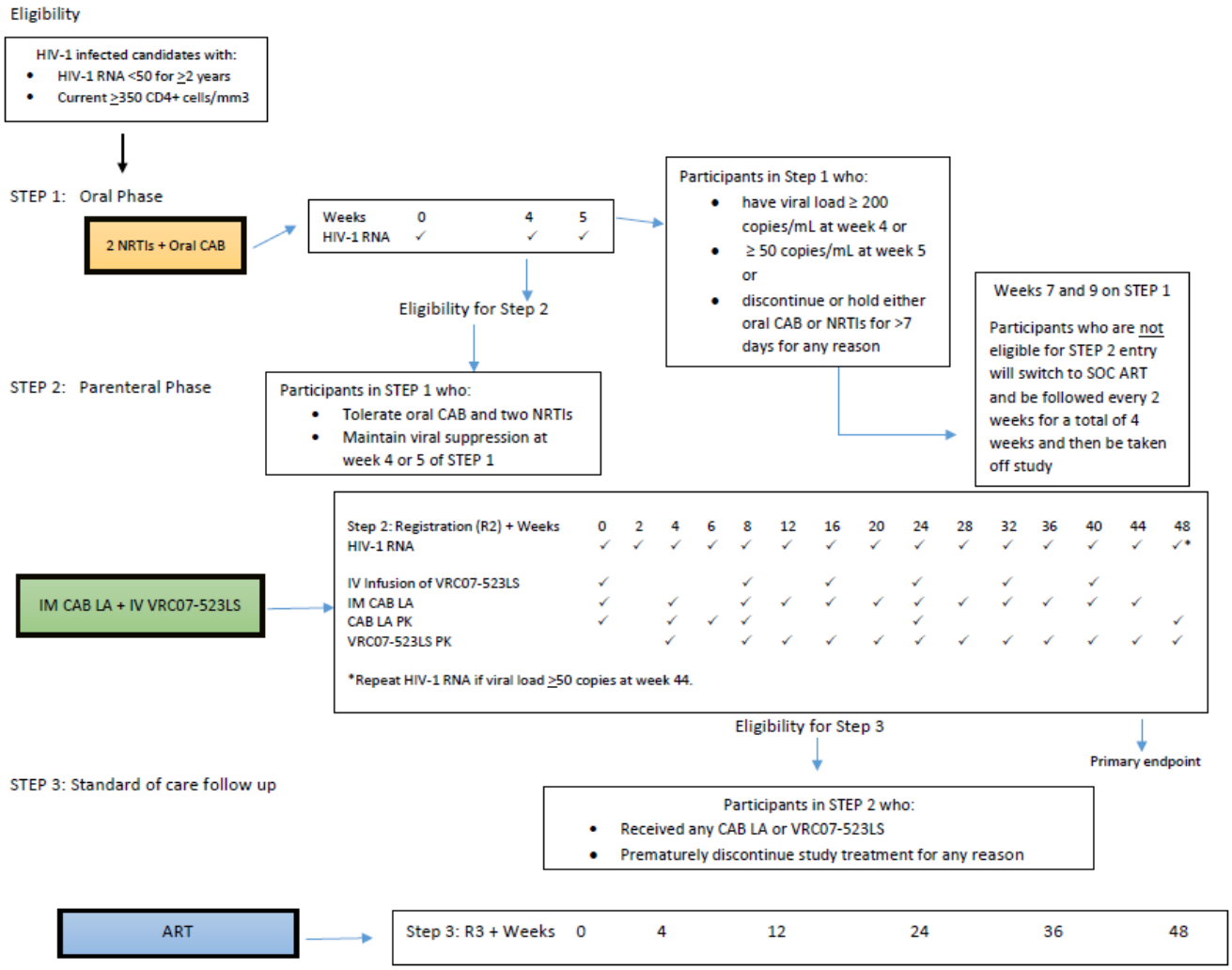
In Step 1, all participants will receive oral CAB 30 mg daily plus their current two NRTIs.

NOTE: For participants currently on Truvada (emtricitabine/tenofovir disoproxil fumarate), or Descovy (emtricitabine/tenofovir alafenamide), or Epzicom (abacavir/lamivudine) without continued access, reimbursement for these drugs will be provided in Step 1.

At entry into Step 2, participants will stop their oral CAB and NRTIs and will receive VRC07-523LS infusion (40 mg/kg) plus CAB LA intramuscular (IM) injection (600 mg). Post entry in Step 2, participants will receive CAB LA IM injection (400 mg) every 4 weeks through week R2+44 plus VRC07-523LS infusion (40 mg/kg) every 8 weeks through week R2+40.

At the last visit in Step 2 (week R2+48) or at premature study discontinuation, all participants who received any CAB LA or VRC07-523LS will enter Step 3 and switch to SOC ART for approximately 48 weeks.

SCHEMA (Cont'd)



1.0 HYPOTHESIS AND STUDY OBJECTIVES

1.1 Hypothesis

The combination of long-acting cabotegravir (CAB LA) and VRC-HIVMAB075-00-AB (VRC07-523LS) is safe and will prevent viral rebound (confirmed HIV-1 RNA ≥200 copies/mL) in individuals who have achieved suppression with conventional antiretroviral therapy (ART).

1.2 Primary Objectives

1.2.1 To evaluate the safety and tolerability of the combination of parenteral VRC07-523LS plus CAB LA in adults living with HIV-1 with well-controlled viral replication

1.2.2 To evaluate the virologic efficacy of the combination of parenteral VRC07-523LS plus CAB LA to prevent viral rebound in adults living with HIV-1 with well-controlled viral replication

1.3 Secondary Objectives

1.3.1 To determine the pharmacokinetic (PK) parameters of the combination of VRC07-523LS and CAB LA and their associations with viral rebound in adults living with HIV-1

1.3.2 To evaluate evidence of anti-idiotype antibodies against VRC07-523LS in samples collected from representative time points throughout the study

1.3.3 To evaluate the safety and tolerability of oral CAB

1.4 Exploratory Objective

1.4.1 To compare genotypic and phenotypic characteristics (viral clonality, neutralization resistance, and integrase resistance) from baseline samples (entry or pre-ART) and failure HIV-1 isolates in individuals who experience viral rebound while receiving the combination of VRC07-523LS and CAB LA.

1.4.2 To evaluate the range of Monogram PhenoSense assay results and its correlation with available demographic and clinical variables for all participants screened.

2.0 INTRODUCTION

2.1 Background

Long-Acting Cabotegravir

Cabotegravir (CAB), formerly GSK1265744, a structural analogue of dolutegravir (DTG), is an integrase strand transfer inhibitor in development in both oral and long-acting formulations. CAB LA is a nanosuspension with optimized solubility and particle size that allows infrequent dosing. Currently in Phase III clinical trials, it was initially selected for development based on its potential for a high genetic barrier to resistance and a PK profile that allows low-dose, once-daily, oral dosing or monthly to bi-monthly parenteral dosing using a nanosuspension formulation. CAB LA PK has been evaluated in Phase 1 studies following repeat administration in individuals without HIV. Following a loading dose of 800 mg intramuscular (IM) and three monthly (every 28 days) maintenance doses, the third monthly 200 mg subcutaneous (SC), 200 mg IM and 400 mg IM injections achieved geometric mean plasma C_{tau} of 1.61μg/mL, 1.72 μg/mL, and 3.22 μg/mL—9.7-, 10-, and 19-fold above the PA-IC_{90} (0.166 μg/mL), respectively [Spreen 2014a; Spreen 2014b; ViiV Healthcare 2014]. Following two quarterly 800 mg IM doses, geometric mean plasma GSK1265744 C_{tau} was 1.11 μg/mL, 6.7-fold above the PA-IC_{90}.

In the LATTE study for HIV treatment, CAB plus two nucleos(t)ide reverse transcriptase inhibitors (NRTIs) once-daily had potent antiviral activity, and the combination of CAB plus rilpivirine once-daily provided antiviral activity similar to efavirenz plus dual NRTIs through week 96 [Margolis 2015]. The 30 mg once daily dose of oral CAB was selected for further development. The safety and efficacy of the combination of CAB LA and LA rilpivirine every 4 or 8 weeks has been demonstrated in the LATTE-2 study [Margolis 2016]. CAB plus rilpivirine (RPV) LA dosing every 4 weeks was selected for the ATLAS and FLAIR Phase III trials [Orkin 2019; Swindells 2019], while both the 4- and 8-week doses are being investigated in ATLAS-2M.

The absorption rate of CAB LA is variable with slower absorption reported in females (35.2% relative to males) and with increasing body mass index [Ford 2014], perhaps due to differences in body fat, lean muscle, and physical activity. While there is a significant difference in absorption rate for males and females, steady state trough concentrations in males and females are similar for similar sized individuals [Landovitz 2017]. CAB has a low potential for drug-drug interactions; CAB is primarily metabolized by uridine diphosphate glucuronosyltransferase (UGT) 1A1 with a minor contribution from UGT1A9 [Reese 2014], and is mainly excreted in feces as unchanged drug [Culp 2014].

Residual concentrations of CAB will remain in the systemic circulation of participants for prolonged periods, more than 1 year in some participants [ÉCLAIR Study 2014] despite stopping treatment (e.g., for tolerability issues or treatment failure). Participants discontinuing CAB LA regimen may be at risk for developing HIV-1 resistance to CAB many weeks after discontinuing injectable therapy. In order to mitigate this risk, alternative ART regimens will be prescribed within 4 weeks after participants stop CAB LA. This is anticipated to result in maintenance of suppression or rapid resuppression of HIV-1 RNA thus minimizing the risk of emergent resistance. The participants in this

study who discontinue CAB LA for any reason will be monitored for approximately 48 weeks from the time of the last CAB LA injection.

Suicidality Monitoring

While CAB remains an investigational product, there has not been a direct association between CAB and suicidality, or a product-associated risk, identified to date. The inclusion of suicidality screening in ongoing CAB studies is primarily intended to create a comprehensive data set on suicidality at the time of product submission, in order to inform regulatory agencies in their review of products being developed for populations at elevated risk of suicidality, including people living with HIV (PLWHIV). This approach is highlighted by the absence of prospective suicidality evaluations in studies of CAB for PrEP, among individuals without HIV. In addition to the value of prospective suicidality monitoring to the overall programmatic analysis of CAB, there is a secondary benefit of prospective suicidality monitoring to individual participants with HIV in clinical trials to ensure that depression and suicidality is detected when present. It is noted, however, that there may be several approaches to this individual participant management, which can also be assumed to be part of the routine medical management. The team is aware that suicidality is being assessed in A5359 (NCT03635788), but in part, this is a larger study, in a different population of individuals who have not been effectively suppressed or routinely followed in clinical care. For A5357 specifically, this study is not intended to be part of the CAB submission package and includes participants who are more effectively tied into care, and have remained suppressed, per study inclusion criteria. With these facts noted, the team proposes use of standard and routine medical care already being offered to individuals in HIV care as the primary means for monitoring suicidality and depression in A5357. As with all studies, adverse events (AEs) of depression and suicidality that emerge while on study will be captured in the study record.

VRC-HIVMAB075-00-AB (VRC07-523LS)

The Vaccine Research Center at the National Institutes of Health (National Institute of Allergy and Infectious Diseases) developed VRC01LS and VRC07-523LS, highly potent and broadly neutralizing HIV-1 human monoclonal antibodies (MAbs) targeted against the HIV-1 CD4+ binding site [Rudicell 2014]. The predecessor of VRC01LS and VRC07-523LS, VRC01, is in clinical trials under IND 113611 for prevention indication, and under IND 126001, IND 126664, and IND 133017 for therapeutic indication. VRC01 was originally discovered in an individual who had lived with HIV-1 for more than 15 years and whose immune system controlled the virus without anti-retroviral therapy [Wu 2012]. The VRC01 sequence was modified by site-directed mutagenesis to increase its binding affinity for the neonatal Fc receptor (FcRn) and the resulting antibody was designated VRC01LS. The LS designation specifies methionine to leucine (L) and asparagine to serine (S) (M428L/N434S, referred to as LS) changes within the C- terminus of the heavy chain constant region far outside of the antigen-binding site [Zalevsky 2010]. Other than the two amino acid difference, VRC01LS is identical to VRC01. VRC01LS has an extended half-life in both serum and mucosal tissue compared to VRC01, persists at higher concentrations in mucosal tissues, and has demonstrated improved protection against primate simian-human immunodeficiency virus (SHIV) infection [Ko 2014]. VRC01LS is currently in clinical trials for PK and safety evaluations in adults without HIV

under IND 125494. The VRC07 (wild-type) heavy chain was identified by 454 deep sequencing based on its similarity to the VRC01 MAb and paired with the VRC01 (wild-type) light chain. The mutations that together define the 523 designations are a glycine to histidine mutation at residue 54 of the heavy chain, a deletion of the first two amino acids, glutamate and isoleucine, from the light chain, and a valine to serine mutation at the third amino acid residue of the light chain. Like VRC01LS, the LS mutation of VRC07-523LS was introduced by site-directed mutagenesis to increase the binding affinity for the neonatal FcRn, resulting in increased recirculation of functional IgG [Ko 2014; Zalevsky 2010], thus increasing plasma half-life.

VRC07-523LS Safety Data

As of January 15, 2018, the VRC 605 study is fully enrolled. Twenty-five (25) of 26 participants received at least one dose of VRC07-523LS (12 SC and 25 IV administrations). One participant withdrew from the study prior to receiving the study product. There have been no serious adverse events (SAEs) and no study safety pauses for AEs. Overall, 15 of 25 participants who received the product (60%) have had at least 1 AE with the maximum severity being Grade 1 for 7 participants and Grade 2 for 6 participants, Grade 3 for 1 participant and Grade 4 for 1 participant. The Grade 3 AE was for an elevated creatinine 56 days after the last product administration. This was most likely related to dehydration following exercise. The creatinine value was determined to be Grade 3, based on the DAIDS Table for Grading the Severity of Adult and Pediatric Adverse Events (DAIDS AE Grading Table) parameter of an increase of 1.5 to 2 times the baseline value, which was still well within the institutional normal range. The Grade 4 AE was for elevated liver enzymes likely related to starting a concomitant medication, fluoxetine, known to cause hepatoxicity, and not related to VRC07-523LS. VRC07-523LS administrations were discontinued for this participant due to the concomitant illness. While the participant was being followed for safety, liver enzymes tests fluctuated again after starting citalopram, which reinforced the assumption that the event was most likely caused by an underlying sensitivity to selective serotonin reuptake inhibitor (SSRI) medications. This Grade 4 laboratory abnormality was not considered life-threatening as it was not clinically significant as there was no hospitalization, jaundice, coagulopathy, bleeding, or ascites. Six mild or moderate AEs were assessed as related to study product including mild dizziness, four occasions of infusion reactions (one mild and three moderate, reported for two participants), and mild abdominal pain. All AEs assessed as related to the study product have resolved without residual effects.

Two participants developed infusion reactions shortly after IV product administration. Symptoms were typical of infusion reactions observed with other MAbs [Patel 2017]. No atypical symptoms or delayed symptoms were seen. Specifically, one participant enrolled in the 40 mg/kg IV group experienced a moderate infusion reaction with chills, rigors, fever, myalgia, and headache beginning 15 minutes after completion of the infusion. The participant was treated with acetaminophen and ibuprofen. All symptoms resolved within 12 hours. Another participant in the 20 mg/kg IV group experienced three separate infusion reactions (n=2 moderate, n=1 mild) after each product infusion. The participant experienced nausea, chills, rigors, malaise, tachycardia, headache, myalgia, and arthralgia. Symptoms began 15 minutes to 1 hour after completion of each product administration and completely resolved within 12 hours. The participant was treated with

acetaminophen and ibuprofen. Overall, product administrations have been generally well tolerated with no unexpected reactions.

For solicited local reactions in the week after VRC07-523LS administrations, one of 17 participants (5.9%) who received the product by IV administration reported mild bruising at the administration site, and 5 of 8 participants (62.5%) who received the product SC reported mild pain/tenderness at the injection site [Investigator's Brochure, Version 4.0, dated February 26, 2018; VRC07-523LS VRC-HIVMAB075-00-AB CONFIDENTIAL 45].

For solicited systemic AEs reported 3 days after product administration, 4 of 17 participants (25%) receiving VRC07-523LS IV reported mild or moderate systemic reactogenicity symptoms. The reported symptoms were malaise (n=2 mild, n=1 moderate), myalgia (n=2 mild, n=1 moderate), mild headache (n=2), and moderate chills (n=2). Five (5) of 8 participants (62.5%) receiving VRC07-523LS SC reported mild systemic reactogenicity symptoms: malaise (n=3), myalgia (n=2), headache (n=3), chills (n=1), nausea (n=1), and joint pain (n=2). Refer to the IB for more details on the VRC07-523LS safety data.

Antiviral Effect of VRC07-523LS

Preliminary viral load data obtained from ACTG study A5378 (NCT02840474) in nine viremic adults living with HIV-1 demonstrated that VRC07-523LS has an in vivo virological effect on viral load when administered as a single 40 mg/kg IV dose [Chen 2019]. These participants were not on ARVs when enrolled into the study and did not start ARVs during the first 14 days of data collection. Eight of the 9 participants had a ≥1.2 $\log_{10}$ copies/mL maximum decrease in viral load. Per the Department of Health and Human Services (DHHS) guidelines, a ≥0.5 $\log_{10}$ copies/mL decrease in viral load is considered to be a positive response to ARV [Panel on Antiretroviral Guidelines for Adults and Adolescents 2018]. Evaluation of the VRC07-523LS antiviral effect continues; data analysis will be conducted to evaluate a timeline, magnitude of decrease in viral load data, and utility of drug sensitivity testing using the monogram assay in predicting virological responses.

PhenoSense Neutralizing Antibody Assay

VRC07-523LS neutralizing antibody susceptibility will be determined using the PhenoSense neutralizing antibody assay platform pioneered by Monogram BioSciences, Inc. This assay generates HIV pseudovirions that express envelope proteins that are representative of the quasispecies of either the cell-associated HIV DNA or circulating plasma HIV RNA. This will enable the interrogation of VRC07-523LS neutralizing antibody susceptibility of PBMC-derived virus from aviremic individuals. Procedures are derived from a well-established assay that has been utilized extensively to evaluate autologous and vaccine elicited neutralizing antibody sensitivity of virions pseudotyped with a population of envelope proteins that are representative of the HIV RNA quasispecies in circulating plasma virus from viremic individuals [Richman 2003].

These methods were used in ACTG NWCS 413 to determine neutralization sensitivity of plasma viruses from treatment naïve individuals (N=61) and PBMC of the same individuals after 1 and 3 years of suppression against a number of broadly neutralizing

monoclonal antibodies (bNAbs) in clinical development. Results showed that VRC07-523LS was potent against many participants' viruses. For PBMC samples from 1 year of ART, median IC50 was 0.135 µg/mL (Q1, Q3 of 0.078, 0.247) and median IC80 was 0.514 µg/mL (Q1, Q3 of 0.245, 0.984). The correlate of clinical activity in this treatment scenario is not known. Eighty-five percent (52/61) of the NWC participant virus swarms fell under the threshold of IC80 <1 µg/mL, and this value is more than 50- to 100-fold over the plasma levels of VRC07-523LS achievable by the proposed dosing strategy. Thus, an IC80 screening cut-off of 1 µg/mL for PBMC-derived virus has been selected to balance the desire for potency of the bNAb and reasonable accrual and enrollment of this study. Of note, Monogram's reporting process is based on IC50 levels. Accordingly, an IC50 of ≤0.25 µg/mL, which correlates with an IC80 of 1 µg/mL, will be used for screening. In addition, we have added a second enrollment condition of a maximum percent inhibition >98% (meaning that the virus was neutralized >98% at 50 µg/ml concentrations of VRC07-523LS). This additional criterion will likely exclude very few additional participants, so will pose minimal logistical challenges, but may help exclude a few individuals who may not be completely sensitive to the bNAb.

2.2 Rationale

Two-Drug Maintenance ART

Conventional antiretroviral (ARV) regimens include the combination of three active oral ARV drugs. However, recent and ongoing studies have demonstrated the safety and effectiveness of several two ARV drug combinations.

The GARDEL study demonstrated that dual therapy with lopinavir/ritonavir plus lamivudine was non-inferior to triple therapy after 48 weeks of treatment, regardless of baseline HIV viral load. The dual therapy regimen showed fewer discontinuations due to safety and tolerability, and virologic failure did not result in protease inhibitor resistance development, preserving a wide range of drugs for second-line ARV therapy [Cahn 2013].

Two Phase 3 trials (SWORD) enrolled 1,024 participants with viral suppression for at least 1 year and no history of virologic failure. Participants were randomized to stay on their combination ART regimen or to switch to a regimen of once-daily DTG plus RPV. Virologic suppression was maintained in 95% to 96% of the participants in both arms at 48 weeks. A fixed-dose combination of these products has recently been approved [Llibre 2017].

In the LATTE study, the combination of oral CAB plus oral rilpivirine once daily provided antiviral activity similar to efavirenz plus dual NRTIs through week 96 and led to fewer side effects [Margolis 2015]. Findings from the phase 2b LATTE-2 trial demonstrated comparable viral suppression rates (plasma HIV-1 RNA <50 copies/mL) at 48 weeks between CAB LA plus long-acting rilpivirine (RPV LA) dosed every 8 weeks (92%) or every 4 weeks (91%) versus three drug oral regimen of investigational CAB plus NRTIs (89%). The combination of these long-acting injectable drugs was safe and well-tolerated [Margolis 2016b]. Efficacy of this combination has been demonstrated through week 96 in LATTE 2 [Margolis 2017]. The combination of CAB LA and RPV LA has also

been shown to maintain viral suppression through week 48 in treatment-naïve and virologically suppressed individuals in the FLAIR and ATLAS studies, respectively [Orkin 2019; Swindells 2019; ATLAS Study (ViiV Healthcare) 2018; FLAIR Study (ViiV Healthcare 2018)].

In addition, the ongoing GEMINI studies demonstrated the efficacy of the combination of another two ARVs, DTG and lamivudine at week 48, in treatment naïve participants [Cahn 2019], and the results of the same regimen in suppressed participants are awaited [TANGO].

Compared with three-drug ART, regimens containing two drugs have the potential to decrease medication burden, cost, and toxicity.

CAB LA Plus VRC07-523LS

Successful engineering of a new generation of bNAbs has created an opportunity for novel exploration of bNAb plus ARV drug(s) as well as bNAb(s) plus bNAb(s) combinations for HIV control. In addition to direct antiviral effects, it is possible that some bNAbs could have an effect on the size of the HIV reservoir through antibody-dependent cell-mediated viral inhibition or antibody dependent cell-mediated cytotoxicity (ADCVI/ADCC), which will be enhanced by using this combination approach. Here we propose to investigate the combination of CAB LA and VRC07-523LS.

The current design also allows for a careful PK characterization of the levels of both compounds required to prevent the re-emergence of viremia. Sequencing of rebound virus will provide insights into variants resistant to the intervention. In addition, in-vitro testing of viruses collected pre-ART (or at study entry) and after virologic failure will yield important information about possible viral factors associated with eventual treatment failure, particularly viral resistance to neutralization by VRC07-523LS.

VRC07-523LS Dose of 40 mg/kg IV Q8 weeks

The pharmacokinetics of VRC07-523LS was modelled using data obtained following its administration to adults without HIV in a Phase 1 dose-escalating trial (NCT03015181 [Gaudinski 2018]). The modelling reflected the observed data (Figure 2.2-1).

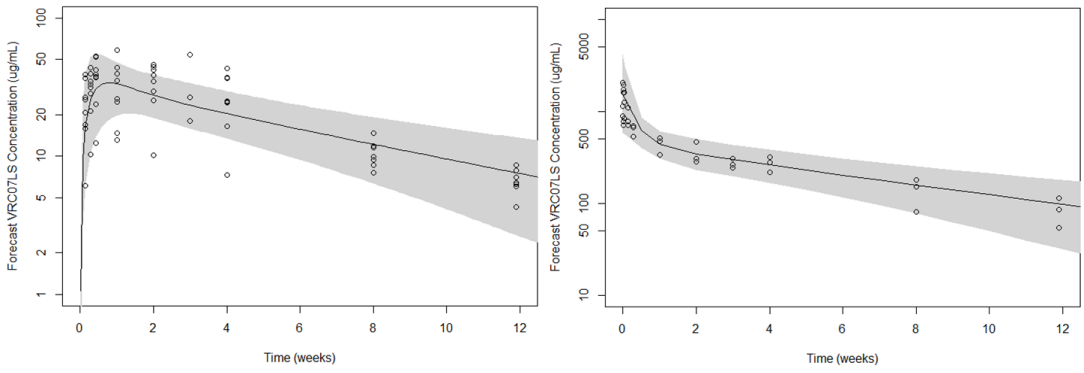


Figure 2.2-1: VRC07-523LS Serum Concentrations following Administration of 5 mg/kg SC and 40 mg/kg IV Overlaid with Median Model Predictions (shading represents the 90% prediction interval).

Predicted median concentrations following a 40 mg/kg IV infusion were 157 [94 –231] µg/mL and 98 [44 - 163] µg/mL at 8 and 12 days respectively. A review of prior bNAb data indicated that an effective serum trough level would need to be equivalent to or exceed a clinical isolate IC90 value (≅9 x IC50) and would have a log-normal standard deviation of 1.7.

The analysis of prior bNAb clinical effectiveness data, pseudovirus neutralization and clinical isolate neutralization suggested that the effective trough would range from the clinical isolate IC90 to >5x IC90 (equivalent to 20x and 100x the pseudovirus neutralization IC50) and that the variance in the in vitro data needed to be factored into the trough.

Trial simulations were performed using:

- The PK
- The PK variance
- Potency (either isolate IC90 or pseudovirus IC50), and
- The variance in potency

to determine the probability that a trial would have >90% of participants with VRC07-523LS concentrations above the nominal target trough concentration (a trial Probability of Success (POS)). Using this approach, the target troughs approximated the 90th percentile of the clinical isolate IC90 (or pseudovirus IC50) incorporating any multiplicative factor.

A 40 mg/kg IV infusion assessed against the clinical isolate IC90 was predicted to have a PoS of 96% [84-100] for a 12-week interval. This predicted PoS declined with reduced dose (30 mg/kg Q12W = 93% [77-99]) and increased with a shorter interval (40 and 30 mg/kg ~99% [90-100]). The PoS was also evaluated against a more stringent threshold of 5x IC90 (reflective of a fold multiplication observed following modelling of prior clinical efficacy data). The 40 mg/kg IV infusion assessed against the 5x clinical isolate IC90 was predicted to have a PoS of 68% [47-86] for a 12-week interval. This predicted PoS for 40 mg/kg IV increased with a shorter Q8W interval to 91% [72-98]).

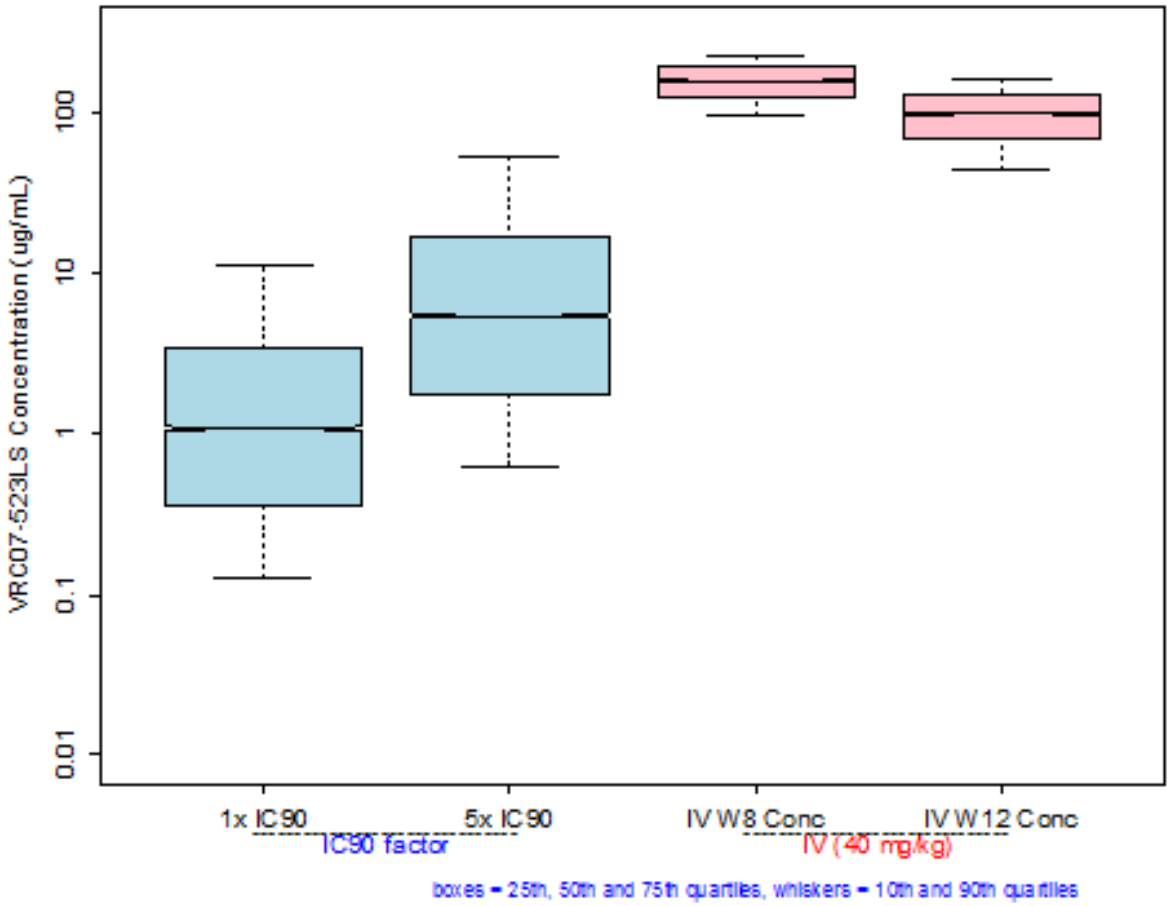


Figure 2.2-2: The VRC07-523LS Clinical Isolate Potencies (Thresholds) and 40 mg/kg IV Trough Concentrations following Q8W and Q12W Administration – Used within the Model to Determine the Probability of a Trial Having >90% of Participants with VRC07-523LS Concentrations above the Nominal Target Trough Concentration.

A dose of 40 mg/kg Q8W was chosen based on the modelling. Whilst a Q12W interval may be sufficient, a Q8W regime provides leeway for any increase in threshold whilst we rely on modelling and do not have any clinical data. This dose and interval provided the most robust treatment over the thresholds evaluated.

Non-inclusion of Control Arms

In lieu of a triple ART SOC control arm, we determined the virologic failure rate on conventional triple ART rate in a population similar to the participants who will enroll in A5357. Specifically, among 2059 participants who suppressed to <50 copies/mL for 96 weeks in two completed ACTG naïve trials (A5257, NCT00811954 and A5202, NCT00118898) and subsequently remained on conventional ART, the cumulative

probability of virologic failure (two consecutive HIV-1 RNAs ≥200 copies/mL or last ≥200 copies/mL) using Kaplan-Meier methods was 1%. By week 192 (when participants had a median of 10 HIV-1 RNA measurements), this cumulative probability of virologic failure was 5%. These estimates were used in the study's statistical considerations.

A CAB LA monotherapy arm was not included because there is already evidence that integrase inhibitor monotherapy is not non-inferior to SOC [Hocqueloux 2019]. The A5357 team agreed with the ACTG's Scientific Agenda Steering Committee's position that a CAB monotherapy control arm should not be included in A5357, recognizing that this design limits our ability to determine the relative contribution of CAB LA or VRC07-523LS to the study results.

Rationale for Virologic Failure Definition

Typically the ACTG defines virologic failure as a confirmed HIV-1 RNA ≥200 copies/mL. This is because previous ACTG studies have shown there is some variability at the lower limit of quantification for the standard virologic assays [Lalama 2015], and that confirmed values of low level viremia are less likely to be associated with future virologic failure [Ribaudo 2009]. Therefore, the primary efficacy outcome of this study will be confirmed HIV-1 RNA ≥200 copies/mL, and a secondary outcome measure will be confirmed HIV-1 RNA ≥50 copies/mL. Additionally, if the primary outcome was changed to a confirmed HIV-1 RNA ≥50 copies/mL, the historical failure probability used in the sample size calculation would be almost doubled, and to obtain a confidence interval with the same upper bound as calculated for this study, would inflate the sample size to a larger degree and render the study **in**feasible.

Rationale for CAB LA Dosing Interval of Q4 Weeks Versus Q8 Weeks

The CAB Q4W dosing regimen achieves the highest exposure of dosing regimens studied in Phase 2 and 3 trials (Q4W or Q8W), and clinical efficacy of CAB LA Q4W as part of a two-drug regimen has been confirmed in Phase 3 studies, whereas Phase 3 results for CAB LA Q8W as part of a two-drug regimen are not yet available.

1) Efficacy: Study 200056 (LATTE-2) is an ongoing, Phase 2b dose-ranging study evaluating the long-term efficacy and safety of a two-drug, two-class combination of CAB LA plus RPV LA given Q4W or Q8W, as compared to an oral three-drug regimen, for maintenance of virologic suppression in treatment-naive adults living with HIV. Week 96 results (Table 2.2-1 below) were supportive of further evaluation of both with the Q4W regimen in the Phase 3 ATLAS and FLAIR studies as well as the Q8W regimen in the Phase 3 ATLAS-2M study. Participants completing the 96-week Injection Phase remained on their randomized LA regimen (either Q4W or Q8W) during the Extension Phase (post Week 96), and those participants randomized to the oral comparator arm were allowed transition to either LA regimen at Week 96. At Week 160, high proportions of participants remained virally suppressed for both CAB LA plus RPV LA Q4W and Q8W [Margolis 2018].

Table 2.2-1: Summary of Study Outcomes (<50 copies/mL) at Weeks 48 and 96 — Snapshot (MSDF) Analysis (ITT-ME Population) in LATTE-2

Endpoint (Week)	Outcome	Q8W IM N=115 n (%)	Q4W IM N=115 n (%)	CAB 30 mg plus ABC/3TC N=56 n (%)	Subtotal IM N=230 n (%)
W48	Virologic Success, n (%)	106 (92)	105 (91)	50 (89)	211 (92)
	Virologic Failure, n (%)	8 (7)	1 (<1)	1 (2)	9 (4)
W96	Virologic Success, n (%)	108 (94)	100 (87)	47 (84)	208 (90)
	Virologic Failure, n (%)	5 (4)	0	1 (2)	5 (2)

Maintenance therapy with Q4W dosing of CAB LA plus RPV LA was recently reported to be non-inferior to standard three-drug oral therapy at Week 48, using the FDA snapshot algorithm [Orkin 2019; Swindells 2019]. Efficacy results from the Q8W dosing used in ATLAS-2M are expected at a later date.

2) PK: The Q4W dosing of CAB that we have selected is also supported by PK data. Figure 2.2-3 shows the concentration-time data for Q4W and Q8W in LATTE-2 demonstrating higher Cτ with Q4W dosing.

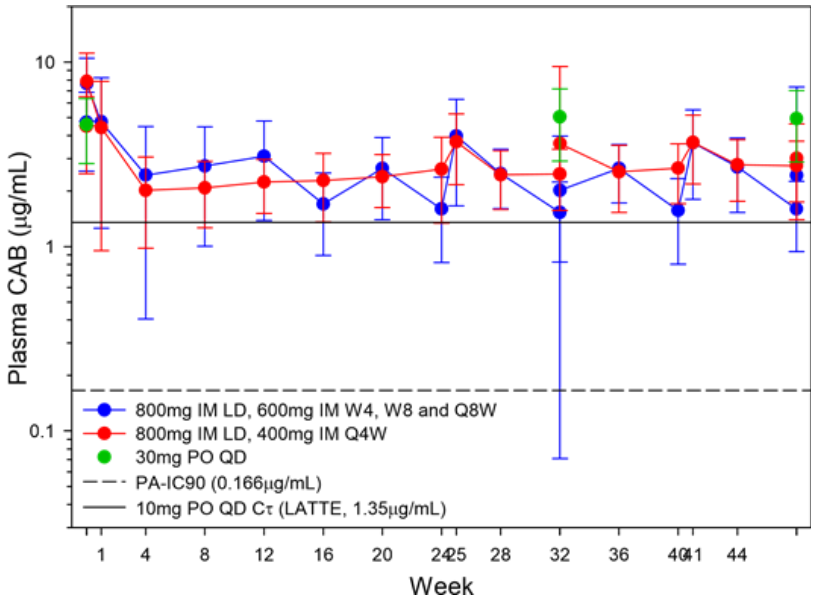


Figure 2.2-3: Observed Mean (SD) Concentration-Time Data following CAB LA Q8W and Q4W and Cτ following 30 mg PO QD through Week 48 (200056, LATTE-2)

Both pre-dose and 2 hour post-injection concentrations are shown at Time Zero, Week 32, and Week 48.

Of note, the loading dose used in LATTE-2 is slightly different from that used in the CAB Phase 3 studies and what is proposed in A5357. The predicted CAB profile for the proposed Q4W regimen based on population PK modelling is shown in Figure 2.2-4, demonstrating CAB levels well above 4X PA IC90 throughout the dosing period.

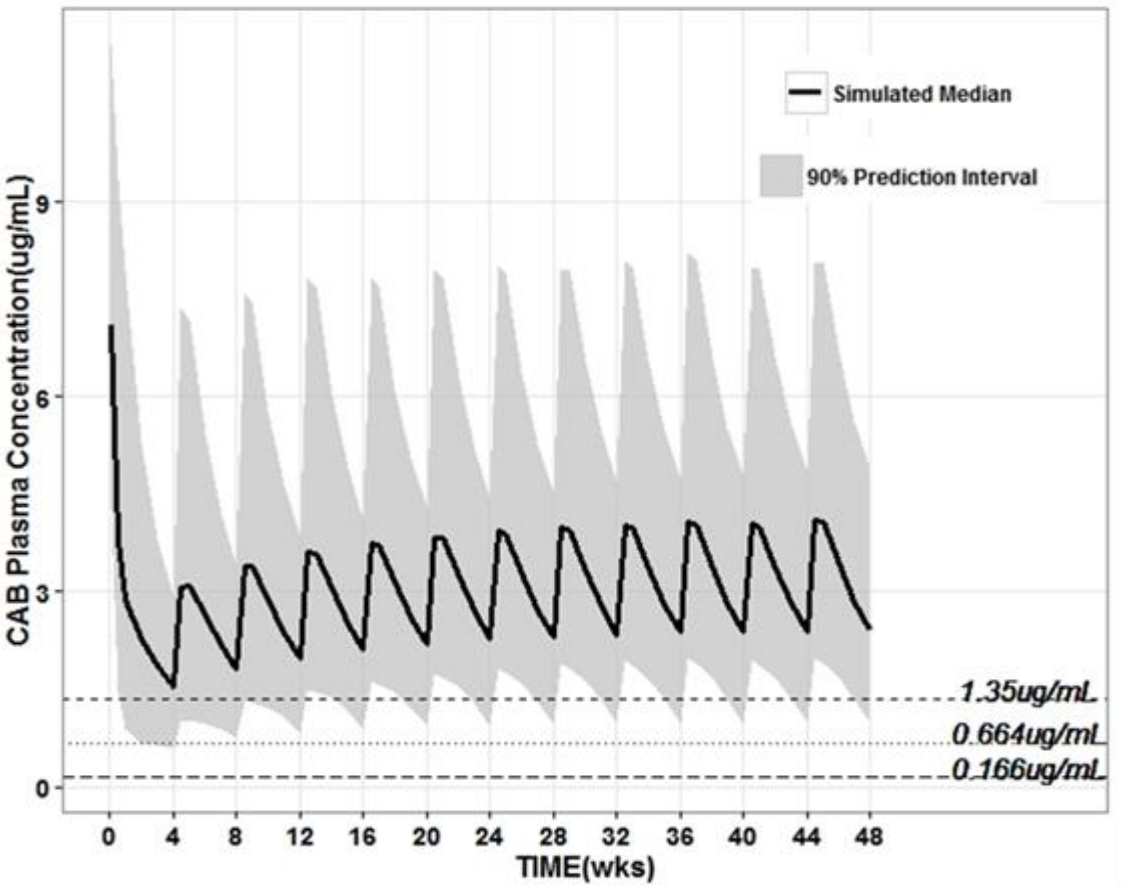


Figure 2.2-4: Simulated* Median (90% Prediction Interval [PI]) CAB Plasma Concentrations versus Time for the CAB LA Q4W Regimen (600 mg IM Day 1, then 400 mg IM Q4W thereafter)

* NOTE: Current simulations based on interim plasma concentration dataset.

^Study schedule of activities includes a 4-week oral lead in. Therefore, Day 1 = day of first injections (Week 4b study visit); Week 4 = second injections (Week 8 study visit).

Medium dashed line at 1.35 µg/mL corresponds to the geometric mean Cpa-concentration following oral CAB 10 mg once daily (LATTE) and is equivalent to 8x PA-IC_{90}.

Dotted line at 0.664 µg/mL corresponds to 4x PA-IC90.

Rationale for Step 3 SOC Follow-up

All participants who receive any dose of CAB LA or VRC07-523LS or prematurely discontinue study treatment in Step 2 will proceed to Step 3, which is the SOC follow-up, beginning at the final study visit in Step 2 or at premature treatment discontinuation. We have included a prolonged follow-up phase because data have shown that CAB LA has a long pharmacologic tail after IM administration (drug can be detected up to 52 weeks after administration in a small proportion of study participants). Current and planned trials of CAB LA include prolonged follow-up phases after last administration of CAB LA in order to generate critical long-term safety data. Specifically, LATTE-2, HPTN 077 and HPTN 083 all include follow-up of 48 to 52 weeks after the final dose of CAB LA [Margolis 2016b; NIAID 2014a; NIAID 2014b]. In alignment with these clinical trials, A5357 will continue safety monitoring and evaluate the pharmacokinetics of CAB LA for approximately 48 weeks after the last injection.

Risk of CAB Monotherapy During A5357

There is the risk that some of the participants in this study could receive CAB monotherapy given that the VRC07-523LS susceptibility testing has not yet been validated in clinical specimens. The team has decided to address this issue in several ways:

1. Study candidates with the lowest quartile of susceptibilities in the new Monogram assay to test the susceptibility of the integrated provirus to VRC07-523LS will be excluded.
2. Participants will be monitored monthly for virologic failure, and if there is any detection of viremia ≥200 copies/mL, it will be confirmed and participants will be switched to SOC triple ART.
3. Study candidates with a history of virologic failure while taking integrase inhibitors will be excluded.

CAB has never been given as monotherapy in individuals living with HIV, and it is not the intention of the team to investigate or support this. However, the limited experience with DTG monotherapy suggests that it takes time to develop resistance to that compound in the presence of virologic failure [Greig 2015]. DTG, and similarly CAB, has a high affinity to its target, resulting in strong and sustained binding [Brenner 2017]. As a consequence, in vitro selection of mutants resistant to DTG is difficult and rare in clinical practice.

We agree with the current DHHS guidelines against DTG monotherapy due to risk of resistance, and opine that the likelihood of significant resistance emergence is low in A5357 given rigorous on-study monitoring. Indeed some European groups have presented cohort data that helps contextualize the risks associated with potential CAB monotherapy. A retrospective hospital database described 33 virally suppressed participants some of them with significant prior ART experience, in whom the treating physician had switched to 50 mg of DTG once daily as a single agent. Only one patient, with prior raltegravir experience and suboptimal adherence developed low-level virologic failure through weeks 4–24 (79 copies/mL; confirmed as 101 copies/mL). HIV RNA genotypic resistance tests in confirmation samples at 4 and 24 weeks detected no integrase mutations. HIV DNA genotypic resistance tests detected the integrase

mutation 118R in 7% of the integrated DNA in PBMCs at 24 weeks [Rojas 2015]. In a single-hospital observational cohort of 28 participants who were maintained on DTG monotherapy, 3 experienced viral rebound with detection of integrase resistance mutations by week 24 [Katlama 2015]. Similar to the study by Rojas et al., all the participants with virologic rebound had previous exposure to an integrase inhibitor. A retrospective cohort of DTG monotherapy maintenance did show emergence of INSTI resistance mutations in 9 of 11 virologic failures [Blanco 2017; Rojas 2016].

In the only randomized trial of DTG monotherapy, monotherapy was non-inferior to combination ART at 24 weeks, suggesting that virologic failure takes time to accrue on monotherapy. However, virologic failure continued to occur thereafter and led to DTG resistance after the participants were viremic for 12 weeks [Wijting 2017].

Overall, while available limited data suggest that it is unlikely that participants will develop resistance to CAB or other integrase inhibitors as a consequence of their participation in the study, the monthly viral load monitoring provides additional safeguards against emergence of clinically significant integrase resistance during the study.

Pregnancy

In one study evaluating CAB in pregnant rats and their newborn pups, there was a higher rate of pups that died at the time of delivery or shortly after delivery in the rats that received 1000 milligrams per kilogram dose of CAB compared to pregnant rats who did not receive CAB. This finding did not occur in pregnant rats who received two lower doses (0.5 and 5 milligrams per kilogram) of CAB. The significance of this finding on human pregnancies is not known. Birth defects have not been observed in animal studies with CAB, to date (refer to the IB for CAB).

The A5357 team is also aware of the recent preliminary results from the TSEPAMO study in Botswana that reported neural tube defects in 4 of 426 (0.9%) babies born to **individuals** who were taking DTG at the time they became pregnant compared to 0.1% occurrence in babies born to **individuals** who were not taking DTG [FDA 2018]. In an updated analysis of the TSEPAMO study, no neural tube defects occurred in an additional 170 babies exposed to DTG at the time of conception, which translated to a revised neural tube defect incidence rate of 0.7% in DTG-exposed babies [Zash 2017]. The TSEPAMO study is ongoing. Information about these recent findings has been included in the informed consent for A5357. In addition, pregnant **individuals** will be excluded from the study, pregnancy testing will be performed on Steps 1 and 2, and **individuals** who become pregnant on study will be taken off the study treatment, and sites will be required to document referral to obstetrical care.

2.3 Significance

Despite the major success of combination ART in suppressing viral replication and preventing disease progression, it is unable to eradicate HIV-1 infection [Siliciano 2014]. The burden of daily medication regimens, drug toxicity, development of drug resistance, and drug cost underscore the need for a continued search for additional complementary

therapeutic modalities. Broadly neutralizing antibodies differ from therapeutic modalities for HIV-1 infection in several respects, and these differences might allow better control of HIV-1 infection. First, they can neutralize the pathogen directly; second, they have the potential to clear the virus and infected cells through engagement of innate effector responses [Igarashi 1999; Nimmerjahn 2008]; and third, immune complexes produced by the passively transferred antibodies may enhance immunity to HIV-1. Since antibodies have longer half-lives than currently prescribed antiretroviral drugs [Klein 2012; Klein 2013], they may also allow for more convenient therapeutic regimens, making them optimal agents for combination therapy with long-acting formulations of conventional ARV drugs. Therefore, bNAbs may have a role as adjuncts to ART or as stand-alone treatment regimens.

Discovery of safe, effective long-acting ART regimens will address a major unmet need in HIV treatment. Specifically, adherence to HIV medications is critical to suppressing HIV RNA levels and preventing the emergence of drug-resistant virus in order to achieve durable clinical and survival benefits. Some HIV studies report the need for >95% adherence to ARV medications to ensure complete virologic suppression [Icovicks 2002; Paterson 2000], and one recent study found over three-fold higher risk of death in participants with less than 95% adherence to contemporary HIV treatment regimens [Lima 2009]. While current HIV regimens are potent, well-tolerated and available as convenient one-pill, once-daily regimens, even simple HIV regimens may pose challenges for some participants. A recent meta-analysis of 84 observational cross-sectional and cohort studies across 20 countries reported that >90% adherence was reported by only 62% of people living with HIV [Ortego 2011]. Thus, interventions to improve adherence in people living with HIV are urgently needed. Parenterally delivered long-acting HIV regimens, such as CAB LA plus VRC07-523LS, have the potential to increase medication compliance and virologic suppression due to directly-observed treatment by providers and elimination of pill burden.

3.0 STUDY DESIGN

A5357 is a phase II, single arm, open-label switch study to assess the safety, tolerability, PK, and antiviral activity of CAB LA plus VRC07-523LS in adults living with HIV-1 with suppressed plasma viremia. At Step 1 entry, all participants will discontinue their current regimen except for NRTIs and initiate oral CAB. For participants currently on Truvada (emtricitabine/tenofovir disoproxil fumarate), or Descovy (emtricitabine/tenofovir alafenamide), or Epzicom (abacavir/lamivudine) without continued access, reimbursement for these drugs will be provided in Step 1.

In Step 1, viral load monitoring will occur at entry and week 4 (and also at week 5 if HIV-1 RNA is 50-199 copies/mL at week 4). Participants tolerating oral CAB plus their current two NRTIs with HIV-1 RNA <50 copies/mL at week 4, or HIV-1 RNA of 50-199 copies/mL at week 4 followed by HIV-1 RNA <50 copies/mL at week 5, will register to Step 2 and receive CAB LA every 4 weeks through week R2+44 plus VRC07-523LS every 8 weeks through week R2+40. Participants who have viral load ≥ 200 copies/mL at week 4 or ≥50 copies/mL at week 5, or who permanently discontinue or temporarily hold oral CAB or NRTIs for >7 days for any reason in Step 1 will be switched to a SOC

regimen and followed on study every 2 weeks for a total of 4 weeks and then be taken off study.

Viral load monitoring in Step 2 will occur every 2 weeks until week R2+8, then every 4 weeks until week R2+48. All participants will complete the week R2+48 visit in Step 2, and this visit will be used to confirm virologic rebound in those with HIV-1 RNA ≥50 copies/mL at week R2+44.

For participants who have a confirmed HIV-1 RNA ≥200 copies/mL during Step 2 or confirmed HIV-1 RNA ≥50 copies/mL at week R2+44 and ≥200 copies/mL at week R2+48, genotypic testing will be performed for protease/reverse transcriptase (PR/RT) and integrase resistance. In addition, samples from the failure confirmation visit and pre-ART or entry (if available) will be tested for viral clonality, integrase resistance, and VRC07-523LS neutralization resistance.

All participants who receive any dose of CAB LA or VRC07-523LS or prematurely discontinue treatment in Step 2 will register to Step 3, the SOC follow-up, at the final study visit in Step 2 or at premature treatment discontinuation. These participants will be registered to Step 3 and will be switched back to a SOC ART regimen, guided by resistance testing, and will undergo study visits at weeks R3+4 and R3+12 and then every 12 weeks for approximately 48 weeks.

4.0 SELECTION AND ENROLLMENT OF PARTICIPANTS

4.1 Step 1 Inclusion Criteria

4.1.1 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 a licensed Western blot or a second antibody test by a method other than the initial rapid HIV and/or E/CIA, or by HIV-1 antigen, plasma HIV-1 RNA viral load.

NOTE: The term “licensed” refers to a US Food and Drug Administration (FDA)-approved kit, which is required for all IND studies.

World Health Organization (WHO) and Centers for Disease Control and Prevention (CDC) guidelines mandate that confirmation of the initial test result must use a test that is different from the one used for the initial assessment. A reactive initial rapid test should be confirmed by either another type of rapid assay or an E/CIA that is based on a different antigen preparation and/or different test principle (e.g., indirect versus competitive), or a Western blot or a plasma HIV-1 RNA viral load.

4.1.2 Clinically stable (i.e., in the opinion of the site investigator, doing well and not sick from treatment) for at least 8 weeks prior to study entry on a three-drug ART regimen that includes a boosted protease inhibitor, a nonnucleoside reverse

transcriptase inhibitor (NNRTI), or an integrase inhibitor, plus two NRTIs, with no history of a switch due to virologic failure.

NOTE: Previous switches for reasons other than virologic failure prior to screening are allowed.

4.1.3 Screening CD4+ T-cell count ≥350 cells/mm^3 obtained within 60 days prior to study entry at any US laboratory that has a Clinical Laboratory Improvement Amendments (CLIA) certification or its equivalent.

4.1.4 All available HIV-1 RNA measurements must be <50 copies/mL within the 2 years prior to study entry except as allowed by the note below.

NOTE: **One** plasma HIV-1 RNA ≥50 copies/mL but <200 copies/mL is allowed if followed by a subsequent HIV-1 RNA value below 50 copies/mL.

4.1.5 Participants must have at least two documented HIV-1 RNA <50 copies/mL within 12 months prior to study entry.

NOTE: The HIV-1 RNA level obtained at the screening visit can be used as the second measurement, but must meet the requirements of section 4.1.6.

4.1.6 Screening plasma HIV-1 RNA <50 copies/mL by any FDA-approved assay with minimum limit of detection of ≤50 copies/mL obtained within 60 days prior to study entry by any US laboratory that has a CLIA certification or its equivalent.

4.1.7 The following laboratory values obtained within 60 days prior to entry at any US laboratory that has a CLIA certification or its equivalent.

- Absolute neutrophil count (ANC) ≥750/mm^3
- Hemoglobin**:**
  - ≥11.0 g/dL for **cisgender** men **and transgender women**
  - ≥10.0 g/dL for **cisgender** women **and transgender men**
- Platelet count ≥100,000/mm^3
- Calculated creatinine clearance (Cockcroft-Gault formula) ≥50 mL/min

NOTE: A program for calculating creatinine clearance by the Cockcroft-Gault method is available at www.fstrf.org.

- Aspartate aminotransferase (AST) (SGOT) ≤2.0 x ULN
- Alanine aminotransferase (ALT) (SGPT) ≤2.0 x ULN

4.1.8 For **persons of child-bearing potential**, negative serum or urine pregnancy test within 48 hours prior to entry by any clinic or laboratory that has a CLIA certification or its equivalent, or is using a point of care (POC)/CLIA-waived test.

NOTE A: **Child-bearing potential** is defined as **persons** who have reached menarche and **persons** who have had menses within the prior 12 months, and have not undergone surgical sterilization. If no menses for a year or longer, the follicle-stimulating hormone (FSH) should be ≤40 IU/mL to be considered of **child-bearing potential**. If an FSH is not available, and they have not had menses in 24 or more consecutive months, they would be considered not to be of **child-bearing potential**. **Persons** who have undergone surgical sterilization (e.g., hysterectomy, bilateral oophorectomy, tubal micro-inserts, tubal ligation or salpingectomy) are considered not to be of **child-bearing potential**.

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

4.1.9 **Persons of Child-bearing Potential**

Persons of child-bearing potential, who are participating in sexual activity that could lead to pregnancy, must agree to use an effective form of contraception from 30 days prior to the first dose of study medication, while receiving the study drugs, and for 30 days after stopping oral medications, or the duration specified in the product label if receiving ARV drugs not supplied by the study, or for approximately 48 weeks after last dose of CAB LA or VRC07-523LS. 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

Persons Who Are Not of **Child-bearing Potential**
Persons who are not of **child-bearing potential** are eligible to start study treatment without requiring the use of contraceptives. Refer to section 4.1.8 for definition of **persons who are of child-bearing potential**.

NOTE: All participants in the study should be counseled on safe sexual practices including the use and benefit/risk of effective barrier methods (e.g., male condom) and on the risk of HIV transmission to a partner without HIV.

4.1.10 **Individuals** aged ≥18 years.

4.1.11 Ability and willingness of participant to provide written informed consent.

4.1.12 Negative HBsAg results obtained within 60 days prior to study entry.

4.1.13 Negative hepatitis C virus (HCV) antibody result obtained within 60 days prior to study entry or, if the HCV antibody result is positive, a negative HCV RNA result obtained within 60 days prior to study entry.

4.1.14 Susceptibility to VRC07-523LS based on IC50 of ≤0.25 µg/mL and a Maximum Percent Inhibition >98% using the Monogram PhenoSense Assay on sample obtained at the screening visit.

NOTE: Participants who had their samples drawn for PhenoSense susceptibility testing to VRC07-523LS at a prior screening as part of any ACTG study and whose screening lab values have expired do not need to repeat the PhenoSense susceptibility testing as part of the re-screening, provided there is no documented detectable HIV viral load since the original screen.

4.1.15 Adequate venous access in at least one arm.

4.1.16 Willingness to continue current two NRTIs and expects to have continued access to NRTIs in Step 1.

NOTE: NRTIs will not be provided by the study. Participants without continued access to NRTIs will be provided reimbursement for these drugs by the study.

4.1.17 Willingness to not actively engage in the conception process for the duration of the study.

4.2 Step 1 Exclusion Criteria

4.2.1 Any previous receipt of humanized or human monoclonal antibody (licensed or investigational).

4.2.2 Weight >115 kg or <53 kg.

4.2.3 AIDS-defining illness within 60 days prior to study entry.

4.2.4 History of a severe allergic reaction with generalized urticarial, angioedema, or anaphylaxis within 2 years prior to study entry.

4.2.5 Currently breastfeeding or pregnant.

4.2.6 Active drug or alcohol use or dependence that, in the opinion of the site investigator, would interfere with adherence to study requirements.

4.2.7 Acute or serious illness that, in the opinion of the site investigator, requires systemic treatment, **quarantine,** and/or hospitalization within **30** days prior to entry.

4.2.8 Use of immunomodulators (e.g., interleukins, interferons, cyclosporine), HIV vaccine, systemic cytotoxic chemotherapy, or investigational therapy within 60 days prior to study entry.

NOTE: Participants receiving stable physiologic doses of glucocorticoids, defined as the equivalent of prednisone ≤10 mg/day, will not be excluded. Stable physiologic glucocorticoid doses should not be discontinued for the duration of the study. In addition, participants receiving inhaled or topical corticosteroids will not be excluded.

4.2.9 Treatment for hepatitis C within 24 weeks prior to study entry.

4.2.10 Vaccinations within 7 days prior to study entry.

NOTE: Participants are encouraged to get routine vaccinations, such as seasonal influenza vaccine outside this window. If vaccination occurs within 7 days prior to study entry, the entry visit should be postponed for at least 7 days after the vaccination.

4.2.11 Initiation of ART during acute HIV-1 infection (as determined by the site investigator by history and/or available medical records).

4.2.12 Personal or known family history of prolonged QT syndrome or, in the opinion of the site investigator, a clinically significant finding on the screening electrocardiogram (ECG) based on an assessment of the screening ECG by that site investigator.

4.2.13 Unstable liver disease (as defined by the presence of ascites, encephalopathy, coagulopathy, hypoalbuminemia, esophageal or gastric varices, or persistent jaundice), known biliary abnormalities (with the exception of Gilbert's syndrome or asymptomatic gallstones).

4.2.14 Moderate or severe hepatic impairment (Class B or C) as determined by Child-Pugh classification.

4.2.15 History of seizures or treatment for seizures within the past 2 years prior to study entry.

NOTE: For candidates with a remote (> 2 year) history of seizure, consult the A5357 CMC for eligibility determination.

4.3 Step 2 Inclusion Criteria

4.3.1 HIV-1 RNA <50 copies/mL at week 4 (Step 1), or HIV-1 RNA of 50-199 copies/mL at week 4 followed by HIV-1 RNA <50 copies/mL at week 5 (Step 1).

4.3.2 **Persons of child-bearing potential** must have a negative serum or urine pregnancy test obtained within 48 hours prior to Step 2 registration.

NOTE: Refer to section 4.1.8 for definition of **child-bearing potential** and acceptable documentation.

4.3.3 Confirmation that female participant agrees to continue to use an effective form of contraception (see section 4.1.9) while on study, and for approximately 48 weeks after last dose of CAB LA or VRC07-523LS.

4.3.4 Confirmation of willingness to not actively engage in the conception process for the duration of the study.

4.4 Step 2 Exclusion Criteria

4.4.1 Discontinuation or temporary hold of oral CAB for >7 consecutive days for any reason during Step 1.

4.4.2 Discontinuation or temporary hold of NRTIs for >7 consecutive days for any reason during Step 1.

4.4.3 Grade 3 or 4 adverse event thought to be related to oral CAB during Step 1 according to the site investigator.

4.4.4 Vaccination (e.g., influenza) within 7 days prior to the Step 2 registration.

4.4.5 Currently breastfeeding or pregnant.

4.4.6 Any Grade ≥2 ALT (>2.5 times ULN) that developed during Step 1.

4.4.7 Current implants and/or direct silicone injections on or around the subcutaneous area where the study product will be administered.

4.4.8 An overlying tattoo (that is located on or around the skin area where the study product will be administered) that, per the site investigator's best clinical judgement, would impede clinical care or management in any way.

4.4.9 Current acute illness that, in the opinion of the investigator, will prevent the participant from complying with study visits.

4.5 Step 3 Inclusion Criterion

4.5.1 Received any CAB LA or VRC07-523LS during Step 2.

NOTE: Participants who prematurely discontinue study treatment for any reason in Step 2 remain eligible for Step 3.

4.6 Step 3 Exclusion Criterion

There are no exclusion criteria to Step 3.

4.7 Study Enrollment Procedures

4.7.1 Prior to implementation of this protocol, and any subsequent full version amendments, each site must have the protocol and the protocol consent form(s) approved, as appropriate, by their local institutional review board (IRB)/ethics committee (EC) and any other applicable regulatory entity (RE). 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.

Upon receiving final IRB/EC and any other applicable approvals for an amendment, 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 the required documents have been received. Site-specific ICF(s) will not be reviewed and approved by the DAIDS PRO, and 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 participant for 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.

Participants from whom a signed informed consent has been obtained may be screened and enrolled, if they otherwise qualify. An ACTG Screening Checklist must be entered through the Data Management Center (DMC) Participant 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

For candidates from whom informed consent has been obtained, but who are deemed ineligible or who do not enroll into the initial protocol step, an ACTG Screening Failure Results form must be keyed into the database.

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

4.8 Co-enrollment Guidelines

Sites are encouraged to co-enroll participants in A5128, “Plan for Obtaining Informed Consent to Use Stored Human Biological Materials (HBM) for Currently Unspecified Analyses.” Co-enrollment in A5128 does not require permission from the A5357 protocol chairs.

For specific questions and approval for co-enrollment in other studies, sites should first check the PSWP or contact the protocol team via email as described in the Study Management section.

5.0 STUDY TREATMENT

Study treatment is defined in Step 1 as oral CAB (oral cabotegravir) and two NRTIs, in Step 2 as CAB LA (injectable cabotegravir) and VRC07-523LS (VRC-HIVMAB075-00-AB), and in Step 3 as SOC ART regimen.

5.1 Study Product

Site pharmacists should consult the *Pharmacy Guidelines and Instructions for DAIDS Clinical Trials Networks* for standard pharmacy operations. Refer to study schema for an overview of steps and study design, and to the investigator’s brochures (IBs) for further information about the study products.

A prescription signed by an authorized prescriber that includes PID and SID must be provided to the site pharmacist before the pharmacist prepares and dispenses study product.

5.2 Study Product Regimen, Administration, and Duration

5.2.1 Regimen and Duration

Step 1 (Oral Phase)
At entry, HIV-1 positive study participants with suppressed viremia will discontinue their current regimen except for NRTIs and initiate oral CAB daily for 5 weeks (-7 days/+14 days). The two NRTIs on Step 1 and SOC ART at weeks 7 and 9 are not considered study products.

Step 2 (Parenteral Phase)
Participants tolerating oral CAB plus two NRTIs who maintain viral suppression (HIV-1 RNA <50 copies/mL at week 4, or HIV-1 RNA of 50-199 copies/mL at week 4 followed by HIV-RNA <50 copies/mL at week 5) will register to Step 2 and receive injectable CAB LA every 4 weeks through week R2+44 and VRC07-523LS every 8 weeks for R2+40 weeks.

NOTE: For participants who register to Step 2, the initial dose of CAB LA will be administered on the same visit day as the final dose of oral CAB on Step 1.

Step 3 (SOC Follow Up)
All participants who received any CAB LA or VRC07-523LS dose during Step 2 will register to Step 3 at the final study visit in Step 2 or at premature treatment discontinuation in Step 2. In Step 3, participants will switch to a SOC regimen and undergo study visits per Table 6.1-3. The SOC ART regimen on Step 3 is not considered study product.

5.2.2 Study Product Administration Overview

Oral CAB 30 mg will be administered as one 30 mg tablet orally once daily, with or without food, for 5 weeks (-7 days/+14 days) during Step 1.

CAB LA 600 mg loading dose will be administered as one 3 mL (600 mg) IM injection in the gluteus medius once, when the participant registers to Step 2. At Step 2 registration, participants will receive the first IM CAB LA dose on the same visit day as the final dose of oral CAB on Step 1.

CAB LA 400 mg maintenance dose will be administered as one 2 mL (400 mg) IM injection in the gluteus medius, starting 4 weeks after the CAB LA 600 mg loading dose and then every 4 weeks through week R2+44 for a total of 11 doses in Step 2.

VRC07-523LS (40 mg/kg) in 100 mL of Sodium Chloride for Injection USP, 0.9% administered as an IV infusion over about 15 to 30 minutes or more as needed using a volumetric pump, starting once the participant registers to Step 2 and then every 8 weeks for a total of six doses through week R2+40 in Step 2.

5.3 Study Product Preparation

The site pharmacist(s) must be proficient in the preparation of injectable study products using aseptic technique under a pharmacy isolator or biological safety cabinet (BSC)

Class II or better. Local regulations and site institutional policies and procedures for use of personal protective equipment, such as gloves, gowns, masks, and safety glasses, must be followed.

5.3.1 CAB LA Preparation

CAB LA 600 mg Loading Dose
The pharmacist must prepare one syringe containing 3 mL (600 mg) of CAB LA study product for the loading dose using aseptic technique under a pharmacy BSC/isolator.

CAB LA 400 mg Maintenance Dose
The pharmacist must prepare one syringe containing 2 mL (400 mg) of CAB LA study product using aseptic technique under a pharmacy BSC/isolator.

Materials required for preparation and administration of CAB LA

1. Appropriate number of CAB LA vials:
   a. To prepare CAB LA Loading dose 600 mg (3 mL) in a syringe, one CAB LA 600 mg/3 mL vial or two CAB LA 400 mg/2 mL vials are needed.
   b. To prepare CAB LA Maintenance dose 400 mg (2 mL) in a syringe, one CAB LA 600 mg/3 mL vial or one CAB LA 400 mg/2 mL vial is needed
2. Becton Dickenson (BD) 3-mL syringe, Leur-Lok Tip, Product No.: 309657 or equivalent
3. Becton Dickinson (BD) 5-mL Syringe, Luer-Lok Tip, Product No.: 309646 or equivalent
4. Needle for aspiration: BD general use sterile hypodermic needle, 21G x 1½ inch (e.g. Precision Glide Needle, Product No.: 305165 or equivalent
5. Needle for intramuscular injection: BD IM sterile hypodermic needle, 23G x 1½ inch (e.g. Precision Glide Needle, Product No.: 305194) or equivalent.

   NOTE: Variable needle lengths and/or needles with different gauges (1½ inch, 2 inch; 21 to 25 gauge) are permitted, if needed, based on available materials at the study site or to accommodate individual body types for IM administration of CAB LA.

Preparation Steps

1. Remove applicable number of CAB LA vial(s) (200 mg/mL concentration in 2 mL or 3 mL fill per vial) from storage. If the vials are stored in the refrigerator (2°C to 8°C), remove the vial(s) from the refrigerator and wait at least 15 minutes to equilibrate to room temperature.

2. Vigorously shake the vial(s) for a full 10 seconds by shaking the vial(s) with long arm movements.
3. Invert the vial(s) and inspect to ensure uniform suspension. If solid remains undispersed, repeat Steps 2-3 until all material is uniformly suspended.

NOTE: It is normal to see small air bubbles at the end of shaking the vial for re-suspension.

4. Using aseptic technique under a pharmacy BSC/isolator, flip off the plastic cap from the vial. Wipe the top of the vial with an alcohol pad (isopropyl alcohol 70% or similar) and allow to dry. Do not touch the rubber stopper at any time.

5. Remove a 3 mL or 5 mL size syringe and 21G x 1½ inch needle (or equivalent) for aspiration. Attach the needle to the Luer connection of the syringe.

6. With the needle sheath on, pull the syringe plunger rod to allow approximately 1 mL of air into the syringe. Remove the needle sheath.

7. With the vial in the inverted position and the syringe with the needle in the upright position, push the needle through vial stopper and inject approximately 1 mL of air into the vial.

8. While keeping the syringe with the needle in the upright position, withdraw needed volume of CAB LA suspension from the vial(s) into the syringe.
   - For LOADING DOSE, withdraw total of 3 mL (600 mg) suspension from the vial(s) into a syringe.
     - If using two CAB LA 400 mg/2 mL vials to prepare the loading dose, a second new aspiration needle should be used to withdraw suspension from the second vial. Remove the first needle that was used to withdraw the suspension out of the first vial and discard properly. Attached the new 21G x 1½ inch needle to the syringe already containing suspension per instructions in Step 5 and repeat Steps 6 and 7 to withdraw the remaining needed volume from the second vial.
   - For MAINTENANCE DOSE, withdraw 2 mL (400 mg) of suspension from a vial into a syringe.

     Since the suspension can contain some air after having shaken the vial, withdraw enough suspension from the vial in order to be able to de-aerate the syringe properly.

9. Remove the needle that was used to withdraw the suspension out of the vial and discard the needle properly.

10. Attach a 23G x 1½ inch (or equivalent) needle to the Luer connection of the prepared CAB LA syringe for IM injection for the participant. Alternatively, the site pharmacist can attach a syringe cap to the prepared syringe. The study staff can then attach the appropriate needle for administration to the prepared syringe in the clinic before administration.

NOTE: The participant-specific prepared CAB LA syringe is to be de-aerated by administrator prior to injection so that the correct volume can be administered.

De-aerate the syringe by first tapping with a finger against the syringe and then by moving the plunger rod carefully forward with the top of the syringe in an upright position until the first drop of suspension appears.

Remove the excess suspension in order to administer the correct volume (3 mL for the LOADING DOSE or 2 mL for the MAINTENANCE DOSE). If needed, collect the excess suspension in a beaker to avoid spilling.

11. Record the time that the suspension was withdrawn from the vial and into the syringe in the participant's pharmacy log. This is the time of preparation.

12. Labeling of Prepared Injectable Study Product

    CAB LA 600 mg Loading Dose
    The participant's loading dose of CAB LA is 600 mg/3 mL in one syringe. Label as CAB LA 600 mg including volume (3 mL), route (IM), PID, SID, date and time of preparation, and date and time of expiration.

    CAB LA 400 mg Maintenance Dose
    The participant's maintenance dose of CAB LA is 400 mg/2 mL in one syringe. Label as CAB LA 400 mg including volume (2 mL), route (IM), PID, SID, date and time of preparation, and date and time of expiration.

    Follow the DAIDS Pharmacy guidelines and local regulations for preparing the participant specific study product label.

    After withdrawal of the CAB LA suspension from the vial into a syringe, it is recommended to inject the suspension immediately. Do not exceed 2 hours between withdrawing the contents of the vial(s) into a syringe (Step 8) and administration to the study participant.

    The prepared CAB LA study product in a syringe must be stored at controlled room temperature between 20°C to 25°C (68° F to 77° F) from the time it is withdrawn into a syringe to the time it is administered.

    Any entered vials and expired filled syringes should be disposed of in accordance with institutional or pharmacy policy.

5.3.2 VRC07-523LS Preparation

A prescription signed by an authorized prescriber must be sent to the pharmacy prior to study product infusion preparation. The prescription must include the participant identifier, weight (kg) from the most recent visit, and calculated VRC07-523LS dose (mg). If the participant's weight on the day of the infusion visit has changed by >10% from the weight written on the prescription sent to the pharmacy, a new prescription must be provided to the pharmacy to prepare a new study infusion dose based on the current actual weight on the day of the visit.

Thawing Instructions
Thaw vials of VRC07-523LS at controlled room temperature (maximum 27°C) for a minimum of 1 hour after removal from freezer.

VRC07-523LS is a highly concentrated protein solution and may develop white, opaque to translucent particles after thawing. When particles are observed, they may disappear after a few hours at controlled room temperature or storage at 2°C to 8°C. Vials of VRC07-523LS containing particles should be placed in the refrigerator as particles may continue to dissipate at 2°C to 8°C. Vials of VRC07-523LS that previously contained particles but subsequently become clear of particles may be used.

Vials that continue to have visible particles after a maximum of 2 weeks at 2°C to 8°C (36°F to 46°F) are not to be used and must be quarantined. Contact the protocol pharmacist for further instructions regarding handling of vials of VRC07-523LS with particles.

Thawed vials for preparation should contain fluid that is a clear, colorless to yellow liquid and no particles are observed. Following thaw, VRC07-523LS vials must either be used to prepare an infusion or placed in a refrigerator at 2°C to 8°C (36°F to 46°F) before reaching the maximum storage of 24 hours at controlled room temperature (maximum 27°C). The thawed VCR01LS vials may be stored up to 2 weeks at 2°C to 8°C (36°F to 46°F).

If stored at 2°C to 8°C (36°F to 46°F), vials must be equilibrated to controlled room temperature (maximum 27°C) for a minimum of 30 minutes and may be held at controlled room temperature (maximum 27°C) for up to 8 hours prior to product preparation.

VRC07-523LS may not be stored in direct sunlight at any time.

IV Infusion Preparation Instructions

Participants' screening weight, entry weight, or last obtained weight may be used for estimating the dose to thaw vials. After removal from 2-8°C, vials of VRC07-523LS should be equilibrated to controlled room temperature (maximum 27°C) for a minimum of 30 minutes prior to preparing IV infusions.

1. Calculate the total milligrams of VRC07-523LS required based on the participant's weight, 40 mg/kg and the total number of vials required based on a 6 mL withdrawal volume containing 600 mg of VRC07-523LS or 2 mL withdrawal volume containing 200 mg of VRC07-523LS.
2. Gently swirl thawed vials for 30 seconds with sufficient force to resuspend any visible particles, yet avoiding foaming. DO NOT SHAKE THE VIALS. Keep the vials upright at all times until ready to withdraw the contents. Do not invert the vial during inspection.
3. Observe vials for particles. If particles are observed refer to the thawing instructions for further information.
4. Add the required volume for the calculated total milligrams of VRC07-523LS needed into 0.9% Sodium Chloride Injection, USP, 100 mL IV bag or glass bottle using aseptic technique to maintain sterility under a pharmacy isolator or Biological Safety Cabinet (Class 2 or better). The 0.9% Sodium Chloride Injection, USP, 100 mL bag will accommodate the additional volume required for the dose of VRC07-523LS to be used in this study. Do not withdraw fluid from the 0.9% Sodium Chloride Injection, USP, 100 mL bag to make room for the volume of study product to be added.
5. Label the IV bag with participant identifier, participant weight (kg), calculated dose of VRC07-523LS (mg) added to the 0.9% Sodium Chloride Injection, USP, 100 mL, the final volume of the bag, lot number, storage instructions, Investigational Use Statement ("Limited by Federal Law to Investigational Use"), and manufacturer information.

After VRC07-523LS study product preparation in IV bags, the prepared VRC07-523LS may be stored at 2°C to 8°C (36°F to 46°F) up to 48 hours or at controlled room temperature (maximum 27°C) for a maximum of 4 hours total including completion of infusion time.

The prepared study IV bag may not be stored in direct sunlight.

If the prepared study IV bag is stored at 2°C to 8°C, it must be equilibrated at controlled room temperature (maximum 27°C) for at least 30 minutes prior to IV administration.

The IV bag will also be labeled with a "DO NOT INFUSE AFTER" date and time as follows:

- Up to 48 hours if stored at 2°C to 8°C
- Up to 4 hours, including completion of infusion, if at controlled room temperature (maximum 27°C).

Any unused portion of a VRC07-523LS vial will not be used for another participant. Any empty vials, unused portion of entered vials, or unused IV solution which contains study product should be discarded in a biohazard containment bag and incinerated or autoclaved in accordance with institutional or pharmacy policy.

VRC07-523LS (IV Administration)
The IV bag label on the IV bag prepared by the pharmacy will include the participant's weight that was used for preparation of the IV bag, the calculated, total amount (mg) of VRC07-523LS added to the 100 mL normal saline bag and the final volume of the bag.

The clinician responsible for administration and another study staff will each check the IV bag label and confirm that the participant identifier is correct and the weight on the bag label is within 10% of the participant's current actual weight before beginning the IV administration.

An in-line filter infusion set must be used for IV administration. In-line filter must comply with the following specifications: 1.2 micron PES (polyether-sulfone) filter membrane, DEHP-free, latex-free (equivalent to Braun # 473994 filter extension set). When the in-line filter is added to the tubing, prime the administration set. Flush the administration set with about 30 mL or appropriate volume of normal saline at the end of product administration.

The investigational study product solution for infusion will be administered IV over about 15 to 30 minutes or more as needed using a volumetric pump. The rate of infusion (mL/hr) will vary based on the total volume needed to administer the full dose. The total time needed to administer the dose may be longer, based on factors such as participant tolerance.

Please see the A5357 MOPS for further detail on administration.

5.3.3 Study Product Formulation and Storage

Oral cabotegravir (CAB) tablets are formulated as white to almost white oval-shaped coated tablets for oral administration. The tablets are packaged in high density polyethylene (HDPE) bottles with child-resistant closure that include an induction seal. The bottles contain 30 tablets and a desiccant. The tablets are to be stored up to 30°C (86°F) in the original container with the desiccant, and protected from moisture.

Cabotegravir Long Acting injectable (CAB LA) is formulated as a sterile white to slightly pink suspension containing 200 mg/ mL concentration of cabotegravir free acid for administration by IM injection. The product is packaged in 2 mL filled (400 mg/2 mL) and 3 mL filled (600 mg/3 mL) per vial. Each vial is for single use and does not require dilution prior to administration. CAB LA injectable suspension in the vial is to be stored up to 30^{o}C (86°F); do not freeze.

VRC07-523LS will be supplied in 10 mL size glass vial with a 6.25 mL fill volume at a concentration of 100 mg/mL and a 3 mL size glass vial with 2.25 mL fill volume at a concentration of 100 mg/mL. The vials contain a clear, colorless to yellow liquid essentially free of visible particles; some opaque or translucent particles may be present. The formulation buffer is composed of 50 mM histidine, 50 mM sodium chloride, 5% sucrose, and 2.5% sorbitol at pH 6.8. The vials are intended for single use and thus do not contain a preservative.

VRC07-523LS product label designates the long-term storage as -35°C to -15°C (-31°F to 5°F). Storage in a continuously monitored, temperature-controlled freezer with temperature excursion between -45°C to -10°C (-49°F to 14°F) is acceptable.

5.4 Pharmacy: Product Supply, Distribution, and Accountability

5.4.1 Study Product Supply

Oral CAB and CAB LA are provided by ViiV Healthcare.

VRC07-523LS **is** provided by the VRC/DAIDS/NIAID.

NOTES: ART supply, other than oral CAB and CAB LA, will not be provided through the study.

Any ART including NRTIs, other than oral CAB and CAB LA, are not to be received, stored, or dispensed by the ACTG pharmacist from the ACTG pharmacy.

NOTE: Previously enrolled Step 1 participants who are re-screened for Step 1 and found to be eligible should be instructed to bring back their remaining oral CAB bottle supply at the study entry visit.

The study participants are to obtain NRTIs outside of the study through routine care, which is the same process they were obtaining their NRTI regimen before entering the study.

For participants currently on NRTIs, including emtricitabine 200 mg/tenofovir disoproxil fumarate 300 mg (Truvada®), abacavir 600 mg/lamivudine 300 mg (Epzicom®), and emtricitabine 200 mg/tenofovir alafenamide 25 mg (Descovy®) in Step 1 without continued access to NRTIs outside of the study through routine care, reimbursement for these drugs will be provided by the ACTG Leadership and Operations Center (LOC) with funding support from ViiV.

5.4.2 Study Product Acquisition/Distribution

Oral CAB, CAB LA, and VRC07-523LS will be available from the NIAID Clinical Research Products Management Center (CRPMC). The site pharmacist should obtain the study products for this protocol by following the instructions in the manual *Pharmacy Guidelines and Instructions for DAIDS Clinical Trials Networks.*

5.4.3 Study Product Accountability

The site pharmacist is required to maintain complete records of all study products. In addition, the site pharmacist must maintain records of the manufacturer and lot # of 0.9% Sodium Chloride for Injection, USP, locally sourced and used to prepare the study infusion. All unused study products in US CRSs must be returned to the NIAID CRPMC (or as otherwise directed by the sponsor) after the study is completed or terminated. The procedures to be followed are in the manual *Pharmacy Guidelines and Instructions for DAIDS Clinical Trials Networks.*

5.5 Concomitant Medications

Participants must be advised to notify their investigator of any current or proposed concomitant medication, whether prescribed or over-the-counter, because of the potential for interactions between such treatments and the study medications. Concomitant medications (prescription and non-prescription) will be permitted during the course of the study at the investigator's discretion except for prohibited medications as described in section 5.5.2.

Whenever a concomitant medication or study agent is initiated or a dose is 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: http://tprc.pharm.buffalo.edu/home/di_search/.

5.5.1 Required Medications

Step 1: Study-provided oral CAB plus two current NRTIs that are obtained as part of clinical care.

Step 2: Study-provided CAB LA plus VRC07-523LS.

Step 3: SOC ART that is obtained as part of clinical care.

5.5.2 Prohibited Medications

The following medications may not be used at any time during this protocol:

- HIV immunotherapeutic vaccines
- Other experimental agents, antiretroviral drugs not otherwise specified in the protocol, cytotoxic chemotherapy, or radiation therapy (see exclusion criterion: section 4.2.8).
- Systemically administered immunomodulators (such as interleukin and interferon agents). This includes topical agents with substantial systemic exposure and systemic effects. Use of topical imiquimod is permitted.

The following medications are prohibited during Step 1 and Step 2 since they could significantly decrease the levels of either formulation of CAB due to enzyme induction:

- Carbamazepine
- Oxcarbazepine
- Phenobarbital
- Phenytoin
- Rifabutin
- Rifampicin / Rifampin
- Rifapentine
- St. John's wort (*Hypericum perforatum*)

NOTE: These agents should be discontinued for a minimum of 4 weeks or a minimum of three half-lives (whichever is longer) prior to the first dose of CAB.

The following medications are prohibited during Step 2 since participants will be receiving CAB LA intramuscular injections:

- Anticoagulation agents for greater than 14 days, with the exception of the use of anticoagulation for deep vein thrombosis (DVT) prophylaxis (e.g., postoperative DVT prophylaxis) or the use of low dose acetylsalicylic acid (≤325 mg). Systemic anticoagulation (including prophylaxis doses) on the day of an IM injection should be avoided.

The following medications are prohibited during Step 3:

- All agents that are prohibited in the most current package insert of each of the antiretroviral drugs the participant is receiving.

5.5.3 Precautionary Medications

CAB oral administration only: Antacid products containing divalent cations (e.g., aluminum, calcium, and magnesium) must be taken at least 2 hours before or at least 4 hours after CAB. Concurrent administration of multivitamins is acceptable.

6.0 CLINICAL AND LABORATORY EVALUATIONS

6.1 Schedule of Evaluations

Table 6.1-1: Step 1 Oral Phase

Evaluation	Screen	Step 1 entry	Step 1 Visits (weeks)		Premature Tx/Study D/C	Step 1 SOC Tx Visits (weeks); see section 6.2.5	
	-60 days		4	5, if needed; see section 6.2.5		7	9
Window			*-7/+14 days; ≥72 hours between these two visits*			*-7/+14 days*	
Documentation of HIV	X						
Medical and Medication History	X	X					
Documentation of Pre-ART HIV-1 RNA and Nadir CD4+ T-cell Count		X					
Clinical Assessments	X	X	X	X	X	X	X
Complete Physical Exam	X						
Targeted Physical Exam		X	X	X	X	X	X
ECG	X						
Dispensation of Study-provided Oral CAB Plus Current Two NRTIs (not provided by the study)		X	X				
Dispensation of SOC ART (not provided by the study)						X	X
Hematology, Liver Function Tests, and Blood Chemistries	X	X	X	X	X		
PT/INR	X						

Evaluation	Screen	Step 1 entry	Step 1 Visits (weeks)		Premature Tx/Study D/C	Step 1 SOC Tx Visits (weeks); see section 6.2.5	
	-60 days		4	5, if needed; see section 6.2.5		7	9
Window			*-7/+14 days; ≥72 hours between these two visits*			*-7/+14 days*	
Urinalysis		X					
Pregnancy Testing	X	X	X	X	X	X	X
Hepatitis Screen	X						
CD4+/CD8+ T-cells	X						
Assess Availability of Pre-ART Plasma/Serum for Storage		X					
Plasma HIV-1 RNA	X	X				X	
Expedited Plasma HIV-1 RNA			X	X			
Susceptibility Testing to VRC07-523LS	X						
HIV-1 Drug Resistance Genotype				X			
ART Adherence Assessment		X	X	X			
Stored Plasma and PBMC for Future Studies		X	X				

Table 6.1-2: Step 2 Parenteral Phase

Evaluation	Step 2	Step 2 Visits (weeks)														VF conf.	Premature Tx/Study D/C
	Registration (R2)	R2 + 2	R2 + 4	R2 + 6	R2 + 8	R2 + 12	R2 + 16	R2 + 20	R2 + 24	R2 + 28	R2 + 32	R2 + 36	R2 + 40	R2 + 44	R2 + 48		
Window		*± 7 days (except for R2+4 and R2+8 which have a -7/+0 day dosing window)*					*± 7 days*								*±14 days*		
Clinical Assessments	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Targeted Physical Exam	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Administration of VRC07-523LS	X				X		X		X		X		X				
Administration of CAB LA	X		X		X	X	X	X	X	X	X	X	X	X			
Hematology, Liver Function Tests, and Blood Chemistries	X		X		X	X	X	X	X	X	X	X	X	X	X		X
Urinalysis	X														X		X
Pregnancy Testing	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X		X
CD4+/CD8+ T-cells	X		X		X	X			X			X			X		X
Plasma HIV-1 RNA	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X (see section 6.2.5)	X	X

Evaluation	Step 2	Step 2 Visits (weeks)														VF conf.	Premature Tx/Study D/C
	Registration (R2)	R2 + 2	R2 + 4	R2 + 6	R2 + 8	R2 + 12	R2 + 16	R2 + 20	R2 + 24	R2 + 28	R2 + 32	R2 + 36	R2 + 40	R2 + 44	R2 + 48		
Window		*± 7 days (except for R2+4 and R2+8 which have a -7/+0 day dosing window)*					*± 7 days*								*±14 days*		
HIV-1 Drug Resistance Genotype															X (see section 6.2.5)	X	
Stored Plasma (for PK of CAB LA)	X		X	X	X				X						X		
Stored Plasma (for Additional PK Studies)		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	
Serum (for VRC07-523LS PK)			X		X	X	X	X	X	X	X	X	X	X	X	X	
Serum (for Antibody to VRC07-523LS)			X		X	X	X	X	X	X	X	X	X	X	X	X	
Distribute Infusion Report Card	X				**X**		**X**		X		**X**		**X**				
Collect Infusion Report Card		X				**X**		**X**		X		**X**		**X**			
Stored Plasma and PBMC (for Future Studies)	X					X			X			X			X	X	X

Table 6.1-3: Step 3 SOC Follow-up

Evaluation	Step 3	Step 3 Visits (weeks)						
	Registration	R3+4	R3+12	R3+24	R3+36	R3+48	VF	Premature
Window	(R3)	*-/+ 14 days*					conf.	Study D/C
Targeted Physical Exam	X	X	X	X	X	X	X	X
Hematology, Liver Function Tests, and Blood Chemistries	X	X	X	X	X	X		X
CD4+/CD8+ T-cells	X	X	X	X	X	X	X	X
Plasma HIV-1 RNA	X	X	X	X	X	X	X	X
HIV-1 Drug Resistance Genotype							X	
Stored Plasma and Serum (for Additional PK Studies)		X	X	X	X	X	X	
ART Adherence Assessment		X	X	X	X	X	X	X
Stored PBMC and Plasma for future studies						X	X	X

6.2 Timing of Evaluations

6.2.1 Screening Evaluations

Step 1 screening evaluations must occur prior to the participant's starting oral CAB.

NOTES: All individuals previously enrolled to Step 1 prior to March 16, 2020, and those screened after that date whose screening lab values have expired, and who choose to re-enroll into A5357, may be re-screened for Step 1. Screening evaluations that are repeated must be documented and keyed on the eCRFs. Previous PhenoSense susceptibility testing to VRC07-523LS, completed as part of any ACTG study, does not need to be repeated as part of the re-screening process, provided there is no documented detectable HIV viral load since the original screen.

Screening evaluations to determine eligibility must be completed within 60 days prior to study entry unless otherwise specified. In addition, data on participants who do not enroll will be captured in a Screening Failure Results form and entered into the ACTG database.

Non-reportable Results of the PhenoSense Assay
If the susceptibility test to VRC07-523LS is resulted as *not reportable*, the participant should be entered as a screen failure. The site may choose to re-screen such a participant once at a later date. The CMC should be contacted at actg.cmcA5357@fstrf.org to assist with this decision.

6.2.2 Step 1 Oral Phase

Step 1 entry evaluations must occur at least 24 hours after screening evaluations and must be completed prior to the initiation of oral CAB.

Participant must begin study treatment within 72 hours after entry.

The week 5 visit (if needed) must occur no earlier than 72 hours after the week 4 visit is completed.

Adherence counseling per standard of care should be undertaken at every visit and whenever a participant is suspected to be poorly adherent to oral therapy.

The availability of the stored pre-ART plasma or serum specimens should be determined.

NOTE: Available pre-ART plasma or serum is NOT required for study entry. If available, pre-ART plasma or serum should be stored.

6.2.3 Step 2 Parenteral Phase

Participants who meet the inclusion criteria in section 4.3 will register to Step 2 within **3** weeks after the last visit on Step 1. Registration to Step 2 must occur on the same visit day as the last oral CAB dose on Step 1.

Safety laboratory evaluations at Step 2 registration will be performed only if not obtained at the last Step 1 visit.

In exceptional circumstances, the protocol team may authorize the use of oral CAB as a short-term "bridging" strategy for participants who have begun CAB LA. This strategy would only be employed to address any potential gap in CAB LA dosing as a result of scheduling conflicts, which would prevent planned dosing. Should a participant need "oral bridging", sites must contact the CMC at actg.cmcA5357@fstrf.org for authorization and guidance for treatment strategies prior to a missed CAB LA dose. Should a participant not notify the site in advance, the CMC must be contacted for further treatment guidance. Refer to the A5357 MOPS for additional information or examples for when the bridging strategy may be utilized.

NOTE: If a participant does not complete a Step 2 study visit within the visit window, sites must notify the CMC at actg.cmcA5357@fstrf.org as soon as possible, ideally no later than 24 hours after the visit window closes. The team will provide further guidance to sites on a case-by-case basis.

6.2.4 Step 3 SOC Follow-up

Participants who meet the inclusion criteria in section 4.5 will register to Step 3 within 2 weeks after the last visit on Step 2. Registration to Step 3 may occur on the same day as the last Step 2 visit.

Safety laboratory evaluations at Step 3 registration will be performed only if not obtained at the last Step 2 visit.

6.2.5 Post-Entry Evaluations

Study visits for Steps 1, 2, and 3 must be scheduled on the weeks indicated in the SOE within the visit windows.

NOTE: Screening and enrollment have re-opened, **and progression through study steps as outlined in the SOE has resumed.**

Week 5 on Step 1
Evaluations listed under week 5 visit in the SOE will occur only for participants who have a detectable viral load on week 4 of Step 1 (HIV-1 RNA ≥50 copies/mL).

NOTE: Safety laboratory evaluations at Step 2 registration will be performed only if not obtained at the last Step 1 visit.

Step 1 SOC Treatment Visits
Participants who have viral load ≥200 copies/mL at week 4 or ≥50 copies/mL at week 5, or who permanently discontinue or temporarily hold oral CAB or NRTIs for >7 days for any reason in Step 1 will be switched to a SOC regimen. These participants will not be eligible for Step 2 and will be followed on study every 2 weeks for a total of 4 weeks and then be taken off study. **NOTE: Previously enrolled Step 1 participants who were instructed to discontinue the Step 1 study treatment and to resume their original complete ART regimen were re-screened for Step 1 when the study re-opened to screening and accrual.**

Week R2+48 Visit on Step 2
All participants will complete the Step 2 week R2+48 visit. Only participants who have HIV-1 RNA ≥50 copies/mL at week R2+44 will have a repeat HIV-1 RNA at the week R2+48 visit. If the HIV-1 RNA ≥200 copies/mL at week R2+48, then genotyping will be performed at this time point.

NOTE: For participants who prematurely discontinue from Step 2, the follow-up duration will be based on the date of the participant's last CAB LA dose regardless of the last VRC07-523LS infusion. Safety laboratory evaluations at Step 3 registration will be performed only if not obtained at the last Step 2 visit.

Confirmation of Suspected Virologic Failure
Virologic failure is defined as two consecutive HIV-1 RNA levels ≥200 copies/mL or last ≥200 copies/mL. Participants with a plasma HIV-1 RNA ≥200 copies/mL will have a confirmation of suspected virologic failure visit as soon as possible and no later than 2 weeks after the first sample was drawn. If this visit coincides with a regularly scheduled visit, the evaluations should be combined. See section 8.7 for management of participants with confirmed virologic failure.

HIV-1 Drug Resistance Genotype
See section 6.3.8 for additional information on genotyping for participants with confirmed virologic failure or participants who have week R2+44 RNA ≥50 copies/mL and week R2+48 RNA ≥ 200 copies/mL.

6.2.6 Discontinuation Evaluations

Evaluations for Registered Participants Who Do Not Start Oral CAB on Step 1
All eCRFs must be completed and keyed for the period up to and including entry. No further follow-up is required.

Premature Study Treatment Discontinuation Evaluations
Participants who permanently discontinue or temporarily hold oral CAB or NRTIs for >7 days for any reason in Step 1 will be switched to a SOC regimen and be followed every 2 weeks for a total of 4 weeks as outlined in the Step 1 SOE.

Participants who prematurely discontinue study treatment for any reason in Step 2 must complete the premature study treatment discontinuation evaluations within 2 weeks after stopping CAB LA and VRC07-523LS. These participants will register to Step 3 and be switched to a SOC regimen and followed per the SOE until study completion.

Participants who become pregnant while on oral CAB, CAB LA, or VRC07-523LS must immediately discontinue oral CAB, CAB LA, and VRC07-523LS and will be switched to an appropriate SOC regimen. They must complete the premature study treatment discontinuation evaluations within 2 weeks after stopping oral CAB, CAB LA, and VRC07-523LS. The site must document participant referral to appropriate obstetrics care. Participants will be encouraged to remain in the study to be followed on study/off study treatment until study completion.

NOTE: Sites must contact the CMC via email at actg.cmca5357@fstrf.org for any instances of premature study treatment discontinuation.

Premature Study Discontinuation Evaluations
Participants who prematurely discontinue study participation after receiving any study treatment or who do not initiate any study treatment in Step 1 or Step 2 will have the premature study discontinuation evaluations performed per the SOE.

Study Completion Evaluations
For Step 3, week R3+48 will be the final study visit for participants.

6.3 Instructions for Evaluations

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 DAIDS AE Grading Table and AE reporting of adverse events requirements.

The protocol team and/or study monitoring entity (e.g., 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 of HIV-1

Section 4.1.1 specifies assay requirements for HIV-1 documentation. HIV-1 documentation of the date of diagnosis must be recorded.

6.3.2 Medical and Medication 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 30 days. In addition, the following diagnoses should be recorded regardless of when the diagnosis was made:

- AIDS-defining conditions (refer to the CDC HIV Classification and the WHO Staging System for HIV Infection and Disease)
- Bone fractures (verbal history accepted)
- Coronary artery disease
- Cancer (exclusive of basal/squamous cell skin cancer)
- Diabetes
- Tuberculosis
- Chronic hepatitis C
- Chronic hepatitis B

The medical history evaluation will be assessed at the screening and entry visit and recorded on the eCRFs at the study entry visit.

A medication history must be present, including start and stop dates. The table below lists the medications that must be included in the history.

Table 6.3.2-1: Medication History

Medication Category	Complete History or Timeframe
Antiretroviral Therapy	Available ARV history
Immune-based Therapy	Within 30 days prior to study entry
Blinded study Treatment	Within 30 days prior to study entry
HIV-1-related Vaccines	Within 30 days prior to study entry
Prescription Drugs	Current use at entry
Alternative Therapies	Current use at entry
Dietary Supplements	Current use at entry
Non-prescription drugs (over-the-counter)	Current use at entry
Sex-hormone medications or sex-hormone analogues or antagonists*	Current use at entry

(*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.)

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

6.3.3 Documentation of Pre-ART HIV-1 RNA and Nadir CD4+ T-cell Count

Document the pre-ART HIV-1 RNA level and nadir CD4+ T-cell count. Participant recall is acceptable.

6.3.4 Clinical Assessments

Complete Physical Exam
A complete physical examination will be performed at the screening visit and is to include at a minimum an examination of the skin, head, mouth, and neck; auscultation of the chest; cardiac exam; abdominal exam; and examination of the lower extremities for edema. The complete physical exam will also include signs and symptoms, diagnoses, and vital signs (height, weight, temperature, pulse, respiration rate, and blood pressure).

Targeted Physical Exam
A targeted physical examination will be performed and is to include vital signs (weight, temperature, pulse, respiration rate, and blood pressure) and injection site reactions. The targeted physical exam will be driven by any previously identified or new signs or symptoms and diagnoses that the participant has experienced since the last visit.

Post entry, see section 8.5 for collection requirements for pregnancy. Refer to section 7.2 for AE collection requirements.

Height
Height (cm) will be recorded at **screening**.

Weight
Weight (kg) will be recorded at every visit.

Signs and Symptoms
At Step 1 entry, signs and symptoms of all grades that occurred within 30 days prior to entry must be recorded as medical history. For post-entry signs and symptoms, refer to section 7.2 for AE reporting requirements.

Diagnoses
After Step 1 entry, refer to section 7.2 for AE reporting requirements.

Active solicitation of adverse events will be done at every study visit.

Concomitant Medications
After Step 1 entry, record all new and discontinued concomitant medications, including sex-hormone medications or sex-hormone analogues or antagonists (see section 6.3.2 for examples), prescription medication, dietary supplements and over-the-counter medications taken since the last visit. Ongoing medications do not need to be recorded at each visit.

ECG
At screening, an ECG will be performed on all participants. The screening ECG results must be recorded at Step 1 entry.

VRC07-523LS Infusion Monitoring
Prior to each VRC07-523LS administration, record temperature, blood pressure, heart rate (pulse), and weight. A targeted physical examination may be conducted (based on signs, reported symptoms, or interim medical history). Sites must observe participants for at least 60 minutes following VRC07-523LS administration. During the monitoring period, participants will be observed for clinical AEs, and vital signs checked every 15 minutes for up to 60 minutes after the completion of infusion.

CAB LA Injection Monitoring
Record injection site reactions or any other signs and symptoms from CAB LA administration at the next scheduled study visit.

6.3.5 Documentation of Study Treatment and SOC ART Administration

Record oral CAB plus two NRTIs in Step 1, including initial dose, any interruption regardless of duration, dose modifications, formulation modifications, and permanent discontinuations.

Record all VRC07-523LS infusions and CAB LA injections in Step 2, including dose administered, time administration initiated, whether administration was temporarily halted for any reason, duration and rate of infusion, and whether the full dose was administered. If the full dose was not administered, the amount (volume and concentration) that was administered should be recorded, along with the reason the full dose was not administered.

Record SOC ART regimen administered on Step 3, including initial dose, any interruption lasting 3 days or longer, dose modifications, formulation modifications, and permanent discontinuations.

6.3.6 Laboratory Evaluations

At screening and entry, record on the eCRF all protocol-required laboratory values regardless of grade. For post-entry assessments, record all creatinine, creatinine clearance, creatine phosphokinase (CPK), and lipase values regardless of grade; record abnormal laboratory findings per section 7.2.

PT/INR
PT/INR will be performed at the local laboratory.

Hematology
Hemoglobin, hematocrit, white blood cell count (WBC), differential WBC, absolute neutrophil count (ANC), absolute eosinophil count, and platelet count will be performed at the local laboratory.

Liver Function Tests
Total bilirubin, AST (SGOT), ALT (SGPT), and alkaline phosphatase will be performed at the local laboratory.

NOTE: For participants on ritonavir boosted atazanavir, total and direct bilirubin should be measured.

Blood Chemistries
Blood urea nitrogen (BUN), creatinine, glucose, creatine phosphokinase (CPK), lipase, and electrolytes (sodium, potassium, chloride, and CO2/bicarbonate) will be performed at the local laboratory.

Creatinine clearance must be recorded each time that a creatinine level is recorded. Creatinine clearance should be estimated by the Cockcroft-Gault equation. A program for calculating creatinine clearance by the Cockcroft-Gault method is available at www.fstrf.org.

Child-Pugh Score
Since albumin is needed for the Child-Pugh calculation, albumin will be performed as part of liver function tests or chemistries.

Urinalysis
Dipstick or microscopic exam may be done; if dipstick results are abnormal, microscopic exam is required.

Pregnancy Test
A pregnancy test will be performed for **persons of child-bearing potential**: serum or urine β-HCG (urine test must have a sensitivity of at least 25 mIU/mL). A serum or urine pregnancy test must be obtained per the SOE.

Record pregnancy and pregnancy outcome per section 8.0. See section 8.5 for management of participants who become pregnant while on study.

Hepatitis Screen
HCV antibody, HCV RNA (if HCV antibody positive; see section 4.1.13**)**, and HBsAg testing per the SOE.

6.3.7 Immunologic Studies

CD4+/CD8+ T-cells
Screening absolute CD4+/CD8+ T-cell count and percentages must be performed within 60 days prior to study entry at a laboratory that possesses a CLIA certification or equivalent (US sites).

Entry and post-entry absolute CD4+/CD8+ T-cell counts and percentages should be performed at the same laboratory, if possible, and that laboratory must possess a CLIA certification or equivalent (US sites).

Assess Availability of Pre-ART Plasma or Serum for Storage
The availability of the stored pre-ART plasma or serum samples will be determined but is NOT required for entry into the study. If available, these specimens should be stored for later testing.

6.3.8 Virologic Studies

Plasma HIV-1 RNA
Screening HIV-1 RNA must be performed within 60 days prior to study entry at a laboratory that possesses a CLIA certification or equivalent (US sites). Eligibility will be determined based on the screening value.

Entry and post-entry plasma HIV-1 RNA must be performed per the SOE. Samples must be processed and shipped to the designated central ACTG testing laboratory (refer to laboratory processing chart [LPC] for shipping information) in an expeditious manner. At weeks 4 and 5 in Step 1, ship the plasma HIV-1 RNA samples on the same day the sample is obtained.

Susceptibility Testing to VRC07-523LS
A sample for susceptibility testing to VRC07-523LS must be obtained at screening and shipped to the designated laboratory for testing (refer to LPC for details). The results of the PhenoSense assay will be available within 4 weeks after testing and will be communicated to sites to determine eligibility for the study. Refer to the A5357 MOPS for additional information on the reporting of the assay results.

NOTE: Previous PhenoSense susceptibility testing to VRC07-523LS, completed as part of any ACTG study, does not need to be repeated as part of the re-screening process, provided there is no documented detectable HIV viral load since the original screen.

HIV-1 Drug Resistance Genotype
An HIV-1 drug resistance genotype (virus population sequencing of reverse transcriptase, protease, and integrase coding regions of the pol gene) will be performed for participants with confirmed virologic failure or participants who

have week R2+44 RNA ≥50 copies/mL and week R2+48 RNA ≥ 200 copies/mL. Refer to the LPC for additional information.

6.3.9 PK Studies

Blood samples will be collected and stored for determination of CAB and VRC07-523LS levels and serum for PK and antibody to VRC07-523LS according to Tables 6.1-2 and 6.1-3.

See section 11.0 for additional details on the planned pharmacokinetic studies.

6.3.10 IRC

Participants will be given an IRC in Step 2 to use as a memory aid for solicited AEs. For this study, solicited AEs occurring during the 3 days after receipt of VRC07-523LS will include: unusually tired, feeling unwell, muscles aches, headache, chills, nausea, and joint pain. Participants will also record highest measured temperature daily.

Participants should be instructed to take their temperature at least once daily, starting with the day of infusion (day 0), after leaving the clinic, through day 3 post-infusion. Temperature should be taken orally in the evening whenever possible. If more than one measurement is made in a day (for example due to feeling unwell), then the highest temperature taken that day should be recorded. Sites will provide thermometers and/or instructions on the use of thermometers to participants as needed.

The IRCs will be reviewed for accuracy and completeness at follow-up visits. Clinicians will collect resolution information for any systemic symptoms that are not resolved after 3 days. Additionally, active solicitation of AEs will be done at every visit. All reportable signs and symptoms from the IRC will be recorded per section 7.2.

6.3.11 ART Adherence Assessment

Adherence to ART medications, including oral CAB and two NRTIs on Step 1 and to SOC ART on Step 3, will be assessed by self-report per the SOE.

The adherence eCRF is posted on the DMC Portal in the Forms Management Utility.

6.3.12 Stored Plasma and PBMC for Future Studies

Cryopreserved plasma and PBMC will be stored per the SOE for future analysis.

For PBMC cryopreservation during the study, all laboratories must be certified for protocol testing by the DAIDS Immunology Quality Assurance Program.

7.0 ADVERSE EVENTS AND STUDY MONITORING

7.1 Definition of Adverse Events

An adverse event (AE) is any unfavorable and unintended sign (including an abnormal laboratory finding), symptom, or diagnosis that occurs in a study participant at or after study entry REGARDLESS of the attribution (i.e., relationship of event to protocol-imposed intervention). This includes any occurrence that is new in onset or aggravated in severity or frequency from the baseline condition.

7.2 Adverse Event Collection Requirements for this Protocol

All AEs must be recorded on the eCRFs if any of the following criteria have been met.

- All Grade ≥3 AEs
- All AEs that led to a change in study treatment/intervention regardless of grade
- All AEs meeting SAE definition or 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.

Diagnoses

Post-entry, all targeted diagnoses listed below and diagnoses that led to a change in Steps 1 and 2 study treatment (i.e., oral CAB and two NRTIs for Step 1 or CAB LA and VRC07-523LS for Step 2) must be recorded regardless of grade.

- Immunologic including AIDS-defining conditions and HIV-associated opportunistic infection (OI)
- Bone fractures (verbal history accepted)
- Cardiovascular including coronary heart disease
- Cancer (exclusive of basal/squamous cell skin cancer)
- Chronic obstructive pulmonary disease (COPD)
- Diabetes
- Tuberculosis (TB)
- Acute hepatitis C
- Chronic hepatitis C
- Chronic hepatitis B
- Acute hepatitis B
- Autoimmune disorders
- Renal disease
- Pregnancy

Signs and Symptoms

Post-entry, Grade ≥3 signs and symptoms and all signs and symptoms that led to a change in study treatment must be recorded regardless of grade.

Laboratory Evaluations
For post-entry assessments, Grade ≥2 laboratory findings and all laboratory findings that led to a change in study treatment must be recorded regardless of grade.

All AEs must be reported in the eCRFs if the reporting criteria have been met for any diagnoses, signs and symptoms, and abnormal laboratory findings as described below.

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: https://rsc.niaid.nih.gov/clinical-research-sites/daids-adverse-event-grading-tables.

Serious Adverse Events (SAEs)
A 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 Reporting of Adverse Event (EAE) to DAIDS

7.3.1 Expedited Reporting of Adverse Events to DAIDS

Requirements, definitions and methods for expedited reporting of 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:

- Oral CAB (oral cabotegravir)
- VRC07-523LS (via infusions)
- CAB LA (injectable cabotegravir)
- Two NRTIs taken on Step 1

In addition to SAEs, sites will report in an expedited manner the following events:

- ALT ≥3x ULN AND total bilirubin ≥2x ULN
- Any seizure event
- ALT ≥8x ULN
- ALT ≥3x baseline ALT with signs/symptoms of acute hepatitis
- ALT ≥5x ULN that persists >2 weeks
- Confirmed abacavir hypersensitivity reaction

7.3.3 Grading Severity of Events

The DAIDS AE Grading Table, corrected Version 2.1, July 2017, must be used and is available on the DAIDS RSC website at https://rsc.niaid.nih.gov/clinical-research-sites/daids-adverse-event-grading-tables.

7.3.4 Expedited AE Reporting Period

- The expedited AE reporting period for this study is as per the EAE Manual.
- 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 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, study conduct (including premature treatment and study discontinuations), virologic failures, and all AEs will be monitored during the trial on a regular basis by the protocol core team. The protocol core team will review the individual safety data frequently to assess the relation of all reported AEs to oral CAB, CAB LA, and VRC07-523LS.

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

To ensure the safety of the participants, the study will be reviewed routinely by an independent ACTG appointed study monitoring committee (SMC) at the earlier of (i) the 25th enrolled participant has reached week R2+24 in Step 2 of the CAB LA plus VRC07-523LS combination or discontinued the study or study treatment prior to this, or (ii) 1 year after the study is open for enrollment. After the first interim review, the study will be routinely monitored annually by the SMC.

An interim review may be triggered prior to this if (i) three or more participants have virologic failures while on Step 2 treatment (see section 10.5 for definition of virologic failures considered in the stopping guideline), (ii) one or more participant(s) experience a death that is assessed by the protocol core team as possibly, probably, or definitely related to CAB LA and/or VRC07-523LS at any time, (iii) two or more participants experience a Grade 4 AE that is assessed by the protocol core team as possibly, probably, or definitely related to CAB LA and/or VRC07-523LS before 25 participants are enrolled and have reached week R2+24 of Step 2, or (iv) four or more participants experience a Grade 4 AE that is assessed by the protocol core team as possibly, probably, or definitely related to CAB LA and/or VRC07-523LS at any time.

If an interim review is triggered, enrollment into Step 1 and Step 2 will be paused pending SMC consultation and participants in Step 1 or Step 2 will continue to follow the intended study design including continuing the step-specific study treatment until the SMC has been consulted. An interim review may also be convened if a concern is identified by the DAIDS clinical representative, the study chairs, or study statisticians in consultation with the team. See section 10.0 for statistical and other considerations related to interim monitoring.

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 ISSUES

8.1 Toxicity

Criteria for participant management, dose interruptions, modifications, and discontinuation of study drugs are delineated only for toxicities attributable to study treatment on Step 1 and Step 2 (i.e., oral CAB and two NRTIs during Step 1 or CAB LA and VRC07-523LS during Step 2). The goal is to maintain participant safety while continuing therapy, if possible. If any individual study drug must be interrupted or discontinued due to toxicity, then the entire regimen must be interrupted or discontinued. Participants who have study treatment discontinued for toxicity should be followed for a total of 4 weeks if the discontinuation occurred in Step 1 or for approximately 48 weeks as part of Step 3 of the protocol if the discontinuation occurred in Step 2. NOTE: If participants discontinue oral CAB in Step 1, they will be considered being on-study/off-study treatment regardless of continuation of their NRTIs.

NOTE: The CMC must be notified at actg.cmca5357@fstrf.org regarding toxicities that result in regimen interruption or discontinuation. The protocol does not allow drug substitution for toxicity management.

The general guidelines presented in sections 8.1.1 to 8.1.3 apply to toxicities that are not specifically discussed elsewhere.

8.1.1 Grade 1 or 2

Participants who develop a Grade 1 or 2 AE or toxicity may continue the Step 1 or Step 2 study treatment. If the participant chooses to discontinue the study treatment, the site should complete the premature treatment discontinuation evaluations, notify the A5357 CMC at actg.cmca5357@fstrf.org, and have the participant attend all remaining study visits.

8.1.2 Grade 3

Grade 3 AE or toxicity must be evaluated and managed by the site investigator according to the SOC. It may be necessary to discontinue the Step 1 or Step 2 study treatment. The A5357 CMC must be notified at actg.cmca5357@fstrf.org regarding AEs or toxicities that result in a change of study treatment. If the site investigator has compelling evidence that the AE or toxicity was NOT caused by the Step 1 or Step 2 study treatment, dosing may continue. If the study treatment is temporarily held, the participant should be re-evaluated closely until the AE or toxicity returns to Grade ≤2, at which time the study treatment may be reintroduced at the discretion of the site investigator or according to standard practice.

If the site investigator determines that a Grade 3 AE or toxicity is an isolated event, the site has the option of confirming the AE or toxicity before holding the study treatment.

If the same Grade 3 AE or toxicity recurs within 4 weeks of reintroducing the study treatment and is thought to be related to the study treatment (per the site investigator), the study treatment must be permanently discontinued. However, if the same Grade 3 AE or toxicity recurs after 4 weeks, but is not thought to be related to the study treatment (per the site investigator), the management scheme outlined above may be repeated.

Participants experiencing Grade 3 AEs or toxicities requiring permanent discontinuation of the study treatment should be followed closely until resolution of the AE or toxicity. The A5357 CMC must be notified at actg.cmca5357@fstrf.org. See section 6.2.6 for management of participants who prematurely discontinue study treatment.

8.1.3 Grade 4

Participants who develop a Grade 4 AE or toxicity thought to be related to study treatment (per the site investigator) must have the Step 1 or Step 2 study treatment temporarily held. If the site investigator has compelling evidence that the AE or toxicity has NOT been caused by the study treatment, dosing may resume when the AE or toxicity has resolved to Grade ≤2. Notify the A5357 CMC at actg.cmca5357@fstrf.org.

Participants experiencing Grade 4 AEs or toxicities requiring permanent discontinuation of the study treatment should be followed closely until resolution of the AE or toxicity to Grade ≤2, and the protocol team must be consulted. See section 6.2.6 for management of participants who prematurely discontinue study treatment.

8.2 Clinical Abnormalities

8.2.1 Liver Function Tests

The Step 1 or Step 2 study treatment may be continued for asymptomatic Grade ≤3 AST/ALT elevations at the discretion of the site investigator, and in consultation with the CMC. All Grade ≥2 ALT elevations must be communicated to the CMC for review and discussion regarding re-testing and/or continuation of study treatment.

For symptomatic Grade 3 (e.g., fatigue, nausea, vomiting, right upper quadrant pain or tenderness, fever, rash, or eosinophilia) or any Grade 4 elevations in AST or ALT with or without symptoms, no further doses of the study treatment should be given, and the CMC should be consulted. **Refer to the eosinophilia grading table below.** In addition, for Grade 3 ALT with bilirubin ≥2 x ULN (attempts should be made to fractionate the bilirubin), the study treatment should be held and the CMC consulted for further guidance.

Table 8.2.1-1: Grading Table for Eosinophilia, by Absolute Eosinophil Count

Grade	Value
1	**1000/µL to 1499/µL**
2	**1500/µL to 1999/µL**
3	**2000/µL to 10,000/µL**
4	**>10,000/µL**

In participants receiving CAB LA plus VRC07-523LS, the study treatment will be stopped if any of the following liver chemistry criteria are met:

- ALT ≥3x ULN and total bilirubin ≥2x ULN
- ALT ≥8x ULN
- ALT ≥3x baseline ALT with signs/symptoms of acute hepatitis
- ALT ≥5x ULN that persists >2 weeks

All participants who permanently discontinue study treatment as a result of liver toxicity should be followed weekly until resolution to Grade ≤2. Participants will be followed on study/off study treatment after study treatment discontinuation.

Careful assessments should be done to rule out other possible causes (e.g., alcohol, non-study-treatment-related toxicity, syphilis, or viral hepatitis) as the cause of Grade 3 or Grade 4 AST/ALT elevations.

Evaluations to be considered (but are not required) include:

- Viral hepatitis serology including: hepatitis A IgM antibody, hepatitis B surface antigen (HBsAg) and hepatitis B core antibody (IgM), hepatitis C RNA, hepatitis E IgM antibody
- Cytomegalovirus IgM antibody
- Epstein-Barr viral capsid antigen IgM antibody (or if unavailable, obtain heterophile antibody or monospot testing)
- Syphilis screening
- Drugs of abuse screen including alcohol
- Serum acetaminophen test (APAP adduct test)
- Serum creatine phosphokinase (CPK) and lactate dehydrogenase (LDH)
- Anti-nuclear antibody, anti-smooth muscle antibody, and Type 1 anti-liver kidney microsomal antibodies
- Liver imaging to evaluate liver disease.

8.2.2 CPK Elevation

A Grade 3 or higher elevation in CPK should result in a repeat assessment within 2 to 4 weeks to ensure the result is transient or due to exercise and will not require a change in study treatment. A history regarding use of drugs known to cause increase of CPK (such as statins) physical activity or exercise preceding the CPK evaluation should be obtained.

Grade 4 elevations in CPK should have a repeat assessment after the participant has abstained from exercise for >24 hours. For persistent Grade 4 CPK elevations that are considered related to study treatment (per the site investigator), the Step 1 or Step 2 study treatment should be discontinued. See section 6.2.6 for management of participants who prematurely discontinue study treatment.

8.2.3 Lipase Elevations and Pancreatitis

Participants with asymptomatic Grade 1 or Grade 2 elevations in lipase may be followed closely for the development of symptoms.

Participants with asymptomatic Grade ≥3 elevations in lipase that are considered related to study treatment by site investigator should have the Step 1 or Step 2

study treatment held until serum lipase returns to Grade ≤2. The lipase assay should be repeated within 2 weeks of any Grade ≥3 result. Participants with persistence of Grade ≥3 lipase in the absence of other diagnoses or reoccurrence of lipase elevation (at Grade ≥2) following reintroduction of study treatment should permanently discontinue the study treatment.

Participants with a confirmed diagnosis of clinical pancreatitis that is considered related to study treatment by a site investigator should have all study treatments held. After complete resolution of the episode, participants may be re-challenged with study treatment after discussion with the A5357 CMC, only if the Investigator has compelling evidence that the event was not caused by study treatment. Upon re-challenge, lipase determinations should be performed every 2 weeks for at least 6 weeks after re-initiation of treatment. With any elevation of lipase of Grade ≥2 or any recurrence of symptoms, the participant should discontinue all study treatments. See section 6.2.6 for management of participants who prematurely discontinue study treatment.

8.2.4 Seizure

Any seizure event will result in permanent discontinuation of the Step 1 or Step 2 study treatment. Local standards should be followed if the event occurred in Step 3.

8.2.5 Suicidal Ideation

Participants with HIV may occasionally present with symptoms of depression and/or suicidality (suicidal ideation or behavior). In addition, there have been reports of depression and suicidal ideation and behavior (particularly in participants with a pre-existing history of depression or psychiatric illness) in some participants being treated with integrase inhibitors, including CAB. Therefore, it is appropriate to monitor participants for suicidality before and during treatment.

Participants should be monitored appropriately and observed closely for suicidal ideation and behavior or any other unusual changes in behavior. It is recommended that the investigator consider mental health consultation or referral for participants who experience signs of suicidal ideation or behavior.

8.3 Allergic Reactions

8.3.1 Allergic Reactions During CAB Administration

Participants may continue CAB during Grade 1 or Grade 2 allergic reactions at the discretion of the site investigator. The participant should be advised to contact the site investigator immediately if there is any worsening of symptoms or if further systemic signs or symptoms develop. Antihistamines, topical corticosteroids, or antipruritic agents may be prescribed.

Participants with Grade ≥3 allergic reactions that are considered to be related to the CAB by site investigator should permanently discontinue the Step 1 or Step 2 study treatment. Participants should be treated as clinically appropriate and followed until resolution of the AE.

See section 6.2.6 for management of participants who prematurely discontinue study treatment.

8.3.2 Allergic Reactions During VRC07-523LS Infusion

Participants who develop a Grade 1 or Grade 2 AE or toxicity during infusion may complete the VRC07-523LS infusion at the discretion of the site investigator, and will be followed carefully. The site investigator may consider reducing the speed of the infusion or prescribing antihistamines, topical corticosteroids, or antipruritic agents as needed. If a participant chooses to discontinue VRC07-523LS, the site should notify the A5357 CMC at actg.cmca5357@fstrf.org and have the participant complete follow-up study visits as part of Step 3. Grade 1 or Grade 2 AEs or toxicities that may be related to VRC07-523LS (per the site investigator) should be handled according to standard clinical practice and documented.

Participants who develop a Grade 3 AE or toxicity during infusion should have VRC07-523LS discontinued and the A5357 CMC should be notified. Grade 3 AEs or toxicities that occur following infusion should be handled according to standard clinical practice and the A5357 CMC should be notified.

Participants who develop a Grade 4 AE or toxicity during infusion will have all study treatments (i.e., CAB LA and VRC07-523LS during Step 2) discontinued. Participants experiencing Grade 4 AEs or toxicities should be followed closely until the resolution of the AE or toxicity to Grade ≤2 and the A5357 CMC must be consulted within 24 hours.

Any participant who has received any dose of study treatment in Step 2 will be followed for approximately 48 weeks as part of Step 3 of the protocol.

Pre-Medication

Pre-medication for infusions is not planned. However, if an infusion reaction occurs during administration or if the participant has a medical history suggesting a potential benefit from pre-medication, the study investigator(s) should determine the appropriate pre-medication. Any pre-medication given will be documented as a concomitant medication.

If minor infusion reactions are observed, administration of acetaminophen 500 mg to 1000 mg, antihistamines, and/or other appropriately indicated medications may be given prior to the start of infusions for subsequent visits.

8.4 Local Reactions

8.4.1 Injection Site Reactions

Injection site reactions (ISRs) will be managed through site investigator assessment and participant infusion report card collection throughout the study. All Grade 3 or Grade 4 ISRs must be discussed with the A5357 CMC (actg.cmca5357@fstrf.org) to determine etiology and assess appropriate continued study participation.

Digital photographs will be obtained where possible for all participants who have an ISR that is either serious or Grade 2 or above and that persists beyond 2 weeks.

ISR discomfort can be managed symptomatically (e.g., cold/warm compress, acetaminophen, ibuprofen) if the reaction is interfering with the participant's ability to perform activities of daily living. If a participant chooses to discontinue CAB LA, the site should notify the A5357 CMC at actg.cmca5357@fstrf.org and encourage the participant to complete follow-up study visits as part of Step 3.

8.5 Pregnancy

Female participants must not participate in the conception process (e.g., active attempt to become pregnant or in vitro fertilization), and if participating in sexual activity that could lead to pregnancy, female participants must use an effective form of contraception while receiving oral CAB, CAB LA, or VRC07-523LS and for 30 days after stopping oral medications, or the duration specified in the product label if receiving ARV drugs not supplied by the study, and for approximately 48 weeks after last dose of CAB LA or VRC07-523LS.

Acceptable contraceptive methods include:

- Contraceptive subdermal implant
- Intrauterine device or intrauterine system
- Combined estrogen and progestogen oral contraceptive
- Injectable progestogen
- Contraceptive vaginal ring
- Percutaneous contraceptive patches

Individuals who become pregnant while on Step 1 or Step 2 must immediately discontinue study treatment and consult with their primary care physicians. Participants should have the premature treatment discontinuation evaluations completed within 2 weeks after stopping study treatment. Participants will be encouraged to remain in the study to be followed on study/off study treatment until study completion.

Sites should have an obstetrical care referral plan in place for **individuals** of child-bearing potential who become pregnant while receiving CAB or within 48 weeks after the

final dose of CAB LA. The obstetrical referral is to provide greater assurance for the appropriate evaluation of the pregnancy, per SOC, following exposure to CAB or within 48 weeks of the final dose of CAB LA. If a study participant becomes pregnant, the site investigator must document i) referral to obstetrical care, and ii) discussion of the study drug(s) received by the participant and any implications for follow-up (e.g., any known risk of neural tube defects) with the obstetrical care team and primary care provider.

If **an individual** has completed the study or chooses to discontinue from the study before the end of the pregnancy, then site staff must request permission to contact the participant regarding **their** pregnancy outcomes and infant outcomes at the end of the pregnancy. Pregnancy and pregnancy outcome will be recorded on the eCRFs. Pregnancy outcomes will be summarized in the final study report. Only pregnancies that occur while a female participant is receiving FDA-approved ARV agents 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.

8.6 Breastfeeding

Female participants who become pregnant and have a live birth while on study should refrain from breastfeeding until 48 weeks from the last dose of study treatment in Step 2 to avoid potential exposure of the infant because non-clinical data suggest that CAB may be present in breast milk.

8.7 Virologic Failure

Refer to section 6.2.5 for confirmation of suspected virologic failure in Step 1.

Participants with confirmed virologic failure on Step 2, per section 6.2.5, will discontinue CAB LA and VRC07-523LS infusions and will continue on study in Step 3 where they will switch to a non-integrase inhibitor SOC regimen pending the results of genotypic testing. The participant should continue on study follow-up with visits and evaluations as outlined in the SOE. The A5357 CMC must be notified.

Participants who experience virologic failure in Step 3 will be managed by the site investigator according to standard practice and guided by results of genotypic testing. Consultation with the A5357 CMC is encouraged.

9.0 CRITERIA FOR DISCONTINUATION

9.1 Permanent and Premature Study Treatment Discontinuation

- Request by the participant to discontinue study treatment.
- Drug-related toxicity (see section 8.1).
- Clinical abnormalities (see section 8.2).
- Allergic reactions (see section 8.3).
- Local reactions (see section 8.4).

- Requirement for prohibited concomitant medications (see section 5.5).
- Pregnancy
- Virologic rebound in Step 1 (see section 6.2.5) or virologic failure in Step 2.
- Clinical reasons believed life threatening by the physician, even if not addressed in the toxicity section of the protocol.
- Completion of treatment as defined in the protocol.

9.2 Premature Study Discontinuation

- Non-initiation of study treatment in Step 1 or Step 2.
- Request by the participant to withdraw.
- Request of the primary care provider if s/he thinks the study is no longer in the best interest of the participant. NOTE: Whenever possible, it is preferable to keep all participants on study even if they have to discontinue study treatment.
- Maintained suppression in Step 1 but ineligible for Step 2.
- At the discretion of the IRB, Food and Drug Administration (FDA), NIAID, Office for Human Research Protections (OHRP), other government agencies as part of their duties, investigator, or industry supporters.

10.0 STATISTICAL CONSIDERATIONS

10.1 General Design Issues

This is an open-label, single arm study to evaluate the safety, tolerability, and virologic efficacy of the combination of CAB LA plus VRC07-523LS in participants with HIV-1 with well-controlled viral replication. Seventy-four participants will be enrolled over approximately 9 to 12 months. It is hypothesized that the parenteral administration of CAB LA plus VRC07-523LS after a lead-in period of oral CAB plus two NRTIs will be safe and efficacious in preventing HIV-1 RNA rebound (virologic failure is defined as confirmed HIV-1 RNA ≥200 copies/mL) up to 44 weeks after initiation of the long-acting combination.

To ensure participants' safety, virologic failures and AEs will be monitored regularly by the core team. An independent ACTG appointed Study Monitoring Committee (SMC) will review the interim study data (see section 7.4, Study Monitoring).

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 ClinicalTrials.gov. Outcomes of interest for secondary and exploratory objectives intended for subsequent publications are to be listed under "Other Outcome Measures".

10.2.1 Primary Outcome Measures

10.2.1.1 Either the occurrence of a Grade 3 or higher AE that is possibly, probably, or definitely related (as judged by the core team) to the CAB LA plus VRC07-523LS combination or premature study treatment discontinuation due to an AE (regardless of grade) that is possibly, probably, or definitely related (as judged by the core team) to the CAB LA plus VRC07-523LS combination.

10.2.1.2 Virologic failure defined as confirmed HIV-1 RNA ≥200 copies/mL at or prior to week R2+44 of the CAB LA plus VRC07-523LS combination.

10.2.2 Secondary Outcome Measures

10.2.2.1 PK parameters of the combination of VRC07-523LS and CAB LA.

10.2.2.2 Viral resistance of breakthrough isolates.

10.2.2.3 Virologic failure (confirmed HIV-1 RNA ≥200 copies/mL) at or prior to week R2+24 of the CAB LA plus VRC07-523LS combination.

10.2.2.4 Virologic failure (confirmed HIV-1 RNA ≥200 copies/mL) or premature discontinuation of the CAB LA plus VRC07-523LS combination at or prior to week R2+44.

10.2.2.5 Confirmed HIV-1 RNA ≥50 copies/mL at or prior to weeks R2+24 and R2+44 of the CAB LA plus VRC07-523LS combination.

10.2.2.6 Confirmed HIV-1 RNA ≥50 copies/mL or premature discontinuation of the CAB LA plus VRC07-523LS combination at or prior to week R2+44.

10.2.2.7 Virologic failure (defined by FDA snapshot algorithm) at week R2+44 of the CAB LA plus VRC07-523LS combination.

10.2.2.8 Measurable levels of anti-idiotype antibodies against VRC07-523LS in samples collected from representative time points throughout the study.

10.2.2.9 Either the occurrence of a Grade 3 or higher AE that is possibly, probably, or definitely related (as judged by the core team) to oral CAB or premature oral CAB discontinuation due to an AE (regardless of grade) that is possibly, probably, or definitely related (as judged by the core team) to oral CAB.

10.2.2.10 Premature discontinuation of oral CAB or the CAB LA plus VRC07-523LS combination.

10.2.2.11 Occurrence of a Grade 3 or higher AE that is possibly, probably, or definitely related (as judged by the core team) to oral CAB or the CAB LA plus VRC07-523LS combination.

10.3 Participant Registration

This is an open-label, single arm study. All participants will be assigned up to a 5 week oral CAB plus two NRTIs lead-in period (Step 1), followed by 44 weeks of CAB LA plus VRC07-523LS (Step 2), and 48 weeks of SOC ART (Step 3). There is no randomization or stratification.

10.4 Sample Size and Accrual

The cumulative probability of participants with virologic failure (confirmed HIV-1 RNA ≥200 copies/mL) at or prior to week R2+44 of the CAB LA plus VRC07-523LS combination will be estimated with a two-sided 95% confidence interval (CI) using Kaplan-Meier methods. Assuming 74 participants are enrolled, 70 initiate CAB LA plus VRC07-523LS, 10% are lost to follow-up and 5% subsequently discontinue CAB LA plus VRC07-523LS, there will be 60 analyzable participants. With 60 analyzable participants, if the observed virologic failure probability is 5.0%, the 95% CI will be [1.7%, 13.7%]. This 95% CI is estimated using the Wilson score method. A 95% CI of [1.7%, 13.7%] would provide proof of concept in support of the investigational strategy. Table 10.4-1 below provides the 95% CI if the virologic failure probability differs from 5.0%. Assuming the true rate of failure is 5%, the sample size will provide >90% power to reject a null failure rate of 20%.

Table 10.4-1 95% CI at Different Virologic Failure Probabilities with a Sample Size of 60 Analyzable Participants

Virologic Failure Probability		95% Wilson Score CI
1%		[0.1%, 7.8%]
2%		[0.4%, 9.4%]
5%		[1.7%, 13.7%]
8%		[3.4%, 17.6%]
10%		[4.7%, 20.1%]
12%		[6.0%, 22.6%]

Using data from participants who remained <50 copies/mL for 96 weeks (approximately 2 years) from two recently completed ACTG naïve trials (A5257 and A5202), we identified 2059 participants who subsequently remained on ART for the rest of follow-up. Forty-eight weeks later, the cumulative probability of virologic failure (two consecutive HIV-1 RNAs ≥200 copies/mL or last ≥200 copies/mL) using Kaplan-Meier methods was 1%, and 192 weeks later (when participants had a median of 10 HIV-1 RNA measurements), this cumulative probability of virologic failure was 5%. As A5357 will measure HIV-1 RNA frequently (>13 measurements on CAB LA plus VRC07-523LS), for the sample size we assumed a virologic failure probability of 5.0%. This is additionally

supported by data from LATTE (Margolis 2015) in which the proportion with protocol-defined virologic failure in the maintenance phase of the study was 2% and those with virologic non-response by the FDA snapshot analysis (≥50 copies/mL) at week 72 of the maintenance phase was 9%.

Regarding the assessment of safety and tolerability (see section 10.2.1.1), a sample size of 70 CAB LA plus VRC07-523LS treated participants will provide a 94% probability of observing a CAB LA plus VRC07-523LS related AE or CAB LA plus VRC07-523LS related treatment discontinuation that would occur in 4% of treated participants.

Accrual is anticipated to take 9 to 12 months. Accrual will be frequently monitored by the core team. It is expected that at least 18 participants will be enrolled within 3 months of the first participant enrollment, and 37 will be enrolled within 6 months. Overall, the study aims to enroll at least 15 (20% of 74) female participants. The core team will also monitor accrual to ensure that ≥70 participants enroll in Step 2. Additional participants will be enrolled into the study if >4 Step 1 participants are ineligible for Step 2.

10.5 Data and Safety Monitoring

The interim reviews will include data on accrual, baseline characteristics, conduct of the study (including premature treatment and study discontinuations), virologic failure, and all reported AEs. The efficacy and the safety triggers for the SMC interim reviews are outlined in section 7.0, with virologic failure stopping guidelines described below.

To protect participants if virologic failure on the experimental regimen turns out to be higher than what may be clinically acceptable, a stringent stopping rule has been put into place. However, to guard against premature study stoppage or modification due to virologic failures that may be attributed to non-adherence or deviations from the specified dosing of the study treatments, virologic failures contributing to the stopping criteria must meet additional criteria to ensure that the pure treatment efficacy is evaluated. Specifically, virologic failure for the study's stopping guideline will be defined as two consecutive HIV-1 RNA levels ≥200 copies/mL on Step 2, while adhering to study treatment (i.e., no missed dose of CAB LA or VRC07-523LS). A missed dose is defined as an unadministered dose, inadequate dose, or any dose outside the window specified in the protocol. Initial HIV-1 RNA measurements ≥200 copies/mL taken prior to Step 2 treatment initiation will be excluded from the evaluation of virologic failure for the stopping guideline. Under this definition of virologic failure, a true failure rate ≤2% is considered to be acceptable. The reference for the threshold is the recent result from the LATTE-2 trial, where the virologic failure rate was 1% through week 96 for the combination of CAB LA plus RPV LA as a maintenance therapy for participants suppressed on ART [Margolis 2017].

Note that the virologic failure definition considered for the stopping guideline has more stringent adherence criteria than the virologic failure definition for the primary outcome, with the intention that the stopping guideline serves the purpose of protecting participants if available data indicate that efficacy of the experimental regimen may be lower than what is clinically acceptable. Table 10.5-1 estimates the choices of the

stopping guideline associated with different sample sizes and the probability that the guideline will be met under various true probabilities of failure. At any time during Step 2, if three or more participants are observed to experience virologic failures defined for the stopping guideline, enrollment into Step 1 and Step 2 will be paused, and SMC will be promptly convened. The SMC, in such an event, is expected to require all participants in Step 1 and Step 2 to enter Step 3 immediately. The stopping criteria will ensure that the trial has a high probability (≥85%) to continue when the true failure rate is ≤2%, and is likely to stop when the true failure rate is unacceptably high (e.g., when the true failure rate is 10%, the trial will stop with a probability of 58%-95% when the sample size is ≥30).

Table 10.5-1: Probability that the SMC Will Consider Stopping the Trial under Various True Failure Probabilities

Number of Participants Examined	Number of failures (observed failure rate)	True Failure Rate					
		1.0%	2.0%	5.0%	8.0%	10%	20%
20	3 (15%)	0.10%	0.71%	7.55%	21.21%	32.31%	79.39%
30	3 (10%)	0.33%	2.17%	18.78%	43.46%	58.86%	95.58%
40	3 (7.5%)	0.75%	4.57%	32.33%	63.06%	77.72%	99.21%
50	3 (6%)	1.38%	7.84%	45.95%	77.40%	88.83%	>99%
60	3 (5%)	2.24%	11.87%	58.26%	86.83%	94.70%	>99%

The SMC safety triggers assume 95% of participants will initiate CAB LA plus VRC07-523LS, and have a low chance (9%) to be triggered if there is a low probability of a treatment related death (0.1%) and Grade 4 AE (1%), but a higher chance (97%) to be triggered if there is a high probability of a treatment related death (1%) and Grade 4 AE (10%).

10.6 Analyses

10.6.1 Primary Analyses

For the primary safety and tolerability analysis (see section 10.2.1.1), all participants who have been exposed to CAB LA and VRC07-523LS will be included and summaries will include the number and percentage of participants experiencing an AE or premature treatment discontinuation defined in section 10.2.1.1 with a Wilson score 95% CI.

For the primary virologic efficacy analysis (see section 10.2.1.2), the cumulative probability of participants experiencing virologic failure at or prior to week R2+44 of the CAB LA plus VRC07-523LS combination will be estimated using Kaplan-Meier methods. If the probability is high, a standard two-sided 95% CI around the true virologic failure probability will be calculated using the adaption of Greenwood's variance estimate with a log(-log) transformation [Kalbfeisch and Prentice, 1980]. However, if the probability is low, Rothman-Wilson two-sided

95% CIs will be estimated [Rothman 1978]. Primary virologic efficacy analysis will be as-treated (i.e., per protocol) only including participant follow-up on the CAB LA plus VRC07-523LS combination. Participants who prematurely discontinue the CAB LA plus VRC07-523LS combination will be censored at the time of discontinuation.

10.6.2 Secondary Analyses

The secondary safety and tolerability outcome (see section 10.2.2.9) will be analyzed in a similar manner to the primary safety and tolerability outcome (see section 10.2.1.1) described in section 10.6.1. A similar approach will also be taken for the secondary safety outcome (see section 10.2.2.11) describing Grade 3 or higher AEs related to oral CAB or the CAB LA plus VRC07-523LS combination, overall and separately. In addition, all reported Grade 3 or 4 AEs (regardless of study treatment relatedness) on oral CAB or the CAB LA plus VRC07-523LS combination will be summarized.

Secondary intent-to-treat (ITT) sensitivity analyses will be conducted for the primary virologic efficacy outcome measure (see section 10.2.1.2). Participants who initiate but then prematurely discontinue LA CAB plus VRC07-523LS will only be censored if lost to follow-up prior to virologic failure and HIV-1 RNA measures on Step 3 (ART) will be used to determine if the participant had virologic failure.

The secondary virologic efficacy outcomes (see sections 10.2.2.3 and 10.2.2.5) will be analyzed in a similar manner to the primary efficacy outcome (see section 10.2.1.2) described in section 10.6.1, but with respect to week R2+24 and/or ≥50 copies/mL. The secondary virologic failure/premature treatment discontinuation outcome (see section 10.2.2.4) will include all participants initiating CAB LA plus VRC07-523LS and consider both virologic failure and premature discontinuation of LA CAB plus VRC07-523LS as failure. The secondary premature treatment discontinuation outcome (see section 10.2.2.10) will include all participants initiating oral CAB and consider premature discontinuation of oral CAB, LA CAB, or VRC07-523LS as failure, and will summarize them overall and separately with reasons for the discontinuation. The secondary virologic rebound/premature treatment discontinuation outcome (see section 10.2.2.6) will include all participants initiating CAB LA plus VRC07-523LS and consider both virologic rebound (HIV-1 RNA ≥50 copies/mL) and premature discontinuation of LA CAB plus VRC07-523LS as failure.

The proportion of participants experiencing virologic failure defined by FDA snapshot algorithm (see section 10.2.2.7) will be presented along with a Wilson score 95% CI.

The percentage of participants with measurable levels of anti-idiotype antibodies will be presented along with a Wilson score 95% CI. Neutralization resistance

and diversity of viral rebound quasispecies will be summarized pre-ART and at virologic failure.

See section 11.0, Pharmacology Plan, for more details on the determination of the PK parameters of the combination of VRC07-523LS and CAB LA. After PK modelling, selected parameters will be associated with viral rebound.

10.7 Unblinding

Not applicable.

11.0 PHARMACOLOGY PLAN

11.1 Pharmacology Objective

The primary pharmacology objective is to determine CAB and VRC07-523LS pharmacokinetics when administered in combination. The rationale for this design is to provide further data on VRC07-523LS pharmacokinetics and determine if CAB pharmacokinetics parameters are influenced by concomitant VRC07-523LS administration.

11.2 Pharmacology Study Design

A population PK study design will be used to describe CAB LA and VRC07-523LS PK. The pharmacology design for A5357 is focused on CAB LA but VRC07-523LS will also be examined. Oral CAB will be administered as the 30 mg tablet orally once daily, with or without food for approximately 5 weeks. CAB LA 600 mg loading dose will be administered as one (600 mg) IM injection in the gluteal muscle once the participant registers to Step 2 on the same visit day as the final dose (30 mg tablet) of oral CAB. CAB LA 400 mg maintenance dose administered as one (400 mg) IM injection in the gluteal muscle starting 4 weeks after the CAB LA 600 mg loading dose and then every 4 weeks through week R2+44 in Step 2.

For CAB LA, plasma will be collected at Step 2 registration. A trough sample will be collected at week R2+4, a peak sample at week R2+6 (2 weeks after the week 4 dose), and at week R2+8 during Step 2. Additional troughs are scheduled to be collected at weeks R2+24 and R2+48. Plasma will also be stored from each study visit, so in case any participant experiences viral breakthrough during the 48 weeks of treatment, these samples also could be analyzed.

11.3 Primary and Secondary Data, Modeling, and Data Analysis

PK data for both compounds will be modeled using a population approach. CAB LA concentration-time data will be incorporated into an existing model developed by GlaxoSmithKline/ViiV. The analysis will focus on determining whether CAB LA is similar to previously collected data when CAB LA was administered alone or with rilpivirine.

VRC07-523LS concentrations will be analyzed by the NIH Vaccine Research Center to further enhance their PK dataset and dosing refinement. An LC/MS/MS assay for CAB has been developed at the UAB PSL to support this study.

11.4 Anticipated Outcomes

It is anticipated that CAB LA PK parameters will fall within the expected range of CAB LA administered alone or with rilpivirine. If not, further PK studies will be needed to determine whether a clinically significant PK interaction exists between CAB LA and VRC07-523LS. It is expected that VRC07-523LS will exhibit a very long half-life, and these data will be used to refine the dose and/or dosing interval if needed.

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 the entering of 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 assure 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

12.3.1 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, and participants' 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, on-site visits to ensure the safety of study participants and data integrity [FDA 2021]. The site will make available study documents for site monitors to review utilizing a secure platform that is HIPAA and 21 CFR Part 11

compliant. Potential platform options include: Veeva SiteVault, site-controlled SharePoint or cloud-based portal, direct access to Electronic Medical Record (EMR), and Medidata Rave Imaging Solutions. Other secure platforms that are 21 CFR Part 11 compliant may be utilized, as allowed by the DAIDS Office of Clinical Site Oversight (OCSO).

12.3.2 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, the site monitors, the FDA, the NIAID, the 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) Review and Informed Consent

This protocol and the informed consent document and any subsequent modifications will be reviewed and approved by the IRB or ethics committee 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, IRB/EC, FDA, NIAID, OHRP, other local, US, and international regulatory entities as part of their duties, or the industry supporter or designee.

13.3 Study Discontinuation

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

14.0 PUBLICATION OF RESEARCH FINDINGS

Publication of the results of this trial will be governed by ACTG policies. Any presentation, abstract, or manuscript will be made available for review by the industry supporter prior to submission.

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 Centers for Disease Control and Prevention and the NIH.

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.

16.0 REFERENCES

ATLAS Study [ViiV Healthcare]. ViiV Healthcare reports positive 48-week results for first pivotal, phase III study for novel, long-acting, injectable HIV-treatment regimen. Last updated August 15, 2018. Available at: https://www.viivhealthcare.com/en-gb/media/press-releases/2018/viiv-healthcare-reports-positive-48-week-results-for-first-pivotal-phase-iii-study-for-novel-long-acting-injectable-hiv-treatment-regimen/ Accessed December 18, 2018.

Blanco JL, Oldenbuettel C, Thomas R, et al. Pathways of resistance in subjects failing dolutegravir monotherapy. [Abstract 42]. In: Program and Abstracts of the 2017 Conference on Retroviruses and Opportunistic Infections (CROI); February 13-16, 2017; Seattle, Washington.

Brenner BG, Wainberg MA. Clinical benefit of dolutegravir in HIV-1 management related to the high genetic barrier to drug resistance. Virus Res 2017;239:1-9.

Cahn P, Andrade-Villanueva J, Arribas JR, et al.; GARDEL Study Group. Dual therapy with lopinavir/ritonavir (LPV/r) and lamivudine (3TC) is non-inferior to standard triple drug therapy in naïve HIV-1 infected participants: 48-week results of the GARDEL study. [Abstract LBPS7/6]. Program and Abstracts of the 14th European AIDS Conference of the European AIDS Clinical Society; October 16-19, 2013; Brussels, Belgium.

Cahn P, Madero JS, Arribas JR, et al. Dolutegravir plus lamivudine versus dolutegravir plus tenofovir disoproxil fumarate and emtricitabine in antiretroviral-naive adults with HIV-1 infection (GEMINI-1 and GEMINI-2): week 48 results from two multicentre, double-blind, randomised, non-inferiority, phase 3 trials. Lancet 2019;393:143-55.

Chen G, Fichtenbaum C, Koletar S, et al. [Abstract IAS 2019]. Safety and Virologic Effect of the HIV-1 Broadly Neutralizing Antibodies, VRC01LS or VRC07-523LS, Administered to HIV-Infected Adults in a Phase 1 Clinical Trial.

Culp A, Bowers G, Gould E, et al. Metabolism, excretion, and mass balance of the HIV integrase inhibitor, cabotegravir (GSK1265744) in humans. [Abstract H-1010]. Proceedings of the 54th Interscience Conference on Antimicrobial Agents and Chemotherapy; 5–9 September 2014; Washington, DC.

ECLAIR Study [GSK Study #201120]. A phase IIa study to evaluate the safety, tolerability and acceptability of long acting injections of the HIV integrase inhibitor, GSK1265744, in HIV uninfected men (ECLAIR). Received February 27, 2014; last updated September 28, 2017. Available at: https://www.gsk-clinicalstudyregister.com/study/201120#rs. Accessed September 25, 2018.

FDA. FDA Drug Safety Communication: FDA to evaluate potential risk of neural tube birth defects with HIV medicine dolutegravir (Juluca, Tivicay, Triumeq). May 18, 2018. Last updated September 6, 2018.

FDA. FDA Guidance on Conduct of Clinical Trials of Medical Products During the COVID-19 Public Health Emergency: Guidance for Industry, Investigators, and Institutional Review Boards, March 2020, Updated on January 27, 2021. Accessed at: https://www.fda.gov/media/136238/download.

FLAIR Study [ViiV Healthcare]. ViiV Healthcare reports positive 48-week results for second phase III study for novel, long-acting, injectable HIV-treatment regimen. Last updated October 30, 2018. Available at: https://www.gsk.com/en-gb/media/press-releases/viiv-healthcare-reports-positive-48-week-results-for-second-phase-iii-study-for-novel-long-acting-injectable-hiv-treatment-regimen/; Accessed December 18, 2018.

Ford SL, Chiu J, Lovern M, et al. Population PK approach to predict cabotegravir (CAB, GSK1265744) long-acting injectable doses for phase 2b. [Abstract H-645]. Proceedings of the 54th Interscience Conference on Antimicrobial Agents and Chemotherapy; 5-9 September 2014; Washington, DC.

Gaudinski MR, Coates EE, Houser KV, et al. Safety and pharmacokinetics of the Fc-modified HIV-1 human monoclonal antibody VRC01LS: a phase 1 open-label clinical trial in healthy adults. PLoS Med 2018;15:e1002493.

Greig SL, Deeks ED. Abacavir/dolutegravir/lamivudine single-tablet regimen: a review of its use in HIV-1 infection. Drugs 2015;75:503-14.

Hocqueloux L, Raffi F, Prazuck T, et al. Dolutegravir monotherapy versus dolutegravir/abacavir/lamivudine for virologically suppressed people living with chronic HIV infection: the randomized non-inferiority MONCAY trial. Clin Infect Dis 2019;69:1498-1505.

Ickovics JR, Cameron A, Zackin R, et al. Consequences and determinants of adherence to antiretroviral medication: results from Adult AIDS Clinical Trials Group protocol 370. Antivir Ther 2002;7:185-93.

Igarashi T, Brown C, Azadegan A, et al. Human immunodeficiency virus type 1 neutralizing antibodies accelerate clearance of cell-free virions from blood plasma. Nat Med 1999;5:211-16.

Kalbfleisch JD, Prentice RL. The Statistical Analysis of Failure Time Data. New York: John Wiley & Sons; 1980.

Katlama C, Soulie C, Blanc C, et al. Dolutegravir monotherapy in patients with suppressed HIV viremia. [Oral Abstract PS4/4]. 15th European AIDS Conference (EACS); 21-24 October 2015; Barcelona, Spain.

Klein F, Halper-Stromberg A, Horwitz JA, et al. HIV therapy by a combination of broadly neutralizing antibodies in humanized mice. Nature 2012;492:118-22.

Klein F, Mouquet H, Dosenovic P, Scheid JF, et al. Antibodies in HIV-1 vaccine development and therapy. Science 2013;341:1199-204.

Ko SY, Pegu A, Rudicell RS, et al. Enhanced neonatal Fc receptor function improves protection against primate SHIV infection. Nature 2014;514:642-5.

Lalama CM, Jennings C, Johnson VA, et al. Comparison of three different FDA-approved plasma HIV-1 RNA assay platforms confirms the virologic failure endpoint of 200 copies per milliliter despite improved assay sensitivity. J Clin Microbiol 2015;53:2659-66.

Landovitz R, Li S, Grinsztejn B, et al. Safety, tolerability and pharmacokinetics of long-acting injectable cabotegravir in low-risk HIV-uninfected women and men: HPTN 077. [Abstract TUAC0106LB]. 9th International AIDS Society Conference on HIV Science; 23-26 July 2017; Paris, France.

Lima VD, Harrigan R, Bangsberg DR, Hogg RS, et al. The combined effect of modern highly active antiretroviral therapy regimens and adherence on mortality over time. J Acquir Immune Defic Syndr 2009;50:529-36.

Llibre JM, Hung C-C, Brinson C, et al. Phase III SWORD 1&2: Switch to DTG+RPV maintains virologic suppression through 48 wks. [Abstract 44LB]. Conference on Retroviruses and Opportunistic Infections (CROI); March 4-7, 2017; Seattle, Washington. Available at: http://www.croiconference.org/sessions/phase-iii-sword-12-switch-dtgrpv-maintains-virologic-suppression-through-48-wks.

Margolis DA, Brinson CC, Smith GHR, et al. Cabotegravir plus rilpivirine, once a day, after induction with cabotegravir plus nucleoside reverse transcriptase inhibitors in antiretroviral-naive adults with HIV-1 infection (LATTE): a randomised, phase 2b, dose-ranging trial. Lancet Infect Dis 2015;15:1145-55.

Margolis DA, González-García J, Stellbrink HJ, et al. Cabotegravir+rilpivirine as long-acting maintenance therapy: LATTE-2 week 32 results. [Abstract 31LB].Presented at Conference on Retroviruses and Opportunistic Infections (CROI); 22-25 February 2016; Boston, Massachusetts; 2016a.

Margolis DA, González-García J, Stellbrink HJ, et al. Long-acting intramuscular cabotegravir and rilpivirine in adults with HIV-1 infection (LATTE-2): 96-week results of a randomised, open-label, phase 2b, non-inferiority trial. Lancet 2017;390:1499-1510.

Margolis DA, González-García J, Stellbrink HJ, et al. Safety, efficacy and durability of long-acting cabotegravir (CAB) and rilpivirine (RPV) as two-drug IM maintenance therapy for HIV-1 infection. LATTE-2 week 160 results. Glasgow HIV, 27-31 October 2018; Glasgow, UK.

Margolis D, Podzamczer D, Stellbrink HJ, et al. Cabotegravir + rilpivirine as long-acting maintenance therapy: LATTE-2 week 48 results. [Abstract 10517]. 21st International AIDS Conference (AIDS 2016); July 18-22, 2016; Durban, South Africa; 2016b.

National Institute of Allergy and Infectious Diseases (NIAID). A phase iia study to evaluate the safety, tolerability and pharmacokinetics of the investigational injectable HIV integrase inhibitor, GSK1265744, in HIV-uninfected men and women. In: ClinicalTrials.gov. Bethesda (MD): National Library of Medicine (US). Registered on June 27, 2014a. NLM Identifier: NCT02178800. Available at: http://www.clinicaltrials.gov/ct2/show/NCT02178800. Last accessed on May 2, 2016.

National Institute of Allergy and Infectious Diseases (NIAID). Safety and efficacy study of injectable cabotegravir compared to daily oral tenofovir disoproxil fumarate/emtricitabine (TDF/FTC), for pre-exposure prophylaxis in HIV-uninfected cisgender men and transgender women who have sex with men. In: ClinicalTrials.gov. Bethesda (MD): National Library of Medicine (US). Registered on June 27, 2014b. NLM Identifier: NCT02720094. Available at: https://clinicaltrials.gov/ct2/show/NCT02720094. Last accessed on May 2, 2016.

Nimmerjahn F, Ravetch JV. Fcgamma receptors as regulators of immune responses. Nat Rev Immunol 2008;8:34-47.

Orkin C, Arasteh K, Hernández-Mora MG, et al. Long-acting cabotegravir + rilpivirine for HIV maintenance: FLAIR week 48 results. [Abstract 140]. In: Program and Abstracts of the 2019 Conference on Retroviruses and Opportunistic Infections (CROI); March 4-7, 2019; Seattle, Washington.

Ortego C, Huedo-Medina TB, Llorca J, et al. Adherence to highly active antiretroviral therapy (HAART): a meta-analysis. AIDS Behav 2011;15:1381-96.

Panel on Antiretroviral Guidelines for Adults and Adolescents. Guidelines for the use of antiretroviral agents in HIV-1-infected adults and adolescents. Department of Health and Human Services (DHHS). Last updated May 30, 2018. Available at http://aidsinfo.nih.gov/ContentFiles/AdultandAdolescentGL.pdf. Last accessed September 25, 2018.

Patel SV, Khan DA. Adverse reactions to biologic therapy. Immunol Allergy Clin North Am 2017;37:397-412.

Paterson DL, Swindells S, Mohr J, et al. Adherence to protease inhibitor therapy and outcomes in patients with HIV infection. Ann Intern Med 2000;133:21-30.

Reese M, Ford S, Bowers G, et al. In vitro drug interaction profile of the HIV integrase inhibitor, GSK1265744, and demonstrated lack of clinical interaction with midazolam. [Abstract PP_20]. Proceedings of the 15th International Workshop on Clinical Pharmacology of HIV and Hepatitis Therapy; 19-21 May 2014; Washington, DC; 2014.

Ribaudo HJ, Lennox J, Currier J, et al. Virologic failure endpoint definition in clinical trials: is using HIV-1 RNA threshold <200 copies/mL better than <50 copies/mL? An analysis of ACTG Studies. [Abstract #580]. Presented at Conference on Retroviruses and Opportunistic Infections (CROI); February 8-11, 2009; Montreal, Canada.

Richman DD, Wrin T, Little SJ, Petropoulos CJ. Rapid evolution of the neutralizing antibody response to HIV type 1 infection. Proc Natl Acad Sci U S A 2003;100:4144-9.

Rojas J, Blanco JL, Lonca M et al. Dolutegravir monotherapy in HIV-infected patients with sustained viral suppression: a 24-week pilot study. [Abstract LBPS4/2]. 15th European AIDS Conference (EACS); October 21-24, 2015; Barcelona, Spain.

Rojas J, Blanco JL, Marcos MA, et al. Dolutegravir monotherapy in HIV-infected patients with sustained viral suppression. J Antimicrob Chemother 2016;71:1975-81.

Rothman KJ. Estimation of confidence limits for the cumulative probability of survival in life table analysis. J Chron Dis 1978;31:557-60.

Rudicell RS, Kwon YD, Ko SY, et al. Enhanced potency of a broadly neutralizing HIV-1 antibody in vitro improves protection against lentiviral infection in vivo. J Virol 2014;88:12669-82.

Siliciano JD, Siliciano RF. Recent developments in the search for a cure for HIV-1 infection: Targeting the latent reservoir for HIV-1. J Allergy Clin Immunol 2014;134:12-19.

Spreen W, Ford SL, Chen S, et al. GSK1265744 pharmacokinetics in plasma and tissue after single-dose long-acting injectable administration in healthy participants. J Acquir Immune Defic Syndr 2014a;67:481-6.

Spreen W, Williams P, Margolis D, et al. Pharmacokinetics, safety, and tolerability with repeat doses of GSK1265744 and rilpivirine (TMC278) long-acting nanosuspensions in healthy adults. J Acquir Immune Defic Syndr 2014b;67:487-92.

Swindells S, Andrade-Villanueva JF, Richmond GJ, et al. Long-acting cabotegravir + rilpivirine as maintenance therapy: ATLAS week 48 results. [Abstract 139]. In: Program and Abstracts of the 2019 Conference on Retroviruses and Opportunistic Infections (CROI); March 4-7, 2019; Seattle, Washington.

ViiV Healthcare. A phase iib study evaluating a long-acting intramuscular regimen of GSK1265744 plus TMC278 for the maintenance of virologic suppression following an induction of virologic suppression on an oral regimen of GSK1265744 plus abacavir/lamivudine in HIV-1 infected, antiretroviral therapy-naive adult participants. In: ClinicalTrials.gov. Bethesda (MD): National Library of Medicine (US). Registered on April 17, 2014. NLM Identifier: NCT02120352. Available at: http://www.clinicaltrials.gov/ct2/show/NCT02120352

Wijting I, Rokx C, Boucher C, et al. Dolutegravir as maintenance monotherapy for HIV (DOMONO): a phase 2, randomised non-inferiority trial. Lancet HIV 2017;4:e547-e554.

Wu X, Wang C, O'Dell S, et al. Selection pressure on HIV-1 envelope by broadly neutralizing antibodies to the conserved CD4-binding site. J Virol 2012;86:5844-56.

Zalevsky J, Chamberlain AK, Horton HM, et al., Enhanced antibody half-life improves in vivo activity. Nat Biotechnol 2010;28:157-9.

Zash R, Jacobson D, Mayond G, et al. Dolutegravir/tenofovir/emtricitabine (DTG/TDF/FTC) started in pregnancy is as safe as efavirenz/tenofovir/emtricitabine (EFV/TDF/FTC) in nationwide birth outcomes surveillance in Botswana. [Oral abstract MOAX0202LB]. 9th IAS Conferenec on HIV Science; July 23-26, 2017; Paris, France.

SAMPLE INFORMED CONSENT

Sponsor / Study Title:	**NIAID / "A Study of Long-Acting Cabotegravir Plus VRC-HIVMAB075-00-AB (VRC07-523LS) to Maintain Viral Suppression in Adults Living with HIV-1"**
Protocol Number:	**A5357**
Principal Investigator: (Study Doctor)	**«PiFullName»**
Telephone:	**«IcfPhoneNumber»**
Address:	**«PiLocations»**

SUMMARY

PURPOSE

The purpose of this study is to test the safety of cabotegravir (CAB) and VRC-HIVMAB075-00-AB (VRC07-523LS, a monoclonal antibody) when these two drugs are given together. It will also look at whether this drug combination can keep the level of HIV (the virus that causes AIDS) controlled and how your body responds to this drug combination.

NUMBER OF PARTICIPANTS

There will be about 74 participants.

LENGTH OF STUDY

The study will last about 2 years for most people. For a small group of participants who are not eligible for the second part of the study, the study will only last about 2 months.

You will have 2 study visits for the first month, and up to 15 more visits over the next 48 weeks. After that, you will have up to 6 study visits over the last 48 weeks of the study.

STUDY TREATMENT

Step 1: oral CAB and two NRTIs
Step 2: long-acting CAB (CAB LA) injections and VRC-HIVMAB075-00-AB (VRC07- 523LS) infusions
Step 3: SOC ART regimen

REQUIRED ACTIVITIES

Sample collections

- At all visits, some blood will be collected from a vein in your arm.
- At most visits, your blood will be stored.
- A small amount of urine will be collected from you.

Special procedures

- Long-acting CAB will be given to you as an injection in the muscles of your buttock.
- VRC07-523LS will be given to you through a vein in your arm. You will be monitored by the study staff for up to 60 minutes after you are given the VRC07-523LS.
- An electrocardiogram (ECG), a procedure that tests how your heart is doing. This is one of the tests that will be used to check your eligibility for this study.

Other evaluations

- On the day that you first receive VRC07-523LS and for 3 days after, you will record your temperature and symptoms on the infusion report card (IRC).

RISKS

The following are possible side effects associated with the study drugs:

- Pain, soreness, redness, swelling, and hardening where you had your CAB injection.
- Allergic reactions (difficulty breathing or shortness of breath, chest discomfort, low blood pressure, hives or rash, blisters or peeling skin, swelling in the mouth and face, redness of the eyes, big lymph nodes)
- Fatigue, dizziness, headache, generally not feeling well, fever, and joint or muscle pains.
- Risks related to blood draws.
- Liver problems or damage (dark urine, yellowing of your skin or of the white of your eyes, pale colored stools, pain or tenderness on your right side)
- Nausea or vomiting
- Loss of appetite
- Mental health problems (depression, suicide attempts, suicide)
- Seizures or convulsions
- Drug resistance

BENEFITS

No direct benefits should be expected from participating in this study. The information learned from this study may help others who are living with HIV-1.

OTHER CHOICES

Your participation in this research study is completely voluntary. Instead of being in this study, you have the option of continuing with your current

treatment or starting a new treatment under the care of your regular doctor or other health care provider.

INTRODUCTION

You are being asked to take part in this research study because you are infected with the human immunodeficiency virus (HIV, the virus that causes AIDS) and because you are taking anti-HIV drugs that are controlling your HIV infection.

This study is sponsored by the National Institutes of Health (NIH). The doctor in charge of this study at this site is **listed on the first page of this form**. Before you decide if you want to be part of this study, we want you to know more about it.

This is a 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 take part in this study, you will be asked to sign **and date** this consent form. You will get a copy to keep.

WHY IS THIS STUDY BEING DONE?

The study is being done to:

- See how safe CAB is when given as an oral pill and to see if it causes side effects in persons living with HIV.
- See whether the combination of an experimental HIV drug, cabotegravir (CAB), and a monoclonal antibody (VRC-HIVMAB075-00-AB [VRC07- 523LS]) is safe.
- See if the CAB-VRC07-523LS drug combination causes side effects in people living with HIV.
- See if the CAB-VRC07-523LS drug combination causes side effects, and, if so, to understand what the side effects are.
- Find out if a combination of CAB and VRC07-523LS would work well when taken together in keeping HIV virus levels low in the body when CAB is given as long-acting injectable drug (given as a shot like a vaccine) and VRC07-523LS is given as infusions (given through a needle in a vein). A long-acting drug stays in the body much longer compared to the usual form of the medications. This kind of drug combination has never been used before for HIV treatment and is not approved for HIV treatment. It is not known whether it will be effective or not.

This study is opening under protocol Version 3.0 because changes, including a change in one of the study drugs, were made to the original version. The new study drug, VRC07-523LS, is expected to be better than the antibody that had been planned for the original version of the study. VRC07-523LS is a fully human antibody that is targeted to attack HIV; it is not targeted to attack any human protein or the antibody's structure.

HOW MANY PEOPLE WILL BE IN THIS STUDY?

About 74 people (**individuals** aged 18 years and older) will take part in this study.

HOW LONG WILL I BE IN THIS STUDY?

You will be in this study for about 101 weeks (about 2 years or so).

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

Information Collected at Screening
There is some information that we collect on everyone who is screened for an ACTG study. As part of your screening visit, some demographic (for example, age, gender, race), clinical (for example, disease condition, diagnosis), and laboratory (for example, CD4 cell count, viral load) information will be collected from you. We also collect information on whether you use (or have used) IV drugs.

We will collect this information even if you do not enroll in this study. This information is collected so that ACTG researchers may determine whether there are patterns or common reasons why people do not join a study.

If you decide to take part in this research study, you will be asked to sign **and date** this consent form and a screening visit will be scheduled to determine if you can join the study. The screening visit will occur prior to your being given any experimental study treatments (i.e., oral CAB in Part 1 of the study and long-acting CAB and VRC07-523LS in Part 2 of the study). Experimental means the study-provided drugs have not been approved by the Food and Drug Administration (FDA).

Part 1
For Part 1 of this study, you will continue taking your nucleoside reverse transcriptase inhibitors (NRTIs) such as lamivudine, tenofovir, and abacavir, but you will stop taking all other HIV medications and replace them with CAB, taken orally as a pill for about 5 weeks.

If your HIV viral load (how much HIV is in your body) is undetectable at the week 4 visit of Part 1 of the study, then you will enter Part 2 of the study. See below study treatment for each part of the study.

If your HIV viral load is detectable at week 4, you will return 1 week later to see if it has been controlled. If your HIV viral load is still detectable at the week 5 visit or if you stopped **oral** CAB for any reason, then you will not be eligible to enter Part 2 of the study. You will remain in Step 1 for another 4 weeks (with study visits every 2 weeks) before being taken off study. During this time, you will take only your local standard of care (SOC) HIV regimen.

Part 2
In Part 2 of the study, you will stop all oral HIV treatment, including your NRTIs. You will be given VRC07-523LS intravenously (or "IV," which means, "through a vein") every 8 weeks for 40 weeks. You will also be given CAB LA, as intramuscular injections in the gluteus medius (a broad muscle on the outer part of the pelvis, which is located on the upper region of the buttock), every 4 weeks for 44 weeks. You will receive the first CAB LA injection on the same visit day as the final dose of oral CAB on Part 1. **To be eligible for Part 2 of the study, you should not have any implants or silicone injections or tattoo that is located on or around the skin area where VRC07-523LS and CAB LA will be given.**

You will need to come to the clinic to receive treatment for Step 2. You will not be given any study drugs to take at home. While you are on Step 2, you must not take other ARVs at home. Part 2 of the study will last for about 48 weeks.

Part 3
After Part 2 of the study, you will enter Part 3 of the study, which will last for another 48 weeks. In Part 3, you will stop CAB LA and VRC07-523LS and resume taking a local SOC HIV regimen.

The drugs in each of part of the study are:

Part 1: Oral CAB as a pill once daily plus two current NRTIs for up to 5 weeks.

Part 2: One 3mL shot of the CAB LA will be given, and then one 2 mL shot of the CAB LA every 4 weeks (intramuscular injections) for 44 weeks plus VRC07-523LS infusion given every 8 weeks (through a needle in a vein) for 40 weeks.

NOTE: The VRC07-523LS dose of 40 mg/kg body weight is based on estimates of how frequently VRC07-523LS should be given so that the amount of VRC07-523LS in your blood would stay at an effective level. In a small study, a single VRC07-523LS dose of 40 mg/kg IV was shown to work against HIV, but the estimated dosing frequency being used in this study (i.e. every 8 weeks over a long time) has not been used in people with HIV before.

Part 3: SOC HIV regimen for 48 weeks.

Oral CAB, CAB LA, and VRC07-523LS will be provided by the study. NRTIs will be required for Part 1 and reimbursement for these drugs will be provided by the study for those participants who are unable to obtain them in Part 1 of the study. There is no study-provided medication in Step 3, and participants will go back to taking their SOC HIV regimen.

For Part 1 of the study, the study staff will let you know how often to take the study regimen and whether to take them with or without food.

For Part 2 of the study, you will be given a thermometer and an infusion report card (like a notebook log) to record your daily temperature and any symptoms you may have for a few days after each VRC07-523LS infusions. The study staff will give you instructions on the use of the infusion report card. At each study visit, you must bring back the infusion report card so that the study staff can review the information you have recorded.

Before you are given the VRC07-523LS infusion, the study staff will check your temperature, blood pressure, heart rate, and weight. You also might have a brief physical exam. During the infusion, you will be asked to sit or recline for about 15 to 30 minutes or more as needed while the drug is given. After you receive the VRC07-523LS infusion, you will remain in the clinic for 1 hour so that the study staff can check your vital signs (weight, temperature, pulse, respiration rate, and blood pressure) and look out for any unusual signs or symptoms.

At each visit of Part 2 of the study, you will need to inform the study staff of any symptoms you may have while taking CAB LA.

CAB (both the oral and **LA** injection forms) and VRC07-523LS are experimental. The VRC07-523LS dose (40 mg/kg) chosen for this study has not yet been studied in a clinical trial.

All other study-required drugs and routine tests are part of standard clinical care.

If you enter this study, you will need to come for clinic visits up to 2 times for the first month or so, then up to 15 times for a year, and lastly up to 6 times during the final year *(A5357 Appendix I: Study Visits provides more detail.)*

Visits where you receive an infusion will last between 1 and 2 hours. Other visits will last about 1 hour. The study staff will tell you how long each visit will last.

You may need to come to the clinic for extra visits if you develop side effects or if you need to switch anti-HIV drugs. During the study, you will receive the results of routine laboratory tests that are done during the study. **The site staff can tell you approximately how much blood will be collected at any visit.**

WHY WOULD THE STUDY DOCTOR TAKE ME OFF THIS STUDY EARLY?

The study doctor may need to take you off the study without your permission if:

- The study is stopped or cancelled.
- Your primary care doctor believes that remaining on the study is no longer what is best for you. NOTE: It is preferred by the study team that you remain on study even if you have to stop study treatment. Since the study is being done to look at safety, the more data are collected from participants who may have to stop study treatment, the better the study becomes with the additional information.
- You are not eligible for Part 2.
- A Safety Monitoring Committee (SMC) recommends that the study be stopped early (A SMC is an outside group of experts that monitors the study.)

Also at any time in the study, you can request to stop participating.
Your study doctor may also need to take you off the study drugs without your permission if:

- Continuing the study drugs may be harmful to you; for example, if the study drugs are making you sick or if the study drugs are not controlling the level of HIV in your blood.

- You need a treatment that you may not take while on the study.
- You become pregnant or start breastfeeding.

If you must stop taking the study drugs before the study is over, the study staff will ask you to continue to be part of the study and return for some study visits and procedures. If you want to stop the study visits, then the study staff will ask you to return to the clinic for a final visit.

If You Have to Stop Taking the Study Drugs Early or You Have to Stop the Study Early
If you stop taking the study drugs or leave the study early, you will be asked to come to the clinic for at least one additional study visit. At this visit, you will have a targeted physical exam, which will assess vital signs, have blood drawn for routine safety blood tests, pregnancy tests, and may have urine, CD4+ T-cell count, viral load, and immune tests. In addition, some of your blood may be stored for future testing required by the study.

If you stop taking the study drugs early, but are willing to remain in the study, you will continue to come in for regularly scheduled study visits. If the discontinuation of study drugs occurred during Part 1 of the study (i.e., while on oral CAB and the current two NRTIs), you will be asked to remain on the study for about 4 weeks. If the discontinuation of study drugs occurred during Part 2 of the study (i.e., while on CAB LA and VRC07-523LS), you will be asked to remain on the study for an additional 48 weeks while on Part 3 of the study. This is because the study staff will need to monitor you since CAB LA can remain in the body for about 48 weeks after the last dose.

During the study:
If you must permanently stop having CAB LA and VRC07-523LS during Step 2 before your study participation is over, the study staff will discuss other options that may be of benefit to you. You will be asked to restart your anti-HIV drugs that you were on before you entered the study or another ART regimen depending on the results of the resistance testing or other considerations by your doctor.

After the study:
After you have completed your study participation at the end of Part 3, the study will not continue to monitor and follow you. Also, the study will not provide you with CAB LA and VRC07-523LS that you received on the study because its use in the general population is still being studied. You will be asked to return to your regular doctor and resume treatment as recommended.

CAN I CHOOSE THE TYPES OF RESEARCH THAT MY SAMPLES AND INFORMATION ARE USED FOR?

Use of Your Samples Required for this Study
The study staff will determine if samples of your blood from before you started HIV medication is already stored at your site or at a central storage facility, or stored from an earlier research study. If a sample is available, the study team will request storage of some of this sample for future testing as part of this study.

During this study, some of your blood samples will be stored and used for testing that is required for this study. The tests that will be done include measurement of the amount of HIV in the blood cells and plasma, measurement of the levels of CAB LA and VRC07-523LS, and tests to determine if there are changes in the immune (infection-fighting) cells before and after administration of CAB LA and VRC07-523LS.

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.

The tests described above are required by this study. If you do not agree to the storage or testing that has been described above, you should not join this study.

WHAT IF I BECOME PREGNANT DURING THIS STUDY?

If you can become pregnant, you must have a pregnancy test before entering the study, and the test result must be available at the study clinical research site. The test must show that you are not pregnant in order for you to take part in the study. You will also be given a pregnancy test at the scheduled visits during Parts 1 and 2 of the study.

If you are pregnant, you will need to stop taking CAB and VRC07-523LS right away and will complete the premature study treatment discontinuation evaluations. You should also not breastfeed for 48 weeks after the last dose of CAB LA. If you are pregnant or become pregnant within 48 weeks after the last dose of CAB LA, you may remain on study during your pregnancy or you may leave the study. If you agree to remain on the study, you will continue to have regularly scheduled study visits and samples collection. Blood tests will be limited to those performed to assess safety, measure the levels of CAB LA and VRC07-523LS (i.e., pharmacokinetic (PK) studies), and measure antibodies to VRC07-523LS in your body. The study staff will talk to you about your choices.

This study will not provide care or cover any cost related to your pregnancy, the delivery of your baby, or the care of your baby. The study will not provide any drugs during pregnancy. You must arrange for your care and your baby's care outside of this study. If you need help finding a health care provider for your pregnancy, the site staff will try to help you with this. You and your primary care doctor will decide which anti-HIV drugs are best for you while pregnant. The study doctor will provide your primary care doctor with information about the study drugs that you have been exposed to in the course of the study.

Long-term follow-up is recommended for babies whose mothers take anti-HIV drugs during pregnancy. The study staff will talk with you about long-term follow-up and the possibility of enrolling your baby in a long-term follow-up study.
Site staff will request to contact you regarding your pregnancy. We will collect information about you and about the delivery and health of your baby (even if your participation in the study has ended).

If you become pregnant, your pregnancy will be reported to an international database (The Antiretroviral Pregnancy Registry) that collects information about pregnancies in **individuals**

taking anti-HIV drugs. This report will not use your name or other information that could be used to identify you.

ARE THERE RISKS RELATED TO PREGNANCY?

You should not take part in this study if you are pregnant or intend to become pregnant in the next 2 years. Mothers should not breastfeed a baby while on this study. Since CAB (oral and **LA** injections) and VRC07-523LS are experimental, the risks to a pregnant **individual** or fetus are not fully known.

If you are having sex that could lead to pregnancy, you must agree not to become pregnant. If you can get pregnant, you must talk to your study doctor about birth control and use it all of the time. You must use an effective form of birth control from 30 days before you start the study until 48 weeks after your last dose of study drugs in Part 2 of the study. If you do not enter Part 2 of the study, then you must continue to use effective birth control for only 30 days after your last oral dose of study drug in Part 1. You must choose one of the birth control methods listed below:

- Intrauterine device or intrauterine system
- Birth control medications that prevent pregnancy given as pills, shots, or placed on or under the skin (i.e., contraceptive subdermal implant, combined estrogen and progestogen oral contraceptive, injectable progestogen, percutaneous contraceptive patches)
- Contraceptive vaginal ring

If you become pregnant while on study, the study staff would like to obtain information from you about the outcome of the pregnancy (even if it is after your participation in the study ends). If you are taking anti-HIV drugs when you become pregnant, your pregnancy will be reported to an international database that collects information about pregnancies in **individuals** taking anti-HIV drugs. This report will not use your name or other information that could be used to identify you.

<u>Breastfeeding</u>
It is unknown whether the study drug passes through the breast-milk and may cause harm to your infant. You must not breastfeed if you are in this study. You should also not breastfeed for 48 weeks after the last dose of CAB LA on Part 2 of the study.

In one study evaluating CAB in pregnant rats and their newborn pups, there was a higher rate of pups that died at the time of delivery or shortly after delivery in the rats that received a 1000 milligrams per kilogram dose of CAB compared to pregnant rats who did not receive CAB. This finding did not occur in pregnant rats who received two lower doses (0.5 and 5 milligrams per kilogram) of CAB. The blood levels of CAB given in this study are expected to be lower than the blood levels in pregnant rats where this finding was observed. The significance of this finding on human pregnancies is not known. Birth defects have not been observed in animal studies with CAB, to date.

<u>Risk of neural tube defects with the HIV-1 Integrase inhibitor dolutegravir (DTG)</u>
In one ongoing birth outcome study, early results show that 4 of 426 (0.9% or nearly 1 in every 100) pregnancies of **individuals** who were taking DTG at the time they became pregnant had

babies with serious brain and spine defects, compared to 0.1% (one in every 1000) pregnancies of **individuals** who were not taking DTG. These defects happen early in pregnancy, within the first month, before many **individuals** even know they are pregnant. In an updated analysis of this same birth outcome study, no neural tube defects occurred in an additional 170 babies exposed to DTG at the time of conception, which translated to a revised neural tube defect incidence rate of 0.7% in DTG-exposed babies.

CAB is not the same drug as DTG. We do know that CAB and DTG belong to the same class of medications and work in a similar way to treat HIV infection. We do not know if CAB can cause nervous system defects in babies. **There may be unknown risks to a pregnancy, embryo, or fetus if you become pregnant.**

ARE THERE BENEFITS TO TAKING PART IN THIS STUDY?

You should not expect any direct benefit from being in this study. CAB and VRC07-523LS have been given to only a small number of people living with HIV-1. The impact of CAB and VRC07-523LS on HIV infection is unknown, and no guarantee of any benefit can be made. The information learned from this study may help others who are living with HIV-1.

WHAT OTHER CHOICES DO I HAVE BESIDES THIS STUDY?

You can choose not to be in this study, continue with your normal medication regimen, and just be followed routinely by your regular doctor or health care provider.

Please talk to your study doctor about these and other choices available to you. Your **study** doctor will explain the risks and benefits of these choices.

WILL I RECEIVE THE RESULTS OF ANY TESTS?

You will receive the results of routine laboratory tests (e.g., blood counts, viral load, liver and kidney tests) that are performed at the study visits. You will be told of any new information learned during the course of the study that might cause you to change your mind about staying in the study. At the end of the study, you will be told when study results may be available and how to learn about them. As with all studies, if we find out important information that may affect your care, you will be provided with those results.

WHAT ARE THE RISKS OF THE STUDY?

If you participate in this study, you will stop taking anti-HIV drugs that have been working well to control HIV. You will be given an experimental combination that has unknown efficacy. There is a risk that HIV could rebound (meaning virologic failure could occur). If HIV rebounds, there is a risk that it could become resistant to CAB and/or other anti-HIV drugs in the same class.

The drugs used in this study may have side effects, some of which are listed below. Please note that these lists do not include all the side effects seen with these drugs. These lists include the more serious or common side effects with a known or possible relationship.

If you have questions concerning additional study drug side effects, please ask the medical staff at your site.

There is a risk of serious and/or life-threatening side effects when non-study medications are taken with the study drugs. 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 while on the study. Also, you must tell the study doctor or nurse before enrolling in any other clinical trials while on this study.

Use of Combination Antiretroviral (ARV) Drugs

Immune Reconstitution Syndrome:
In some people living with advanced HIV, symptoms from other infections or certain diseases may occur soon after starting combination anti-HIV treatment but can also occur later. Some of these symptoms may be life threatening. If you start having new symptoms or notice that existing symptoms are getting worse after starting your ARV therapy, tell your healthcare provider right away.

The use of potent ARV drug combinations may be associated with an abnormal placement of body fat and wasting. Some of the body changes include:

- Increase in fat around the waist and stomach area
- Increase in fat on the back of the neck
- Thinning of the face, legs, and arms
- Breast enlargement

Risks of only Receiving Two NRTIs with Oral CAB

Two NRTIs plus oral CAB is a three-drug combination that is expected to keep HIV controlled. However, there is a risk that there may be side effects from oral CAB or that the combination may not work either because of HIV resistance to one or more of the drugs or if the combination is not taken correctly.

Risks of Study-Provided Drugs

Cabotegravir (CAB) Tablets and CAB Long Acting Injections

The following serious effects may occur with the use of CAB:

- Hypersensitivity reactions. This is a type of allergic reaction that may start as a rash. If you develop a rash while taking CAB, contact your healthcare provider right away, especially if you also have:
  - Blisters or peeling skin
  - Fever
  - General ill feeling
  - Extreme tiredness
  - Muscle or joint pain

  - Blisters or sores in your mouth
  - Redness of the eyes
  - Swelling around your eyes, face, mouth, lips, or tongue
  - Trouble breathing
- Liver problems. Contact your healthcare provider right away if you have any of the following possible symptoms of a liver problem:
  - Yellowing of your skin or of the whites of your eyes (jaundice)
  - Dark or tea-colored urine
  - Pale colored stools
  - Nausea (feeling sick to your stomach) or vomiting
  - Loss of appetite
  - Pain, aching, or tenderness on your right side, below your ribs
- Depression, suicide attempts, or suicide, especially in people with pre-existing history of depression or other mental health problems. If your mental health problems worsen or if you develop suicidal thoughts, call your healthcare provider right away. **If you feel in crisis, you can call 911 and/or a Nationwide Suicide Hotline that is answered 24 hours a day with a skilled, trained counselor. One example is the National Suicide Prevention Lifeline at 1-800-273-TALK (8255).**
- Seizures/convulsions: If you have a history of seizures at any point in your life, please let your study doctor know.

Additional side effects include:
- Headache
- Upper respiratory tract infection. Symptoms may include:
  - Sore throat
  - Cough
  - Runny nose
  - Fever
  - Trouble breathing
- Fever
- Fatigue
- Nausea
- Diarrhea
- Lack of energy or weakness
- Abdominal pain and discomfort
- Back pain
- Trouble sleeping
- Abnormal dreams
- Dizziness
- Joint aches and pains
- Muscle pain and/or breakdown of muscles
- Abnormal liver blood tests
- Increase in the level of enzymes produced in the muscles (creatine phosphokinase)

VRC-HIVMAB075-00-AB (VRC07-523LS)
VRC07-523LS is a type of monoclonal antibody that was developed after the first monoclonal antibody, VRC01. VRC07-523LS has not been tested in studies. Some safety information has been collected from other studies using VCR01LS in people, but these studies have not been completed. A small group of people without HIV and nine people with HIV have received VRC07-523LS and have tolerated it well so far.

With antibody products, most side effects occur within the first 24 hours. This product may have serious allergic reactions, but this is unlikely. These reactions can be life-threatening.

- Anaphylaxis is one type of allergic reaction that may occur soon after an antibody product is given. It includes difficulty breathing, low blood pressure, hives or rash, and swelling in the mouth and face.
- Serum sickness is a delayed type of allergic reaction that may occur several days to 3 weeks after an antibody product is given. It is characterized by hives or rash, fever, big lymph nodes, muscle pains, joint pains, chest discomfort, and shortness of breath.
- You may also experience an increase in liver enzymes, which can be a sign of liver damage.

We expect that there will be a low risk of serious allergic reactions with VRC07-523LS because VRC07-523LS is a fully human antibody that attacks a virus. Some antibodies of the type that attack human proteins are known to increase the risk of serious infections. VRC07-523LS is not expected to increase the risk of serious infections because, as noted above, it attacks a virus.

It is possible that VRC07-523LS will have unexpected effects on the course of your HIV infection, such as changes in CD4+ T-cell count and viral load levels, changes in antiretroviral (ARV) drug sensitivity, or other unknown effects. In addition to the possible risks that are listed above, VRC07-523LS may have other side effects that we do not know about. Participation in this study may limit your eligibility for other future monoclonal antibody studies.

In addition to the side effects listed above, other side effects may include: pain, headache, fever, nausea and vomiting, dizziness, trouble breathing, shortness of breath, tiredness, tightening of the muscles around the bronchial tubes, change in blood pressure (low/high), chills, diarrhea, itchiness, rash, hives, swelling (lip or face), increased heart rate, and chest pain; fainting may occur after receiving the injection, which may result in falling with injury, shaking, stiffening, and other seizure-like activity have also been reported.

Among 25 participants who received VRC07-523LS in a clinical trial, 6 had mild or moderate side events. These included mild dizziness, infusion reactions, and abdominal pain. All the side effects were judged to be related to VRC07-523LS and all of them resolved without any lasting effects. Other symptoms that participants reported included mild bruising at the administration site, mild pain/tenderness at the injection site, general discomfort (not feeling well), muscle aches, headache, chills, nausea, and joint pain.

We will give you any information (including about risks) that becomes available and that may affect your willingness to continue in the study.

This is the first time CAB LA and VRC07-523LS have been given together, so there may be risks associated with this combination that are unknown.

General Side Effects of Injections - Long Acting Medications

The drugs that you will be given by injections in this study are long acting, meaning they stay in your body for a long time. The study medication will be given on a regular set schedule so that the amount of medication in your blood would stay at an effective level. Following an injection of CAB LA, the medication stays in your body for months. In some people, low levels of CAB may be present for more than a year. If you develop a side effect to CAB LA after the injection, there will be no way to remove the drug from your body. You will be taking these drugs as tablets first, which stay in the body for a shorter amount of time. This will help the study staff understand if you might have problems with the drugs when received as an injection. If it appears that you would, based on lab tests before Part 1 ends, then you will not be eligible for Part 2.

If you develop a symptom from these drugs, every effort to treat the symptoms will be made. The amount of drug will decrease over time and will eventually disappear.

During the time that drug is leaving your body, your HIV virus could develop resistance (stop working) to these medicines, even if it is many weeks or months since you last took the drug. When discontinuing long acting HIV treatment, it will be very important to start taking other HIV medications, as recommended by your doctor, to help prevent your HIV from developing resistance to HIV medications. This is why you will re-start your anti-HIV drugs in Part 3 of the study.

Injection Site Reactions

Side effects at the location where you received injections (Injection Site Reactions, ISRs) have been seen with CAB LA. Common side effects could include:

- Pain or redness, swelling, itching, bruising, lumps, and irritation where you receive the injection(s). Most reactions resolve in a week or less.
- The injections that you receive will be given to you in the muscles of your buttock (gluteal muscle).

Study staff may take pictures of ISRs that are thought to be serious and last longer than 2 weeks.

Vasovagal Reactions

Receiving injections can cause some people to feel lightheaded or feel like they might pass out. This reaction, called a “vasovagal reaction,” can occur with many medical procedures. It resolves quickly and is not a direct threat to your health. *[Sites: This text can be modified to fit local cultural language sensitivities; however, the meaning of the precautionary statement must remain.]*

Other Drugs Available Through Routine Care

FTC, TAF, epzicom, abacavir, and lamivudine are available through routine care (i.e., not study-provided drugs) and have the associated risks, as described below. Please refer to the current package insert for additional risks information on these drugs.

Nucleoside Analogues
Lactic acidosis (elevated lactic acid levels in the blood) and severe hepatomegaly (enlarged liver) with steatosis (fatty liver) that may result in liver failure, other complications, or death have been reported with the use of ARV nucleoside analogues alone or in combination. The liver complications and death have been seen more often in **individuals** on these drug regimens. Some nonspecific symptoms that might indicate lactic acidosis include:

- Unexplained weight loss
- Stomach discomfort
- Nausea, vomiting
- Fatigue
- Cramps
- Muscle pain
- Weakness
- Dizziness
- Shortness of breath

Emtricitabine (FTC, Emtriva®)
The following side effects have been associated with the use of FTC:

- Headache
- Dizziness
- Tiredness
- Inability to sleep, unusual dreams
- Loose or watery stools
- Nausea or vomiting
- Abdominal pain
- Rash, itching, which sometimes can be a sign of an allergic reaction
- Darkening of the skin on the palms of the hands and/or soles of the feet
- Increased cough
- Runny nose
- Abnormal liver function tests, which could mean liver damage
- Increases in pancreatic enzyme (a substance in the blood), which could mean a problem with the pancreas
- Increased triglycerides (a type of fat found in the blood)
- Increased creatine phosphokinase (a substance found in the blood), which could mean muscle damage

NOTE: If you are living with both hepatitis B and HIV-1, your liver function may be affected and symptoms caused by hepatitis may get worse if you stop FTC.

Some side effects of FTC may not need any medical attention. As your body gets used to the medicine, these side effects may disappear.

Tenofovir Alafenamide (TAF)
The following side effects have been associated with the use of TAF:

- Nausea, vomiting, gas, loose or watery stools
- Generalized weakness

- Dizziness
- Depression
- Headache
- Abdominal pain
- Worsening or new kidney damage or failure
- Inflammation or swelling and possible damage to the pancreas and liver
- Shortness of breath
- Rash
- Allergic reaction: symptoms may include fever, rash, nausea, vomiting, loose or watery stools, abdominal pain, achiness, shortness of breath, a general feeling of illness, or a potentially serious swelling of the face, lips, and/or tongue
- Bone pain and bone changes such as thinning and softening, which may increase the risk of breakage
- Muscle pain and muscle weakness
- Sleeping problems

NOTES:
- If you are living with both hepatitis B and HIV-1, your liver function may be affected and symptoms caused by hepatitis may get worse if you stop TAF.
- Because there is only a small amount of information on TAF in pregnant and breastfeeding **individuals**, you should not use TAF during pregnancy or if breastfeeding.

Emtricitabine (FTC)/Tenofovir Alafenamide (TAF), Descovy®
No new or unexpected side effects are observed with the FTC 200 mg/TAF 25 mg combination tablet than those observed when each drug is given separately.

Abacavir (ABC, ZIAGEN®)
The following side effects have been associated with the use of abacavir:

People taking abacavir may have a serious allergic reaction that involves several organs of the body. This reaction can be severe or may rarely cause death. Your risk of this allergic reaction is much higher if you have a certain type of gene called HLA-B*5701. Your doctor can determine if you have this by doing a blood test. If you have tested positive for this blood test before, do not take abacavir and let your doctor know right away. If you have two or more of the following while taking abacavir, stop taking the abacavir and call your doctor right away:
- Fever
- Rash
- Upset stomach, vomiting, loose or watery stools, abdominal pain
- General feeling of illness, extreme tiredness, achiness
- Shortness of breath, cough, sore throat.

This serious reaction usually appears within the first six weeks after starting this drug but can occur at any time during treatment. This reaction can be severe and can lead to death especially if abacavir is not stopped. IF YOU STOP ABACAVIR BECAUSE OF AN ALLERGIC REACTION, YOU SHOULD NEVER TAKE ABACAVIR OR ANY OTHER ABACAVIR-CONTAINING MEDICINE AGAIN.

A more severe or fatal allergic-type reactions can occur within hours after abacavir is restarted in people who have stopped abacavir therapy for any reason. If you were taking abacavir, be sure to contact the medical staff at the site before restarting abacavir. Your doctor may want to test your blood for HLA-B*5701. If your doctor decides that it is safe for you to restart abacavir, you may need to be monitored more closely in the clinic or in the hospital.

IF YOU THINK YOU MIGHT BE DEVELOPING A REACTION TO ABACAVIR, STOP ABACAVIR AND CONTACT THE **STUDY** DOCTOR AT THE SITE IMMEDIATELY.

Other than a serious allergic reaction, additional side effects may include:
- Upset stomach
- Vomiting
- Vague overall feeling of discomfort
- Feeling tired
- Decrease in appetite
- Loose or watery stools
- Pancreatitis (inflammation of the pancreas), with one or more of the following: stomach pain, nausea or vomiting
- Headache

Note: It is unclear if abacavir may be associated with heart disease. If you have risk factors for heart disease tell your doctor.

Lamivudine (3TC, EPIVIR®)
The following side effects have also been associated with use of lamivudine:
- Headache
- Feeling tired
- Dizziness
- Numbness, tingling, and pain in the hands or feet
- Depression
- Trouble sleeping
- Rash
- Upset stomach, vomiting, nausea, loose or watery stools
- Pancreatitis (inflammation of the pancreas), which may cause death. If you develop pancreatitis, you may have one or more of the following: stomach pain, nausea, and vomiting
- Abnormal pancreatic and liver function blood tests

Persons who are living with both hepatitis B and HIV should be warned that their liver function may be affected, and symptoms associated with hepatitis (an acute inflammation of the liver) may worsen after lamivudine has been stopped. Although most of these cases have resolved without treatment, some deaths have been reported.

Lamivudine (3TC)/Abacavir (ABC), Epzicom®
No new or unexpected side effects are observed with the ABC 600 mg/3TC 300 mg combination tablet than those observed when each drug is given separately.

Risks Associated with Procedures and Other Risks

Electrocardiogram (ECG)
You may have local skin irritation and redness where the adhesive patches are placed on your skin.

Blood Draw or Intravenous (IV) Placement
Taking blood may cause some discomfort, bleeding, bruising, and/or swelling where the needle enters the body, and in rare cases it may result in fainting. There is a small risk of infection. Placement of an intravenous catheter can cause bleeding, swelling, or bruising where the needle enters the body.

Intramuscular Injections
Although trained study staff will administer the CAB LA injections, it is possible that the person giving you your injection could accidentally give the injection too deeply or not deeply enough, missing the muscle and entering your skin, blood stream or a nerve. The risks of injecting a long acting drug outside of the muscle are not well understood but could include having drug levels that are either too low or too high. The risk of having levels that are too low is that the drug may not work well to control your HIV virus. The risks of having high levels of CAB LA in your body are not well known at this time.

Social Harm
Although the study site will make every effort to protect your privacy and confidentiality, it is possible that your involvement in the study as a participant could become known to others if it is not already and that social harms may result (because you could become labeled as being infected with HIV). For example, you could be treated unfairly or discriminated against by family members, friends, and/or the community.

Other Non-study Medicines
There is a risk of serious and/or life-threatening side effects when non-study medicines are taken with study drugs. For your safety, you must tell your **study** doctor or the study nurse about all medicines you are taking before you start the study and also before starting any new medicines while on the study. Also, you must tell your **study** doctor or the study nurse before enrolling in any other clinical trials while on this study.

Unforseen Risks
Since the study drug is investigational, there may be other risks that are unknown.

Virologic Failure
CAB LA and VRC07-523LS may not control your viral load levels as well as your current ART.

Drug Resistance
Although the study team does not think it likely, you may develop resistance to CAB or other integrase inhibitors as a consequence of participating in this study.

WHAT ABOUT CONFIDENTIALITY?

We will do everything we can to protect your privacy. In addition to the efforts of the study staff to help keep your personal information private, we have a Certificate of Confidentiality from the U.S. Federal Government. This certificate means that researchers cannot be forced to tell people who are not connected with this study, such as the court system, about your participation. Also, any publication of this study will not use your name or identify you personally.

Your records may be reviewed by the U.S. Food and Drug Administration (FDA), the ACTG, the U.S. Office for Human Research Protections (OHRP), or other local, US, and international regulatory entities as part of their duties**, the study site, Advarra IRB** (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. Having a Certificate of Confidentiality does not prevent you from releasing information about yourself and your participation in the study.

Even with the Certificate of Confidentiality, if the study staff learns of possible child abuse and/or neglect or a risk of harm to yourself or others, we will be required to tell the proper authorities.

A description of this clinical trial will be available on www.ClinicalTrials.gov, as required by US law. This Website will not include information that can identify you. At most, the **W**ebsite will include a summary of the results. You can search this **W**ebsite at any time.

WHAT ARE THE COSTS TO ME?

There will be no cost to you for the study-provided drugs, CAB (oral and LA injections) and VRC07-523LS, study-related visits, physical examinations, required laboratory tests, or other procedures. This study will not provide you with other ARV drugs. If you are not able to obtain the two NRTIs that are required in Part 1 of the study, then the study will reimburse you if you have to purchase these drugs. You, your insurance company, or your health care system may need to assume the cost of drugs not provided by the study. 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.

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. **The cost for this treatment could be charged to you or your insurance company.**-There is no program for compensation either through this institution or the **National**

Institutes of Health (NIH). You will not be giving up any of your legal rights by signing **and dating** this consent form.

WILL I RECEIVE ANY PAYMENT?

«Compensation»
You may be reimbursed for your time and travel expenses as part of your participation in this study. [If applicable:] We will reimburse you for the cost of [describe: e.g., traveling to your study visits]. You will be reimbursed approximately [e.g., 2 weeks, 1 month, etc.] after you submit your travel receipts to the study staff.

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 or leave this study at any time. Your decision will not have any impact on your participation in other studies conducted by NIH and will not result in any penalty or loss of benefits to which you are otherwise entitled. You will still be able to receive drugs to treat your HIV outside this study.

We will tell you about new information from this or other studies that may affect your health, welfare, or willingness to stay in this study. If you want the results of the study, let the study staff know.

WHOM TO CONTACT ABOUT THIS STUDY?

During the study, if you experience any medical problems, suffer a research-related injury, or have questions, concerns or complaints about the study, please contact the study doctor at the telephone number listed on the first page of this consent document. If you seek emergency care, or hospitalization is required, alert the treating physician that you are participating in this research study.

An institutional review board (IRB) is an independent committee established to help protect the rights of research participant. If you have any questions about your rights as a research participant, and/or concerns or complaints regarding this research study, contact:

- **By mail:**
  Study Subject Adviser
  Advarra IRB
  6100 Merriweather Dr., Suite 600
  Columbia, MD 21044
- **Or call toll free: 877-992-4724**
- **Or by email: adviser@advarra.com**

Please reference the following number when contacting the Study Subject Adviser: Pro00057341.

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 below **and date it**.

_____	_____
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

APPENDIX I: **STUDY VISITS**

I. Schedule for Clinic Visits

The study staff can answer any questions you have about individual study visits, the evaluations that will occur, or how long each visit will be. The tables below can be used as a quick reference.

A. Appendix Table 1A-1: Schedule for Part 1

Evaluation or Test	Screen	Study Entry	Post-Entry Visits: Oral CAB and NRTIs (week 4 &, if needed, week 5)	Early Discontinuation	Start SOC Treatment (follow-up every 2 weeks for 1 month)
Consent	√				
HIV documentation	√				
Pre-ART HIV-1 RNA and Nadir CD4+ T-cell count documentation		√			
Clinical Assessments	√	√	√	√	√
Complete physical examination	√				
Brief physical examination		√	√	√	√
Medical/medication history	√	√			
Hepatitis screen	√				
CD4+/CD8+ T-cells	√				
Plasma HIV-1 RNA	√	√	√		√ (Wk 7)
Blood sample (for VRC07-523LS susceptibility test)	√				
Blood sample collection (for routine safety tests)	√	√	√	√	
Urinalysis		√			
Pregnancy test	√	√	√	√	√
Study medications dispensed		√	√(Wk 4)		
Non-study provided medications dispensed					√
Confirm availability of pre-ART sample and store, if available		√			
Electrocardiogram (ECG)	√				
Genotype testing			√ (Wk 5)		
Adherence questionnaire		√	√		
Stored blood samples (for future studies)		√	√ (Wk 4)		

B. Appendix Table 1A-2: Schedule for Part 2

Evaluation or Test	Part 2 Entry	Post-Entry Visits				Confirm Virologic Failure	Early Discontinuation
		Most Visits	Some Visits	End of CAB LA and VRC07-523LS (week 44)	Week 48		
Brief physical examination	√	√		√	√	√	√
Clinical assessments	√	√		√	√	√	√
Blood sample collection (for routine safety tests)	√	√		√	√		√
Urinalysis	√				√		√
Pregnancy test	√	All visits					√
CD4+/CD8+ T-cells	√		√		√		√
Plasma HIV-1 RNA	√	√		√	If needed	√	√
Study medications administered	√	√		√			
Stored blood samples (for future studies)	√		√		√	√	√
Genotype testing					√	√	
Stored plasma (for PK of CAB LA)	√		√		√		
Serum collection (for VRC07-523LS PK)		√		√	√	√	
Serum collection (for antibody to VRC07-523LS)		√		√	√	√	
Stored plasma (for additional PK studies)		√		√	√	√	
Infusion report card **distribution**	√	√					
Infusion report card collection		√		√			

C. Appendix Table 1A-3: Schedule for Part 3

Evaluation or test	Part 3 Entry	Post-Entry Visits (SOC ART)		Confirm Virologic Failure	Early Discontinuation
		Weeks 4, 12, 24, 36	Final Visit (week 48)		
Brief physical exam	√	√	√	√	√
Blood sample collection (for routine safety tests)	√	√	√		√
CD4+/CD8+ T-cells	√	√	√	√	√
Plasma HIV-1 RNA	√	√	√	√	√
Genotype testing				√	
Stored PBMC and plasma			√	√	√
Stored plasma and serum (for additional PK studies)		√	√	√	
Adherence questionnaire		√	√	√	√

II. Description of Visits

Screening Visit: After you have read and signed the consent form, you will have several evaluations done to make sure that you meet the requirements for joining the study. You will have a special procedure done called an ECG that will measure the electrical activity of your heart. This is a simple and painless test to show how the heart is doing.

Entry (Part 1 of study): If you are eligible to join the study, you will enter the study. As part of the entry visit, you will switch to the study-provided drug (oral CAB) and continue your current NRTIs. You will be seen at the clinic at 4 weeks (and possibly at 5 weeks) after you enter the study. If the level of HIV in your blood (also known as viral load) goes up to a higher level than what is required while on study, you will be seen at the clinic every 2 weeks for a month (about 30 days) and then will be taken off the study.

Part 2 of study: If the study drugs are working well for you at the end of week 4 or week 5 in Part 1, you will start Part 2 (about 5 weeks after you enter the study). When you enter Part 2 of the study, you will have routine safety labs done only if these tests were not done at the final visit on Part 1 of the study.

You will stop taking the anti-HIV drugs you were on during Part 1 of the study and start taking CAB LA every 4 weeks for 44 weeks and VRC07-523LS every 8 weeks for 40 weeks on Part 2 of the study. You will be seen in the clinic every 2 weeks until week 8, and then every 4 weeks until week 48. If your viral load is over 200 copies/mL, you will have a repeat test done. If the repeat test is still over 200 copies/mL, you will be required to stop the study drugs and your doctor will select a new regimen for you. However, you will be followed on study but off study treatment until the final study visit. Your viral load will be checked at week 48 only if it is not suppressed at week 44.

If you received one dose of CAB LA or VRC07-523LS in Part 2, you will enter Part 3 (the SOC follow-up, see below) at the final visit on Part 2 of the study.

Part 3: In Part 3 of the study, the anti-HIV drugs you received on Part 2 will no longer be provided to you. You will need to start taking the anti-HIV drugs that you were on before you entered this study or another ART depending on the results of the resistance testing. When you enter Part 3 of the study, you will have routine safety labs done only if these tests were not done at the final visit on Part 2 of the study. After you enter Part 3, you will be seen in the clinic at 1 month, 3 months, and then every 3 months for 48 weeks.

Early Discontinuation: If you leave the study before you have been told that your time in the study is ended, you will be asked to return for one final visit.

III. Explanation of Evaluations

Consent and contact information collected
After you read the consent form and have had a chance to ask questions about the study, you will sign **and date** the consent form if you want to continue to be evaluated for study participation. You will also be asked how to be contacted in case you miss a visit or there are problems with your tests, and whether you give the study team permission to contact you.

HIV infection confirmed
If an HIV test has to be done, you may have to sign a separate consent form before this is done. You will be told the results of the HIV test as soon as it is available.

Physical examination
You will have a physical exam and will be asked questions about your health and about any medicines you have taken or are taking now.

Electrocardiogram (ECG)
ECG is a test to measure heart activity. Small adhesive pads connected to wires from the ECG machine will be painlessly placed on your chest and arms. You will be asked to lie down, remain still, and breathe normally for a few minutes during the test.

Blood collected
Blood will be collected from you for various tests during the study. These include: routine safety laboratory tests, HIV-1 viral load (a test that shows how much HIV is in your blood), CD4 count (a test that shows how many infection-fighting cells you have in your blood), liver function tests, and levels of study drugs. Blood will be collected and stored at some other visits.

The site staff can tell you how much blood will be collected at any visit.

Pregnancy test
If you are able to become pregnant, you will be asked to give a small urine or blood sample for a pregnancy test.

HIV-1 Resistance testing
Your blood will be used to see which anti-HIV drugs might work best for you.

Urine collection
You will be asked to provide a small amount of urine that will be used in safety tests.

Adherence Questionnaire
You will be asked how you are feeling when you were taking the anti-HIV drugs and if there were any changes in your medicines since your last visit.

Infusion Report Card (IRC)
You will receive an IRC to take home and use as a memory aid for side effects, on which you will record temperature and symptoms daily, starting on the day of VRC07-523LS infusion, after you leave the clinic, and continue for 3 days until the IRC is completed.

IV. Consent for Use of Samples in Other Studies

Use of Your Other Stored Samples
Some blood that is collected from you during the study might be left over after all required study testing is done. This blood will be stored and, if you give your consent below, may be used for future ACTG-approved research that is not yet planned. This means that researchers who are not part of the protocol team may use your information and samples in different types of future ACTG research to fight HIV and other related diseases without asking you again for your consent.

Some of these research studies may include testing of your genes or your DNA (your own genetic information), as described below. We do not know whether a type of testing called whole genome sequencing, or WGS, might be done. In WGS, researchers look at all of your genes and at almost all of your DNA. In "standard" genetic testing, researchers look at specific genes or subsets of genes, but not at all genes. It is hard to predict the exact amount of blood that will be left over after all required study testing is completed, but it will be no more than 10 tablespoons.

As noted above, none of your samples will have any private information about you on their labels. You may decide whether this "extra" blood may be stored and, if so, whether additional testing may be performed on it. You may withdraw your consent for research on your extra samples at any time and the specimens will be discarded.

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 is not likely to ever know who you are.

Your blood will be kept frozen for an indefinite length of time. We cannot ensure that you will be told of the results of the research done on your blood.

For each of the questions below, choose the response that matches what you want by putting your initials in the space provided. Please ask the staff any questions that you have before you indicate your selections.

Research Without Human Genetic Testing – OPTIONAL (Research on leftover blood; no human genetic testing)

If you agree, some of your blood that is left over after all required study testing is done may be stored (with usual protection of your identity) and used for ACTG-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 blood.

OR

____ (initials) I understand but I do not agree to this storage or possible use of my blood.

Research With Human Genetic Testing – OPTIONAL (Human genetic research on leftover blood)

The ACTG has two studies that collect samples and consent for genetic testing.

In the US, this study is A5128, Plan for Obtaining Informed Consent to use Stored Human Biological Materials (HBM) for Currently Unspecified Analysis

Outside the US, this study is A5243, Plan for Obtaining Human Biological Samples at Non-U.S. Clinical Research Sites for Currently Unspecified Genetic Analyses

Your site might ask you if you would like to participate in the study that is being done where you live. If you would like to participate, you will sign and date a separate consent form.

Your extra samples will not be used for human genetic testing unless you sign and date a consent form for A5128 or A5243.

If you agree, some of your blood will be saved (with protectors of identity that will not have your name on the sample) and tested in the future (after the study is done) to help understand how CAB and VRC07-523LS and methods of preventing HIV work. Some genetic tests may be done (after the study has been completed) to see if different types of immune responses to CAB LA and VRC07-523LS are related to genetic differences in people. You will not receive the results of these studies because they are experimental tests.

Please initial below if you agree to have any of your blood used for ACTG-approved HIV-related research that includes human genetic testing, and may include whole genome sequencing (WGS).

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

OR

____ (initials) I understand but I do not agree to this storage or possible use of my blood.

If you decide now that your samples can be stored for research to be done at a later date, you may change your mind at any time. If you change your mind, you must contact your study doctor or nurse and let them know that you do not want your samples used for research to be done at a later date. Every effort will then be made to destroy your left-over samples.

Sharing Genetic Data - OPTIONAL

Genetic Research Databases: If you agreed to possible genetic testing of your blood above, researchers may want to share genetic information (with protection of your identity) with other researchers around the world, so that they can learn more about the causes and treatment of diseases. They may store this information in dbGaP, a genetic database maintained by the National Institutes of Health, as well as in other protected databases.

____ (initials) I understand and I agree to this possible sharing of my genetic data.

OR

____ (initials) I understand but I do not agree to this possible sharing of my genetic data.