A5359

The LATITUDE Study
Long-Acting Therapy to Improve Treatment SUccess in Daily LifE

A Phase III Study to Evaluate Long-Acting Antiretroviral Therapy in Non-adherent HIV-Infected Individuals

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

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The National Institute of Allergy and Infectious Diseases

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The National Institute of Mental Health
The National Institute on Drug Abuse

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Antiretroviral Therapy Strategies Transformative Science Group (ARTS TSG):	**Timothy Wilkin, MD, MPH, Chair**
Protocol Co-Chairs:	**Jose Castillo-Mancilla, MD** **Aadia Rana, MD**
Protocol Co-Vice Chairs:	**Raphael Landovitz, MD, MSc** **Karen Tashima, MD**
DAIDS Clinical Representatives:	**Tia Morton, RN, MS** **Lawrence Fox, MD, PhD**
Clinical Trials Specialist:	**Chanelle Wimbish, BS, CCRP**

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ACTG
AIDS CLINICAL TRIALS GROUP

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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 US 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 (eg, 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

A5359 is a multicenter study open to all ACTG US clinical research sites (CRSs) including Puerto Rico.

PROTOCOL TEAM ROSTER

Co-Chairs
Jose Castillo-Mancilla, MD
University of Colorado Hospital CRS
Infectious Diseases/Medicine
12700 East 19th Avenue, B168
Aurora, CO 80045
Phone: 303-724-4934
E-mail: jose.castillo-mancilla@cuanschutz.edu

Aadia Rana, MD
Alabama CTU
845 19th Street South, BBRB 206
Birmingham, AL 35205
Phone: 205-934-1268
E-mail: airana@uabmc.edu

Co-Vice Chairs
Raphael Landovitz, MD, MSc
University of California, Los Angeles CARE Center CRS
Center for Clinical AIDS Research & Education
911 Broxton Avenue, Suite 200
Los Angeles, CA 90024
Phone: 310-825-3782
E-mail: rlandovitz@mednet.ucla.edu

Karen Tashima, MD
The Miriam Hospital (TMH) CRS
M-974112
164 Summit Avenue
Providence, RI 02906
Phone: 401-793-4089
Phone: 401-793-4979
E-mail: ktashima@lifespan.org

DAIDS Clinical Representatives
Lawrence Fox, MD, PhD
TRP/DAIDS/NIAID/NIH
HIV Research Branch
5601 Fishers Lane
Room 9E41
Rockville, MD 20852
Phone: 240-627-3069
E-mail: lfox@niaid.nih.gov

Tia Morton, RN, MS
DAIDS/NIAID/NIH/HIVRB
5601 Fishers Lane
Room 9E48
Rockville, MD 20852
Phone: 240-627-3073
E-mail: frazierti@niaid.nih.gov

Clinical Trials Specialist
Chanelle Wimbish, BS, CCRP
ACTG Network Coordinating Center
Social & Scientific Systems, Inc.,
A DLH Holdings Company
8757 Georgia Avenue, 12th Floor
Silver Spring, MD 20910
Phone: 301-628-3367
E-mail: chanelle.wimbish@dlhcorp.com

Statisticians
Irena Brates, MSPH
Statistical and Data Analysis Center
Harvard T.H. Chan School of Public Health
FXB Building, Room 625
651 Huntington Avenue
Boston, MA 02115-6017
Phone: 617-432-2809
E-mail: ibrates@sdac.harvard.edu

Statisticians (Cont'd)
Ellen S. Chan, MSc
Statistical and Data Analysis Center
Harvard T.H. Chan School of Public Health
651 Huntington Avenue
FXB 539
Boston, MA 02115
Phone: 617-432-4879
E-mail: echan@sdac.harvard.edu

Lu (Summer) Zheng, PhD
Statistical and Data Analysis Center
Harvard T.H. Chan School of Public Health
FXB Building, Room 613
651 Huntington Avenue
Boston, MA 02115-6017
Phone: 617-432-3021
E-mail: szheng@sdac.harvard.edu

Data Manager
Sara Sieczkarski, PhD
ACTG Data Management Center
Frontier Science and Technology Research Foundation, Inc.
4033 Maple Road
Amherst, NY 14226
Phone: 716-834-0900 x7372
E-mail: sieczka@frontierscience.org

Primary DAIDS Pharmacist
Katherine Shin, PharmD, RPh
OCSO/DAIDS/NIAID/NIH
Pharmaceutical Affairs Branch
5601 Fishers Lane
Room 9D30
Rockville, MD 20852
Phone: 240-627-3047
E-mail: kashin@niaid.nih.gov

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

Pharmacologists
Ed Acosta, PharmD
Alabama Therapeutics CRS
University of Alabama at Birmingham School of Medicine
1670 University Boulevard
Volker Hall, Room 258
Birmingham, AL 35294-0019
Phone: 205-934-2655
E-mail: eacosta@uab.edu

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

Charles Venuto, PharmD
University of Rochester Adult HIV Therapeutic Strategies Network CRS
265 Crittenden Boulevard
Rochester, NY 14642
Phone: 585-276-5622
E-mail: charles.venuto@chet.rochester.edu

Virologist
Jonathan Li, MD, MMSc
Brigham and Women's Hospital
Harvard Medical School
65 Landsdowne Street, Room 435
Cambridge, MA 02139
Phone: 617-768-8476
E-mail: jli@bwh.harvard.edu

Investigators
Omar Galarraga, PhD
The Miriam Hospital (TMH) CRS
121 South Main Street,
G-S121-7
Providence, RI 02912
Phone: 401-863-2331
E-mail: omar_galarraga@brown.edu

Investigators (Cont'd)
Steven Shoptaw, PhD
UCLA Vine Street Clinic CRS
10880 Wilshire Boulevard, Suite 1800
Los Angeles, CA 90024
Phone: 310-794-6206
E-mail: sshoptaw@mednet.ucla.edu

Michael Stirratt, PhD
NIMH Division of AIDS Research
5601 Fishers Lane, Rm 9G28, MSC 9830
Bethesda, MD 20892
Phone: 240-627-3875
E-mail: stirrattm@mail.nih.gov

David Wohl, MD
Chapel Hill CRS
Suite 2100, Bioinformatics Building
130 Mason Farm Road
Chapel Hill, NC 27514
Phone: 919-843-2723
E-mail: wohl@med.unc.edu

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

Laboratory Technologist
Cheryl Jennings, BS
Rush University Medical Center
Clinical Retrovirology Research Laboratory
859 Jelke Building
1750 West Harrison Street
Chicago, IL 60612
Phone: 312-942-5954
E-mail: cheryl_jennings@rush.edu

Community Scientific Subcommittee (CSS) Representative
Michael Dorosh, MA
University of Colorado Hospital CRS
38 W. Maple Avenue
Denver, CO 80223-1839
Phone: 303-777-5737
E-mail: michael@ontheten.org

Industry Representatives
Ronald D'Amico, DO, MSc
Five Moore Drive
Research Triangle Park
Durham, NC 27709
Phone: 919-315-7489
E-mail: Ronald.d.damico@viivhealthcare.com

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

Kati Vandermeulen, MSc
Janssen Pharmaceutical**s** Inc.
Turnhoutseweg 30
Beerse, 2340
Belgium
Phone: 324-735-31109
E-mail: kvanderm@its.jnj.com

Rodica Van Solingen-Ristea, MD
Janssen **R&D**
Turnhoutseweg 30
Beerse, 2340
Belgium
Phone: +32 478-63-2199
E-mail: rvsolin1@its.jnj.com

Industry Representatives (Cont'd)
Paul Wannamaker
ViiV Healthcare
5 Moore Drive
Mail Stop 5.3C
Research Triangle Park, NC 27709
Phone: 919-259-2554
E-mail: paul.g.wannamaker@viivhealthcare.com

Laboratory Data Managers
Frederic Bone
Frontier Science & Technology Research Foundation, Inc.
4033 Maple Road
Amherst, NY 14226
Phone: 716-834-0900
E-mail: bone@frontierscience.org

Kathleen Shepherd, MPH
Frontier Science Foundation, Inc.
4033 Maple Road
Amherst, NY 14226
Phone: 716-834-0900 x7370
E-mail: kshepherd@frontierscience.org

Laboratory Specialists
Ceora Beijer, BS
ACTG Laboratory Center at UCLA (ALC-UCLA)
675 Charles E. Young Drive S
Los Angeles, CA 90095
Phone:
E-mail: cbeijer@milabcentral.org

Kathie Ferbas, PhD
ACTG Laboratory Center at UCLA (ALC-UCLA)
675 Charles E. Young Drive South
Los Angeles, CA 90095
Phone: 310-780-3639
E-mail: kferbas@milabcentral.org

STUDY MANAGEMENT

All questions concerning this protocol should be sent to actg.leada5359@fstrf.org via email. The appropriate team member will respond with a "cc" to actg.leada5359@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.prota5359 email group. Include the protocol number in the email subject 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 protocol team.

- Send an email message to actg.leada5359@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 pharmacologists.

- Send an email message to actg.leada5359@fstrf.org (ATTN: **Ed Acosta, Jen Kiser, and** Charles Venuto).

Data Management

- For nonclinical questions about transfers, inclusion/exclusion criteria, electronic case report forms (eCRFs), randomization/registration, and other data management issues, contact the data manager. Completion guidelines for eCRFs and participant completed CRFs can be downloaded from the FSTRF website at www.frontierscience.org.
- For transfers, reference the Study Participant Transfer SOP 119, and contact Sara Sieczkarski directly.
- For other questions, send an email message to actg.leada5359@fstrf.org (ATTN: Sara Sieczkarski).
- Include the protocol number, PID, and a detailed question.

Randomization/Participant Registration
For randomization/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 e-mail message to actg.user.support@fstrf.org or call 716-834-0900 x7302.

Computer and Screen Problems
Contact the User Support Group at the Data Management Center (DMC).
- 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.leada5359@fstrf.org (ATTN: **Chanelle Wimbish**).

Copies of the Protocol
To request a hard copy of the protocol, send a message to ACTGNCC@dlhcorp.com via email. Electronic copies can be downloaded from the ACTG Web site (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 **Chanelle Wimbish** at **chanelle.wimbish@dlhcorp.com.**

Study Product
For questions or problems regarding study product, dose, supplies, records, and returns, email Katherine Shin and Cynthia Parker, protocol pharmacists, at kashin@niaid.nih.gov and cindy.parker@nih.gov.

Study Drug Orders
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 A5359 team members.
- Send an email to actg.leada5359@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

ABC	abacavir
AE	adverse event
AIDS	acquired immunodeficiency syndrome
ALT	alanine aminotransferase
ANC	absolute neutrophil count
ART	antiretroviral therapy
ARV	antiretroviral
AST	aspartate aminotransferase
BUN	blood urea nitrogen
CAB	cabotegravir (GSK1265744)
CDC	Centers for Disease Control and Prevention
CEI	conditional economic incentives
CKD-Epi	**Chronic Kidney Disease Epidemiology Collaboration equation**
CLIA	Clinical Laboratory Improvement Amendments
CRPMC	NIAID Clinical Research Products Management Center
DAERS	DAIDS Adverse Events Reporting System
DBS	dried blood spots
DMC	Data Management Center
EAE	expedited adverse event
EC	Ethics Committee
eCRF	electronic case report form
FDA	Food and Drug Administration
GCLP	Good Clinical Laboratory Practice
HCV	hepatitis C virus
HRU	healthcare resource utilization
IM	intramuscular
IND	investigational new drug
INSTI	integrase strand transfer inhibitor
IQA	Immunology Quality Assurance
IRB	Institutional Review Board
IRC	infusion report card
ISR	injection site reaction
IUD	intrauterine device
IV	intravenous

LA	long-acting
LPC	laboratory processing chart
mg	milligram
MOPS	Manual of Procedures
OHRP	Office for Human Research Protections
OLI	oral lead-in
PBMC	peripheral blood mononuclear cell
PI/cobi	boosted protease inhibitor
PID	patient identification number
PK	pharmacokinetics
PSWP	protocol specific webpage
RPV	rilpivirine
RSC	Regulatory Support Center
SAE	serious adverse event
SID	study identification number
SOE	schedule of evaluations
SOC	standard of care
VL	viral load
WBC	white blood cell
WHO	World Health Organization

SCHEMA

A5359

The LATITUDE Study
Long-Acting Therapy to Improve Treatment SUccess in Daily LifE

A Phase III Study to Evaluate Long-Acting Antiretroviral Therapy in Non-adherent HIV-Infected Individuals

DESIGN

A phase III, prospective, randomized, open-label trial comparing Long-Acting (LA) Antiretroviral therapy (ART) with rilpivirine (RPV) LA and cabotegravir (CAB) LA versus Standard of Care (SOC) in previously non-adherent individuals. The study has four steps.

In Step 1, participants will be initiated on a SOC oral induction regimen consisting of a ≥3-drug ART regimen with ≥2 drugs predicted to be fully active including a boosted protease inhibitor (PI/cobi) and/or an integrase strand transfer inhibitor (INSTI) for up to 24 weeks. Participants who achieve milestones will be eligible to receive conditional economic incentives (CEI) at Step 1 (section 5.7).

Step 1 participants are eligible to enter Step 2 if virologic suppression criteria for randomization are met at or after Step 1, week **4** (but before Step 1, week 24). Virologic suppression criteria are defined as: a) HIV-1 RNA ≤200 copies/mL or b) HIV-1 RNA of 201-399 copies/mL followed by HIV-1 RNA ≤200 copies/mL prior to Step 1, week 24. Eligible participants will enter Step 2 and be randomized 1:1 to switch to oral RPV + oral CAB for 4 weeks (optional) followed by RPV-LA + CAB-LA every 4 weeks (Q4) until the end of Step 2 or to continue on SOC for 52 weeks (see Table 5.2.1-2).

At the completion of Step 2, eligible participants randomized to SOC will have the option to register to Step 3 and cross over to the LA strategy, which includes oral RPV + oral CAB for 4 weeks (optional see section 5.2.1) followed by RPV-LA + CAB-LA Q4 weeks until the end of Step 3; participants already on RPV-LA + CAB-LA in Step 2 will continue on this regimen in Step 3 for 52 weeks (see Table 5.2.1-3).

At the completion of Step 3, participants will transition to locally sourced RPV-LA + CAB-LA, (if possible and available) and will no longer be followed on study. If access to locally sourced RPV-LA + CAB-LA cannot be attained or participant requests to switch to oral ART, those participants will enter Step 4 and be followed for 52 weeks on locally sourced oral ART. If **the participant can access** LA ART during follow-up in Step 4, and the participant and provider decide to restart LA ART,

they will be allowed to do so. In that case, the participants will not be followed by the study after restarting LA ART.

In addition, any participant who receives at least one dose of CAB-LA or RPV-LA, and prematurely discontinues study treatment prior to the end of Step 3, will complete their Step (2 or 3) off treatment, and then register to Step 4 to be followed on locally sourced oral ART for 52 weeks after his or her last dose of any LA injectable.

DURATION

Up to 180 weeks (up to 24 weeks in Step 1, 52 weeks in Step 2, 52 weeks in Step 3, and up to 52 weeks in Step 4).

SAMPLE SIZE

A maximum of 640 participants in Step 1 for Step 2 to achieve an accrual target of 320 participants (160 in each arm).

POPULATION

ART-experienced, **non-pregnant people** with HIV**-1** who are ≥18 years of age with:

- Evidence of non-adherence according to at least one of the following criteria:
  - Poor virologic response within 18 months prior to study entry (defined as <1 $\log_{10}$ decrease in HIV-1 RNA or HIV-1 RNA >200 copies/mL at two time points at least 4 weeks apart) in individuals who have been prescribed ART for at least 6 consecutive months.
  - Loss to clinical follow-up within 18 months prior to study entry with ART non-adherence for ≥6 consecutive months. Lost to clinical follow-up is defined as either no contact with provider or missed 2 or more appointments in a 6-month period. ART non-adherence is defined as a lapse in ART ≥7 days (consecutive or non-consecutive), in the 6-month period where they were lost to clinical follow-up per participant report.
- No evidence of any clinically relevant RPV or INSTI resistance-associated mutations through commercially available resistance testing analyses (historically or upon screening).
- Ability of site clinician, in conjunction with participant, to construct a ≥3-drug ART regimen with ≥2 drugs predicted to be fully active, including a boosted PI/cobi and/or an INSTI. Drugs for oral regimens will be made available to study participants according to PSWP.

REGIMEN

Step 1, Induction: All participants will receive SOC (oral induction ART regimen) with CEI for up to 24 weeks.

Step 2, Randomization: Participants who achieve virologic suppression criteria at or after Step 1, **w**eek **4**, will be randomized to Step 2 in a 1:1 ratio to either of the **two** treatment arms:

- Arm A: Oral RPV + oral CAB for 4 weeks (optional) followed by RPV-LA + CAB-LA Q4 weeks until the end of Step 2 (Table 5.2.1-2).

- Arm B: Continuation of SOC for 52 weeks.

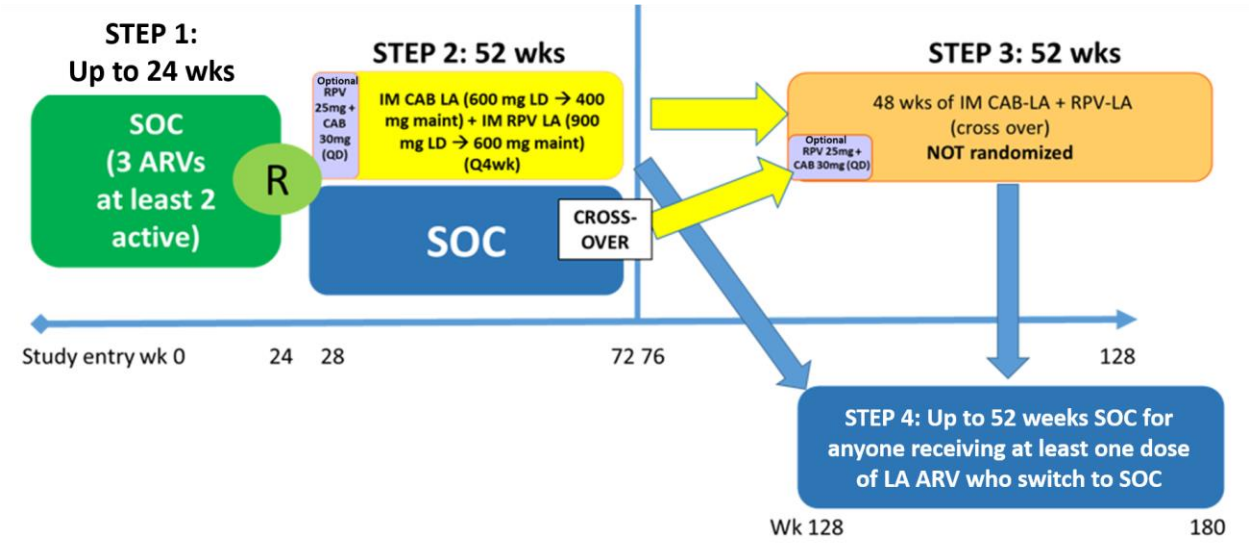
Step 3, Continuation/Crossover:

- Arm A participants (LA ART arm) will continue on RPV-LA + CAB-LA Q4 weeks for 52 weeks until completion of Step 3.

- Arm B participants (SOC arm) who are virologically suppressed (HIV-1 RNA ≤200 copies/mL) at Step 2, week 48, or HIV-1 RNA of 201-399 copies/mL at Step 2, week 48, followed by HIV-1 RNA ≤200 copies/mL by Step 2, week 52, will have the option to switch to oral RPV + oral CAB for 4 weeks (optional) followed by RPV-LA + CAB-LA Q4 weeks until the end of Step 3 (Table 5.2.1-3).

Step 4, Observation: All participants who enter Step 4, as outlined in study design above, will be followed until they complete 52 weeks on locally sourced oral ART or restart LA ART if it becomes available.

Standardized adherence support will be provided by sites throughout each step of the study (refer to the Manual of Procedures [MOPS]).



Schema Figure 1: Schema Diagram

1.0 HYPOTHESIS AND STUDY OBJECTIVES

1.1 Hypothesis

After achieving suppression during a period of incentivized standard of care (SOC) (up to 24 weeks), long-acting (LA) antiretroviral therapy (ART) consisting of RPV-LA + CAB-LA will be a more successful therapy compared to a SOC regimen in keeping previously non-adherent persons with HIV on treatment and virologically suppressed.

1.2 Primary Objective

To compare regimen **efficacy** of LA ART (using RPV-LA and CAB-LA) to SOC in previously non-adherent persons with HIV by 48 weeks of follow-up after an incentivized oral induction period.

1.3 Secondary Objectives

1.3.1 To compare virologic efficacy between LA ART using RPV-LA and CAB-LA and SOC at 48 weeks following an incentivized oral induction period in previously non-adherent persons with HIV.

1.3.2 To assess the safety and tolerability of the LA ART regimen versus the SOC regimen in previously non-adherent persons with HIV after an incentivized oral induction period.

1.3.3 To estimate the HIV-1 RNA viral decline at 4, 8, 12, 16 and 20 weeks after initiation of oral ART in Step 1 in previously non-adherent persons with HIV utilizing CEI to promote adherence.

1.3.4 To assess participant acceptability and treatment satisfaction with LA ART versus SOC.

1.3.5 To assess adherence (self-reported, self-efficacy, and missed or delayed injections [defined as 8 days beyond scheduled injection day] for LA ART), among previously non-adherent persons with HIV randomized to LA ART versus SOC.

1.3.6 To compare the rates of new drug-resistance mutation development in individuals who develop virologic failure between the LA ART versus SOC and determine factors associated with emerging drug resistance.

1.4 Exploratory Objectives

1.4.1 To assess long-term durability of LA ART in Step 3 for persons with HIV with a history of non-adherence randomized to LA ART.

1.4.2 To assess virologic efficacy of returning to an oral ART regimen after receiving at least one dose of LA ART.

1.4.3 To evaluate factors associated with viral suppression during Step 1 including socio-demographic, substance abuse, health, and behavioral health-related measures.

1.4.4 To evaluate factors associated with maintenance of virologic suppression at Step 2, week 48, including socio-demographic, substance abuse, health, and behavioral health- related measures within each arm.

1.4.5 To evaluate factors associated with virologic suppression at Step 3, week 48, including socio-demographic, substance abuse, health, and behavioral health measures.

1.4.6 To evaluate factors associated with virologic suppression at Step 4, week 48, including socio-demographic, substance abuse, health, and behavioral health measures.

1.4.7 To develop a repository of biologic samples (i.e., plasma and hair) for future research on ART adherence (e.g., ART concentration in dried blood spots (DBS) and hair), inflammation and immune activation in previously non-adherent persons with HIV.

1.4.8 To assess cost-effectiveness of an LA ART strategy with an incentivized oral induction period versus SOC in previously non-adherent persons with HIV.

1.4.9 To assess quality of life in participants randomized to LA ART versus SOC.

1.4.10 To assess stigma associated with HIV in participants randomized to the LA ART versus SOC.

1.4.11 To assess healthcare resource utilization (HRU) in Steps 1 through 3.

1.4.12 To assess efficacy of LA ART, effect of CEI or adherence and behavioral measures specifically in young adults with HIV (18-24 years old) with a history of non-adherence.

1.4.13 To examine the association of HIV treatment outcomes, including virologic failure, at Step 2 and Step 3 with corresponding CAB-LA and RPV-LA pre-dose trough concentrations.

1.4.14 To examine relationship between the hair and DBS concentrations of ARTs with self-reported adherence measures.

2.0 INTRODUCTION

2.1 Background

Durable viral suppression remains the main objective of ART for individuals **with HIV**. However, achieving an undetectable viral load (VL) continues to be a challenge for many individuals in clinical practice [1, 2]. Among the obstacles that hinder ART success, suboptimal drug adherence is responsible for most episodes of failure to achieve and maintain virologic suppression. Up to 25% of individuals on chronic ART may experience episodes of non-adherence, and only a small proportion of adults with HIV in the US are virologically suppressed [3], a suboptimal outcome from both an individual and public health perspective. Thus, improving ART adherence remains of critical importance in HIV treatment.

Rationale for the use of LA ART as an alternative for individuals in whom oral ART is a challenge

Despite the potency of currently available orally administered ART regimens, high levels (≥80-85%) of adherence to daily dosing are still necessary to maintain viral suppression [2, 4]. Although ideal, this level of adherence is unachievable in some individuals due to a wide range of structural, behavioral, social and clinical barriers including patient recollection of scheduled doses, competing priorities (i.e., employment, child care, transportation) stigma, and active mental illness or substance use [5, 6, 7]. Newer LA ART regimens offer the possibility of improving virologic suppression outcomes in previously non-adherent individuals, given the benefits associated with infrequent dosing and the opportunity to implement directly-observed therapy in this population [8, 9]. Recent modeling data have also demonstrated that LA ART could improve survival in non-adherent individuals, while offering a significant cost advantage when compared to SOC [10].

Currently, the combination of GSK1265744 LA (CAB-LA) plus rilpivirine (RPV) LA is the only LA regimen being evaluated for the treatment of HIV infection [8, 11, 12]. CAB-LA is a novel INSTI that can be administered orally or as a LA intramuscular injection [12]. Its oral formulation has been evaluated in an ongoing phase II dose-ranging study randomizing participants to three doses of oral CAB in combination with 2 nucleoside reverse transcriptase inhibitors (NRTIs) in a 24-week lead-in period followed by two-drug maintenance with once-daily oral CAB and RPV versus 2 NRTIs plus once-daily efavirenz (EFV) in treatment-naïve, persons with HIV (LATTE trial) [8, 9]. Recently published 96-week data demonstrated comparable rates of virologic suppression between all CAB dosing arms vs. EFV, with similar incidence of adverse events and the identification of 30 mg/day as the oral CAB dose for further study [13]. Based on these results, the CAB-LA nanoformulation (half-life ~20-50 days) [12], is currently undergoing evaluation in combination with RPV-LA (half-life ~35 days) [14] after a 20-week induction period with oral CAB plus abacavir/lamivudine versus continuation of oral induction in treatment-naïve, persons with HIV (LATTE-2, NCT02120352). Results from this trial demonstrate high levels of viral suppression with CAB-LA and RPV-LA at 96 weeks with comparable response rates among those injected every 4 and 8 weeks (87% in Q4W vs. 94% in Q8W maintained HIV-1 RNA <50 c/mL at W96 compared to 84% on PO) [14].

The First Long-Acting Injectable Regimen (FLAIR; NCT02938520) study is a Phase III non-inferiority study that enrolled 629 treatment-naïve persons with HIV. Participants who achieved viral suppression to <50 copies/mL after 20 weeks of oral daily ART induction with ABC/3TC/DTG were randomized 1:1 to continuation of this oral regimen or switch to IM CAB-LA 400 mg + RPV-LA 600 mg Q4W [15]. The 48-week results from FLAIR demonstrated that 94% of participants in the IM CAB-LA + RPV-LA arm maintained viral suppression to <50 copies/mL, in comparison with 93% of participants in the continuation of daily oral ABC/3TC/DTG arm. This met the pre-specified non-inferiority margin for CAB-LA + RPV-LA, which was set at 6%. Safety and tolerability of IM CAB-LA + RPV-LA were similar to oral daily ABC/3TC/DTG, with 3% versus 1% of adverse events leading to discontinuation in the IM and SOC arms, respectively. Regarding participant preferences, 99% of respondents preferred the IM CAB-LA + RPV-LA over the daily oral therapy. In total, three participants randomized to IM CAB-LA + RPV-LA (all with HIV-1 subtype A1) had confirmed virologic failure with evidence of treatment-emergent resistance for non-nucleoside reverse transcriptase inhibitor (NNRTI) (E138E/A/K/T, K101E) and INSTI (L74I, G140R, Q148R) [15].

The Antiretroviral Therapy as Long-Acting Suppression (ATLAS; NCT02951052) study is also a non-inferiority, randomized phase III study that is evaluating continuation of daily oral SOC ART versus CAB-LA 400 mg IM + RPV-LA 600 mg IM Q4W in persons with HIV with long-standing virologic suppression on a standard-of-care oral regimen [16]. In ATLAS, 616 persons with HIV with at least 6 months of virologic suppression were randomized 1:1 to each arm. At 48 weeks, 92% versus 95% of participants in the LA IM and SOC arms, respectively, maintained viral suppression <50 copies/mL, demonstrating non-inferiority of IM CAB-LA + RPV-LA Q4W in comparison with the SOC arm (similar to FLAIR, a 6% non-inferiority margin was pre-specified). Similar to FLAIR, tolerability and safety were comparable between both arms (2% adverse events in the SOC arm versus 3% in the IM arm, with 1% of injection site reactions [ISRs] leading to discontinuation in the IM arm), with higher participant satisfaction in the CAB-LA + RPV-LA arm [16]. Virologic failure with NNRTI (E138E/A/K, V108I) and/or INSTI (L74I, N155H) -associated mutations was confirmed in three participants in the CAB-LA+ RPV-LA arm, two had A/A1 and one had subtype AG), two of which had NNRTI resistance-associated mutations at baseline (demonstrated by archived HIV-1 DNA).

ATLAS-2M (NCT03299049) randomized approximately 1,020 persons with HIV with virologic suppression receiving oral daily SOC ART or IM CAB 400 mg LA + RPV 600 mg LA Q4W (as part of ATLAS) to either IM CAB-LA + RPV-LA Q4W or Q8W. Similar to ATLAS, this study was designed to demonstrate non-inferiority and safety and tolerability of IM CAB 600 mg LA + RPV 900 mg LA Q8W compared to Q4W IM CAB 400 mg LA + RPV 600 mg LA, which was confirmed to be non-inferior to SOC in ATLAS and FLAIR after a 48-week follow-up [17].

Based on the results of FLAIR and ATLAS, a New Drug Application (NDA) seeking approval for CAB-LA 400 mg + RPV-LA 600 mg IM Q4W was submitted to the FDA on April 29, 2019. On December 21, 2019, the FDA provided a Complete Response Letter to this application citing reasons related to the Chemistry Manufacturing and Controls, without any new concerns about safety.

In addition to the registrational phase III studies, data on the compassionate use program of CAB-LA + RPV-LA IM in 35 patients from 10 countries have recently become available. This program, which used the same dosing as the FLAIR/ATLAS studies (including a one-month oral lead-in [OLI] in some cases), enrolled patients with advanced disease who required parenteral ART and had no key CAB or RPV-associated mutations. From the 28 patients who entered the compassionate use with detectable viremia (10 without administration of oral CAB + RPV lead-in period), 16 (57%, 4/10 without OLI) achieved virologic suppression (<50 copies/mL) with CAB + RPV LA IM, with a median (range) duration of follow-up of 11 (1-47) months, and a median (range) time to virologic suppression of 6 (1-31) months. At the time of last follow-up, 22/35 (63%) remained virologically suppressed to <50 copies/mL. Of the 7/35 patients who were virologically suppressed at the time of initiation of oral CAB + RPV, 6/7 remained suppressed at their last follow-up. Among five (14%) patients who had incomplete virologic responses and stopped CAB-LA + RPV-LA IM treatment, four had NNRTI resistance-associated mutations and two had INSTI resistance-associated mutations at failure [18].

In Phase III studies, virologic failure was confirmed in ~1% of study participants across FLAIR, ATLAS, and ATLAS-2M. In multivariate analysis of pooled data from those three studies, BMI ≥30 kg/m^2, HIV-1 subtype A6/A1, the presence of RPV-associated mutations, and lower week 8 RPV trough concentrations were all significantly associated with increased odds of virologic failure in 13 out of 1039 participants. While less than 1% of participants with zero or one of those risk factors at baseline had virologic failure, this was confirmed in 25% of participants who had at least two baseline factors and in one participant who had all three factors at baseline [19].

Regarding safety in the compassionate use program, the most common adverse events reported were ISRs, but no patients discontinued CAB-LA + RPV-LA due to these. Five patients reported serious adverse events (one of them treatment related), but all continued CAB-LA + RPV-LA IM. In this cohort, three patients died, but none of these events were related to treatment.

Direct-to-Inject

Data on the use of CAB-LA + RPV-LA without the CAB + RPV OLI have also become recently available. Within the FLAIR study, 111 participants transitioned from oral ART to CAB-LA + RPV-LA without the use of the OLI (i.e., direct-to-inject), while 121 received the OLI. At week 124, one participant in each arm had HIV-1 RNA ≥50 copies/mL, and one participant in the direct-to-inject group developed confirmed virologic failure at week 112. Regarding safety, adverse events leading to withdrawal were infrequent, and the number of participants experiencing serious adverse events was comparable between arms. One participant in the direct-to-inject arm had a Grade 4 drug-related adverse event (mixed cellularity Hodgkin's lymphoma) [**20**].

On January 21, 2021, the US Food and Drug Administration (FDA) approved injectable CAB and RPV for the treatment of adults **living with HIV-1** who are virologically suppressed on a stable ART regimen with no known or suspected resistance to either CAB or RPV or a history of treatment failure. The FDA approved the injectable

combination to be administered once a month. Oral CAB was also approved to be used in combination with oral RPV for 1 month prior to starting treatment with the injectable [**21**].

Although these are encouraging and supportive results, none of these studies or the FDA approval relate to the use of LA ART regimens in previously non-adherent individuals. Since non-adherent individuals are one of the main population targets of these LA formulations, addressing this gap is of critical importance to accelerate implementation of these new regimens in the individuals who might benefit from them most.

Rationale for the use of short-term CEI to support adherence with LA ART
Although infrequent dosing will be a very attractive treatment option for many persons with HIV on ART, achieving viral suppression through a short-acting "conventional" oral ART regimen (i.e., dosed daily) is still required prior to transitioning to a maintenance strategy using LA ART. The need for stable and suppressive oral ART represents a major hurdle to the use of an LA ART strategy in those who have challenges to adherence. Thus, useful interventions to improve adherence during this period will still be required.

While a wide variety of interventions have been shown to improve adherence to ARTs, no optimal strategy is applicable to all populations. Evidence-based strategies to address ART adherence include adherence counseling, interactive text messaging, and efforts to address mental health and substance abuse in concert with adherence support. Behavioral interventions have been found to have a modest effect on ART adherence in meta-analyses and are commonly used to varying degrees in standard clinical practice. Behavior modifications through economic incentives have had positive results in studies done for smoking cessation, weight loss, medication adherence, and illicit drug abstinence [**22-25**], particularly if the reward is temporally proximate to the behavior change [**26, 27**]. In the HIV arena, CEI have resulted in improvement in ART adherence in substance users [**28-34**], retention in care, and viral suppression [**35, 36**]. A potential drawback to the use of CEI has been the durability and sustainability of their beneficial effect, limiting their utility to promote high-level adherence over a prolonged horizon and beyond the incentive period [**26, 27, 35**]. To date, data have demonstrated that CEI are successful in promoting adherence for up to 48 weeks, mainly while the incentives remain in place [**33**]. Project Hope, a completed **three**-arm randomized controlled trial (RCT), tested 6 months of patient navigation (PN) and PN plus contingency management (PN+CM) versus treatment as usual (TAU) on 12-month viral suppression rates [**37**]. Average payment to an incentivized PN+CM participant was $668. While there was no difference in viral suppression at 12 months among the three arms, attendance at an HIV care visit at 6 months was highest in the PN+CM arm (PN=79%, PN+CM=87%, TAU=69%, p(PN vs TAU)=.003); p(PN+CM vs PN)=.014) at 6 months and was significantly different between arms. If used as a time-limited intervention to support a short-term behavior, CEI could prove highly effective to optimize adherence and achieve viral suppression in preparation to the use of LA ARV in previously non-adherent individuals. Currently, no data on the efficacy of this approach

are available; however, a substantial analogy to short-term potent effects exists across a wide variety of medical and social contexts [**35, 38, 39**].

The CEI sizes in this protocol are comparable to what has been demonstrated successful among previously non-adherent patients with $100/quarter [**32, 40**] for VL reductions and suppression. In HPTN-065 trial, a multi-site RCT testing CEI on linkage to care and viral suppression, a $70 gift certificate to attain VL was associated with 10% higher proportion of patients with an undetectable VL at care clinics, where fewer than 65% of patients had an undetectable VL at the start of the study [**36**].

Reflecting the myriad barriers that patients with challenges to adherence may face, studies evaluating CEI also included additional strategies to promote adherence including reinforcement of the behavior based on a standard measure and delivered in close proximity with the successful behavior; medication counseling or coaching [**33**]; digital reminders and pill organizers [**33**]; and case management and substance abuse counseling as indicated [**30, 37**]. Similarly, an approach using CEI in this setting will also need to incorporate evidence-based strategies such as case management support and patient-navigation to enhance treatment and care adherence [**41, 42**].

To address the above-mentioned gaps, we propose a randomized study that will compare an LA ART therapeutic strategy to best current practice in previously non-adherent persons with HIV. Given the need to achieve and sustain viral suppression using an oral, short-acting regimen before transitioning to maintenance LA ART therapy, in this strategy we also propose to implement CEI as an intervention aimed at reinforcing early adherence to oral ARTs during the Step 1 OLI phase only (see Design section of the Schema). The CEI program will be complemented by an array of other evidence-based behavioral support approaches for adherence. Each study site is required to create a site-specific adherence intervention plan. The protocol team will assist in developing, implementing and monitoring the adherence intervention plan for each study site.

2.2 Rationale

The proposed study seeks to compare the efficacy, safety, and durability of two different strategies to treat participants with a history of sub-optimal adherence and control of their HIV infection: LA ART versus all-oral SOC/Best Available Regimen after an incentivized induction period of all oral ART. The main advantages of LA ART in this population include infrequent dosing and directly observed therapy during the LA ART phase. To assess the safety and efficacy of this strategy we propose a comparator arm that consists of the best available therapy in the absence of LA ART.

3.0 STUDY DESIGN

This is a phase III, four-step, randomized, open label, controlled study that will assess if LA ART therapy is effective in persons with HIV with a prior history of non-adherence compared to SOC.

Step 1, Induction
Previously non-adherent individuals will be enrolled and undergo a period (up to 24 weeks) of induction SOC ART regimen using conditional economic incentives (CEI). Participants who achieve virologic suppression criteria at or after Step 1, week **4**, defined as: a) HIV-1 RNA ≤200 copies/mL or b) HIV-1 RNA of 201-399 copies/mL followed by HIV-1 RNA ≤200 copies/mL by Step 1, week 24, will be eligible to enter Step 2.

NOTE A: CEI to support adherence will be provided to all participants during Step 1 oral induction phase only. Participants will continue to receive study visit remuneration as per usual site practice throughout study participation (Steps 1-4).

NOTE B: Participants who do not achieve virologic suppression will complete study at Step 1, week 24.

Step 2, Randomization
Eligible participants will be randomized at Step 2 entry in a 1:1 ratio to either of the two treatment arms:

Arm A (LA ART): A combination of oral RPV + oral CAB for 4 weeks (optional) followed by the LA ART Phase, consisting of a two-drug regimen using RPV-LA + CAB-LA Q4 weeks until the end of Step 2 (Table 5.2.1-2). The option to initiate LA ART at the Step 2 Randomization visit without oral RPV + oral CAB is at the discretion of the site investigator of Record (IoR) and participant (see section 2.1, Direct-to-Inject).

Arm B (SOC): Continuation of the SOC for 52 weeks.

Step 3, Continuation/Crossover
Arm A participants will continue on RPV-LA + CAB-LA Q4 weeks for 52 weeks until the end of Step 3. Arm B participants (continuation of SOC) who achieve virologic suppression (HIV-1 RNA ≤200 copies/mL) at Step 2, week 48, or HIV-1 RNA of 201-399 copies/mL at Step 2, week 48, followed by HIV-1 RNA ≤200 copies/mL by Step 2, week 52, will have the option to cross over at the end of Step 2 to oral RPV + oral CAB for 4 weeks (optional) followed by RPV-LA + CAB-LA every 4 weeks until the end of Step 3 (Table 5.2.1-3). Arm B participants who do not wish or are not eligible to cross over will complete study follow-up at Step 2, week 52.

If RPV-LA + CAB-LA becomes available before a participant finishes Step 3, and the participant chooses to continue RPV-LA + CAB-LA as part of their clinical care, their follow-up in the study will end at the completion of Step 3. If for some reason the participant chooses not to continue LA ART at the end of Step 3 or if LA ART is not available, the participant will register to Step 4 and will be followed on locally sourced oral ARV for 52 weeks.

Step 4, Observation
Participants who register to Step 4 will be followed for up to 52 weeks on oral ART. In addition, any participant who receives at least one dose of CAB-LA or RPV-LA at any step, and prematurely discontinues the LA ART prior to end of Step 3, will complete their respective Step (either Step 2 or 3) on study/off study treatment, and will register to Step 4 and followed to complete 52 weeks total on oral ART after their last dose of any LA injectable.

If LA ART becomes available during follow-up in Step 4, and the participant and provider decide to restart LA ART, they will be allowed to do so. In that case, the participants will not be followed by the study after restarting LA ART.

Justification for Step 4: Given the long pharmacokinetic tail of the LA ART formulations, Step 4 has been implemented to ensure ongoing ART and virologic suppression during a period of potential vulnerability when participants could have drug concentrations that may be below the necessary therapeutic thresholds for virologic suppression.

Standardized adherence support will be provided by sites throughout each step of the study (refer to MOPS).

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 FDA-approved kit, which is required for all IND studies.

WHO (World Health Organization) and CDC (Centers for Disease Control and Prevention) 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 **HIV-1 Plasma VL >200 copies/mL within 12 months prior to study entry by any US laboratory that has a Clinical Laboratory Improvement Amendments (CLIA) certification or its equivalent, unless participant has been lost to clinical follow-up (see 4.1.3 NOTE) and no viral load result is available within the last 12 months.**

4.1.3 Evidence of non-adherence to ART according to at least one of the following criteria:

4.1.3.1 Poor virologic response within 18 months prior to study entry (defined as <1 log_{10} decrease in HIV-1 RNA or HIV-1 RNA >200 copies/mL at two time points at least 4 weeks apart) in individuals who have been prescribed ART for at least 6 consecutive months.

4.1.3.2 Lost to clinical follow-up within 18 months prior to study entry with ART non-adherence for ≥6 consecutive months.

NOTE: Lost to clinical follow-up is defined as either no contact with provider or missed ≥**1** appointment in a 6-month period. ART non-adherence is defined as a lapse in ART ≥7 days (consecutive or non-consecutive), in the 6-month period where they were lost to clinical follow-up per participant report.

4.1.4 No evidence of any clinically relevant RPV or INSTI resistance-associated mutations (see MOPS for list of exclusionary mutations) through commercially available genotypic (or phenotypic if available) analyses from any laboratory that has a CLIA certification or equivalent within 60 days of study entry, nor history of such mutations on review of prior **HIV-1 drug** resistance tests by the site investigator. **For participants in whom a screening HIV-1 conventional genotype cannot be resulted by the testing laboratory, review of historical genotypes and treatment history by the IoR can be used to satisfy this criterion (see section 6.3.8).**

4.1.5 Ability of site clinician, in conjunction with participants, to construct an oral induction ARV regimen that must include at least three ARVs of which at least two must be predicted to be fully active. The regimen must, include PI/cobi and/or an INSTI based on screening and/or historic resistance testing.

4.1.6 Laboratory values obtained within 60 days prior to study entry by any laboratory that has a CLIA certification or its equivalent:

- Hemoglobin ≥9.0 g/dL
- Absolute neutrophil count (ANC) ≥600/mm^3
- Alanine aminotransferase (ALT) ≤3 x ULN
- Creatinine Clearance (CrCl) ≥50 mL/min estimated by **Chronic Kidney Disease Epidemiology Collaboration equation (CKD-Epi)**

4.1.7 For participants of reproductive potential, negative serum or urine pregnancy test with a sensitivity of ≤25 mIU/mL at screening. This will be repeated again at study entry.

NOTE: Participants are considered to be NOT of reproductive potential if: 1) they have had amenorrhea for at least 12 consecutive months prior to study entry (i.e., who have had no menses within 12 months prior to study entry), and have a

documented FSH >40 IU/mL; OR 2) an FSH level is not available, but they have had 24 consecutive months of amenorrhea (in the absence of medications known to induce amenorrhea); OR 3) they report having undergone surgical sterilization (e.g., hysterectomy, or bilateral oophorectomy, or bilateral tubal ligation/hysteroscopic tubal occlusion).

4.1.8 Contraception **R**equirements

Participants of Reproductive Potential
Participants of reproductive potential, who are participating in sexual activity that could lead to pregnancy, must agree to use at least one of the listed highly effective methods for 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 study drugs not supplied by the study, or 52 weeks after stopping RPV-LA or CAB-LA. 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

Participants Who Are Not of Reproductive Potential
Participants who are not of reproductive potential are eligible to start study drugs without requiring the use of contraceptives. Any statement of self-reported sterility or that of her partner's must be entered in the source documents.

NOTE A: Acceptable documentation of lack of reproductive potential is the participant's self-reported history of surgical sterilization, menopause, or male partner's azoospermia.

NOTE B: ALL participants in the study should be counseled on safer 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**.

4.1.9 Age ≥18 years.

4.1.10 Ability and willingness of participant or legal guardian/representative to provide written informed consent.

4.2 Step 1 Exclusion Criteria

4.2.1 Currently pregnant, planning to become pregnant during the study period, or currently breastfeeding.

4.2.2 Participants determined by the Site Investigator to have a high risk of seizures, including participants with an unstable or poorly controlled seizure disorder.

NOTE: A participant with a prior history of seizure may be considered for enrollment if the Investigator believes the risk of seizure recurrence is low. All cases of prior seizure history should be discussed with the A5359 protocol leadership team (actg.leada5359@fstrf.org) prior to enrollment.

4.2.3 Advanced liver disease (as defined by any of the following: 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) OR history of liver cirrhosis.

4.2.4 History of or current active hepatitis B (HBV) infection defined as positive HBV surface antigen test or any detectable HBV DNA in participants with isolated HBcAb and HBV DNA as follows:

4.2.4.1 Participants positive for HBsAg are excluded

4.2.4.2 Participants negative for anti-HBs but positive for anti-HBc (negative HBsAg status) and any detectable HBV DNA are excluded

NOTE: Participants positive for anti-HBc (negative HBsAg status) and positive for anti-HBs (past and/or current evidence) are immune to HBV and are not excluded. **If prior documentation of immunity is available, repeat testing at screening is not required.**

4.2.5 Current or anticipated need for chronic anti-coagulation therapy.

4.2.6 Unwilling to receive injections, or unable to receive gluteal injections.

4.2.7 Tattoo or other condition over gluteus region, which may interfere with interpretation of injection site reaction.

4.2.8 Previous use of CAB.

4.2.9 **Any a**cute or serious illness, **within 7 days prior to entry,** requiring systemic treatment and/or hospitalization **that may render the participant unable to receive study medication, in the opinion of the site investigator**.

4.2.10 Any serious medical or psychiatric condition, which may render the participant unable to receive study medication in the opinion of the site investigator.

4.2.11 Known allergy/sensitivity or any hypersensitivity to components of study drug(s) or their formulation.

4.2.12 Requirement for any medication that is prohibited with a study medication.

4.3 Step 2 Inclusion Criteria

Meeting virologic suppression criteria at or after Step 1, week **4**, defined as:
a) HIV-1 RNA ≤200 copies/mL

OR

b) HIV-1 RNA of 201-399 copies/mL followed by HIV-1 RNA ≤200 copies/mL by Step 1, week 24

NOTE: The HIV-1 RNA viral load that will be used to determine eligibility for randomization must have been collected within 4 weeks (28 days) of the Step 2 randomization visit.

4.4 Step 2 Exclusion Criteria

4.4.1 Permanent discontinuation of study treatment for any reason during Step 1.

4.4.2 Participants who never started study treatment in Step 1 (see section 6.2.4).

4.4.3 Currently pregnant, planning to become pregnant during the study period, or currently breastfeeding.

4.5 Step 3 Inclusion Criteria

4.5.1 Willingness to continue for those in Arm A or begin to receive LA ART for those in Arm B.

4.5.2 Arm B participants: HIV-1 RNA ≤200 copies/mL at Step 2, week 48, or HIV-1 RNA of 201-399 copies/mL at Step 2, week 48, followed by HIV-1 RNA ≤200 copies/mL by Step 2, week 52.

NOTE: For Arm B participants continuing on to Step 3, the HIV-1 RNA viral load that will be used to determine eligibility for Step 3 registration must have been collected within 4 weeks (28 days) of the Step 3 registration visit.

4.6 Step 3 Exclusion Criteria

4.6.1 Permanent discontinuation of study treatment (LA ART for Arm A and oral ART for Arm B) for any reason during Step 2.

4.6.2 Confirmed Virologic Failure during Step 2.

4.6.3 (Only for Arm B in Step 2) Currently pregnant, planning to become pregnant during the study period, or currently breastfeeding.

4.7 Step 4 Inclusion Criteria

4.7.1 Any participant who has received at least one dose of CAB-LA or RPV-LA AND does not have access to available LA ART through their provider.

OR

4.7.2 Does not wish to continue LA ART.

4.8 Step 4 Exclusion Criteria

There are no exclusion criteria for Step 4.

4.9 Study Enrollment Procedures

4.9.1 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 RE 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 candidate for study entry has been identified, details will be carefully discussed with the participant. The participant (or, when necessary, the legal representative if the participant is under guardianship) will be asked to read and

sign the approved protocol consent form.

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

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.

4.9.2 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.

4.9.3 Randomization/Participant Registration

For participants 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 completed and keyed into the database.

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

4.10 Co-enrollment Guidelines

- US 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 A5359 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 as oral cabotegravir (CAB), cabotegravir long-acting injectable (CAB-LA), oral rilpivirine (RPV), rilpivirine long-acting injectable (RPV-LA), and the oral ARVs (abacavir (ABC)/lamivudine (3TC), ABC/dolutegravir (DTG)/3TC, darunavir (DRV)/cobicistat (cobi), DTG, emtricitabine (FTC)/tenofovir alafenamide (TAF) that are provided through the study and any locally sourced oral antiretroviral product prescribed in Step 1 and Step 2.

5.1 Study Product

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

5.2 Study Product Regimens, Administration, and Duration

5.2.1 Regimen

Step 1: Induction
All participants who meet eligibility criteria will initiate an ART regimen of ≥3 drugs with ≥2 drugs predicted to be fully active. The regimen must include a boosted PI/cobi and/or an INSTI. Oral antiretroviral study products provided through the study are included in Table 5.2.1-1 below. If it is determined that it is in a participant's best interest to be prescribed a regimen that is not included in Table 5.2.1-1, locally sourced antiretroviral products are allowed. Please note that, if the oral antiretroviral product is provided through the study (i.e., included in Table 5.2.1-1), participants MUST use the study supply. All participants are eligible to receive CEI for achieving visit and virologic benchmarks at Step 1 (Table 5.7-1).

Table 5.2.1-1: Oral ART for Step 1 and Arm B of Step 2 Provided Through the Study

Single Tablet Regimen
1. ABC/DTG/3TC 600 mg/50 mg/300 mg (Triumeq®) one tablet orally once daily with or without food
Combination Regimen
2. FTC/ TAF 200 mg/25 mg (Descovy®) one tablet orally once daily with or without food + DTG 50 mg (Tivicay®) one tablet orally once daily with or without food
3. FTC/ TAF 200 mg/25 mg (Descovy®) one tablet orally once daily with or without food + DRV/cobi 800 mg/150 mg (Prezcobix®) one tablet orally once daily with food
4. FTC/ TAF 200 mg/25 mg (Descovy®) one tablet orally once daily with or without food + DTG 50 mg (Tivicay®) one tablet orally once daily with or without food + DRV/cobi 800 mg/150 mg (Prezcobix®) one tablet orally once daily with food
5. ABC/ 3TC 600 mg/300 mg (Epzicom®) one tablet orally once daily with or without food + DRV/cobi 800 mg/150 mg (Prezcobix®) one tablet orally once daily with food
6. ABC/ DTG/3TC 600 mg/50 mg/300 mg (Triumeq®) one tablet orally once daily with or without food + DRV/cobi 800 mg/150 mg (Prezcobix®) one tablet orally once daily with food

7. RPV 25 mg (Edurant®) one tablet once daily with a meal + DRV/cobi 800 mg/150 mg (Prezcobix®) one tablet orally once daily with food + NRTI (FTC/TAF 200 mg/25 mg or abacavir/3TC 600 mg/300 mg) one tablet orally once daily with or without food)
8. RPV 25 mg (Edurant®) one tablet once daily with a meal + DTG 50 mg (Tivicay®) one tablet orally once daily with or without food + NRTI (FTC/TAF 200 mg/25 mg or ABC/3TC 600 mg/300 mg) one tablet orally once daily with or without food

Step 2: Randomization
At Step 2 randomization, eligible participants will be randomized 1:1 to one of the following two arms (see Table 5.2.1-2):

Arm A (LA ART):
Participants will discontinue Step 1 ART regimen and receive RPV plus CAB orally once daily for 4 weeks followed by RPV-LA plus CAB-LA Q4 weeks for 48 weeks.

RPV 25 mg orally once daily and CAB 30 mg orally once daily for 4 weeks followed by:

RPV-LA 900 mg Loading Dose and CAB-LA 600 mg Loading Dose IM followed in 4 weeks by:

RPV-LA 600 mg Maintenance Dose and CAB-LA 400 mg Maintenance Dose IM every 4 weeks for 44 weeks.

Alternatively, participants may initiate Long-Acting (LA) injectable ART at the Step 2 Randomization visit *without* oral RPV+ oral CAB at the discretion of the site IoR and participant. In this case, the participant will initiate RPV-LA 900 mg Loading Dose and CAB-LA 600 mg Loading Dose IM at the Step 2 Randomization visit, followed in 4 weeks by RPV-LA 600 mg Maintenance Dose and CAB-LA 400 mg Maintenance Dose IM every 4 weeks for 48 weeks.

Arm B (SOC):
Participants will continue their SOC oral ART regimen for 52 weeks.

Table 5.2.1-2: Dosing Regimen in Step 2

	Registration	Week 4b	Weeks 8-52
Step 2: Arm A (LA ART)			
Regimen	Optional Oral Lead-in (OLI): RPV 25 mg orally once daily and CAB 30 mg orally once daily for 4 weeks	LA ART Loading Dose: RPV-LA 900 mg and CAB-LA 600 mg IM	LA ART Maintenance Dose: RPV-LA 600 mg and CAB-LA 400 mg IM every 4 weeks

Alternative Regimen Dosing	LA ART Loading Dose: RPV-LA 900 mg and CAB-LA 600 mg IM	LA ART Maintenance Dose: RPV-LA 600 mg and CAB-LA 400 mg IM every 4 weeks
Step 2: Arm B (SOC)		
Regimen	SOC	

Step 3: Continuation/Crossover
Participants randomized to LA ART in Step 2 will continue RPV-LA + CAB-LA Q4 weeks for 52 weeks. In addition, eligible participants randomized to SOC in Step 2 will initiate oral RPV + CAB for 4 weeks (optional) followed by RPV-LA + CAB-LA Q4 weeks until the end of Step 3.

Arm A:
Participants in Arm A in Step 2 will continue RPV-LA 600 mg Maintenance Dose and CAB-LA 400 mg Maintenance Dose IM every 4 weeks for 52 weeks.

Arm B:
Participants in Arm B in Step 2 will switch from SOC oral ART to:

RPV 25 mg orally once daily and CAB 30 mg orally once daily for 4 weeks followed by:

RPV-LA 900 mg Loading Dose and CAB-LA 600 mg Loading Dose IM followed in 4 weeks by:

RPV-LA 600 mg Maintenance Dose and CAB-LA 400 mg Maintenance Dose IM every 4 weeks for 44 weeks.

Alternatively, Step 2, Arm B, participants may initiate LA ART at the Step 3 registration visit without oral RPV + oral CAB at the discretion of the site IoR and participant. In this case, the participant will initiate RPV-LA 900 mg Loading Dose and CAB-LA 600 mg Loading Dose IM at Step 3 Registration visit, followed in 4 weeks by RPV-LA 600 mg Maintenance Dose and CAB-LA 400 mg Maintenance Dose IM every 4 weeks until the end of Step 3.

Table 5.2.1-3: Dosing Regimen in Step 3

	Registration	Week 4b	Weeks 8-52
Step 3: Arm A (LA ART)			
Regimen	LA ART Maintenance Dose: RPV-LA 600 mg and CAB-LA 400 mg IM every 4 weeks		
Step 3: Arm B (SOC) Crossover Regimen			
Regimen	Optional OLI: RPV 25 mg orally once daily and CAB	LA ART Loading Dose: RPV-LA 900 mg and	LA ART Maintenance Dose:

	Registration	Week 4b	Weeks 8-52
	30 mg orally once daily for 4 weeks	CAB-LA 600 mg IM	RPV-LA 600 mg and CAB-LA 400 mg IM every 4 weeks
Alternative Regimen Dosing	LA ART Loading Dose: RPV-LA 900 mg and CAB-LA 600 mg IM	LA ART Maintenance Dose: RPV-LA 600 mg and CAB-LA 400 mg IM every 4 weeks	

Step 4: Observation
Any participant who has completed Step 3 and does not have access to locally sourced available LA ART (CAB-LA and RPV-LA) will register to Step 4 for 52 weeks. Any participant who has received at least one dose of CAB-LA or RPV-LA and withdraws from LA dosing during the study will be followed on oral ART for 52 weeks after their last dose of any LA injectable. Oral ART (SOC) in Step 4 will be locally sourced and will not be provided by the study.

Prescriptions
A new prescription that includes the patient identification number (PID) and study identification number (SID) and signed by an authorized prescriber must be provided to the site pharmacist before the pharmacist prepares and dispenses study product.

Quantity of Oral Study Product Supply to Dispense
The site pharmacist should dispense enough oral study products so the participant has about 1 month of buffer supply. The oral study products should be prepared and dispensed by the site pharmacist in original whole bottles. The oral tablets should not be transferred from the original bottle to a prescription vial for dispensation by the site pharmacist.

Drug substitutions
Drug substitutions, if deemed appropriate by the site investigator, will be permitted during Step 1 and in the Step 2, Arm B (SOC arm). All substitutions and indications for the substitutions are to be recorded on the eCRFs. The site pharmacist must be informed in writing that the previous regimen is to be discontinued.

5.2.2 Administration

- CAB 30 mg administered as one 30 mg tablet orally once daily, with or without food for 4 weeks (optional).
- CAB-LA 600 mg loading dose administered as one 3 mL (600 mg) IM injection in the gluteal muscle once at the Step 2 randomization if no OLI, or at Step 2, week 4, visit after 4 weeks of oral CAB + RPV therapy.

- CAB-LA 400 mg maintenance dose administered as one 2 mL (400 mg) IM injection in the gluteal muscle starting 4 weeks after the CAB-LA 600 mg loading dose and then every 4 weeks until the end of the Step.
- RPV 25 mg administered as one 25 mg tablet orally once daily, with a meal for 4 weeks (optional).
- RPV-LA 900 mg loading dose administered as one 3 mL (900 mg) IM injections in the gluteal muscle once at the Step 2 randomization if no OLI, or at Step 2, week 4, visit after 4 weeks of oral CAB + oral RPV therapy.
- RPV-LA 600 mg maintenance dose administered as one 2 mL (600 mg) IM injection in the gluteal muscle starting 4 weeks after the RPV-LA 900 mg loading dose and then every 4 weeks until the end of the step.
- CAB-LA and RPV-LA injections will be administered by study staff in a clinical setting during the same clinic visit.
- ART in Step 1 and Arm B of Step 2 – The site clinician, in conjunction with participant, should determine the optimal ART regimen per protocol for each participant and dosed per package insert and site clinician's discretion.

NOTE: If the participant misses an injection and the time since the last RPV-LA and CAB-LA injection was greater than 8 weeks (56 days) from the previous injection, the participant will need to be administered a new loading dose of both RPV-LA (900 mg) and CAB-LA (600 mg) prior to continuing the maintenance dose. If the last injection of RPV-LA and CAB-LA occurred less than or equal to 8 weeks (56 days) from the previous injection, the participant will be continued on the maintenance dose of RPV-LA (600 mg) and CAB-LA (400 mg).

5.2.3 Study Duration

Participants will be followed for a maximum duration of 180 weeks with up to 24 weeks in Step 1, 52 weeks in Step 2, 52 weeks in Step 3, and up to 52 weeks in Step 4 (if LA ART is not locally accessible and/or if participant has received at least one dose of LA ART and does not wish to continue LA ART).

5.3 Study Product Preparation, and Formulation

5.3.1 Preparation of Injectable Study Products

The Pharmacist of Record must be proficient in the preparation of study products using aseptic technique under a pharmacy Biological Safety Cabinet (BSC) Class II or better. For individual protection measures such as personal protective equipment (PPE), local requirements and regulations are to be followed. PPE may include disposable gloves, gowns, respirator and safety glasses.

5.3.1.1 CAB-LA Injectable Study Product Preparations

Materials required for preparation and administration of CAB-LA 600 mg (3 mL) and CAB-LA 400 mg (2 mL) dose:

1. CAB-LA 600 mg/3 mL vial or CAB-LA 400 mg/2 mL vial(s)
   - *For CAB-LA 600 mg/3 mL Loading Dose*, one (1) CAB-LA 600 mg/3 mL vial or two (2) CAB-LA 400 mg/2 mL vials are needed
   - *For CAB-LA 400 mg/2 mL Maintenance Dose*, one (1) CAB-LA 600 mg/3 mL vial or one (1) CAB-LA 400 mg/2 mL vial is needed

2. Becton Dickinson (BD) 3-mL size syringe, Luer-Lok Tip, Product No.: 309657 or equivalent

3. Becton Dickinson (BD) 5-mL size 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). Longer needle lengths may be needed for participants based on body habitus and/or with higher body mass indexes (BMIs, example >30), to ensure that injections are administered intramuscularly as opposed to subcutaneously.

Preparation Steps:

1. Remove required vial(s) of CAB-LA from storage. If the vials are stored in the refrigerator (2°C to 8°C), remove vial(s) from the refrigerator and wait at least 15 minutes to equilibrate to room temperature. If stored refrigerated, record for each individual CAB-LA vial the point in time that the vial has been taken out of the refrigerator on the participant's pharmacy log.

   - *For CAB-LA 600 mg/3 mL Loading Dose*, remove one (1) 600 mg/3 mL vial or two (2) 400 mg/2 mL vials from storage
   - *For CAB-LA 400 mg/2 mL Maintenance Dose*, remove one (1) 600 mg/3 mL vial or one (1) 400 mg/2 mL vials from storage

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 resuspension.

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 (or equivalent) needle 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 the 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 CAB-LA 600 mg/3 mL Loading Dose*, withdraw total of 3 mL (600 mg) of CAB-LA suspension from the vial(s) into a syringe.
   - If using two CAB-LA 400 mg/2 mL vials to prepare the 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. Attach the new 21G x 1½ inch needle to the syringe already containing suspension per instructions in Step 5 and repeat Steps 6 through 8 to withdraw the remaining needed volume from the second vial.
   - *For CAB-LA 400 mg/2 mL Maintenance Dose*, withdraw a total of 2 mL (400 mg) of CAB-LA suspension from the 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 in a 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 needle in an upright position until the first drop of suspension appears. Remove the excess suspension in order to administer the correct volume. If needed, collect the excess suspension in a beaker to avoid spilling.

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

12. Label the prepared syringe as CAB-LA 600 mg (3mL) for the Loading Dose or as CAB-LA 400 mg (2 mL) for the Maintenance Dose. Also include on the label the participant's PID, route of administration (IM), date and time of preparation, and date and time of expiration. Follow the DAIDS Pharmacy Guidelines and local regulations for preparing participant specific labels.

13. 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 administering to the study participant.

14. 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.

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

5.3.1.2 RPV-LA Injectable Study Product Preparations

Materials required for preparation and administration of RPV-LA 900 mg (3 mL) and RPV-LA 600 mg (2 mL) dose:

1. RPV-LA 900 mg/3 mL vial or RPV-LA 600 mg/2 mL vial(s)
   - *For RPV-LA 900 mg/3 mL Loading dose*, one (1) RPV-LA 900 mg/3 mL vial or two (2) RPV-LA 600 mg/2 mL vials are needed

- *For RPV-LA 600 mg/2 mL Maintenance dose*, one (1) RPV-LA 900 mg/3 mL vial or one (1) RPV-LA 600 mg/2 mL vials is needed

2. Becton Dickinson (BD) 3-mL size syringe, Luer-Lok Tip, Product No.: 309657 or equivalent

3. Becton Dickinson (BD) 5-mL size 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)

Preparation Steps:

6. Remove required vial(s) of RPV-LA from the refrigerator and wait 15 minutes to equilibrate to room temperature. Record for each individual RPV-LA vial the point in time that the vial has been taken out of the refrigerator on the participant's pharmacy log. The maximum time out of the refrigerator is 24 hours at a maximum temperature of 25ºC.
   - *For RPV-LA 900 mg/3 mL Loading Dose*, remove one (1) 900 mg/3 mL vial or two (2) 600 mg/2 mL vials from storage
   - *For RPV-LA 600 mg/2 mL Maintenance Dose*, remove one (1) 900 mg/3 mL vial or one (1) 600 mg/2 mL vial from storage

7. Hand-shake the vial(s) moderately for a minimum of 10 seconds to ensure a homogeneous suspension. After resuspending, it is recommended to use the suspension immediately.

8. Invert the vial to inspect for any sediment. If sediment is observed, repeat Step 2.

9. Using aseptic technique under a pharmacy Biological Safety Cabinet or isolator, flip off the plastic cap from the vial. Wipe the top of each vial with a single-use sterile alcohol pad of isopropyl alcohol 70% and allow the alcohol to dry. Do not touch the rubber stopper at any time.

10. Remove a 3 mL or a 5 mL size syringe from the blister pouch and appropriate aspiration needle to withdraw the suspension from the vial. Attach the needle to the Luer connection of the syringe.

11. Remove needle sheath and, with vial in the upright position, push the needle through the vial stopper and inject the amount of air equal to the needed amount of suspension into the vial.

12. Withdraw needed volume of RPV-LA suspension from the vial(s) into the syringe.
    - *For RPV-LA 900 mg/3 mL Loading Dose*, withdraw total of 3 mL (900 mg) of RPV-LA suspension from the vial(s) into a syringe.
    - If using two RPV-LA 600 mg/2 mL vials to prepare the 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 a new 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 RPV-LA 600 mg/2 mL Maintenance Dose*, withdraw a total of 2 mL (600 mg) of RPV-LA suspension from the vial into a syringe.

13. 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.

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

15. Attach a 23G x 1½ inch (or equivalent) needle to the Luer connection of the prepared RPV-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 RPV-LA in a syringe is to be de-aerated by administrator prior to injection so that the correct volume can be administered.

16. De-aerate the syringe by first tapping with a finger against the syringe and then by moving the plunger rod carefully forward with the needle in an upright position until the first drop of suspension appears. Remove the excess suspension in order to administer the correct volume. If needed, collect the excess suspension in a beaker to avoid spilling.

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

18. Label the prepared syringe as RPV-LA 900 mg (3 mL) for the Loading Dose or as RPV-LA 600 mg (2 mL) for the Maintenance Dose. Also include on the label the participant's PID, route of administration (IM), date and time of preparation, and date and time of expiration. Follow the DAIDS Pharmacy Guidelines and local regulations for preparing participant specific labels.

19. After withdrawal of the RPV-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 7) and administering to the study participant.

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

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

5.3.2 Study Product Formulation

- CAB 30 mg oral tablet in bottles is to be stored up to 30°C (86°F) in the original container and protected from moisture.
- CAB-LA injectable suspension in single use vial containing 400 mg/2 mL or 600 mg/3 mL is to be stored up to 30°C (up to 86°F). Do not freeze. The concentration of CAB-LA for both 2 mL and 3 mL filled vials is 200 mg/mL.
- RPV 25 mg oral tablet (Edurant®) in bottles is to be stored in the original bottle protected from light at 25°C (77°F); excursions permitted to 15° to 30°C (59° to 86°F) [See USP Controlled Room Temperature].
- RPV-LA injectable suspension in single use vial containing 600 mg/2 mL or 900 mg/3 mL is to be stored in the original container protected from light between 2°C to 8°C (36°F to 46°F). Do not freeze. The concentration of RPV-LA for both 2 mL and 3 mL filled vials is 300 mg/mL.
- Emtricitabine and tenofovir alafenamide 200 mg/25 mg tablet (Descovy®) is to be stored below 30°C (86°F). Keep container tightly closed. Dispense only in original container.
- Abacavir and lamivudine(3TC) 600 mg/300 mg tablet (Epzicom®) is to be stored at 25°C (77°F); excursions permitted to 15° to 30°C (59° to 86°F) [See USP Controlled Room Temperature].

- Darunavir and cobicistat 800 mg/150 mg tablet (Prezcobix®) is to be stored at 20° to 25°C (68° to 77°F); excursions permitted to 15° to 30°C (59° to 86°F) [See USP Controlled Room Temperature].
- Dolutegravir 50 mg tablet (Tivicay®) is to be stored at 25°C; excursions permitted to 15° to 30°C (59° to 86°F) [See USP Controlled Room Temperature].
- Abacavir, dolutegravir, and lamivudine(3TC) 600 mg/50 mg/300 mg (Triumeq®) is to be stored at 25°C; excursions permitted to 15° to 30°C (59° to 86°F) [See USP Controlled Room Temperature]. Dispense in the original package, protected from moisture with the bottle tightly closed. Do not remove desiccant.

5.4 Pharmacy: Product Supply, Distribution, and Accountability

5.4.1 Study Product Acquisition/Distribution

All oral ART provided through the study for Steps 1 and 2 (see Table 5.2.1-1), oral CAB, oral RPV, CAB-LA and RPV-LA for Steps 2 and 3 will be provided by ViiV and will be available through the NIAID Clinical Research Products Management Center (CRPMC). The site pharmacist should obtain the study drug(s) for this protocol by following the instructions in the manual *Pharmacy Guidelines and Instructions for DAIDS Clinical Trials Networks*.

5.4.2 Study Product Accountability

The site pharmacist is required to maintain complete records of all study drugs received from the NIAID CRPMC and subsequently dispensed. All unused study drugs 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.

5.4.3 Ensuring Study Product Supply during the COVID-19 Pandemic or Other Extenuating Circumstances as Approved by Protocol Team Leadership

Notify the site Pharmacist of Record (PoR) and provide a prescription for any participant randomized to the long-acting injectable arm in Step 2 that may require oral bridging therapy (up to 1 month is allowed) with oral cabotegravir/rilpivirine (CAB/RPV) due to a missed visit (either anticipated or already missed). The site PoR can order 1-month supplies of oral CAB and oral RPV from the CRPMC via the online ordering system per PID per order. The site PoR should notify both protocol pharmacists, Katherine Shin (kashin@niaid.nih.gov) and Cynthia Parker (cindy.parker@nih.gov), for each PID in need of oral bridging therapy. The protocol pharmacists will work with the site pharmacist to provide assistance.

If oral CAB/RPV is unavailable or more than 1 month of oral bridging is needed by a participant, sites should instruct the participant to reinitiate his or her

regimen from Step 1. The oral study products provided through the study via CRPMC may be limited in supply during the COVID-19 pandemic. In rare circumstances, additional consideration for the use of oral bridging may be appropriate; contact the study leadership team (actg.leada5359@fstrf.org) for individual circumstances, such as limited site study product supply, anticipated prolonged absence, or other unpredictable instances (see also section 6.2.3.1) . In emergency situations, such as the COVID-19 pandemic, the Pharmacy Guidelines and Instructions for DAIDS Clinical Trials Networks permits shipment or courier of study product from the site directly to participants. The pharmacist should refer to the section on "Shipping Study Product to a Participant" in this manual for detailed procedures. If this method is to be implemented, each site pharmacist must develop appropriate procedures for the shipment or courier of study product to the identified participant in accordance with these guidelines, and must include appropriately documented chain of custody. This method should only be used if permissible per local institutional and IRB/EC policies.

All questions related to study product management should be directed to the protocol pharmacists, Katherine Shin and Cynthia Parker.

If sites cannot, at minimum, dispense oral study products and maintain contact with the participant to assess safety because of institutional or local guidelines related to the response to the COVID-19 pandemic, then participants should be referred back to their local clinical providers to obtain local SOC ARVs and medical care.

5.5 Concomitant Medications

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

Additional drug information may be found on the ACTG Precautionary and Prohibited Medications Database located at: http://tprc.pharm.buffalo.edu/home/di_search/.

5.5.1 Required Medications

Prophylaxis for those who are at risk for opportunistic infections is strongly recommended. Investigators should refer to the US Public Health Service/Infectious Diseases Society of America "Guidelines for Prevention and Treatment of Opportunistic Infections in HIV-Infected Adults and Adolescents (https://aidsinfo.nih.gov/contentfiles/lvguidelines/adult_oi.pdf)." Although recommended as an alternative in the guidelines, rifabutin for the prophylaxis of Mycobacterium avium-intracellulare complex should be avoided.

5.5.2 Prohibited Medications

The following concomitant medications or therapies are not permitted at any time during the study regardless of randomized treatment arm:

- HIV immunotherapeutic vaccines or monoclonal antibodies.
- Other experimental agents, ARV drugs not otherwise specified in the protocol, cytotoxic chemotherapy, or radiation therapy (see Exclusion Criteria: section 5.2).
- Systemically administered immunomodulators (such as interleukin and interferon agents). Including interferon for treatment of HCV infection. This includes topical agents with substantial systemic exposure and systemic effects. Use of topical imiquimod is permitted.
- Chronic use of systemic (oral or parenteral) glucocorticoids at doses above physiologic replacement must be avoided due to their immunosuppressive effect; however, short treatment courses with oral prednisone/ prednisolone/methylprednisolone (e.g., adjunctive treatment of pneumocystis pneumonia with ≤21 days of tapering prednisone) are allowed. A single dose of systemic dexamethasone is permitted (more than a single dose in a treatment course may cause significant decrease in RPV plasma concentration and is prohibited). Topical, inhaled, or intranasal use of glucocorticoids will be allowed.

Prohibited Medications with Concurrent Use of CAB or RPV:
For participants receiving either formulation of CAB and RPV, the following medications could significantly decrease the levels of CAB and/or RPV due to enzyme induction and therefore are prohibited and must not be administered concurrently:

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

Hepatitis C infection therapy with direct-acting agents (DAA) is allowed during the entire study. However, participants on an HIV ART regimen in Step 1 or Step 2 that contains a protease inhibitor (PI) are prohibited from co-administration of anti-HCV PI as part of their DAA regimen either alone or as part of a fixed-dose combination (e.g., Ombitasvir/Paritaprevir/RTV plus Dasabuvir). Please refer to DHHS guidelines Table 15 (https://clinicalinfo.hiv.gov/sites/default/files/guidelines/documents/AdultandAdolescentGL.pdf).

Prohibited Medications with Concurrent Use of Oral RPV:
Participants must discontinue the following (or change to an allowable alternative) while receiving treatment with oral RPV:

- Proton pump inhibitors, such as esomeprazole, lansoprazole, omeprazole, pantoprazole, rabeprazole
- Systemic dexamethasone (more than a single dose)

If the participant cannot discontinue use or change to an allowable alternative while receiving treatment with RPV, the participant should not be randomized into the study.

Prohibited Medications with Concurrent Use of Either Long-acting Agent:
In addition, for participants receiving CAB-LA and RPV-LA, use of anticoagulation agents for greater than 14 days is prohibited, 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.

NOTE: Any prohibited medications that decrease CAB or RPV concentrations should be discontinued for a minimum of 4 weeks or a minimum of three half-lives (whichever is longer) prior to the first dose, and any other prohibited medications should be discontinued for a minimum of 2 weeks or a minimum of three half-lives (whichever is longer) prior to the first dose.

5.5.3 Precautionary Medications

A full list of precautionary medications will be listed in the PSWP.

5.6 Adherence

5.6.1 Adherence Assessment

Adherence to all oral study medications will be assessed by a validated adherence assessment at the intervals indicated in section 6.1, Schedule of Evaluations (SOE). In addition to self-report, ART adherence and drug exposure will also be evaluated through drug concentrations in hair and DBS. These matrices provide a quantitative measure of cumulative drug exposure (usually weeks or months) that complement plasma drug levels (which are subject to white coat adherence) and are predictive of viral suppression in diverse populations (refer to the MOPS).

5.6.2 Adherence Monitoring and Support

This study seeks to enroll participants with a history of non-adherence to medications, a group not traditionally targeted for recruitment in ACTG trials. Since CEI alone might not be sufficient to encourage adherence, addressing the

challenges to adherence in this study population will be imperative to ensure study retention and allow for complete interpretation of study results.

In addition to the CEI used during the induction period, sites will be required to develop a multi-component adherence support protocol utilizing the framework of the Guidelines for Improving Entry Into and Retention in Care and ARV Adherence for Persons With HIV: Evidence-Based Recommendations From an International Association of Physicians in AIDS Care Panel, with a focus on the recommendations to promote adherence to visits and improve adherence to ART (see MOPS) [43]. In addition, multiple methods of participant recruitment and retention will be utilized, including appointment reminder via phone call, email, SMS and social media in a HIPAA-compliant fashion. We expect these recommendations will enhance current study adherence and retention efforts by ACTG sites.

The A5359 MOPS will provide recommendations on frequency of between-visit contact with study participants. Recommendations for best practices for addressing toxicity and adherence barriers will also be outlined in the MOPS.

5.7 Conditional Economic Incentives (CEI)

Adherence benchmarks using study visit and HIV-1 RNA decline will be evaluated during Step 1 and CEI will be provided to participants if the predetermined milestones are met during this period (Table 5.7-1). As described above, the rationale behind limiting the cash incentives to the induction phase is to utilize them as a time-limited intervention to support adherence to oral therapy in individuals with a history of sub-optimal adherence to oral medications and to improve the chance that viral suppression will be achieved before transitioning to LA ART.

Participants are eligible to receive CEI totaling up to $675 for completion of Step 1. At Step 1, week 2, a $75 incentive will be provided for completion of a return study visit. At Step 1, weeks 4 and 8, participants who have a decrease of >1 $\log_{10}$ and >2 $\log_{10}$ in HIV-1 RNA compared to HIV-1 RNA at entry, respectively, or achieve an HIV-1 RNA decline to ≤200 copies/mL, or complete a virtual visit under COVID-19 pandemic guidelines, will be incentivized $75 for each milestone met.

Starting at Step 1, week **4**, participants who achieve an HIV-1 RNA ≤200 copies/mL will be eligible to receive the remainder of the CEI scheduled for Step 1 and proceed to Step 2 randomization (Table 5.7-1). As an example, if a participant meets virologic suppression criteria for randomization at Step 1, week 12, the CEI for week 12+16+20 ($450) will be disbursed at that time and the participant will proceed to Step 2 randomization; or if a participant meets virologic suppression criteria for randomization at Step 1, week 16, the CEI for week 16+20 ($300) will be disbursed at that time and the participant will proceed to Step 2 randomization. If the Step 1, week **4, 8,** 12, 16, or 20, HIV-1 RNA is 201-399 copies, the participant will not receive CEI at that visit, but can be incentivized if the confirmation viral load visit is ≤200 copies/mL. This confirmation visit needs to be completed before Step 1, week 24.

If a participant skips visit(s), he or she can be eligible for an incentive not received in a previous missed visit; e.g., if participant misses the Step 1, week 8, visit, he or she can be eligible for the $75 incentive of dropping more than 2 log10 copies in HIV RNA at Step 1, week 9, 10, or 11, visits.

Participants who do not achieve the benchmarks at any point will not receive the CEI.

Table 5.7-1: CEI from Entry to Week 20, and Additional Continuity Visits Due to the COVID-19 Pandemic

Step 1, Week	Milestone	Incentive
2	Completed visit (in person or virtual)	$75.00
4	HIV-1 RNA >1 $\log_{10}$ drop or HIV-1 RNA ≤200 copies/mL or completed virtual visit	$75.00*
8 **(if needed)**	HIV-1 RNA >2 $\log_{10}$ drop or HIV-1 RNA ≤200 copies/mL or completed virtual visit	$75.00*
12 **(if needed)**	HIV-1 RNA ≤200 copies/mL or completed virtual visit	$150.00*
16 (if needed)	HIV-1 RNA ≤200 copies/mL or completed virtual visit	$150.00*
20 (if needed), or Confirmation viral load after week 20 (but prior to week 24)	HIV-1 RNA ≤200 copies/mL	$150.00
Additional Continuity Visits during the COVID-19 pandemic (only applicable if in-person visits are not permitted by the site's institution)	HIV-1 RNA ≤200 copies/mL or completed virtual visit	$150.00

* NOTE: Virally suppressed participants (≤200 copies/mL) who receive CEI at week **4, 8,** 12, or week 16 will be eligible for randomization into Step 2 and should not continue further visits in Step 1, and will additionally receive the CEI that would have been distributed at the later Step 1 visits.

All CEIs will be additional to site's usual compensation for participation in the study (i.e., attending study visits and completing assessments). Since there will be a short lapse between study visits and virologic assay results, incentives may be provided using a debit card system, which will allow for funds to be added remotely once the data become available, although in person incentive distribution will also be permitted. Study participants will be notified immediately via phone call, text SMS, email, or other preferred communication method after their benchmark is achieved.

No other steps will be incentivized financially beyond standard site-specific compensation for study visit attendance.

6.0 CLINICAL AND LABORATORY EVALUATIONS

6.1 Schedule of Evaluations

Table 6.1-1: Step 1: Induction

Evaluations	Screening	Entry (0)	Step 1, Week 2	Step 1, Week 4	Step 1, Week 8	Step 1, Week 12	Step 1, Week 16	Step 1, Week 20	Visit to confirm HIV-1 RNA if Week **4, 8,** 12, 16, or 20 HIV-1 RNA = 201-399	Step 1, Week 24[A]	Premature Treatment Discontinuation[B]	Premature Study Discontinuation
Visit Window	Within 60 days prior to entry	Within 72 hours after registration	±1 **W**eek						Before Step 1, Week 24	±1 Week	Within 14 days	Within 14 days
SOC (All Participants)		X	X	X	X	X	X	X				
Documentation of HIV-1	X											
Baseline Demographics		X										
Medical History	X	X										
Medication History	X	X										
Clinical Assessments		X	X	X	X	X	X	X		X	X	X
Complete Physical Exam	X											
Targeted Physical Exam		X	X	X	X	X	X	X		X	X	X
Hematology	X			X		X		X		X	X	X
Blood Chemistries, including Cr Clearance	X			X		X		X		X	X	X

Evaluations	Screening	Entry (0)	Step 1, Week 2	Step 1, Week 4	Step 1, Week 8	Step 1, Week 12	Step 1, Week 16	Step 1, Week 20	Visit to confirm HIV-1 RNA if Week **4, 8,** 12, 16, or 20 HIV-1 RNA = 201-399	Step 1, Week 24[A]	Premature Treatment Discontinuation[B]	Premature Study Discontinuation
Visit Window	Within 60 days prior to entry	Within 72 hours after registration	±1 **W**eek						Before Step 1, Week 24	±1 Week	Within 14 days	Within 14 days
Liver Function Tests	X	X		X		X		X		X	X	X
Fasting Lipid Profile		X								X		
Urinalysis	X		If clinically indicated (see section 6.3.6)									
Pregnancy Test	X	X	If suspected	X[C]	X[C]	X[C]	X[C]	X		X[C]	X	X
Urine Drug Toxicology		X[D]	X	X	X	X	X	X				
CD4+/CD8+	X	X				X				X	X	X
HIV-1 RNA[E]	X	X		X	X	X	X	X	X	X	X	X
HIV-1 Genotype[E]	X	If Clinically Indicated (see section 6.3.8)										
DBS (venipuncture) for participants on TAF, 3TC, FTC or ABC		X		X		X				X	X	X
Stored **plasma and PBMCs from** Whole Blood		X			X	X				X	X	X
Hepatitis B and C Serology	X[R]											
ECG	X											

Evaluations	Screening	Entry (0)	Step 1, Week 2	Step 1, Week 4	Step 1, Week 8	Step 1, Week 12	Step 1, Week 16	Step 1, Week 20	Visit to confirm HIV-1 RNA if Week **4, 8,** 12, 16, or 20 HIV-1 RNA = 201-399	Step 1, Week 24[A]	Premature Treatment Discontinuation[B]	Premature Study Discontinuation
Visit Window	Within 60 days prior to entry	Within 72 hours after registration	±1 **W**eek						Before Step 1, Week 24	±1 Week	Within 14 days	Within 14 days
Hair Collection (optional)		X				X				X	X	X
Sociodemographic Questionnaire		X										
C-SSRS, DVST, HIV Stigma Mechanism Measure Questionnaires		X									X	X
HRU Questionnaire		X				X						
GAD-7, HIV-ASES, PHQ-9 Questionnaires		X				X		X			X	X
Self-Report of Adherence Questionnaire		X	X	X	X	X	X	X	X	X	X	X
Documentation of Site Adherence and Retention Support		Every six months at each site beginning with enrollment of its first participant										
AUDIT-C, DUDIT, Smoking Questionnaires	X					X		X			X	X
Conditional Economic Incentives			X	X	X	X	X	X	X[F]			

Refer to the SOE FOOTNOTES section for the footnote explanations.

NOTE: Once a participant meets eligibility criteria for randomization (at or after Step 1, week **4**) subsequent visits for Step 1 should not be completed and they should proceed to the Step 2 randomization visit.

Table 6.1-2: Step 2: Randomization to LA ART vs. Oral SOC – Arm A

Evaluations	Step 2, Randomization[G]	Step 2, Week 4a[H]	Step 2, Week 4b	Step 2, Week 8	Step 2, Week 12	Step 2, Week 16	Step 2, Week 20	Step 2, Week 24	Step 2, Week 28	Step 2, Week 32	Step 2, Week 36	Step 2, Week 40	Step 2, Week 44	Step 2, Week 48	Step 2, Week 52	Confirmation of Virologic Failure	Premature Treatment Discontinuation	Premature Study Discontinuation
Visit Window Arm A		±4 **D**ays for non-OLI; +1 week for OLI	+6 **D**ays	±4 **D**ays	±1 **W**eek for non-OLI; ±4 days for OLI	±1 **W**eek									±1 **W**eek	7-21 **D**ays after HIV VL >200	Within 14 days	Within 14 days
Dispense Oral RPV + CAB	X[I]																	
RPV-LA + CAB-LA Injection	X[J]		X	X	X	X	X	X	X	X	X	X	X	X	X			
Clinical Assessments	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
Injection Site Evaluation	X[J]		X	X	X	X	X	X	X	X	X	X	X	X	X			
Hematology		X						X						X				
Blood Chemistries, including Cr Clearance		X	X					X						X				
Liver Function Tests		X		X		X		X		X		X		X				
Fasting Lipid Profile	X													X				
Urinalysis	If clinically indicated (see section 6.3.6)																	
Urine Pregnancy Test (pre-dose)	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X		X	X
Urine Drug Toxicology	X	X		X	X	X	X	X	X	X	X	X	X	X	X			

Evaluations	Step 2, Randomization[G]	Step 2, Week 4a[H]	Step 2, Week 4b	Step 2, Week 8	Step 2, Week 12	Step 2, Week 16	Step 2, Week 20	Step 2, Week 24	Step 2, Week 28	Step 2, Week 32	Step 2, Week 36	Step 2, Week 40	Step 2, Week 44	Step 2, Week 48	Step 2, Week 52	Confirmation of Virologic Failure	Premature Treatment Discontinuation	Premature Study Discontinuation
Visit Window Arm A		±4 **D**ays for non-OLI; +1 week for OLI	+6 **D**ays	±4 **D**ays	±1 **W**eek for non-OLI; ±4 days for OLI	±1 **W**eek									±1 **W**eek	7-21 **D**ays after HIV VL >200	Within 14 days	Within 14 days
CD4+/CD8+	X							X						X		X	X	X
HIV-1 RNA[E]	X	X		X		X		X			X			X	X	X	X	X
HIV-1 Genotype[E]	If Clinically Indicated (see section 6.3.8)															X	If clinically indicated (see section 6.3.8)	
Stored **plasma and PBMCs from** Whole Blood[K]	X	X						X			X			X			X	X
PK Trough Sample[L]	X		X	X	X	X		X		X	X	X		X	X	X	X	X
ECG	X													X				
Hair Collection (optional)	X			X				X			X			X		X	X	X
Pill Counts		X[I]																
Sociodemographic Questionnaire	X																X	X
HIVTSQs-status Questionnaire[M]	X							X									X	X
HIVTSQc-change Questionnaire[M]														X				

Evaluations	Step 2, Randomization[G]	Step 2, Week 4a[H]	Step 2, Week 4b	Step 2, Week 8	Step 2, Week 12	Step 2, Week 16	Step 2, Week 20	Step 2, Week 24	Step 2, Week 28	Step 2, Week 32	Step 2, Week 36	Step 2, Week 40	Step 2, Week 44	Step 2, Week 48	Step 2, Week 52	Confirmation of Virologic Failure	Premature Treatment Discontinuation	Premature Study Discontinuation
Visit Window Arm A		±4 **D**ays for non-OLI; +1 week for OLI	+6 **D**ays	±4 **D**ays	±1 **W**eek for non-OLI; ±4 days for OLI	±1 **W**eek									±1 **W**eek	7-21 **D**ays after HIV VL >200	Within 14 days	Within 14 days
Dichotomous Preference Questionnaire														X			X	X
CEI Withdrawal Questionnaire	X			X														
C-SSRS, DVST, HIV Stigma Mechanism Measure Questionnaires	X													X			X	X
HRU Questionnaire	X			X		X		X			X			X				
GAD-7, HIV-ASES, PHQ-9 Questionnaires								X						X			X	X
Documentation of Site Adherence and Retention Support	Every six months at each site beginning with enrollment of its first participant.																	
AUDIT-C, DUDIT, Smoking Questionnaires								X						X			X	X

Refer to the SOE FOOTNOTES section for the footnote explanations.

Table 6.1-3: Step 2: Randomization to LA ART vs. Oral SOC – Arm B

Evaluations	Step 2, Randomization	Step 2, Week 4a[H]	Step 2, Week 8	Step 2, Week 12[N]	Step 2, Week 16	Step 2, Week 20[N]	Step 2, Week 24	Step 2, Week 28[N]	Step 2, Week 32[N]	Step 2, Week 36	Step 2, Week 40[N]	Step 2, Week 44[N]	Step 2, Week 48	Visit to confirm HIV-1 RNA if Step 2, Week 48 HIV-1 RNA = 201-399	Step 2, Week 52	Confirmation of Virologic Failure	Premature Treatment Discontinuation[B]	Premature Study Discontinuation
Visit Window Arm B		±1 **W**eek	±1 **W**eek											Before Step 2, Week 52	±1 **W**eek	7-21 **D**ays after HIV VL >200	Within 14 days	Within 14 days
Dispense Oral SOC	X	X	X		X		X			X			X					
Clinical Assessments	X	X	X		X		X			X			X				X	X
Targeted Physical Exam	X	X	X		X		X			X			X				X	X
Hematology		X					X						X					
Blood Chemistries, including Cr Clearance		X					X						X					
Liver Function Tests		X					X						X					
Fasting Lipid Profile	X												X					
Urinalysis	If clinically indicated (see section 6.3.6)																	
Urine Pregnancy Test	X	X	X	X[N]	X	X[N]	X	X[N]	X[N]	X	X[N]	X[N]	X		X		X	X
Urine Drug Toxicology	X	X	X		X		X			X			X		X			
CD4+/CD8+	X						X						X			X	X	X

Evaluations	Step 2, Randomization	Step 2, Week 4a[H]	Step 2, Week 8	Step 2, Week 12[N]	Step 2, Week 16	Step 2, Week 20[N]	Step 2, Week 24	Step 2, Week 28[N]	Step 2, Week 32[N]	Step 2, Week 36	Step 2, Week 40[N]	Step 2, Week 44[N]	Step 2, Week 48	Visit to confirm HIV-1 RNA if Step 2, Week 48 HIV-1 RNA = 201-399	Step 2, Week 52	Confirmation of Virologic Failure	Premature Treatment Discontinuation[B]	Premature Study Discontinuation
Visit Window Arm B		±1 **W**eek	±1 **W**eek											Before Step 2, Week 52	±1 **W**eek	7-21 **D**ays after HIV VL >200	Within 14 days	Within 14 days
HIV-1 RNA[E]	X	X	X		X		X			X			X	X	X	X	X	X
HIV-1 Genotype[E]	If Clinically Indicated (see section 6.3.8)															X	If clinically indicated (see section 6.3.8)	
DBS (venipuncture) on TAF, 3TC, FTC, or ABC	X		X				X			X			X			X	X	X
Stored **plasma and PBMCs from** Whole Blood[K]	X	X					X			X			X				X	X
ECG	X												X					
Hair Collection (optional)	X		X				X			X			X			X	X	X
Sociodemographic Questionnaire	X																X	X
HIVTSQs-status Questionnaire[M]	X						X						X				X	X
CEI Withdrawal Questionnaire	X		X															
C-SSRS, DVST, HIV Stigma Mechanism Measure Questionnaires	X												X				X	X
HRU Questionnaire	X		X		X		X			X			X					

Evaluations	Step 2, Randomization	Step 2, Week 4a[H]	Step 2, Week 8	Step 2, Week 12[N]	Step 2, Week 16	Step 2, Week 20[N]	Step 2, Week 24	Step 2, Week 28[N]	Step 2, Week 32[N]	Step 2, Week 36	Step 2, Week 40[N]	Step 2, Week 44[N]	Step 2, Week 48	Visit to confirm HIV-1 RNA if Step 2, Week 48 HIV-1 RNA = 201-399	Step 2, Week 52	Confirmation of Virologic Failure	Premature Treatment Discontinuation[B]	Premature Study Discontinuation
Visit Window Arm B		±1 **W**eek	±1 **W**eek											Before Step 2, Week 52	±1 **W**eek	7-21 **D**ays after HIV VL >200	Within 14 days	Within 14 days
GAD-7, HIV-ASES, PHQ-9 Questionnaires							X						X				X	X
Self-Report of Adherence Questionnaire	X	X	X		X		X			X			X		X	X	X	X
Documentation of Site Adherence and Retention Support	Every six months at each site beginning with enrollment of its first participant.																	
AUDIT-C, DUDIT, Smoking Questionnaires							X						X				X	X

Refer to the SOE FOOTNOTES section for the footnote explanations.

Table 6.1-4: Step 3: LA ART Continuation/Crossover to LA ARV

Evaluations	Step 3, Registration[O]	Step 3, Week 4a[H]	Step 3, Week 4b (All Participants)	Step 3, Week 8	Step 3, Week 12	Step 3, Week 16	Step 3, Week 20	Step 3, Week 24	Step 3, Week 28	Step 3, Week 32	Step 3, Week 36	Step 3, Week 40	Step 3, Week 44	Step 3, Week 48	Confirmation of Virologic Failure	Step 3, Week 52	Premature Treatment Discontinuation	Premature Study Discontinuation
Visit Window (Arm A)		±1 **W**eek		±1 **W**eek											7-21 **D**ays after HIV VL >200	±1 **W**eek	Within 14 days	Within 14 days
Visit Window (Arm B)		±4 **D**ays for non-OLI; +1 week for OLI	+6 **D**ays	±4 **D**ays	±1 **W**eek for non-OLI; ±4 days for OLI	±1 **W**eek									7-21 **D**ays after HIV VL >200	±1 **W**eek	Within 14 days	Within 14 days
Dispense Oral RPV + CAB (Arm B)	X[I]																	
RPV-LA + CAB-LA Injection	X[J]		X	X	X	X	X	X	X	X	X	X	X	X		X		
Clinical Assessments	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
Injection Site Evaluation	X[J]		X	X	X	X	X	X	X	X	X	X	X	X		X	X	X
Hematology		X						X			X					X		
Blood Chemistries, including Cr Clearance		X						X			X					X		
Liver Function Tests		X		X		X		X			X					X		
Fasting Lipid Profile																X		

Evaluations	Step 3, Registration[O]	Step 3, Week 4a[H]	Step 3, Week 4b (All Participants)	Step 3, Week 8	Step 3, Week 12	Step 3, Week 16	Step 3, Week 20	Step 3, Week 24	Step 3, Week 28	Step 3, Week 32	Step 3, Week 36	Step 3, Week 40	Step 3, Week 44	Step 3, Week 48	Confirmation of Virologic Failure	Step 3, Week 52	Premature Treatment Discontinuation	Premature Study Discontinuation
Visit Window (Arm A)		±1 **W**eek		±1 **W**eek											7-21 **D**ays after HIV VL >200	±1 **W**eek	Within 14 days	Within 14 days
Visit Window (Arm B)		±4 **D**ays for non-OLI; +1 week for OLI	+6 **D**ays	±4 **D**ays	±1 **W**eek for non-OLI; ±4 days for OLI	±1 **W**eek									7-21 **D**ays after HIV VL >200	±1 **W**eek	Within 14 days	Within 14 days
Urinalysis	If clinically indicated (see section 6.3.6)																	
Urine Pregnancy Test (pre-dose)	X		X	X	X	X	X	X	X	X	X	X	X	X		X	X	X
Urine Drug Toxicology		X		X	X	X	X	X	X	X	X	X	X	X		X		
CD4+/CD8+								X						X	X	X	X	X
HIV-1 RNA[E]				X		X		X			X			X	X	X	X	X
HIV-1 Genotype[E]	If Clinically Indicated (see section 6.3.8)														X	If Clinically Indicated (see section 6.3.8)		
Stored P**lasma and PBMCs from** Whole Blood[K]	X	X						X			X					X		
PK Trough Sample[L]	X		X	X	X	X		X		X	X	X		X	X	X	X	X
ECG	X													X				
Hair Collection (optional)	X				X			X			X			X	X		X	X

Evaluations	Step 3, Registration[O]	Step 3, Week 4a[H]	Step 3, Week 4b (All Participants)	Step 3, Week 8	Step 3, Week 12	Step 3, Week 16	Step 3, Week 20	Step 3, Week 24	Step 3, Week 28	Step 3, Week 32	Step 3, Week 36	Step 3, Week 40	Step 3, Week 44	Step 3, Week 48	Confirmation of Virologic Failure	Step 3, Week 52	Premature Treatment Discontinuation	Premature Study Discontinuation
Visit Window (Arm A)		±1 **W**eek		±1 **W**eek											7-21 **D**ays after HIV VL >200	±1 **W**eek	Within 14 days	Within 14 days
Visit Window (Arm B)		±4 **D**ays for non-OLI; +1 week for OLI	+6 **D**ays	±4 **D**ays	±1 **W**eek for non-OLI; ±4 days for OLI	±1 **W**eek									7-21 **D**ays after HIV VL >200	±1 **W**eek	Within 14 days	Within 14 days
Pill Counts (Arm B)		X[I]																
HIVTSQs-status Questionnaire[M]								X									X	X
HIVTSQs-change Questionnaire (Arm B only)[M]														X				
Dichotomous Preference Questionnaire (Arm B)														X			X	X
C-SSRS, DVST, HIV Stigma Mechanism Measure Questionnaires														X			X	X
HRU Questionnaire		X			X			X			X			X				
GAD-7, HIV-ASES, PHQ-9 Questionnaires								X						X			X	X
Documentation of Site Adherence and Retention Support	Every six months at each site beginning with enrollment of its first participant																X	X
AUDIT-C, DUDIT, Smoking Questionnaires								X						X			X	X

Refer to the SOE FOOTNOTES section for the footnote explanations.

Table 6.1-5: Step 4: Observation on SOC (Oral ART locally sourced, not provided by study). Participants Who Received at Least One Dose of LA ART

Evaluations	Step 4 - Observation					Study D/C or Premature Discontinuation[Q]
	Step 4, Registration[P]	Step 4, Week 24	Step 4, Week 52	Confirmation of Virologic Failure	Premature Treatment Discontinuation[B]	
Visit Window	±4 **W**eeks			7-21 **D**ays after HIV VL >200	Within 14 days	Within 14 days
Clinical Assessments	X	X	X		X	X
Targeted Physical Exam	X	X	X		X	X
Injection Site Evaluation	X					
Hematology	X	X	X		X	X
Blood Chemistries, including Cr Clearance	X	X	X		X	X
Liver Function Tests	X	X	X		X	X
Fasting Lipid Profile	X		X		X	X
Urinalysis	If clinically indicated (see section 6.3.6)					
Pregnancy Test	If suspected. Participants of Child Bearing Potential on DTG must have a pregnancy test monthly.					
CD4+/CD8+	X		X	X	X	X
HIV-1 RNA[E]	X	X	X	X	X	X
HIV-1 Genotype[E]	If Clinically Indicated (see section 6.3.8)			X	If Clinically Indicated (see section 6.3.8)	
Stored P**lasma and PBMCs from** Whole Blood[K]	X	X	X		X	X
PK Trough Sample for storage only	X			X	X	X

Evaluations	Step 4 - Observation					Study D/C or Premature Discontinuation[Q]
	Step 4, Registration[P]	Step 4, Week 24	Step 4, Week 52	Confirmation of Virologic Failure	Premature Treatment Discontinuation[B]	
Visit Window	±4 **W**eeks			7-21 **D**ays after HIV VL >200	Within 14 days	Within 14 days
HIVTSQ Questionnaire						X
GAD-7, HIV-ASES, PHQ-9 Questionnaires						X
Documentation of Site Adherence and Retention Support	Every six months at each site beginning with enrollment of its first participant.					
C-SSRS, DVST, HIV Stigma Mechanism Measure						X
AUDIT-C, DUDIT, Smoking Questionnaires						X

Refer to the SOE FOOTNOTES section for the footnote explanations.

SOE FOOTNOTES:

[A] For participants who are not eligible or choose not to continue onto Step 2 only.
[B] The treatment discontinuation visit should only be completed if the participant discontinues oral ART including study provided and/or locally sourced ART.
[C] For participants of child-bearing potential who are on a DTG-containing regimen, perform a pregnancy test at the visits indicated. For all other participants of child-bearing potential, pregnancy test is performed only if clinically suspected.
[D] Only Step 1, Entry urine drug toxicology screen results will be returned to the participant for purposes of referral (see section 6.3.6).
[E] **HIV-1 RNA and HIV-1** genotype testing to be done at local **or central laboratory. Refer to the A5359 LPC for more information.**
[F] Only if not provided at Step 1, week 20.
[G] Step 2 randomization will occur after Step 1, week **4**, if the participant has met virologic suppression criteria for randomization. The HIV-1 RNA viral load that will be used to determine eligibility for randomization must have been collected within 4 weeks (28 days) of the randomization visit. Participant must begin treatment within 72 hours after Step 2 randomization.
[H] Participants who are randomized to LA ART in Step 2, or crossing over from SOC to LA ART in Step 3, and who are opting to start oral CAB and RPV at the Step 2 Randomization visit or Step 3 Registration visit, must have results from the week 4a clinical and laboratory evaluations available and reviewed by the IoR or their designee prior to the injections. Week 4 evaluations may be combined to occur on the same day if safety lab results (all except HIV-**1 RNA**) are available, or over several days. Participants continuing LA ART in Step 3 can combine Step 3 week**s** 4a/4b evaluations on the same visit.
[I] Only for participants opting to start oral CAB and RPV at the Step 2 Randomization visit or Step 3 Registration visit (see section 6.2.3).
[J] Only for participants opting to start LA ART injections at Step 2 Randomization visit OR Step 3 Registration visit (see section 6.2.3). These participants must combine the week**s** 4a and 4b visits.
[K] Stored **plasma and PBMCs from** whole blood will NOT be collected for **people** who become and remain pregnant during Steps 2 and 3 (section 8.22).
[L] A pre-dose trough sample will also be obtained for storage at study visits in which a participant missed a prior scheduled study visit.
[M] For those randomized to Arm A, the “HIVTSQ change” questionnaire will be administered at the Step 2, week 48, visit. For those randomized to Arm B, the “HIVTSQ change” questionnaire will be administered at the Step 3, week 48, visit. For all other visits, the “HIVTSQ status” questionnaire will be administered.
[N] Only **people** of child bearing potential on a DTG-containing regimen must attend visit weeks 12, 20, 28, 32, 40, and 44.
[O] Participants may register to Step 3 immediately following their Step 2, week 52 visit. The HIV-1 RNA viral load that will be used to determine eligibility for Step 3 registration for participants randomized to Arm B in Step 2 must have been collected within 4 weeks (28 days) of their Step 3 registration visit. Participants randomized to Arm B must begin study treatment within 72 hours after registration to Step 3.

[P] Participants who received at least one dose of CAB-LA or RPV-LA will register to Step 4 after completing Step 2 per the SOE or after completing Step 3 per the SOE. Visits in Step 4 must be scheduled ±4 weeks.

[Q] Participants who complete 52 weeks of oral ART after their last dose of LA ART, but prior to Step 4, week 52, will need to complete a study discontinuation visit.

[R] If the last negative HBV test is more than 6 months prior to enrollment, then repeat testing should be performed at screening.

6.2 Timing of Evaluations

6.2.1 Screening Evaluations

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

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

On March 18, 2020, the ACTG leadership placed a temporary pause on enrollment due to the COVID-19 pandemic. Participants who were in screening or completed screening prior to the pause in enrollment, but have exceeded the screening window, could be rescreened after the pause was lifted by the ACTG leadership on August 11, 2020.

6.2.2 Entry Evaluations

Entry evaluations may occur on the same day as screening. Participant must begin treatment within 72 hours after registration to Step 1.

6.2.3 Post-Entry Evaluations

6.2.3.1 On-Treatment Evaluations

Step 1:
Evaluations must occur after the entry visit. The Step 1, week 2, through Step 1, week 24, visits should be scheduled per the window in the SOE.

Step 1, week 24, evaluations are only performed for those participants who are not eligible or choose not to move onto Step 2.

Step 2:
Participants will be randomized in Step 2 after they meet the virologic suppression criteria for randomization at or after Step 1 week **4** (see SOE, Table 6.1-2). The HIV-1 RNA viral load that will be used to determine eligibility for randomization must have been collected within 4 weeks (28 days) of the randomization visit. Participant must begin treatment within 72 hours after Step 2 randomization. After randomization, for Arm A participants, the visits for the second and third CAB-LA/RPV-LA dose (Step 2, week 8, and Step 2, week 12, visits for OLI participants; Step 2, week 4, and Step 2, week 8, for non-OLI

participants) should be scheduled per the window in the SOE and section 6.4. All subsequent CAB-LA/RPV-LA injections visits in Step 2 should be scheduled per the window in the SOE. For Arm B participants, all study visits should be scheduled per the window in the SOE.

Step 2 LA ART Initiation with CAB + RPV OLI Step 2, Week 4a, **or** Step 3, Week 4a, Visit
Participants who are randomized to Arm A in Step 2 and participants who are crossing over to LA ART in Step 3 and initiating oral CAB + RPV, must have results from the Step 2, **w**eek 4a, or Step 3, **w**eek 4a, visit, respectively. Clinical and laboratory evaluations results must be reviewed by the IoR or their designee prior to the injections. Week 4a evaluations may occur on a single day or over several days in accordance with the visit windows.

Participants who are randomized to Arm A and are continuing on LA ART in Step 3 do not need to wait for laboratory evaluations results before receiving their injections.

Step 2, Week 4b, and Step 3, Week 4b, Visits with CAB + RPV OLI
Participants who are randomized to Arm A in Step 2, will receive additional evaluation and LA ART injection per the window in the SOE. Clinical and laboratory evaluations results must be reviewed by the IoR or their designee prior to the injections.

Participants who are randomized to Arm B in Step 2 and are transitioning to LA ART in Step 3, will receive additional evaluation and LA ART injection per the window in the SOE and must have results from the **w**eek 4a visit. Clinical and laboratory evaluations results must be reviewed by the IoR or their designee prior to the injections.

Step 2 LA ART Initiation without CAB + RPV OLI
At the discretion of the site IoR, a participant may opt to forgo the oral CAB + oral RPV, and proceed directly to injection at the Step 2 randomization visit. In this case, the first injections are administered at the Step 2 randomization visit. The next injections will be administered at Step 2, week 4a. The Step 2, week**s** 4a and 4b, visits are combined. Please refer to SOE Table 6.1-2 Step 2: Randomization to LA ART vs. Oral SOC – Arm A footnotes (I, J).

In exceptional circumstances, the protocol team may authorize the use of oral CAB and oral RPV as a short-term “bridging” strategy for participants who have begun CAB-LA/RPV-LA (for COVID-19 pandemic bridging instructions, please refer to section 6.2.3.3 below). This strategy would only be employed to address any potential gap in CAB-LA + RPV-LA dosing due to the COVID-19 pandemic and other

extenuating circumstances (see section 5.4.3) as approved by the A5359 team leadership such as limited site study product supply, anticipated prolonged absence, or other unpredictable or unforeseen events. Should a participant need "oral bridging," sites must contact the protocol leadership team at actg.leada5359@fstrf.org for authorization and guidance for treatment strategies prior to a missed CAB-LA + RPV-LA dose. Should a participant not notify the site in advance, the protocol leadership team must be contacted for further treatment guidance.

In Clarification Memo #2, **for Version 1.0,** dated April 13, 2020, sites were instructed to defer entry into Step 2 following the ACTG leadership's temporary pause on enrollment due to the COVID-19 pandemic. The ACTG leadership lifted this pause in August 2020.

Transition from Step 2, Week 52, to Step 3 Registration
Participants can register to Step 3 immediately following their Step 2, week 52, visit. Participants who were randomized to Arm A in Step 2 should continue their study visits as outlined in the SOE. Participants who were randomized to Arm B in Step 2 must begin study treatment within 72 hours after registration to Step 3. The HIV-1 RNA viral load that will be used to determine eligibility for Step 3 registration for participants randomized to Arm B in Step 2 must have been collected within 4 weeks (28 days) of their Step 3 registration visit. Step 2, week 52, evaluations and results do not need to be repeated nor keyed at the Step 3 registration study visit (if completed on the same day).

Step 3 LA ART Initiation with CAB + RPV OLI
In Step 3, for participants who were randomized to Step 2, Arm B, visits for the second and third CAB-LA/RPV-LA dose (Step 3, week 8, and Step 3, week 12) should be scheduled per the window in the SOE and section 6.4. All subsequent CAB-LA/RPV-LA injection visits in Step 3 should be scheduled per the window in the SOE.

Step 3 LA ART Initiation without CAB + RPV OLI
At the discretion of the site IoR and study participant, a Step 2, Arm B, participant crossing over to LA ART in Step 3 may opt to forgo the oral CAB + oral RPV, and proceed directly to injection at the Step 3 registration visit. In this case, the first injections are administered at the Step 3 registration visit. The next injections will be administered at Step 3, week 4a. The Step 3, week 4a and 4b, visits are combined. Please refer to SOE Table 6.1-4 Step 3: LA ART Continuation/Crossover to LA ART.

Transition from Step 2, Week 52, to Step 4 Registration
Participants who received at least one dose of CAB-LA or RPV-LA can register to Step 4 immediately or within 4 weeks (28 days) following their

Step 2, week 52 visit. Follow-up within Step 2 after the last injection will count towards follow-up in Step 4.

Transition from Step 3, Week 52, to Step 4 Registration
Participants who received at least one dose of CAB-LA or RPV-LA can register to Step 4 immediately or within 4 weeks (28 days) following their Step 3, week 52, visit. Follow-up within Step 3 after the last injection will count towards follow-up in Step 4.

6.2.3.2 Event-Driven Evaluations

Step 1:
At Step 1, weeks **4, 8**, 12, 16, and 20, if HIV-1 RNA is between 201-399 copies/mL, a repeat HIV-1 RNA will be performed at a laboratory that possesses a CLIA certification or equivalent by Step 1, week 24. If the repeat HIV-1 RNA is ≤200 copies/mL, then the participant is eligible for randomization.

Step 2:
For participants who randomized to Arm B, if their Step 2, week 48, sample is between 201-399 copies/mL, a repeat HIV-1 RNA will be performed at a laboratory that possesses a CLIA certification or equivalent by Step 2, week 52. If the repeat HIV-1 RNA is ≤200 copies/mL, then the participant is eligible to register for Step 3 to cross over to LA ART.

Step**s** 2 through 4: Confirmation of Virologic Failure
Virologic failure is defined as follows:

- Confirmed HIV-1 RNA >200 copies/mL after Step 2 randomization.

Participants in whom virologic failure is suspected (HIV-1 VL >200 copies/mL at any visit after the Step 2 randomization visit) should return to the clinic for evaluations per the SOE within 7-21 days after the date of the initial plasma HIV-1 RNA >200 copies/mL.

If the initial sample was collected during a treatment interruption, sites are encouraged to address toxicity or adherence issues before taking the confirmatory sample, if possible, within the allowed window. If the evaluations at the time of confirmed virologic failure coincide with a regularly scheduled visit, the evaluations should be combined.

For participants who enter Step 3 from Step 2 SOC arm, Step 3 virologic failure is defined as confirmed HIV-1 RNA >200 copies/mL after Step 3, week 0.

If the initial sample was collected during a treatment interruption, sites are encouraged to address toxicity or adherence issues before taking the confirmatory sample, if possible, within the allowed window. If the evaluations at the time of confirmed virologic failure coincide with a regularly scheduled visit, the evaluations should be combined.

If virologic failure is confirmed, management of ART will be left to the discretion of the site investigator. If stopping study treatment, the participant will complete the Premature Treatment Discontinuation evaluations and continue to be followed on study/off study treatment or be followed on study/on oral ART if they received at least one dose of CAB-LA/RPV-LA per section 6.2.4. **Refer to the A5359 LPC for testing requirements.**

6.2.3.3 COVID-19 Pandemic Guidance

Study Visits during the COVID-19 Pandemic Restrictions
The study team recognizes that each site's situation will be unique regarding the timing of reopening for study visits and procedures (if these were affected), and the extent to which they will be implemented. The study team suggests that sites should not resume regular operations unless:

- Local governance bodies allow the reinitiation of in-person research activities,

AND

- The site has the capacity to perform monthly visits, specimen collection, and injection administration.

NOTE: Please refer to DAIDS memorandum "Guidance for Resuming ACTG Clinical Research Activities Post-COVID-19 Restrictions" dated May 29, 2020 for additional instructions and recommendations.

Data Collection during the COVID-19 Pandemic "Stay-At-Home" Order
Study visits may be conducted remotely (e.g., telephone, telehealth) in the following situations:

- A participant is unable to attend a visit because of illness, inability to travel, or concern for potential exposure to COVID-19.
- The site is temporarily unable to conduct non-essential visits in the clinic.

Sites should document which visits were conducted remotely, attempt to obtain as much of the visit-specific required information as possible, based on the SOE, and record the information on the relevant eCRF. The impacted visits and rationale must be reported and documented following instructions provided by the team or network leadership. Both the team and IRB must be apprised of overall strategies that are employed at the site, and these documents should be placed in the regulatory binder for the study. The individual research participant's chart will contain information about what assessments were done remotely, or were missed, or other deviations because of COVID-19.

For all visits, site staff should not inactivate eCRFs but should follow guidelines provided by the DMC regarding documentation of missed evaluations due to COVID-19.

Step 1:
Step 1 participants should be maintained on their Step 1 regimen (if possible). Study visits should be conducted as per local institutional guidelines (this could include implementing virtual and over-the-phone visits to provide adherence support and completion of study questionnaires). Study labs may be deferred unless the IoR considers them critical to assess safety.

Conditional Economic Incentives (CEIs) should be deployed as per the protocol and subsequent LOAs if the participant:
1) Meets the criteria as outlined in the protocol (Table 5.7-1) if the site is still conducting visits, or
2) Completes virtual or over-the phone visits as per the institution's current research visits policy.

If a participant has not yet reached the virologic suppression criteria for randomization in Step 1, continue to conduct study visits per the SOE through week 16. At these visits, record data in the corresponding visit week folder. For in-person evaluations that cannot be completed, please follow the guidelines provided by the DMC regarding documentation. These guidelines are located under "Medidata Rave Resources" on the DMC Portal.

After a participant completes the Step 1, week 16, visit, continue to conduct visits every 4 weeks and perform the week 16 evaluations (per Table 6.1-1) at each visit until the COVID-19 restrictions are lifted.

NOTE: Do not perform the Step 1, week 20, evaluations indicated in Table 6.1-1 (Step 1: Induction).

Record the Step 1 visits conducted every 4 weeks after week 16 in an Unscheduled Visit folder. Continue to count visit weeks from Entry for the source documents. On the eCRFs, you will be asked the date of the visit when using the Unscheduled Visit folder. Contact the DMC if additional eCRFs are required. Include "COVID-19" when indicating the reason for an unscheduled visit.

For participants who have completed the Step 1, week 20, visit:
If the participant's HIV-1 RNA viral load was ≥400 copies/mL, the participant should complete the Step 1, week 24, visit as scheduled (remotely, as needed). If the participant's HIV-1 RNA viral load is <400 copies/mL, continue to conduct visits every 4 weeks, performing the Step 1, week 16, evaluations per the SOE. Record these visits in an Unscheduled Visit folder. Include "COVID-19" when indicating the reason for an unscheduled visit.

Participants are eligible to receive both CEIs as outlined above in Table 5.7-1 AND study visit compensation for every visit conducted while in Step 1.

Once the COVID-19 restrictions are lifted, the participants enrolled in Step 1 who were undergoing repeated week 16 evaluations (i.e., those who completed Step 1, week 16) will return for a study visit where the Step 1, week 20, evaluations will be conducted or be randomized to Step 2, if eligible as above. For participants who already completed Step 1, week 20, evaluations prior to the pause in study visits, they may proceed with randomization provided their HIV-1 RNA was ≤200 copies/mL and that this was obtained within 4 weeks (28 days). If HIV-1 RNA was obtained >4 weeks (28 days), repeat testing will be necessary.

Step 2 (Both Arms):
During special operations instituted under the national emergency declaration for the COVID-19 pandemic, sites will continue to collect and process for HIV-1 RNA evaluation for all Step 2 visits that are completed in person by a local CLIA-approved laboratory.

Step 2 (Arm A):
If injections can be administered safely at the institution for those participants randomized to Arm A, injections should be continued after documentation of a negative pregnancy test. Sites could consider minimizing contact during these visits by conducting study questionnaires and performing telehealth evaluations for injection site reactions (if available and per institutional policies).

Laboratory assessments may be limited to safety labs at the discretion of the IoR and per local institutional guidance.

If injections cannot be provided for any reason, consider bridging with 1 month of oral CAB/RPV or Step 1 regimen (see above in section 5.4.3). Participants currently receiving the CAB/RPV OLI should be transitioned to their Step 1 regimen. Participants in this group (receiving CAB/RPV OLI and then transitioned to their previous Step 1 regimen) will continue follow-up visits monthly and have assessments performed according to the SOE (as possible). Data should be recorded in the corresponding visit week folder.

Sites should inform the A5359 protocol team leadership (actg.leada5359@fstrf.org) when initiating participants on oral bridging therapy during the COVID-19 pandemic per section 6.2.3, On-Treatment Evaluations, Step 2, **w**eek 4b, and Step 3, **w**eek 4b, Visit, in the protocol. Sites may also consider reinitiating the ART regimen used in Step 1 if injections cannot be provided.

If study visits in Step 2 are curtailed, continue to conduct safety follow-up visits (per the Step 2, Arm A, SOE) by phone or telehealth to determine if a participant receiving site-prescribed study products has had adverse events (AEs) or serious adverse events (SAEs) that require medical follow-up. Study questionnaires can be administered over the phone per the SOE. Timely medical follow-up is still required for participants experiencing AEs or SAEs. SAEs will need to be reported to DAIDS via DAERS as per guidelines.

Once the COVID-19 restrictions are lifted, the participants enrolled in Step 2, Arm A, will return for a study visit where the next scheduled evaluations will be conducted (i.e., participants will be treated as if this upcoming visit were their next scheduled injection visit after discontinuation of injections). Prior to the reinitiation of injectable LA CAB + RPV, participants will need to have documentation of viral suppression (HIV-1 RNA ≤200 copies/mL). If HIV-1 RNA is >200 copies/mL, a repeat HIV-1 RNA can be obtained within 14 days to assess if reinitiating injectable LA CAB + RPV is appropriate. Refer to the subsection, Data Collection after Resumption of In-Person Clinical Research Activities Post-COVID-19 Restrictions, below for further guidance.

Step 2 (Arm B):
Arm B visits may be treated as other non-essential study visits at some sites in accordance with their local institutional guidance/policies during the COVID-19 pandemic. In these situations, study visits should be conducted according to local institutional guidance and policies. Research personnel can conduct all study visits by phone or telehealth to determine if a participant receiving site-prescribed study products has had AEs or SAEs that require medical follow-up and EAE reporting. Study questionnaires can be administered over the phone.

If study visits in Step 2 are curtailed, conduct safety follow-up visits by phone or telehealth to determine if a participant has had an AE or SAE. Study questionnaires can be administered over the phone per the SOE. Timely medical follow-up is still required for participants experiencing AEs or SAEs. SAEs will need to be reported to DAIDS via DAERS as per guidelines.

NOTE: The CEIs will not be extended to participants in Step 2.

Step 3
Please refer to instructions for Step 2 (Arm A).

Data Collection after Resumption of In-Person Clinical Research Activities Post-COVID-19 Restrictions

Step 1: (including transition from Step 1 into Step 2)
If a site was able to continue with study visits throughout the COVID-19 "stay-at-home" orders, the site may continue to conduct study visits and procedures per the SOE.

If a participant was maintained on their Step 1 study-supplied regimen, they should continue this regimen.

If a participant was required to switch to locally sourced ART due to barriers accessing study-supplied regimen, the study team will allow continuation of this locally sourced ART. Any ART changes will need to be properly documented in the corresponding eCRF.

If a site was unable to conduct in-person study visits or virtual visits for a participant, the study team would recommend that participants resume study visits and procedures in accordance to what would have been their next scheduled visit (per the SOE).

If any participant was required to repeat Step 1 visits due to site restrictions, the participant can now proceed to the next scheduled visit to determine eligibility for transition and randomization to Step 2, or be randomized to Step 2, if eligible. If the participant was determined to be eligible for randomization prior to suspension of Step 1 to Step 2 transition, they can proceed to randomization, provided the last HIV-1 RNA was obtained ≤4 weeks (28 days) prior to the visit and was ≤200 copies/mL. If the HIV-1 RNA was obtained >4 weeks (28 days) prior, this will need to be repeated and confirmed ≤200 copies/mL prior to transition to Step 2.

Sites should confirm the availability of LA ART and oral SOC supply with their site PoR. The site PoR should notify both protocol pharmacists,

Katherine Shin (kashin@niaid.nih.gov) and Cynthia Parker (cindy.parker@nih.gov), for any additional need of study products. The protocol pharmacists will work with the site PoR to provide assistance.

As of August 11, 2020, Step 1 progression may resume. This will allow participants to transition from Step 1 into Step 2 as follows:

Step 2 (Arm A):
If a site was able to continue with study visits throughout the COVID-19 "stay-at-home" order, the sites may continue to conduct study visits and procedures per the SOE.

If a participant was required to transition back to either their Step 1 oral SOC regimen or received/remained on oral CAB/RPV bridging, resumption or initiation of injections will be based on the timing of the last HIV-1 RNA and the timing of the last injection.

HIV-1 RNA:
If the last HIV-1 RNA was obtained ≤4 weeks (28 days) prior to the visit AND was ≤200 copies/mL, the participant can resume injections based on the timing of their last injection (outlined below).

If the last HIV-1 RNA was obtained >4 weeks (28 days) prior to the visit, the site should obtain an HIV-1 RNA (which can be performed at a local lab) and proceed with reinitiation of injectable LA ART if it is ≤200 copies/mL. If the HIV-1 RNA is >200 copies/mL, the site should follow the confirmation of virologic failure procedures outlined in section 6.2.3. If the confirmation HIV-1 RNA is ≤200 copies/mL, proceed with injection.

NOTE: See section 6.3.8 regarding collection of viral loads.

Timing of the last injection:
If the last injection occurred <8 weeks prior to the visit, participants may resume maintenance dose of injectable RPV 600 mg/CAB 400 mg.

If the last injection occurred ≥8 weeks prior to the visit, participants will require a new loading dose of IM RPV 900 mg/CAB 600 mg, which will be followed by the maintenance dose of injectable RPV 600 mg/CAB 400 mg 4 weeks later (in a similar fashion as when they initiated injectable ART in Step 2).

Step 2 (Arm B):
If a site was able to continue with study visits throughout the COVID-19 "stay-at-home" order, the site may continue to conduct study visits and procedures per the SOE.

When in-person visits resume, sites should continue to conduct study visits and procedures per the SOE.

6.2.4 Discontinuation Evaluations

Evaluations for Participants Who Do Not Start Study Treatment in Step 1
Participants who do not begin study treatment in Step 1 will be followed on study/off study treatment until Step 1, week 24, and then be taken off study. Participants will not have Step 1 evaluations performed per protocol requirements; however, their clinical chart will be abstracted for CD4+/CD8+, and plasma HIV-1 RNA assessments until Step 1, week 24, i.e., the equivalent of end of Step 1. Participants who do not wish to be followed on study should have screening and entry forms completed and keyed and then be taken off study.

Evaluations for Randomized Participants Who Do Not Start Study Treatment in Step 2
Participants who do not begin study treatment in Step 2, will be followed on study/off study treatment until Step 2, week 52, and then be taken off study. However, they will only be required to have clinical assessments, CD4+/CD8+ and plasma HIV-1 RNA performed per protocol requirements until Step 2, week 52, i.e., the equivalent of end of Step 2. If applicable, they may also have a urine pregnancy test at the treatment discontinuation visit.

Evaluations for Participants Who Do Not Start Injectable Study Treatment in Step 3
Participants randomized to SOC (Arm B) in Step 2 who do not wish to begin study treatment in Step 3 will be taken off study with no further evaluations required.

Participants randomized to CAB-LA/RPV-LA (Arm A) in Step 2 and who received at least one dose of CAB-LA/RPV-LA in Step 2, who do not wish to continue study treatment in Step 3 will register to Step 4 at the completion of Step 2.

Evaluations for Participants Who Do Not Start oral ART in Step 4
Participants who do not begin oral ART in Step 4, will be followed on study/off study treatment until Step 4, week 52, and then be taken off study. Participants will not have Step 4 evaluations performed per protocol requirements; however, their clinical chart will be abstracted for CD4+/CD8+ and plasma HIV-1 RNA assessments until Step 4, week 52, i.e., the equivalent of end of Step 4.

Premature Discontinuation of Study Treatment
Discontinuation of study treatment is defined as following:

Step 1 participants: discontinuation of all oral ART regimen (this includes study provided and/or locally sourced ART).

Step 2, Arm A, participants: Discontinuation of oral CAB/RPV and not initiating LA injections, or discontinuation of LA injections.

Step 2, Arm B, participants: Discontinuation of all oral ART regimen (including study provided and/or locally sourced ART).

NOTE: Switching oral ART from study provided to locally sourced is NOT considered as discontinuation of study treatment.

Step 3 participants: Discontinuation of oral CAB/RPV and not initiating LA injections, or discontinuation of LA injections.

Step 4 participants: Discontinuation of all oral ART regimen.

Participants who prematurely discontinue treatment at any step will have the Premature Treatment Discontinuation evaluations performed within 14 days after stopping study treatment per the SOE.

Participants who prematurely discontinue study treatment during Step 1 are encouraged to be followed on study/off study treatment per the SOE until the end of Step 1.

Arm B participants who permanently discontinue all oral ART regimen prematurely during Step 2 should be followed on study/off study treatment per the SOE until the end of Step 2; Arm A participants should be followed on study/on oral ART per the SOE until the end of Step 2 and then register to Step 4. Arm A participants will be followed until the participant completes 52 weeks on oral ART after their last dose of LA ART, which could include weeks accrued during Step 2 for a total of 52 weeks.

Participants who prematurely discontinue study treatment during Step 3 should be followed on study/on oral ART per the SOE until the end of Step 3 and then register to Step 4. Participants will be followed until the participant completes 52 weeks on oral ART after their last dose of LA ART, which could include weeks accrued during Step 3 for a total of 52 weeks.

Participants who prematurely discontinue oral ART on Step 4, are encouraged to be followed on study/off oral ART per SOE until the end of Step 4.

Premature Study Discontinuation Evaluations
Participants who prematurely discontinue participation in the study should report to the clinic to have the Premature Study Discontinuation evaluations performed within 14 days.

Participants who complete 52 weeks of oral ART after their last dose of LA ART, but prior to Step 4, week 52, will need to complete a study discontinuation visit.

Study Completion Evaluations
Participants who are not eligible to enter Step 2 will have final study visit at Step 1, week 24.

Step 2, Arm A participants who are not eligible or choose not to continue on LA ART in Step 3 will register to Step 4 at the completion of Step 2 and will be followed until they complete 52 weeks on locally sourced oral ART.

Step 2, Arm B participants who are not eligible or choose not to crossover to LA ART in Step 3 will have their final study visit at Step 2, week 52.

Participants who complete Step 3 and choose not to continue (or cannot access) LA ART at the end of Step 3, will register to Step 4 and have their final study visit at Step 4, week 52.

If participants can access LA ART during follow-up in Step 4, and the participant and provider decide to restart LA ART prior to Step 4, week 52, they will discontinue study follow up and complete a study discontinuation visit before restarting LA ART.

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 Division of AIDS Table for Grading the Severity of Adult and Pediatric Adverse Events (DAIDS AE Grading Table), and AE reporting of adverse events requirements.

The protocol team and/or study 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 is not recorded on the eCRF.

6.3.2 Medical History

The medical history must include all signs and symptoms regardless of grade and all diagnoses identified by the ACTG criteria for clinical events and other diagnoses regardless of grade within the past 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 heart disease
- Cancer (exclusive of basal/squamous cell skin cancer)
- Diabetes
- Tuberculosis
- Chronic hepatitis C
- Chronic hepatitis B
- History of SARS-CoV-2 infection or COVID-19

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

6.3.3 Medication History

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 6.3.3-1: Medication History

Medication Category	Time Frame
ART	Complete History
Immune-based therapy	Within 12 months prior to study entry
Blinded study treatment	Within 12 months prior to study entry
HIV-1-related vaccines	Complete History
Prescription drugs for treatment of opportunistic infections	Within 30 days prior to study entry
Prescription drugs for prophylaxis of opportunistic infections	Within 30 days prior to study entry
Prescription drugs (other)	Within 30 days prior to study entry
Alternative therapies	Within 30 days prior to study entry
Dietary supplements	Within 30 days prior to study entry
Sex-hormone medications or sex-hormone analogues or antagonists*	Within 12 months prior to study entry except as noted below

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

6.3.4 Clinical Assessments

Complete Physical Exam
A complete physical examination, at screening, 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 (temperature, pulse, respiration rate, and blood pressure), height, and weight for BMI calculation.

Targeted Physical Exam
A targeted physical examination will be performed per the SOE and is to include vital signs (weight, temperature, pulse, respiration rate, and blood pressure) and is to be driven by any previously identified or new adverse events/targeted events (as described in below bullets), that the participant has experienced since the last visit or at this visit.

Injection Site Reaction
Injections will start in Step 2. For those randomized to Arm A in Step 2, and for all participants in Step 3, evaluate each injection site immediately after injection and at each subsequent visit and describe per section 8.18.

Refer to section 7.2 for AE collection requirements.

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

- Sex-hormone medications or sex-hormone analogues or antagonists (see section 6.3.3 for examples).
- Any new or discontinued prescription medications, especially those listed in section 6.3.3, including lipid-lowering agents, contraceptives, systemic steroids, other immune modulatory drugs, investigational drugs, and study-prohibited medications taken since the last study visit, including actual or estimated start dates and stop dates.

Study Treatment Modifications
Record all study drug modifications, including initial doses, participant-initiated and/or protocol-mandated modifications, inadvertent and deliberate oral ART interruptions of more than 7 consecutive days, missed or delayed LA injections (defined as 8 days beyond scheduled injection day) since the last visit. Record any permanent discontinuation of treatment.

6.3.5 Procedures

Intramuscular LA ART injection:
Starting in Step 2, Arm A, at study visits (dosing interval of Q4 weeks) and for all participants in Step 3.

6.3.6 Laboratory Evaluations

At screening and entry for each step, all laboratory values must be recorded on the eCRF. For post-entry assessments, record on the eCRF all laboratory values for ALT, AST, alkaline phosphatase, total bilirubin, total cholesterol, HDL cholesterol, low density lipoprotein (LDL) cholesterol (calculated), triglycerides, and glucose regardless of grade as indicated on SOE; record abnormal laboratory findings as per section 7.2.

Hematology (CBC)
Hemoglobin, hematocrit, white blood cell count (WBC), differential WBC, ANC, and platelet count will be performed in real time at the local laboratory.

Blood Chemistries (Basic Metabolic Panel)
Blood urea nitrogen (BUN), creatinine, glucose, and electrolytes (sodium, potassium, chloride, and CO_2/bicarbonate) will be performed in real time at the local laboratory.

Calculated CrCl is required as estimated by the **CKD-Epi** (refer to section 4.1.6). This requires the recording of all values of serum creatinine regardless of grade.

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

NOTE A: If participant develops symptoms suggestive of hepatitis, perform LFTs within 2 weeks of visit.

NOTE B: Indirect bilirubin should be calculated from the total and direct bilirubin values. Indirect bilirubin should be reported according to protocol reporting requirements. Direct bilirubin does not need to be reported.

Fasting **L**ipid Profile
Total cholesterol, HDL cholesterol, low density lipoprotein (LDL) cholesterol (calculated), triglycerides, will be obtained and all values will be recorded in the eCRFs regardless of grade.

Participants will be fasting (nothing to eat or drink except water, decaffeinated black coffee without sugar, and required prescription medications for at least 8

hours). If participants are in a non-fasting state, they must come back within 96 hours for a fasting blood draw and evaluation.

Urinalysis
Urinalysis will be performed at Screening. Post-entry, urinalysis will only be performed if clinically indicated. Perform a microscopic examination if dipstick urinalysis is abnormal or when deemed necessary by the investigator.

Pregnancy Test
For participants of reproductive potential: serum or urine β-HCG. Pregnancy tests must have a sensitivity of ≤25 mIU/mL. Pregnancy testing will be repeated as indicated in the SOEs. Refer to section 8.0 for pregnancy and pregnancy outcome reporting requirements.

For Step 1, Step 2, and Step 4, all participants of child bearing potential who are on a DTG-containing regimen must have a pregnancy test performed at least monthly. If a pregnancy test cannot be performed because the participant is unable to attend study visits, the IoR has the discretion either to continue the DTG-containing regimen or to switch the participant to another regimen.

NOTE: In Step 2 and Step 3, participants of reproductive potential must have a negative pregnancy test result prior to initiating LA ART.

Urine Drug Toxicology
Urine drug toxicology will be performed at entry for purposes of referral for support if indicated. Urine drug toxicology screens will be collected per the SOE but results will not be returned to the participant (except the test performed at entry). The specimen will be checked for: cocaine, amphetamines, methamphetamines, barbiturates, benzodiazepines, marijuana (THC), opiates (including morphine and oxycodone), PCP, methadone. The specimen will also be checked for quality assurance by measuring the specimen temperature at the time of collection with an acceptable range of 92-96°F at time of collection.

6.3.7 Immunologic Studies

CD4+/CD8+
Obtain absolute CD4+/CD8+ T-cell count and percentages within 60 days prior to entry from a laboratory that possesses a CLIA certification or equivalent. During the study, CD4+/CD8+ T-cell count and percentage assays must be performed as indicated in the SOE by a laboratory that possesses a CLIA certification or equivalent.

6.3.8 Virologic Studies

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. Eligibility will be determined based on the screening value.

Specimens **for entry and all post-entry HIV-1 RNA, will also be performed at a laboratory that possesses a CLIA certification or equivalent as outlined in the** A5359 **LPC**.

HIV-1 Genotype
All participants will **have** HIV **genotype testing (including NRTI, NNRTI, PI, and INI resistance)** within 60 day prior to study entry. For the screening genotype, previous results verifiable by reports from a CLIA-certified laboratory (refer to Department of Health and Human Services (DHHS) Guidelines for the use of antiretroviral agents in HIV-1-infected adults and adolescents, **June 2021**: **(https://clinicalinfo.hiv.gov/sites/default/files/guidelines/documents/adult-adolescent-arv/guidelines-adult-adolescent-arv.pdf)** obtained within 60 days prior to screening are acceptable as long as the results are available prior to entry.

A conventional genotype is recommended for HIV-1 drug resistance testing for all participants. For participants in whom an HIV-1 RNA conventional genotype cannot be resulted by the testing laboratory, review of historical genotypes and treatment history by the IoR can be used to satisfy this criterion.

When a participant is suspected to have virologic failure, a specimen for HIV-1 RNA and HIV-1 genotyping will be collected. If virologic failure is confirmed, the **HIV-1 genotype will be tested according to the A5359 LPC**.

Stored **Plasma and PBMCs from** Whole Blood
Whole blood **will be collected and processed into stored** plasma **and PBMCs according to the A5359 LPC.**

Hepatitis B and C Serology
For participants with known HBV immunity, prior documentation of positive HBsAb is acceptable. If documentation is not available, HBsAb, HBsAg, and HBcAb will be obtained at screening. Negative HBV tests (i.e., negative HBsAb, HBsAg, and HBcAb) performed within 6 months prior to enrollment need not be repeated. If the last negative test result is more than 6 months prior to enrollment, then testing should be performed at screening. Results must be available prior to study entry so that participants who have active HBV can be excluded from participating in the study.

Participants who have positive HBcAb but negative HBsAg and HBsAb (isolated HBcAb positive status) must have HBV DNA PCR performed and confirmed as negative for participant to be eligible for A5359.

Hepatitis C antibody testing will be done per the SOE. See sections 4.2.4 and 4.2.5 for details.

6.3.9 Other Laboratory Studies

Electrocardiogram (ECG)
ECG for corrected QT (QTc) measurement will be obtained per the SOE (see section 8.13).

6.3.10 Adherence Assessments

- Dried Blood Spots (DBS) cards will be created and stored for participants on TAF, FTC, 3TC or ABC. **Refer to the A5359 LPC.**
- Hair collection (100 strands) per SOE (Optional). **Refer to the A5359 MOPS and A5359 LPC.**
- Pill Counts conducted per SOE (Step 2, **w**eek 4, Arm A/Step 3, **w**eek 4, Arm B, for participants who initiated oral RPV/CAB).

6.3.11 Questionnaires (see MOPS for details and when a referral for psychiatric care or drug treatment is warranted)

- Sociodemographic Self-Report Questionnaire
- The Alcohol Use and Disorders Identification Test (AUDIT – C)
- Drug Use Disorders Identification Test (DUDIT)
- Smoking Questionnaire
- Patient Health Questionnaire – 9 (PHQ-9)
- General Anxiety Disorder Assessment (GAD-7)
- HIV Treatment Adherence Self-Efficacy Scale (HIV-ASES)
- HIV Stigma Mechanism Measure
- HIV Treatment Satisfaction Questionnaires (HIVTSQs-status and HIVTSQc-change)
- Self-Report of Adherence
- Columbia-Suicide Severity Rating Scale (C-SSRS)
- Domestic Violence Screen Tool: (DVST)
- Health Resource Utilization Questionnaire (HRUQ)
- Conditional Economic Incentive Withdrawal Questionnaire (CEI Withdrawal)
- Dichotomous Preference Questionnaire
- Checklist of Adherence/Retention Measures (at site level only)

6.3.12 Incentives

CEI will be paid to participants according to Table 5.7-1 and Step 1 SOE.

6.3.13 Pharmacokinetic Studies (refer to section 11.0)

Refer to the **A5359** LPC for collection, processing, storage, and shipping details.

The date and time of the last three doses of oral ARV taken or last dose of RPV-LA and CAB-LA injected prior to each pharmacokinetic (PK) sample must be recorded. PK **specimens** consist of dried blood spots, hair, and **plasma** for PK trough levels.

6.4 Visit Windows

The target visit windows for all visits, including injection visits, are outlined in the SOE (section 6.1). Visits conducted outside of the target visit windows are allowable with the following instructions for those receiving RPV-LA and CAB-LA:

If the time since the last RPV-LA and CAB-LA injection was greater than 8 weeks (56 days) from the previous injection, a participant will need to be administered a new loading dose of both RPV-LA (900 mg) and CAB-LA (600 mg) prior to continuing the maintenance dose. If the last injection of RPV-LA and CAB-LA occurred less than or equal to 8 weeks from the previous injection, the participant will be continued on the maintenance dose of RPV-LA (600 mg) and CAB-LA (400 mg).

The reason for any injection received outside the injection target window will be recorded on the eCRF. Per protocol, for non-OLI participants, the target window for the week 4b and week 8 injections is 24-32 days since the previous injection. The target window for the week 12 injection is 21-35 days since the previous injection. For OLI participants, the target window for the week 8 and week 12 injections is 24-32 days since the previous injection. The target window for all other injections for all participants is 21-35 days since the previous injection.

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 during the conduct of the study REGARDLESS of the attribution (i.e., relationship of event to medical treatment/study product/device or procedure/intervention). This includes any occurrence that is new in onset or aggravated in severity or frequency from the baseline condition.

7.2 Adverse Event Collection Requirements for this Protocol

All AEs must be recorded on the eCRF 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

- New diagnosis of hepatitis B
- New diagnosis of hepatitis C
- All Grade ≥2 neurologic and psychiatric events
- All seizure regardless of grade
- Any bone fracture
- New onset of Diabetes or preexisting Diabetes with Grade ≥2 Diabetes AE
- Cancer (exclusive of basal/squamous cell skin cancer)
- Tuberculosis
- ALT ≥3x ULN AND total bilirubin ≥2x ULN
- New diagnosis of COVID-19 or SARS-CoV-2 infection, regardless of grade

NOTE A: Uterine pregnancy does not require reporting as an AE (unless other SAE criteria are met), but must still be recorded in the eCRFs.

NOTE B: SAEs or events meeting EAE reporting requirements should also be entered into the DAIDS Adverse Experience Reporting System DAERS system as indicated.

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

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

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

7.3 Expedited Adverse Event (EAE) Reporting to DAIDS

7.3.1 Expedited Reporting of Adverse Event to DAIDS

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

The DAIDS Adverse Experience Reporting System (DAERS), an internet-based reporting system, must be used for EAE reporting to DAIDS. In the event of system outages or technical difficulties, EAEs may be submitted using the DAIDS

EAE Form. This form is available on the DAIDS RSC website at https://rsc.niaid.nih.gov/clinical-research-sites/paper-eae-reporting.

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

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

7.3.2 Reporting Requirements for this Study

The SAE Reporting Category, as defined in Version 2.0 of the DAIDS EAE manual, will be used for this study (the definition of an SAE is also included in the manual).

The study agents for the purposes of EAE reporting are:

- Oral CAB 30 mg oral tablet
- CAB LA injectable suspension (200 mg/mL)
- Oral RPV 25 mg tablet
- RPV LA injectable suspension (300 mg/mL)
- DTG 50 mg as either Tivicay or Triumeq
- In participants for whom a protease inhibitor-based regimen is chosen: DRV/cobi as Prezcobix
- In participants for whom a non-nucleoside-based regimen is chosen: RPV (Edurant)
- Additionally, regimens would include separate NRTIs as either Epzicom or Descovy (except in those participants who receive Triumeq)
- FDA approved oral therapy used to construct SOC (locally sourced)

7.3.3 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

The Protocol Leadership Team will monitor the conduct and safety of the study via regular summaries of accrual, study discontinuation (Step 1 only), protocol deviations, data completeness and adverse events pooled across treatment arms, as appropriate.

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.

The study will undergo interim review at least annually by a DAIDS-appointed Data Safety Monitoring Board (DSMB). The first interim review will occur approximately 6 months after the enrollment of the first study participant. 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 Progress Data and Safety Monitoring Plan (SPDSMP) developed by Statistical and Data Management Center (SDMC) prior to enrollment of the first participant.

8.0 CLINICAL MANAGEMENT ISSUES

8.1 Toxicity Management

8.1.1 Only toxicities related to study medications provided through this study (CAB-LA, RPV-LA, other oral regimens) or required for certain arms of this study (oral CAB, oral RPV) will be considered in the Toxicity **M**anagement section. The grading system is located in the DAIDS AE Grading Table, corrected Version 2.1, July 2017: https://rsc.niaid.nih.gov/clinical-research-sites/daids-adverse event-grading-tables.

8.1.2 For toxicities attributed to one or more of the study medications, the following dosing modifications can be considered:

- All study medications may be held
- One or more of the study drugs may be switched per section 5.0

If there is interruption of one of the study drugs for which no immediate substitution is possible, then all ART drugs should be interrupted.

Participants who have switched to any non-study ART drug should manage toxicity for that drug per SOC.

If there is a treatment-limiting toxicity resulting from one of the drugs in the fixed-dose combination of FTC/TAF the individual formulations of FTC or TAF can be given along with a drug substitution (see section 5.2.1), if necessary.

NOTE: The study leadership team must be notified by e-mail regarding toxicities that result in a change in regimen (actg.leada5359@fstrf.org).

Dosage reductions for oral ART administered in the study in Step 1 and Step 2 are permitted with guidance from the package insert for the respective agent.

There will be no dose reduction for CAB-LA or RPV-LA.

8.2 Grade 1 or 2

Participants who develop a Grade 1 or 2 AE or toxicity may continue study medications without alteration of the dosage, except as stated in sections 8.5-8.22. For participants experiencing Grade 1 or 2 AEs who choose to discontinue all study medications, the site investigator should complete premature discontinuation of study therapy evaluations, contact the study leadership team (actg.leada5359@fstrf.org), and the participant should be encouraged to complete follow-up protocol study evaluations.

NOTE: If participants discontinue study medications due to experiencing Grade 1 or 2 AEs, this should be noted in the eCRF as the reason for discontinuation.

8.3 Grade 3

If the investigator has evidence that the AE has *not* been caused by study medications, dosing may continue. Participants who develop a Grade 3 AE or toxicity thought to be related to a study medication, except as stated in sections 8.5 -8.22 below, should have an ART drug substitution or their study medications withheld, at the site investigator's discretion. The participant should be reevaluated weekly until the AE returns to Grade ≤2 or baseline, at which time the study medications may be reintroduced, at the discretion of the site investigator or according to standard practice.

If the same Grade 3 AE, excluding those AEs noted in the following sections, recurs within 4 weeks of restarting treatment, the suspected study medication must be permanently discontinued. However, if the same Grade 3 AE recurs after 4 weeks, the management scheme outlined above may be repeated.

Participants experiencing Grade 3 AEs requiring permanent discontinuation of all study medications should be followed weekly until resolution of the AE and should be encouraged to complete the premature study treatment discontinuation evaluations and be followed on study/off study treatment (see section 6.2.4). The study leadership team (actg.leada5359@fstrf.org) must be notified, and drug substitution can be considered as discussed in section 5.0.

8.4 Grade 4

Participants who develop a Grade 4 symptomatic AE or toxicity related to study product, will have all study medications permanently discontinued, except as stated in sections 8.5-8.22 below. Participants experiencing Grade 4 AEs requiring permanent discontinuation of all study medications should be followed weekly until resolution of the AE and encouraged to complete the premature study treatment discontinuation evaluations and be followed on study/off study treatment (see section 6.2.4).

The study leadership team (actg.leada5359@fstrf.org) must be notified by e-mail regarding toxicities that result in a change in regimen.

8.5 Rash (with or without systemic symptoms or mucosal or target lesions)

In the event that a participant experiences rash (with or without systemic symptoms), they should be evaluated for the possibility of a cutaneous AE associated with DRV or other medications.

8.5.1 Grade 2 Rash

If thought to be related to the study medications, antihistamines, topical corticosteroids, or a brief course of systemic corticosteroids, at the discretion of the site investigator, may be prescribed and participants may continue all study medications. If the rash progresses, then manage as per section 8.5.2 or 8.5.3.

If the rash is considered to be most likely due to concomitant illness then that illness should be managed as per SOC. If the rash is considered to be due to a non-protocol medication, discontinuation of the likely causative agent should be undertaken. If no other causative factor is found after clinical evaluation, the participant should be treated symptomatically until the rash resolves.

8.5.2 Grade 3 Rash

If thought to be related to the study medications, participants should either discontinue all drugs or consider switching from the likely causative agent. If the rash progresses and all study medications have not yet been stopped, then manage as per section 8.5.3.

8.5.3 Grade 4 Rash

Participants should discontinue all study medications. If the site investigator establishes that there is a definitive alternate explanation for the Grade 4 rash, other than the protocol medications, then the protocol medications may be restarted once the rash has resolved to Grade 2 or less. Otherwise, the participant should have their ART changed to alternate medications.

8.5.4 Abacavir Hypersensitivity Reaction (HSR)

It is required that investigators screen for the HLA-B*5701 allele in any participant for whom an abacavir (ABC)-containing product will be used as part of their best-available NRTI regimen and for whom HLA-B*5701 status is unknown (even if the participant has previously tolerated ABC). Use of ABC in participants known to carry this allele is not allowed. For all participants, appropriate counseling and monitoring for any signs of HSR should be instituted in conjunction with local guidelines.

In any participant treated with ABC, the clinical diagnosis of suspected HSR must remain the basis of clinical decision-making. Even in the absence of the HLA-

B*5701 allele, participants developing signs and symptoms suggestive of a systemic HSR after initiation of an ABC-containing regimen should discontinue all study drugs and seek medical evaluation immediately. The study leadership team should be notified of a clinically suspected HSR as soon as possible and subsequent management should be discussed with the leadership. Withholding ABC should not be delayed, however and ABC must not be reinitiated due to the potential for a severe or even fatal reaction. After resolution of the signs and symptoms, sites can reinitiate a regimen that contains the best NRTI combination that does not include ABC.

All clinically-suspected ABC HSR events must be reported to DAIDS as an EAE (see section 7.3.2).

Clinical Description

The diagnosis of hypersensitivity to ABC remains a clinical diagnosis. There is no pathognomonic clinical sign or laboratory finding that suggests or confirms the diagnosis. Overall, in clinical studies conducted before the introduction of screening for the HLA-B*5701 allele, approximately 5% of participants receiving ABC develop an HSR that in rare cases has proved fatal. HSR is characterized by the appearance of symptoms indicating multi-organ/body system involvement. Symptoms usually appear within the first 6 weeks of starting treatment with ABC (median time to onset is 9 days), but may occur at any time while on therapy, and most often include fever, rash, gastrointestinal symptoms (nausea, vomiting, diarrhea, or abdominal pain), respiratory symptoms (dyspnea, sore throat, cough), and lethargy or malaise. Other signs and symptoms may include musculoskeletal symptoms (myalgia, rarely myolysis, and arthralgia), headache, paresthesia, and edema. Respiratory tract symptoms (dyspnea, sore throat, and cough) have been observed in approximately 20% of participants who experience HSR. Some participants with HSRs were initially thought to have respiratory tract disease (pneumonia, bronchitis, pharyngitis) or a flu-like illness.

Physical findings may include lymphadenopathy and, occasionally, mucous membrane lesions (conjunctivitis and/or mouth ulceration). The rash is variable and may be absent, but often appears maculopapular or urticarial. Laboratory abnormalities that may accompany ABC hypersensitivity include elevated transaminases, CK, or creatinine or lymphopenia.

The misattribution of the symptoms of HSR to another medical condition or delay in diagnosis of hypersensitivity has resulted in ABC being continued or reintroduced, leading to more severe presentation of HSR or death. Therefore, the diagnosis of HSR should be carefully considered for participants presenting with symptoms of these diseases, even if another medical diagnosis seems likely.

Symptoms related to HSR worsen with continued therapy and usually resolve upon discontinuation of ABC. Restarting ABC following an HSR results in a prompt return of symptoms within hours. This recurrence of the HSR may be

more severe than on initial presentation and may include life-threatening anaphylaxis, hypotension, liver, renal and respiratory failure, and death. Regardless of their HLA-B*5701 status, participants who develop this HSR must discontinue ABC and MUST NOT be rechallenged with any ABC-containing product (e.g., Ziagen, Epzicom, or Triumeq).

Management of HSR
Symptoms usually start to resolve (within 24 hours) after stopping therapy. Symptomatic support, such as intravenous fluids for those who develop hypotension, is advised. There are no clinical data demonstrating the benefit of antihistamines or corticosteroids in the management of hypersensitivity. Nevertheless, symptomatic and/or supportive treatment may be reasonable following ABC discontinuation. Laboratory and other investigations which may be useful in the evaluation and treatment of ABC HSR include, but may not be limited to, measurement of ALT, AST, CK, serum creatinine, WBC differential count, and chest x-ray, if respiratory symptoms are present.

Regardless of their HLA-B*5701 status, participants who have had a clinically suspected HSR must be advised to never again take an ABC-containing product (e.g., Ziagen, Epzicom, or Triumeq). ABC therapy SHOULD NOT be restarted following a clinically suspected HSR, because more severe symptoms will occur within hours and may include life-threatening hypotension and death. Fatal HSRs have been associated with re-initiation of ABC therapy. Participants, who develop signs or symptoms of HSR, MUST contact their doctor immediately for advice. The site investigator must be notified and provide sign-off for those participants who discontinue ABC due to HSR. In order to avoid restarting the ABC-containing product, participants who have experienced a clinically suspected HSR should be asked to return the remaining tablets to the pharmacy.

There have been infrequent reports of HSR following reintroduction of ABC, where the interruption was preceded by a single key symptom of hypersensitivity (rash, fever, malaise/fatigue, gastrointestinal symptoms or a respiratory symptom). If a decision is made to restart ABC in these participants in consultation with the study leadership team, this should be done only under direct medical supervision.

On very rare occasions, hypersensitivity reactions have been reported in patients who have restarted therapy and who had no preceding symptoms of a hypersensitivity reaction. If a decision is made to restart ABC, this must be done only if medical care can be accessed readily by the participant.

NOTE: HLA B*5701 screening will not be provided by the study.

8.6 Skin Hyperpigmentation

Changes in skin hyperpigmentation, if assessed as being related to FTC, can be followed without modification of therapy, at the discretion of the site investigator. If the participant is on his/her initial regimen and the skin hyperpigmentation is felt to be toxicity limiting, sites may replace FTC with 3TC.

8.7 Creatinine Clearance

Any participant experiencing a calculated CrCl <50 mL/min should have the value confirmed within 14 days. For those participants being treated with 3TC or FTC as part of their oral regimen who experience a confirmed (2 consecutive) reduction in CrCl to <50 mL/min, 3TC or FTC should be dose reduced as indicated by the package insert. For a confirmed CrCl to <30 mL/min, TAF should be discontinued with substitution as recommended in section 5.0. If the site investigator determines that another condition caused the decrease in CrCl, then TAF may be restarted if approved by the protocol team. Participants should be followed as medically indicated until the serum creatinine clearance returns to Grade ≤2. If 3TC or FTC is to be continued, dosing will need to be adjusted per the package insert. For those participants being treated with a co-formulated regimen containing TAF, the TAF containing regimen should be discontinued with substitution as recommended in section 5.0. If the site investigator determines that another condition caused the decrease in CrCl, then TAF may be restarted if approved by the protocol team. Participants should be followed as medically indicated until the serum creatinine returns to Grade ≤2. If 3TC or FTC is to be continued, dosing will need to be adjusted per the package insert.

8.8 Nausea (with or without vomiting) and/or Diarrhea

Although common, nausea following initiation of therapy with study medications usually subsides or resolves during the first few weeks of treatment.

With the onset of Grade ≥1 nausea, advise participants to take study medications with food. Participants may also be treated as needed with anti-emetics given orally or by suppository.

In participants with persistent nausea, consideration should be given for evaluation of pancreatitis, hepatitis, or hyperlactatemia/lactic acidosis, with evaluation for each if clinically indicated.

For Grade 1 or 2 diarrhea, therapy should be continued with symptomatic treatment that may include antimotility agents. If Grade ≥3 diarrhea occurs and is unresponsive to antimotility agents, and for which an alternative etiology (e.g., infectious diarrhea) is not established, all study medications should be interrupted until resolution of diarrhea to Grade ≤2 or return to baseline. If Grade ≥3 diarrhea recurs upon the resumption of the study medications, all study medications should be interrupted and study drugs can be selectively substituted or alternative ART can be selected, at the discretion of the site investigator.

8.9 Hypertriglyceridemia/Hyperlipidemia

If elevated triglyceride or lipid levels are measured in a non-fasting blood draw, repeat the draw after an 8-hour fast. Only levels done in a fasting state should be used to determine toxicity management. Participants with asymptomatic Grade ≥3 triglyceride, total cholesterol, or LDL elevations may continue ART, at the discretion of the site investigator. Please see the recent recommendations of the ACTG Cardiovascular Disease Focus Group (https://www.actgnetwork.org/members/download/other/lipid901.pdf) for full discussion of management of hyperlipidemia in the context of HIV-1 disease.

8.10 Liver Enzymes

ALT Elevations
All study medications may be continued for asymptomatic Grade ≤3 ALT elevations, at the discretion of the site investigator. Careful assessments should be done to rule out the use of alcohol, non-study drug-related drug toxicity, or viral hepatitis as the cause of Grade 3 elevations. The possibility of hyperlactatemia/lactic acidosis syndrome should also be explored (see section 8.15).

All study medications should be held for symptomatic Grade 3 and all Grade 4 elevations until the symptoms resolve and toxicity grade returns to Grade ≤2. Participants will be followed with weekly ALT assessments until they return to Grade ≤2.

For confirmed Grade 4 elevation in ALT, all study medications should be held and ALT followed weekly until the toxicity grade returns to Grade ≤2 or baseline.

In the individuals who are receiving the LA ART regimen, RPV-LA + CAB-LA 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

8.11 Hyperglycemia

Participants with Grade ≥3 hyperglycemia may continue their study medications at the discretion of the site investigator and be managed with oral hypoglycemic medications or insulin, but this should be discussed with the study leadership team.

8.12 CPK Elevation

A CPK can be checked in cases of suspected rhabdomyolysis. Grade 3 or 4 elevation in CPK should result in a repeat assessment within 4 weeks after the participant has abstained from exercise for ≥72 hours 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.

For persistent Grade 4 CPK elevations that are considered possibly or probably related to the study medications, study medications should be discontinued and the participant will be followed on study/off study treatment.

8.13 Prolonged QTc

A participant that meets either criterion below will have study medications stopped, but will remain in study follow-up. The QT correction formula (Bazett or Fridericia) used to determine study medications discontinuation should be the same one used throughout the study.

8.13.1 Change from baseline: QTc >60 ms

Study medications discontinuation decisions are to be determined by the site investigators in consultation with the study leadership team. A decision to permanently discontinue study product will be based on an average QTc value of triplicate ECGs. If an ECG demonstrates a prolonged QT interval, obtain two more ECGs within one hour, and then use the averaged QTc values of the three ECGs to determine whether the participant should permanently discontinue study product.

8.14 Hyperlactatemia/Lactic Acidosis

The relevance of asymptomatic lactic acid elevations is unclear, and lactates are not part of the routine safety evaluations for this study. Routine lactate monitoring is not currently recommended.

A sometimes-fatal syndrome of lactic acidosis, often associated with evidence of hepatic steatosis, is a recognized but rare complication of NRTI therapy. This syndrome is felt to be secondary to mitochondrial toxicity induced by the inhibitory effect of NRTIs on DNA polymerase gamma, a key enzyme needed for mitochondrial DNA synthesis. Current knowledge regarding this syndrome is incomplete. Obesity and prolonged NRTI exposure may be risk factors. Symptoms of lactic acidosis frequently involve non-specific symptoms such as fatigue, weakness, and fever, but in the majority of cases also involve symptoms suggestive of hepatic dysfunction such as nausea, vomiting, abdominal or epigastric discomfort, abdominal distension, hepatomegaly, and new onset of elevated liver enzymes. A high index of suspicion may be required to diagnose this condition.

The following case definition of symptomatic hyperlactatemia/lactic acidosis will be used in this protocol:

<u>Symptomatic Hyperlactatemia/Lactic Acidosis</u>
New, otherwise unexplained and persistent (≥2 weeks) occurrence of one or more of the following symptoms:

- Nausea and vomiting
- Abdominal pain or gastric discomfort
- Abdominal distention
- Elevated LFTs
- Unexplained fatigue
- Dyspnea

AND

Lactate level >2x ULN confirmed by repeat lactate level analysis.

NOTE: All lactates >2x ULN should be repeated as soon as possible, generally within 1 week. If the second result confirms hyperlactatemia (>2x ULN), participants should immediately discontinue their study medications and the study leadership team (actg.leada5359@fstrf.org) should be contacted to plan further treatment. See the ACTG Web site for guidelines for the collection of lactate specimens: https://www.actgnetwork.org/members/download/other/Metabolic/VenousLactate SOP.doc

8.15 Lipase Elevations and Pancreatitis

Pancreatitis will be reported as either clinical (i.e., symptomatic) or chemical (i.e., persistent elevation in enzymes without any symptoms). The principal enzyme abnormality that will be used for making diagnoses is the lipase level, as this is the most specific. If obtained, amylase determinations will be recorded on the eCRF. For both symptomatic and asymptomatic participants suspected of having pancreatitis, triglyceride levels should be drawn with lipase values.

In cases where study medications are temporarily held, re-challenge with study medications may be performed (with permission from the study leadership team). Re-challenge will occur after complete resolution of the episode in a setting in which other concomitant illness or drugs might have reasonably contributed to the development of pancreatitis. Upon re-challenge, lipase determinations should be performed every 2 weeks for at least 6 weeks after reinitiation (see allowable drug substitutions in section 5.0). Any elevation of lipase of Grade ≥2 or any recurrence of symptoms during this period will lead to permanent discontinuation of the suspected study medications.

8.15.1 Symptomatic Elevations in Lipase (gastrointestinal symptoms, particularly abdominal pain).

The severity of clinical pancreatitis will be recorded as the highest severity level of any of the associated clinical signs and symptoms.

8.15.1.1 Grade 1 or 2

Participants may continue study medications at the discretion of the site investigator. Repeat lipase within 2 weeks. If lipase remains elevated but is Grade <3 and symptoms persist, order a computed tomography (CT) scan (or other radiologic test). If pancreatic enlargement and/or peripancreatic inflammation is demonstrated, diagnose clinical pancreatitis. If the CT scan (or other radiologic test) shows no evidence of pancreatitis, continue to monitor lipase every 2 weeks until symptoms and lipase abnormalities resolve.

8.15.1.2 Grade ≥3

Exclude other possible diagnoses (e.g., renal insufficiency causing false elevations in lipase). If none are found, diagnose as clinical pancreatitis.

8.15.2 Asymptomatic Elevations in Lipase

For those without symptoms that are incidentally found to have lipase of Grade ≥3, repeat testing within 2 weeks will be performed. Persistence of asymptomatic elevation of lipase of Grade ≥3 will qualify as a diagnosis of chemical (asymptomatic) pancreatitis. For a diagnosis of asymptomatic chemical pancreatitis, at the discretion of the study leadership team (actg.leada5359@fstrf.org), it may be decided that all study medications should be held. Asymptomatic, chemical pancreatitis will be listed as mild, regardless of enzyme elevation. Further details regarding the definitions of pancreatitis and the proposed management of drug regimens in the setting of pancreatitis can be found on the ACTG Web site at: https://www.actgnetwork.org/members/download/other/pancdefv2.doc.

8.16 Anemia/Neutropenia

If a participant experiences treatment-limiting (in the opinion of the site investigator) anemia or neutropenia, substitution with an alternative drug can be requested. Alternatively, anemia may be managed by transfusions and recombinant erythropoietin, and neutropenia may be managed with granulocyte-colony stimulating factor (G-CSF) or granulocyte-macrophage colony-stimulating factor (GM-CSF), at the discretion of the investigator. Once the anemia or neutropenia has returned to baseline, all study medications can be restarted.

8.17 Peripheral Neuropathy

Participants should be monitored for the development of peripheral neuropathy, which is usually characterized by numbness, tingling, and/or pain in the feet or hands. If a participant without previous history of neuropathy develops Grade ≥2 neuropathy and the investigator attributes the neuropathy to a study NRTI, that NRTI may be replaced with an alternative

NRTI. Similarly, if a participant with history of neuropathy develops worsening neuropathy Grade ≥3 that is attributed to a study NRTI by the study investigator, that NRTI may be replaced with and alternative NRTI. If the neuropathy is attributed to CAB, CAB-LA, or RPV-LA the investigator should contact the study leadership team for instructions. Treatment of the peripheral neuropathy should be defined by the clinician.

8.18 Injection Site Reactions

Injection Site Reaction (ISR) will be assessed at every study visit in Step 2 for participants randomized to Arm A and for all participants in Step 3.The study leadership team must be informed of all Grade 3 or 4 ISRs to determine etiology and assess appropriate continued study participation. 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. ISR grading will be done according to the DAIDS AE Grading Table referenced above.

8.19 Seizure

Any seizure event will result in permanent discontinuation of LA therapy.

8.20 Drug Substitutions

Drug substitutions, if deemed appropriate by the site investigator, will be permitted during Step 1 and in the SOC arm (Arm B) for Step 2. All substitutions and indications for the substitutions are to be recorded on the eCRFs. The site PoR must be informed in writing that the previous regimen is to be discontinued.

8.21 Immune Reconstitution Inflammatory Syndrome (IRIS)

IRIS events are not caused by a specific or individual drug, but rather are the result of being on a successful ARV treatment regimen. Management of events judged by the site investigator to be IRIS may be managed at the discretion of the site investigator. IRIS events should be recorded in the eCRFs, however, no EAE reporting is required, unless the event meets the criteria for "serious" as discussed in section 7.3. Further details regarding IRIS can be found on the ACTG Web site at:
https://www.actgnetwork.org/members/download/other/iris.doc.

8.22 Pregnancy

Step 1:
Participants who become and remain pregnant during Step 1 will be followed on study, until Step 1, week 24, and blood collections should be limited to safety labs (including HIV viral load). Oral ART regimen will be determined by local provider. These participants will not be eligible to enroll into Step 2.

If the pregnancy results in early termination or loss, the participant can continue on study and advance to Step 2 (if eligible).

Step 2 and Step 3:
Given the anticipated long pharmacokinetic tail of CAB-LA and RPV-LA (resulting in continued exposure in these participants, even after one single dose), participants who become pregnant during Step 2, Arm A, or Step 3 who have already received at least one dose of RPV-LA + CAB-LA injection will be able to continue on study treatment if the benefit of treatment is deemed to be higher than the potential risk in the opinion of the IoR, and the participant wishes to continue LA ART. These participants could move onto the next study step upon completion of their current Step (if eligible).

Although the use of combination ART during pregnancy significantly decreases the risk of vertical transmission, data for CAB-LA and RPV-LA in pregnant **individuals** remain limited. **Thus**, participants randomized to Step 2, Arm A, or Step 3 who become pregnant while receiving oral CAB + RPV (but have not received any CAB-LA/RPV-LA) will have to discontinue study treatment and will need a new regimen in accordance with current guidelines for treatment of persons with HIV who become pregnant while on ART. These participants can remain on study but will not be eligible to enroll into the next study step.

Participants who become pregnant while in Step 2, Arm B, can remain on study until Step 2, week 52. Oral ART regimen will be determined by local provider. Only those participants in Step 2, Arm B, who are not pregnant (including those whose pregnancy results in early termination or loss in Step 2) at the time of their Step 3 Registration visit would be considered eligible for crossover.

Blood collections for participants who become and remain pregnant during Steps 2 and 3 should continue as per the SOE with the exception of Stored **Plasma and PBMCs from** Whole Blood.

Step 4:
Participants who become pregnant during Step 4 may continue study visits as outlined in the SOE. Oral ART regimen will be determined by local provider.

All participants who become pregnant while on study will be followed through the postpartum period to determine the effects of the study regimens on birth outcomes in the exposed infants. For participants who become pregnant while receiving CAB, DTG, or within one year of the last dose of CAB-LA, please see the MOPs for further management.

Participants who become pregnant, and who have access to an International Maternal Pediatric Adolescent AIDS Clinical Trials Group (IMPAACT) trial site, should be encouraged to enroll in the P1026s Pregnancy PK study.

The intrapartum complications, pregnancy, and pregnancy outcome will be recorded on the eCRFs. Pregnancies that occur on study should be reported prospectively to The

Antiretroviral Pregnancy Registry. More information is available at www.apregistry.com. Phone: 800-258-4263; Fax: 800-800-1052.

Pregnancy Reporting
Any intrapartum complications, pregnancy, and pregnancy outcome (including pregnancy loss) for the participant and infant (if known) for any participant who becomes pregnant at any step should be recorded on the eCRFs. If a participant has completed the study or chooses to discontinue from the study before the end of the pregnancy, then site staff should complete a study discontinuation visit within 2 weeks and request permission to contact her regarding pregnancy outcomes at the end of pregnancy.

9.0 CRITERIA FOR DISCONTINUATION

9.1 Permanent and Premature Treatment Discontinuation

- Drug-related toxicity (see section 8.1 Toxicity)
- Requirement for prohibited concomitant medications (see section 5.4)
- Pregnancy during Step 2 or Step 3 CAB-RPV oral induction (if applicable). See section 8.22.
- Breastfeeding at any time
- Completion of treatment as defined in the protocol
- Request by participant to terminate treatment
- Clinical reasons believed life threatening by the physician, even if not addressed in the **T**oxicity section of the protocol

9.2 Premature Study Discontinuation

- Failure by the participant to attend three consecutive study visits; this criteria needs to be discussed with the Study Leadership Team (actg.leada5359@fstrf.org) prior to discontinuation. (For participants in Step 2, please see section 6.2.4 for more details.)
- 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
- At the discretion of the IRB/Ethics Committee, Food and Drug Administration (FDA), NIAID, Office for Human Research Protections (OHRP), other government agencies as part of their duties, investigator, or industry supporter

10.0 STATISTICAL CONSIDERATIONS

10.1 General Design Issues

A5359 is a phase III, four-step, randomized, open-label study that will assess if LA ART is efficacious compared to a SOC in persons with HIV with prior history of non-adherence who achieve viral suppression during the oral induction period. In Step 1,

previously non-adherent individuals will be enrolled and undergo a brief period (up to 24 weeks) of all-oral induction using incentivized adherence. If participants achieve virologic suppression (HIV-1 RNA ≤200 copies/mL) at or after Step 1, week **4**, they will register to Step 2 and be randomized 1:1 to switch to LA ART (oral RPV + CAB for 4 weeks followed by RPV-LA + CAB-LA Q4 weeks for 48 weeks or direct injection of RPV-LA + CAB-LA for 52 weeks). At the completion of Step 2, eligible participants randomized to SOC will have the option to register to Step 3 and cross over to the LA ART (oral RPV + CAB for 4 weeks followed by RPV-LA + CAB-LA Q4 weeks for 48 weeks or direct injection of RPV-LA + CAB-LA for 52 weeks); participants randomized to LA ART arm in Step 2 will have the option to register to Step 3 and continue the LA ART for another 52 weeks. At the completion of Step 3, participants will transition to RPV-LA + CAB-LA, if possible and available. If access to RPV-LA + CAB-LA cannot be attained or participant requests to switch to oral ART, those participants will register to Step 4 and be followed for 52 weeks on oral ART. In addition, any participant who receives at least one dose of CAB-LA or RPV-LA, and prematurely discontinues LA ART prior to end of Step 3, will be followed on oral ART for 52 weeks after their last dose of any LA injectable.

The primary analyses of efficacy and safety for the study will be performed after the last participant completes Step 2 follow-up. Efficacy analyses will use an intention-to-treat (ITT) approach including all participants who are randomized to the treatment arms, regardless of status on randomized treatment. To assess the robustness of the efficacy results, sensitivity analyses will be performed based on a modified ITT approach including all participants who were randomized to the treatment arms and received at least one dose of study treatment at/or after randomization and an as-treated analysis restricting to participants who remained on randomized treatment. Safety analyses will be as-treated, with participant follow-up censored at treatment discontinuation. The results of the primary analysis at the end of Step 2 follow-up will be published following the ACTG publication SOP. Step 1 results may be summarized and shared with the study team upon last participants' completion of Step 1. Analysis of long-term outcome measures will be performed upon completion of the study.

The primary efficacy outcome measure of the study is regimen failure, which is a composite outcome measure of virologic failure and discontinuation of randomized treatment. This outcome measure was chosen for the following reasons. First, A5359 is a strategy trial to assess whether LA ART treatment is more successful in keeping participants who are previously non-adherent virologically suppressed and in the treatment program than the standard of care oral regimen. Secondly, LA ART requires regular injections, hence tolerability to the regimen/injectable is considered to be essential to efficacy. Finally, given the study population of participants with history of non-adherence, participants in the LA ART arm will be exposed to the significantly increased risk of developing drug resistance if they are lost to follow-up and do not obtain oral ART coverage for the long half-life of LA ART. Although it is felt that regimen failure is the appropriate outcome measure to understand the efficacy of the study regimen, pure virologic failure as well as treatment-related failure secondary outcome measures are also central in interpreting study results. Assessing similarity or discordance between analyses of different outcome measures and analysis approach

(ITT vs. modified ITT vs. as-treated) will help understand the relative performance of the regimens and help clinicians weigh the efficacy/tolerability trade-offs and apply them to clinical practice.

10.2 Outcome Measures

Primary and secondary outcomes 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(s) and results reporting to ClinicalTrials.gov. Outcomes related to other objectives intended for subsequent publications are listed under Other Outcome Measures.

10.2.1 Primary Outcome Measure

Occurrence of regimen failure in Step 2.

NOTE A: **Regimen failure is defined as the occurrence of** the first of the following two events **at any time post randomization and Step 2, week 48, visit**:

- Virologic failure (as defined in sections 6.2.3 and 10.2.2.1)
- Permanent discontinuation of randomized study treatment

NOTE B: Permanent discontinuation of randomized study treatment is defined as the first of the following events:

- Participants randomized to LA ART arm prematurely discontinue oral RPV or CAB before Step 2, week 4.
- Participants randomized to LA ART arm never initiate RPV or CAB injectable.
- Participants randomized to LA ART arm prematurely discontinue RPV or CAB injectable.
- Participants randomized to SOC arm prematurely discontinue oral ART regimen. Switching to another oral ARV is not considered treatment discontinuation.
- Participants prematurely discontinue study treatment/participation for any reason including death and loss to follow-up.

NOTE C: Participants who complete randomized study treatment without experiencing a virologic failure on Step 2 will be censored at Step 2, **week 48, visit.**

NOTE D: To assess the robustness of the results, sensitivity analyses will be performed in which all participants (regardless of randomized treatment received) who become pregnant without experiencing a virologic failure or permanent discontinuation of study treatment before confirmation of pregnancy will be censored at the study visit week when pregnancy was confirmed.

NOTE E: During the COVID-19 pandemic, clinical research operation might be disrupted or affected at sites. At sites where a COVID-19 disruption is determined, participants randomized prior to the COVID-19 pandemic will have their follow-up time censored at the start of the disruption period.

10.2.2 Secondary Outcome Measures

10.2.2.1 **Occurrence of** virologic failure in Step 2 **at any time post randomization and week 48 visit.**

NOTE A: Time will be measured from the Step 2 randomization.

NOTE B: Virologic failure confirmation will be determined based on any two consecutive evaluations meeting the virologic failure criterion regardless of the time between them.

NOTE C: Participants discontinuing the study/Step 2 (for any reason, including death and end of study step) will be handled as follows:

- Participants with an unconfirmed virologic failure (HIV-1 RNA >200 copies/mL) will be considered as virologic failure at the study visit week of the unconfirmed value.
- All remaining participants will have their **follow-up** time censored at the study week of the last measured plasma HIV-1 RNA sample on Step 2.
- For as-treated analysis, a participant's **follow-up** time will be censored at discontinuation of randomized treatment.

NOTE D: Same as NOTE E in section 10.2.1

10.2.2.2 **Occurrence of** treatment-related failure in Step 2 **at any time post randomization and week 48 visit**

NOTE A: Time will be measured from the Step 2 randomization.

NOTE B: Treatment-related failure is defined as the first of the following events:

- Virologic failure (as defined in sections 6.2.3 and 10.2.2.1)
- Treatment discontinuation due to AE

NOTE C: For participants **who do not experience treatment-related failure, their follow-up** time will be censored at the last study visit week on Step 2 **up to week 48 visit.**

For as-treated analysis, **their follow-up time** censored at discontinuation of randomized treatment.

NOTE D: Same as NOTE E in section 10.2.1

10.2.2.3 Virologic non-success (defined by FDA Snapshot algorithm) at Step 2, week 48

10.2.2.4 Plasma HIV-1 RNA level < 50 copies/mL and ≤200 copies/mL at scheduled study visits on Steps 1 and 2

10.2.2.5 Occurrence of adverse event (as defined in section 7.2) during Steps 1 and 2

10.2.2.6 **Occurrence of** discontinuation of randomized treatment in Step 2 **at any time post randomization and week 48 visit**

10.2.2.7 Summary score of HIV Treatment Satisfaction Questionnaire (HIVTSQ) in Step 2

10.2.2.8 Occurrence of missed or delayed (defined as 8 days beyond scheduled injection day) injections for participants who received LA ART in Step 2

10.2.2.9 Summary scores of HIV Treatment Adherence Self-Efficacy Scale in Step 1 and Step 2.

10.2.2.10 New drug-resistance mutation in participants with virologic failure in Step 2

10.2.2.11 Occurrence of Injection Site Reactions (ISR) during Step 2

10.2.2.12 Participant self-reported dichotomous preference questionnaire

10.2.3 Other Outcome Measures

10.2.3.1 Time to regimen failure in Step 3.

NOTE: Time will be measured from Step 3 entry until the first of virologic failure and discontinuation of study treatment. Participants who complete Step 3 on study treatment without experiencing virologic failure will be censored at Step 3, **week 48, visit**.

10.2.3.2 **Occurrence of** virologic failure on LA ART in Steps 2 and 3.

NOTE: Time will be measured from initial dose of RPV + CAB until virologic failure **up to Step 3, week 48, visit**.

10.2.3.3 Plasma HIV-1 RNA level <50 copies/mL and ≤200 copies/mL at scheduled study visits on Steps 3 and 4.

10.2.3.4 Occurrence of AEs (as defined in section 7.2) during Step 3.

10.2.3.5 Summary scores of HIV stigma measures.

10.2.3.6 Summary score of QOL measure.

10.2.3.7 Counts of the following HRU units: hospitalizations for any reason (ward, length of stay), emergency room visits for any reason, additional clinician office visits for any reason (participant self-report).

10.2.3.8 Participants' self-reported opinions (e.g., dissatisfaction) about CEI withdrawal.

10.2.3.9 Occurrence of Injection Site Reactions (ISR) during Step 3.

10.2.3.10 Summary scores of substance abuse, health and behavioral-health measures.

10.2.3.11 Summary of socio-demographics measures

10.2.3.12 Self-reported adherence in Step 1

10.2.3.13 Self-reported adherence for participants who randomized to SOC arm in Step 2

10.2.3.14 Occurrence of missed or delayed (defined as 8 days beyond scheduled injection day) injections for participants who received LA ART in Step 3

10.2.3.15 Site Adherence/Retention Measures in Steps 1 and 2

10.3 Randomization

There is no randomization in Step 1. In Step 2, eligible participants will be randomized 1:1 to each of the two arms of the study. Randomization will be carried out using permuted blocks across sites with dynamic balance within site via a computer algorithm at the SDMC. There is no randomization in Step 3 and Step 4.

10.4 Sample Size and Accrual

Superiority of the LA ART (oral induction followed by CAB LA + RPV LA) compared to SOC will be assessed based on the primary comparison of the cumulative probability of regimen failure by Step 2, week 48.

A maximum of 640 participants need to be enrolled in Step 1, for Step 2 to achieve an accrual target of 320 participants (160 in each arm). Screening and enrollment into Step 1 will stop when 320 participants have enrolled into Step 2. The sample size estimation is based on the following considerations:

- The study should have approximately 80% power to show superiority of the LA ART compared to daily SOC with respect to the Step 2, week 48, cumulative probability of regimen failure (defined in section 10.2.1).
- The study should have at least 80% power to show superiority of the LA ART compared to daily SOC with respect to the Step 2, week 48, cumulative probability of virologic failure (defined in section 10.2.2.1).
- The cumulative probability of virologic failure by Step 2, week 48, is estimated to be 25% for the SOC arm and 9% for the LA ART strategy. The reference rate for the SOC is based on ACTG A5241 study of HIV salvage therapy in treatment-experienced participants with cumulative virologic failure rate at week 48 of 24.9% in the add-NRTIs arm and 24.6% in the omit-NRTIs arm [**44**]. The estimated rate for the LA ART strategy is based on LATTE-2 Q4W results (<1% with HIV-1 RNA <50 copies/mL at week 48 and <1% with virologic failure) while taking into consideration of treatment-experienced study population with history of non-adherence.
- The cumulative probability of regimen failure by Step 2, week 48, is estimated to be 50% for the SOC arm and 34% for the LA ART strategy assuming 5% treatment-related failures other than virologic in both arms.
- The lost to follow-up rate (non-treatment related) will be constant during the study follow-up with a Step 2, week 48, cumulative lost to follow-up rate of 25% for each arm taking into consideration of possible impact of COVID-19 pandemic on clinical research activities.
- Sample size inflation of 2% is allowed to account for interim monitoring.
- PASS 15 [PASS 15 Power Analysis and Sample Size Software (2017). NCSS, LLC. Kaysville, Utah, USA, ncss.com/software/pass] was used to calculate the sample size requirement with above parameter settings for an O'Brien-Fleming group-sequential design with two interim reviews comparing two independent proportions using a two-sided Fisher's exact test at a significance level of 0.05.
- Sample size may be further adjusted to account for potential censoring due to COVID-19 disruption.

Table 10.4-1: Power to Claim Superiority Based on Step 2 Sample Size of 320 (N=160 per arm) with 25% Lost to Follow-up Rate Assuming Various Underlying Week 48 Cumulative Failure Rates

Outcome Measure	Step 2, Week 48 Cumulative Failure Rates		Power to Claim Superiority of LA ART Compared to SOC
	LA ART	SOC	
Regimen Failure	35%	50%	73%
	34%	50%	79%
	30%	46%	80%
Virologic Failure	11%	25%	75%
	9%	25%	88%
	7%	23%	91%

Table 10.4-2: Sample Size Required to Provide 80% Power to Assess Superiority of LA ART Compared to SOC Assuming Various Underlying Step 2, Week 48, Cumulative Regimen Failure Rates

Effect Size	Cumulative Probability of Regimen Failure by Step 2, Week 48		Step 2 Total N	Step 1 Total N (to account for LOFU and failure to suppress)	
	SOC	LA ART		40% LOFU and failure to suppress	50% LOFU and failure to suppress
16%	50%	34%	320	534	640

Given the targeted study population of previously non-adherent, persons with HIV, it is further assumed that 50% of participants who enroll in Step 1 will be lost to follow-up and/or ineligible to enter Step 2. This rate was revised up based on limited data observed prior to the COVID-19 pandemic. In the March 2020 DSMB review, based on data entered as of February 24, 2020, the observed failure rate to enroll to Step 2 was 43% with 95% CI of 33-54%. Furthermore, the team took into account the potential continued impact of the COVID-19 pandemic on clinical research operations. Thus, the study targets to enroll a maximum of 640 participants in Step 1 to achieve the accrual goal for Step 2. Depending on the actual proportion of the Step 1 participants eligible to enroll in Step 2, the accrual to Step 1 may be closed earlier prior to reaching 640 participants.

It is anticipated that the study will meet its Step 2 accrual target in **36** to **48** months after sites are enrolling excluding the period when study enrollment was paused due to the COVID-19 pandemic.

10.5 Data and Safety Monitoring

The study will be reviewed by DSMB appointed by DAIDS. The first review will occur approximately 6 months after the accrual of the first participant. Subsequent reviews will

take place at approximately yearly intervals after the first review, or per request by the DSMB. These reviews will assess study conduct and safety. Two interim efficacy reviews are planned when approximately 33% and 67% of the total information on the primary outcome measure is anticipated to be available. Interim efficacy analyses will be based on group-sequential repeated confidence intervals for the difference between treatment groups, using the Lan-DeMets approach with an O'Brien-Fleming spending function. Table 10.5-1 below gives examples of extreme results that might lead to DSMB action at each scheduled review. Each scenario assumes between a 20%-28% cumulative probability of failure by week 48 in the superior group. If the confidence interval excludes zero, demonstrating that one arm is superior to the other, or if external results convincingly establish the superiority of one arm over the other, consideration should be given to recommending modification of the study. Interpretation and the consistency of the primary analysis with the results for secondary efficacy outcome measures and safety should be considered by the DSMB prior to recommending stopping a study arm.

Table 10.5-1: Examples of Extreme Results Based on the Proposed Timing of the Interim Review Using O'Brien-Fleming Spending Function

Interim Review #	Confidence Level	Anticipated Number of Participants in Each Group at or after Step 2, Week 48	Number (%) Failures		Estimated CI on the Difference of Cumulative Regimen Failure
			Superior Group	Inferior Group	
1	99.98%	50	10 (20%)	27 (54%)	[0.4%, 67.6%]
			13 (26%)	31 (62%)	[1.6%, 70.4%]
2	98.8%	100	30 (30%)	48 (48%)	[1.0%, 35.0%]
			39 (39%)	57 (57%)	[0.5%, 35.5%]

At each interim efficacy review, we will also assess whether there is an unacceptable increase in AEs in the LA ART arm compared to the SOC arm. This interim safety analysis will be based on a 95% confidence interval of the difference between the treatment groups (LA ART – SOC) in the cumulative probability of adverse event by week 48. If the lower bound of the 95% confidence interval is greater than 15%, demonstrating that the LA ART arm has a significant unacceptable increase in AEs, consideration should be given to recommending modification of the study. Table 10.5-2 below gives examples of extreme results that might lead to DSMB action at each scheduled review.

Table 10.5-2: Examples of Extreme Scenarios Based on the Proposed Timing of the Interim Review and 15% is the Maximum Acceptable Increase in AEs

Interim Review #	Anticipated Number of Participants in Each Group at or after Step 2, Week 48	Number (%) with AEs		Estimated 95% CI on the Difference (LA ART-SOC)
		LA ART Arm	SOC Arm	
1	50	25 (50%)	88 (16%)	[16.8%, 51.2%]
		23 (46%)	66 (12%)	[17.7%, 50.5%]
2	100	50 (50%)	20 (20%)	[17.5%, 42.5%]
		46 (46%)	18 (18%)	[15.7%, 40.3%]

An additional interim review will be triggered if more than 60% of participants with Step 1 HIV-1 VL evaluations used to determine Step 2 eligibility (or loss to follow up in Step 1) fail to enroll to Step 2 at any time or if an unexpectedly high **proportion of participants with** virologic failure (>35%) in Step 2 is observed in either arm (with at least 50 participants with evaluable data). This virologic failure trigger is supported and based on data from the ACTG A5241 (OPTIONS) study with an overall failure rate of 24.7% for both arms combined. In our sample size calculation, we expect a virologic failure rate of 25% in Arm B in Step 2. Observed rate greater than 35% will likely suggest a true virologic failure rate greater than the 25% expected.

All interim reviews (planned or unplanned) will include by arm information on safety and the following information on study conduct: accrual, losses to follow-up, adherence to study visits, evaluations and study regimen, data completeness, and virtual/missed visit summary during the COVID-19 pandemic.

Routine monitoring, which will be performed for the study leadership team, includes the following pooled over arms: accrual, study status, safety, data timeliness, quality and completeness, proportion of participant enrolling in Step 2, and virtual/missed visit summary during the COVID-19 pandemic.

Interim accrual goals are as follows: 50 participants randomized in Step 2 by 12 months following Step 1 first enrollment. Not attaining these interim accrual goals may trigger an unplanned interim review.

An endpoint adjudication committee consisting of one or more independent clinicians will review regimen and virologic failures.

10.6 Analyses

Full details of the proposed analyses for primary and secondary outcome measures will be described in the Primary Statistical Analysis Plan. For other outcome measures, full details of proposed analyses will be described in a separate statistical analysis plan.

10.6.1 Primary Analyses

Comparison of treatment arms will be made using the difference in the Kaplan-Meier estimate for the week 48 cumulative probability of regimen failure. Specifically, Kaplan-Meier estimates of the 48-week cumulative probabilities of regimen failure and associated Greenwood variance will be calculated. A Z-test and corresponding two-sided confidence interval will then be constructed using the difference between the treatment arms and associated variance of the difference. The final confidence interval will be adjusted for Type I error spent at the interim efficacy analyses, to preserve an overall two-sided Type I error rate of 0.05 for the trial. If the study is monitored per planned (2 interim reviews with O'Brien-Fleming spending function), at the end of Step 2, 95.4% CI will be used to examine the superiority of the LA ART arm. All participants who randomized to the treatment arms will be included in the analysis, regardless of status on the randomized treatment. Sensitivity analysis using a modified ITT population and an as-treated population will also be performed. The modified ITT population consists of all participants who were randomized to the treatment arms and received at least one dose of study treatment at/or after randomization.

NOTE A: Due to the COVID-19 pandemic, participants enrolled in Step 2 prior to the COVID-19 pandemic at clinical research sites where a period of disruption is determined will be censored at the start of the disruption period. Additional supportive analyses may also be conducted to explore the impact of COVID-19 with guidance from FDA, statistical, or clinical research literature on approaches for analyzing clinical trial data impacted by COVID-19.

NOTE B: Additional analysis will be carried out to explore the potential impact of relaxed transition criteria from Step 1 to Step 2 in Version 2. Participants enrolled under Versions 1 and 2 will be compared and primary outcome measures will be tabulated separately.

For more details, please refer to the primary Statistical Analysis Plan.

10.6.2 Secondary Analyses

Cumulative probability of virologic failure and treatment-related failure by Step 2, week 48, will be estimated and compared using the same approach outlined for the primary comparison.

The proportion of participants with virologic non-success defined by FDA Snapshot algorithm at Step 2, week 48, will be summarized and compared between the two arms using a Fisher's exact test.

The proportions of participants with HIV-1 RNA <50 copies/mL and ≤200 copies/mL at each study week on Step 1 will be estimated and plotted over time with 95% confidence intervals. Similar summaries will be produced for each study week on Step 2 by randomized treatment arms and comparison between the two arms at weeks 24 and 48 will use a Fisher's exact test.

The proportion of participants reporting AEs in Step 2 will be tabulated for each treatment arm.

All reported AEs will be tabulated by steps and separately by randomized treatments for Step 2.

Cumulative probability of discontinuation of randomized treatment will be estimated and compared using the same approach outlined for the primary comparison.

Summary score of HIVTSQs will be summarized by study arm and compared using a Wilcoxon rank-sum test between arms.

Adherence and behavioral measures will be summarized by scheduled study week and separately by randomized treatments for Step 2. Missed and delayed LA injection will be summarized by scheduled study week in those who initiated LA ART.

The frequency of new HIV-1 drug resistance mutations at **confirmation of** virologic failure on Step 2 will be tabulated and compared using a Wilcoxon rank sum test between the two treatment arms. Factors associated with emerging drug resistance will be examined.

All grade ISRs will be summarized and tabulated by schedule study weeks during Step 2.

10.6.3 Other Analyses

Cumulative probability of regimen failure and cumulative probability of virologic failure at Step 3, week 48, will be summarized with a two-sided 95% confidence interval for all participants who enrolled in Step 3 overall and by their Step 2 randomized treatment.

Virologic failure on LA ART in Steps 2 and 3, and as-treated analyses, will be summarized using cumulative incidence estimation, incorporating the competing event of treatment discontinuation.

The proportions of participants with HIV-1 RNA <50 copies/mL and ≤200 copies/mL at each study week on Steps 3 and 4 will be estimated and plotted over time with 95% confidence intervals.

All other outcome measures will be summarized and tabulated by schedule week and compared by treatment arm as applicable.

If the sample size permits, analyses of primary, secondary, and other (e.g. self-reported opinions about CEI withdrawal) outcome measures will also be carried out in the subset of young adults with HIV (18-24 years old) using the same aforementioned analytical approaches.

11.0 PHARMACOLOGY PLAN

11.1 Pharmacology Objectives

11.1.1 To examine the association of HIV treatment outcomes, including virologic failure, at Step 2 and Step 3 with corresponding CAB-LA and RPV-LA pre-dose trough concentrations.

11.1.2 To examine relationship between the hair concentrations of ARTs with self-reported adherence measures.

11.1.3 To examine relationship between the DBS concentrations of ARTs with self-reported adherence measures.

11.2 Pharmacology Study Design

11.2.1 Blood Samples

- At Step 2 (for participants randomized to Arm A), pre-dose trough blood samples for quantification of CAB and RPV plasma concentrations will be obtained at Step 2 randomization and Step 2, weeks 4b, 8, 12, 16, 24, 32, 36, 40, 48, and 52, visits for storage and future assay of CAB and RPV plasma concentrations to be performed in the participants who develop virologic failure. A pre-dose trough sample will also be obtained for storage and future assay of CAB and RPV plasma concentrations at study visits in which a participant has missed a prior scheduled study visit, at the time of study/treatment discontinuation, or at the time of confirmation of virologic failure.
- At Step 3 (all participants), pre-dose trough blood samples for quantification of CAB and RPV plasma concentrations will be obtained at Step 3 registration and Step 3, weeks 4b, 8, 12, 16, 24, 32, 36, 40, 48, and 52, visits for storage and future assay of CAB and RPV plasma concentrations

to be performed in the participants who develop virologic failure. A pre-dose trough sample will also be obtained for storage and future assay of CAB and RPV plasma concentrations at study visits in which a participant has missed a prior scheduled study visit, at the time of study/treatment discontinuation, or at the time of confirmation of virologic failure.

- At Step 4 (all participants), pre-dose trough blood samples for quantification of CAB and RPV plasma concentrations will be obtained at Step 4 registration. A pre-dose trough sample will also be obtained for storage and future assay of CAB and RPV plasma concentrations at the time of study/treatment discontinuation, or at the time of confirmation of virologic failure.

11.2.2 Hair Samples (all participants, optional)

- At Step 1, hair samples for quantification of ART drug concentrations will be obtained at Entry and Step 1, week 12, and Step 1, week 24.
- At Step 2, hair samples for quantification of ART drug concentrations will be obtained at Step 2 Randomization, Step 2, week 8; Step 2, week 24; Step 2, week 36; and Step 2, week 48.
- At Step 3, hair samples for quantification of ART drug concentrations will be obtained at Step 3 Registration, Step 3, week 12; Step 3, week 24; Step 3, week 36; and Step 3, week 48.
- Hair samples will also be obtained at confirmation of virologic failure, time of treatment discontinuation, and time of study discontinuation.

11.2.3 DBS Samples (for those on TAF/FTC or ABC/3TC)

- At Step 1, DBS samples for quantification of ART drug concentrations will be obtained at Entry, Step 1, week 4, Step 1, week 12, and Step 1, week 24.
- At Step 2, DBS samples for quantification of ART drug concentrations will be obtained at Step 2 Randomization, Step 2, week 8; Step 2, week 24; Step 2, week 36; and Step 2, week 48, for those randomized to continuation of oral SOC.
- DBS will also be obtained at confirmation of virologic failure, time of treatment discontinuation, and time of study discontinuation.

11.3 Primary and Secondary Data, Modeling, and Data Analysis

CAB and RPV samples will be assayed at the University of Alabama Pharmacology Specialty Laboratory using methods approved by the DAIDS Clinical Pharmacology Quality Assurance program. ARV concentrations in hair samples will be analyzed in the UCSF Hair Analytical Laboratory. For both CAB-LA and LA-RPV formulations, the pre-dose trough concentrations will be summarized by geometric means and interquartile ranges at each study visit. Concentrations of each drug may also be combined for

summary and comparison of variables of interest after steady-state concentrations are achieved.

11.4 Anticipated Outcomes

We anticipate that participants who were previously non-adherent to ARV therapy and develop virologic failure during CAB-LA and RPV-LA will have lower pre-dose trough concentrations compared to historical data from persons with HIV without documented non-adherence who have also received CAB-LA and/or LA-RPV and have remained virologically suppressed.

12.0 DATA COLLECTION AND MONITORING

12.1 Reporting Protocol Deviations

Refer to the MOPs for the definition of protocol deviation. The site principal investigator and personnel are responsible for identifying, and reporting deviations. Once protocol deviations are identified, corrective actions are to be developed by the site and implemented promptly. Protocol deviations must be sent to the IRB/EC per their guidelines.

Protocol deviations as defined by the MOPS must be recorded on the study protocol deviation eCRF. Please see the MOPs for instructions on how to use the eCRF for reporting protocol deviations.

12.2 Records to Be Kept

Electronic case report form screens (eCRFs) 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 randomization/registration.

12.3 Role of Data Management

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

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

12.4 Clinical Site Monitoring and Record Availability

Monitoring visits may be conducted on-site or remotely. Remote visits may include remote source document verification using methods specified for this purpose by NIAID. Remote monitoring visits may be performed in place of, or in addition to, onsite visits to

ensure the safety of study participants and data integrity [**45**]. The site **must** make available study documents for site monitors to review utilizing a secure platform that is HIPAA and 21 CFR Part 11 compliant. **The Data Management Center will configure Medidata Remote Source Review (RSR) and make it available to all sites. We encourage sites to use the DMC-provided Medidata RSR platform but other** potential platform options include: Veeva SiteVault, site-controlled SharePoint or cloud-based portal, **and** direct access to Electronic Medical Record (EMR). Other secure platforms that are 21 CFR Part 11 compliant may be utilized, as allowed by the DAIDS Office of Clinical Site Oversight (OCSO).

13.0 PARTICIPANTS

13.1 Institutional Review Board (IRB) Review and Informed Consent

This protocol and the informed consent documents (Informed Consent Form and Appendix II) 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 (or person with power of attorney for participants who cannot consent for themselves). 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 or legal guardian, 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, or international regulatory entities, other government agencies as part of their duties, or the industry supporter(s) 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(s).

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(s) 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 National Institutes of Health.

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

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APPENDIX I: INFORMED CONSENT FORM

Sponsor / Study Title:	**NIAID/DAIDS / "A Phase III Study to Evaluate Long-Acting Antiretroviral Therapy in Non-adherent HIV-Infected Individuals (The LATITUDE Study)"**
Protocol Number:	**A5359**
Principal Investigator: (Study Doctor)	**«PiFullName»**
Telephone:	**«IcfPhoneNumber»**
Address:	**«PiLocations»**

This form is for use in a research study that may involve participants who may or may not have the capacity to consent to take part in the study. When the participant cannot legally consent to take part, pronouns "you" and "your" should be read as referring to the participant rather than the person (legally authorized representative) who is signing this form for the participant. In cases where the participant's representative gives consent, the participant should be informed about the study to the extent possible given his/her understanding. During the course of the study, if the participant regains the capacity to consent, informed consent will be obtained from the participant and the participant offered the ability to leave the study if desired.

SUMMARY

PURPOSE
This is a research study and your participation in this study is voluntary. The purpose of this study is to test if injectable, long-acting, anti-HIV (human immunodeficiency virus) drugs that are given every month can be used safely and effectively in individuals who are infected with HIV and who have had problems taking daily medications in the past. The study will also look at how well these study drugs are tolerated.

STUDY TREATMENT
There will be study treatment provided and required in this study. The study drugs are oral cabotegravir, oral rilpivirine, long-acting injectable cabotegravir, and long-acting injectable rilpivirine. Oral rilpivirine is currently approved by the US Food and Drug Administration (FDA) for treating HIV/AIDS in treatment-naïve individuals who have never taken antiretroviral (ARV) drugs. Oral cabotegravir, long-acting cabotegravir, and long-acting rilpivirine are currently approved by the US FDA for treating HIV/AIDS in people who are well-controlled on their current treatment regimen and who have never changed their medications because they stopped working.

NUMBER OF PARTICIPANTS
There will be a maximum of 640 participants in Step 1 to reach 320 participants in Step 2, which has two study treatment groups of 160 participants each.

LENGTH OF STUDY
The study will last between 6 months and 3 ½ years, depending on whether you successfully complete each step. There are four steps in the study (up to 24 weeks in Step 1 with about 7 study visits, 52 weeks in Step 2 with about 14 study visits, 52 weeks in Step 3 with about 14 study visits, and up to 52 weeks in Step 4 with about 2 study visits).

REQUIRED ACTIVITIES
Blood and urine collections
- At most study visits, some blood will be collected from a vein in your arm.
- At most study visits, you will be asked to provide a urine sample.

Special procedures
You will be asked to come to the clinic fasting (no food or drink except water, decaffeinated black coffee without sugar, and your prescription drugs for the 8 hours just before the study visit) for some study visits. If you did not fast before a required fasting study visit, you will be asked to come back to the clinic for another blood draw after you have fasted.

RISKS
Risks of participating in this study include side effects from the study drugs used in this study.

BENEFITS
You could possibly benefit from the study by having additional support to help you take your study treatment.

OTHER CHOICES
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 a person with HIV and you have had problems taking daily medications. This study is sponsored by the National Institutes of Health (NIH). The study doctor is in charge of this study at this study site. Before you decide if you want to be a part of this study, we want you to know about the study.

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?

This study is being conducted to test if injectable, long-acting anti-HIV drugs that are given every month can be used safely and effectively in people with HIV and who have had problems taking daily medications in the past. This study is also being conducted to evaluate how well are these study drugs tolerated.

The drugs being looked at in this study are oral cabotegravir, oral rilpivirine, long-acting injectable cabotegravir and long-acting injectable rilpivirine. A long-acting drug means it stays in the body much longer compared to the usual form of the drugs. Oral rilpivirine is currently approved by the U.S. Food and Drug Administration (FDA) for treating HIV/AIDS in treatment-naïve individuals who have never taken antiretroviral (ARV) drugs. Oral cabotegravir, long-acting cabotegravir and long-acting rilpivirine are currently approved by the US FDA for treating HIV/AIDS in people who are well-controlled on their current treatment regimen and who have never changed their medications because they stopped working.

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

If you agree to join this study, you will be asked to sign and date this consent form. After you have signed and dated the form, you will be asked some questions and will undergo some tests at the screening visit to see if it is safe for you to join the study.

Study visits may be conducted remotely (for example, telephone, telehealth) if you are unable to attend a visit because of illness, inability to travel, concerns for potential exposure to COVID-19, or the clinic is temporarily unable to conduct non-essential visits in the clinic.

<u>Screening</u>
The screening visit will take about 1-2 hours. About 2 tablespoons of blood will be drawn.

- You will be asked about your medical history including your HIV history.
- You will be asked about any medicines you have taken in the last 12 months.
- You will also be asked about any anti-HIV medications that you may have ever taken.
- You will have a physical exam. The study staff will check your vital signs such as temperature, blood pressure, breathing, weight, and pulse.
- You will have blood drawn for routine blood tests and HIV viral load (VL, the amount of virus in your blood sample) and CD4+ cell count (the number of white blood cells that fight infection).
- You may have blood drawn for resistance testing (a test to see if the virus in your blood is likely to respond to study drugs).
- You may have blood drawn to test for hepatitis B and C (viruses that can affect your liver).
- You will have an electrocardiogram (ECG).
- You will have urine collected for urinalysis.
- You will be asked to complete a questionnaire that will ask questions about: mental health, smoking, alcohol and substance use.

- If you are a participant able to become pregnant, you will have a pregnancy test. Pregnant participants, or participants who want to become pregnant in the next 4 years, cannot enter the study.
- An HIV test may be required to document your HIV status.
- You will be asked to provide forms of additional contact including, but not limited to: mailing address, email address, home/cell phone, and additional emergency contacts (for example, someone from your family, a friend, or case manager).
- You will be asked to sign a release of information to allow the study staff to consult with your HIV provider regarding your study participation.

Information Collected at Screening
There is some information that we collect on everyone who is screened for an ACTG (AIDS Clinical Trials Group) 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 and/or common reasons why people do not join a study.

Entry
Within 60 days of your screening visit, you will come to the clinic for entry evaluations. This visit will last about 2 hours and you will need to be fasting. You will have about 4 tablespoons of blood drawn. You will also have some questionnaires given at entry.

- You will have a physical exam and be asked about your medical history.
- You will be asked about any medicine changes you have had since your screening visit.
- You will have blood drawn for routine blood tests including liver function testing, CD4+, and HIV viral load.
- You will have blood drawn for storage for future HIV-related ACTG approved research tests.
- You will have urine collected for a drug screen, which will test for the presence of recreational drugs. The test results will be available to you, the study doctor**,** and may be available to your doctor. You may be referred for additional services based on the results of these tests.
- You will have a blood draw for dried blood spots (drops of blood collected on a piece of paper) and will also have the option to provide about 100 strands of hair (obtained within 1 cm of the scalp) collected to measure levels of anti-HIV medications.
- If you are a participant able to become pregnant, a pregnancy test will be done before you begin your study medications.
- You will be asked to come to the clinic fasting (no food or drink except water, decaffeinated black coffee without sugar, and your prescription drugs for the 8 hours just before the visit) for lipid testing. If you did not fast before a required fasting visit, you will be asked to come back to the clinic for another blood draw after you have fasted.
- You will be asked to complete a questionnaire that will ask questions about: mental health, domestic violence, healthcare utilization and medication adherence.

If you qualify to participate in this study, you will initially be prescribed an oral anti-HIV regimen that your study doctor will recommend based on your previous drug regimens and the results of your HIV resistance tests. Your anti-HIV drugs will be provided to you at this study visit. If your study drugs start making you sick or stop working for you, your study doctor can switch you to another regimen.

Post-Entry Step 1

During Step 1, the study doctor will consult with your HIV provider to determine which anti-HIV medications will be safe and most likely to decrease your HIV VL. The study will provide these anti-HIV medications to you at no charge **unless it is decided that you should stay on medication provided by your local provider.** This step will last approximately 24 weeks. During this step, you will be closely monitored to see if the study drugs that you were started on are working and you will be asked to return to clinic at Step 1, weeks 2, 4, 8, 12, 16, 20, and 24, depending on your viral load results. Study visits will last about 1 hour. You will have about 3-4 tablespoons of blood drawn. At most of the study visits:

- You will have a physical exam and be asked about any medications that you may be taking.
- You will be given questionnaires to complete, which may include questions about how you take your medications, health and behavior questions, and about your smoking, alcohol and drug use habits and demographics. You may also have pill counts where you will be asked to bring back all left over pills and pill bottles so that we can see how well you are taking the study drugs.
- You will have blood collected for routine blood tests, HIV viral load, CD4+ and CD8+, and study drug levels (including plasma and dried blood spots). You will not have blood taken at Step 1, week 2.
- If you are a participant who can become pregnant and/or if you think you might be pregnant, you will be asked to provide a blood or urine specimen for pregnancy testing. If you are taking dolutegravir, you will be asked to provide a specimen for pregnancy testing at every visit.
- You will be asked to give urine specimens for recreational drug testing and to monitor for possible drug effects on your kidney function. The drug testing results will not be given to you or the study clinic providers.
- Blood may be drawn and stored for future HIV-related ACTG approved research tests.
- You will have the option to provide about 100 strands of hair (obtained within 1 cm of the scalp) collected to measure levels of anti-HIV medications. This test will be an optional procedure.

Conditional Economic Incentives (CEI)

Because taking your pills every day is an important part of making sure the study treatment works, you will receive additional financial incentives (also known as conditional economic incentives or CEI) if you achieve some specific “milestones” related to the results of your study treatment during this first part of the study, according to the following plan:

- $75 if you complete a study visit at Step 1, week 2.
- $75 if you have a ten-fold decrease (for example from 1000 copies to 100 copies) in your HIV VL at Step 1, week 4, and a 100-fold (for example from 10,000 copies to 100 copies)

decrease in your HIV VL at Step 1, week 8, visit compared to your VL at the beginning of the study entry OR if your HIV VL is equal to or less than 200 copies at weeks 4 or 8.
- **$600 if your HIV VL is equal to or less than 200 copies at week 4; $525 if your HIV VL is equal to or less than 200 copies at week 8;** $450 if your HIV VL is equal to or less than 200 copies at Step 1, week 12; $300 if your HIV VL is equal to or less than 200 copies at Step 1, week 16; and $150 if your HIV VL is equal to or less than 200 copies at Step 1, week 20. Your total amount of incentive will not be reduced if you achieve an HIV VL equal to or less than 200 early during Step 1.
- A completion of a Step 1 virtual visit during the COVID-19 pandemic restrictions will also meet criteria for disbursement of the incentives.

If you do not achieve the milestones, you will not receive the additional conditional economic incentives (but you will receive the usual compensation given for attending your study visit). You will, however, be allowed to continue on the study and you may be eligible for the next available economic incentive. For example, you may not qualify for an incentive at Step 1, week 4, but you could still receive it at Step 1, weeks 8, 12, 16, and/or 20, based on these milestones. The CEI will stop at Step 1, week 20.

The CEIs in this study are intended to enhance your possibility of reaching an undetectable HIV VL by the end of Step 1. This is important because you can only be eligible for randomization (assigned by chance as if by the toss of a coin) in Step 2 if your HIV VL is equal to or less than 200 copies, in order for you to be a candidate to receive long-acting therapy. CEIs have shown to be most helpful for short periods of time; in most studies, the effect of using them stops after an individual stops receiving them. Therefore, we only plan to provide CEIs during Step 1, for up to 20 weeks. After week 20 in Step 1, all CEIs will be discontinued for all participants.

After the CEIs are discontinued, you may feel disappointed about not receiving them. This is expected and should improve overtime. Keep in mind that you will still receive the usual compensation for your participation in the study, as it is customary in the studies performed by the AIDS Clinical Trials Group. The study personnel will be able to answer any questions you may have about the CEIs. As mentioned, the CEIs are only intended to be a temporary intervention as part of a research study.

Please indicate and initial below to ensure that you understand that:
a) The CEIs will only be implemented during Step 1 and;
b) All CEIs will be discontinued for all participants once they are eligible for Step 2.

_____ Study Participant's initials

<u>Step 2</u>
To be eligible to move on to Step 2, your HIV VL will need to be equal to or less than 200 copies at or after the Step 1, week **4**, study visit. If your HIV VL is greater than 200 copies but less than 400 copies, you will need to come in for a retest within 2 weeks. If your HIV VL is less than or equal to 200 copies by Step 1, week 20, or at your retest, you will be randomized (assigned by chance as if by the toss of a coin) to one of two study groups in the next phase of the study,

known as Step 2 randomization study visit. Your chance of being assigned to one of the study groups is one out of two (50%). You will be told which study group you are in. The study groups are as follows:

Study Group A – Switch your anti-HIV regimen to an initial short course of daily oral cabotegravir and rilpivirine tablets for 4 weeks, followed by long-acting injectable cabotegravir + long-acting injectable rilpivirine administered to you every 4 weeks. You and your study doctor may decide to skip the short course of daily oral cabotegravir and rilpivirine and directly start the injectable regimen at the start of Step 2.

Study Group B – Continue on your current regimen.

If you are assigned to Study Group A, your anti-HIV regimen will be switched to a combination of oral cabotegravir + oral rilpivirine for 1 month. After 1 month on the new oral study drug, you will return to the clinic to have your safety labs checked to make sure that it will be safe for you to receive the study drug as a long-acting injectable. If your lab results confirm that it is safe for you to receive an injection, you will be asked to come to the clinic within 1 week to receive your first injection of long-acting anti-HIV medications. You and your study doctor may decide to skip the short course of daily oral cabotegravir and rilpivirine and directly start the injectable regimen at the start of Step 2.

At that study visit, you will receive 2 injections: a loading dose of 3 mL (less than a teaspoon) of long- acting cabotegravir plus a loading dose of 3 mL of long-acting rilpivirine, both in the gluteal muscle (in the buttocks). You will need to return to clinic within 4 weeks (28 days) for an additional dose of long-acting anti-HIV study drugs. In all of the following study visits, you will receive 2 injections which will include 2 mL of long-acting cabotegravir plus 2 mL of long-acting rilpivirine, both in the gluteal muscle. You will be asked to return to the clinic every 4 weeks for injections and study procedures. on Step 2, weeks 4, 8, 12, 16, 20, 24, 28, 32, 36, 40, 44, 48, and 52. If more than 8 weeks pass between your injections you will need to receive another loading dose of 3 mL of long- acting cabotegravir plus a loading dose of 3 mL of long-acting rilpivirine, both in the gluteal muscle.

If you are assigned to Study Group B, you will continue your current anti-HIV regimen. You will be asked to return to the clinic for a study visit on Step 2, weeks 4, 8, 16, 24, 36, 48, and 52. Study visits will last about 1 hour.

During most of these study visits in Step 2 (regardless of which study group you are randomized to), you will have about 3-4 tablespoons of blood drawn. In addition:

- You will have a physical exam, including an evaluation of the site where you are receiving the injection (Study Group A only).
- You will have an ECG at Step 2, Randomization, and Step 2, week 48.
- You will be asked about any side effects and about any medications that you may be taking.

- You will be given questionnaires to complete, which may include questions about how you take your medications, pill counts, mental health and behavior questions, domestic violence, stigma, self-efficacy, treatment satisfaction, demographics and about your smoking, alcohol and drug use habits.
- You will have blood collected for routine blood tests, HIV viral load, CD4+ and CD8+, and study drug levels. You may also have and HIV resistance test (HIV genotype).
- You will have the option to provide about 100 strands of hair (obtained within 1 cm of the scalp) collected to measure levels of anti-HIV medications. This test will be an optional procedure.
- You may be asked to give urine specimens for drug toxicology and to monitor for possible drug effects on your kidney function. Neither you nor your clinic provider will receive the results of the drug tests.
- If you are a participant who is capable of becoming pregnant, you will be asked to give urine specimen**s** for a pregnancy test at various times during the study. You must have a negative pregnancy test result before receiving the first injection. If you are taking dolutegravir, you will be asked to provide a specimen for pregnancy testing at every visit. Otherwise in Study Group B, you will be asked to provide a specimen for a pregnancy test only if you or your study doctor thinks you could be pregnant.
- Blood may be drawn and stored for future HIV-related ACTG approved research tests.
- At Step 2 randomization and Step 2**,** week 48, you will be asked to come to the clinic fasting (no food or drink except water, decaffeinated black coffee without sugar, and your prescription drugs for the 8 hours just before the visit) for lipid testing. If you did not fast before a required fasting visit, you will be asked to come back to the clinic for another blood draw after you have fasted.

Step 3

To be eligible to move on to Step 3, your HIV VL will need to be equal to or less than 200 copies at the Step 2, week 48, visit. If your HIV VL is greater than 200 copies but less than 400 copies, you will need to come in for a retest within 2 weeks. If your HIV VL is less than or equal to 200 copies by Step 2, week 52, you may enter into Step 3.

In Step 3, all participants will receive the long-acting injectable study drugs. If you had previously been receiving the long-acting injectables, you will continue to do so and come to the clinic every 4 weeks during this Step through week 52. If you have never received long-acting study drugs, your anti-HIV regimen will be switched to a combination of oral cabotegravir + oral rilpivirine for 1 month. After 1 month on the new oral study drug, you will return to the clinic to have your safety labs checked to make sure that it will be safe for you to receive the study drug as a long**-**acting injectable. If your lab results confirm that it is safe for you to receive an injection, you will be asked to come to the clinic within 1 week to receive your first injection of long-acting anti-HIV study drugs. You will need to return to clinic within 4 weeks (28 days) for an additional dose of long-acting anti-HIV study drugs. You and your study doctor may decide to skip the short course of daily oral cabotegravir and rilpivirine and directly start the injectable regimen at the start of Step 3. All participants in Step 3 will come to the clinic every 4 weeks for injections and study procedures on Step 3, Registration and on Step 3, weeks 4, 8, 12, 16, 20,

24, 28, 32, 36, 40, 44, 48, and 52. Study visits will last about 1 hour. In Step 3, you will have about 1-2 tablespoons of blood drawn. At most study visits:

- You will have a physical exam including an evaluation of the site where you are receiving the injection.
- You will have an ECG at Step 3, Registration, and Step 3, week 48.
- You will be asked about any side effects and any medications that you may be taking.
- You will be given questionnaires to complete, which may include questions about smoking, mental health, self-efficacy, stigma, domestic violence, treatment satisfaction, alcohol and drug use, and health care utilization.
- You will have blood collected for routine blood tests, HIV viral load, CD4+ and CD8+, and for drug concentrations. You may also have an HIV resistance testing (HIV genotype).
- You will have an evaluation of the site where you are receiving the injections.
- You will have the option to provide about 100 strands of hair (obtained within 1 cm of the scalp) collected to measure levels of anti-HIV medications. This test will be an optional procedure.
- You may be asked to give urine specimens for drug toxicology and to monitor for possible drug effects on your kidney function. Neither you nor your clinic provider will receive the results of the drug tests.
- If you are a participant who is capable of becoming pregnant, you will be asked to give a urine for a pregnancy test. You must have a negative pregnancy test result before receiving the first injection. If you are taking dolutegravir, you will be asked to provide a specimen for pregnancy testing at every visit.
- Blood may be drawn and stored for future HIV-related ACTG approved research tests.
- At week 52, you will be asked to come to the clinic fasting (no food or drink except water, decaffeinated black coffee without sugar, and your prescription drugs for the 8 hours just before the visit) for lipid testing. If you did not fast before a required fasting visit, you will be asked to come back to the clinic for another blood draw after you have fasted.

If you are a participant who is able to become pregnant, a pregnancy test will be done at various visits in Steps 1, 2 and 3, if pregnancy is suspected, to make sure that you are not pregnant. Pregnancy testing must be performed before each injection. You will need to inform the study staff know if you change your birth control method or if you suspect you might be pregnant.

Step 4

If you received at least one dose of long-acting injectable study drug during the study, you will need to be observed on oral HIV medications for 52 weeks after your last dose of injectable therapy. You will complete the study visits for the **s**tep you are in (either Step 2 or Step 3) and then enter Step 4 to complete 52 weeks total on oral HIV study drugs. Please note that after completing Step 3, long-acting injectable medication will not be provided by the study, and will only be available to participants if it is available through your doctor's office. If you decide to continue this treatment, you may not need to enter Step 4.

In Step 4 of the study, you will obtain HIV pill medications from your doctor. You will come for study visits every 6 months for 1 year. You will have labs drawn and complete questionnaires at

those study visits. Study visits will last about 1 hour. You will have about 1-2 tablespoons of blood drawn. At most visits:

- You will have a physical exam. At Step 4, Registration, you will have an evaluation of the site where you receive your final injection.
- You will be asked about any side effects and any medications that you may be taking.
- You will be given questionnaires to complete, which may include questions related to your mental health, self-efficacy, treatment satisfaction, smoking, substance use, and how you take your medications.
- You will have blood collected for routine blood tests, HIV viral load, CD4+, CD8+ and drug concentrations.
- You may be asked to give urine specimens and to monitor for possible drug effects on your kidney function. You may also have an HIV resistance testing (HIV genotype).
- If you are a participant who is capable of becoming pregnant and you think you may be pregnant, you will be asked to give a urine sample for a pregnancy test. If you are taking dolutegravir, you will be asked to provide a specimen for pregnancy testing at every visit.
- At Step 4 registration and week 52 you will be asked to come to the clinic fasting (no food or drink except water, decaffeinated black coffee without sugar, and your prescription drugs for the 8 hours just before the visit) for lipid testing. If you did not fast before a required fasting visit, you will be asked to come back to the clinic for another blood draw after you have fasted.
- Blood may be drawn and stored for future HIV-related ACTG approved research tests.

<u>Virologic Failure Confirmation Study Visit</u>
If your HIV VL has not decreased enough or your HIV VL increases at or after entry into Step 2, you will return for an additional visit and have a second HIV VL test between 7 - 21 days of the previous HIV VL testing. At this study visit:

- You will have blood drawn for HIV VL, CD4+ and CD8+ and drug concentrations. You may also have a blood draw for HIV resistance testing (HIV genotype)
- You will have a blood draw for dried blood spots (if this happens during Steps 1 or 2) and will also have the option to provide about 100 strands of hair (obtained within 1 cm of the scalp) collected to measure levels of anti-HIV drugs (if this happens during Steps 1 through 3).
- You will be given a questionnaire to complete, which will include questions about how you take your medications.

Your study doctor may keep you on your current study drugs, or you may be switched to another study drug regimen selected by your study doctor. If you are switched to a different study drug regimen not provided by the study, you will need to obtain that regimen from your study doctor. You will continue to come in for your regular study visits as described above until the end of the study.

Premature Discontinuation of Study Therapy Visit

If you stop taking the study drugs before the end of the study or if you had virologic failure, you will be asked to return to the clinic for additional evaluations. This visit will last about 1 hour. You will have about 3 tablespoons of blood drawn. You also will be asked to continue to be part of the study and attend study visits even though you are no longer taking the study drugs.

- You will have a physical exam. The clinic staff will check your vital signs such as temperature, blood pressure, breathing, and pulse. You may have an evaluation of your injection site if you were receiving injections.
- You will be asked about the reasons why you discontinued the study drugs, about side effects and about any medicine changes you have had since screening.
- You will have blood drawn for routine blood tests, HIV viral load, CD4+ and CD8+, drug levels, and HIV genotype (if clinically indicated). You will also have a lipid profile if you are in Step 4.
- You will have a blood draw for dried blood spots (Step 2 only) and will also have the option to provide about 100 strands of hair (obtained within 1 cm of the scalp) collected to measure levels of anti-HIV medications.
- You will be given questionnaires to complete, which may include questions about how you take your medications, pill counts, health and behavior questions, and about your smoking, alcohol and drug use habits.
- You may be asked to give urine specimens.
- If you are a participant who is capable of becoming pregnant, you will be asked to give a urine for a pregnancy test.
- Blood may be drawn and stored for future HIV-related ACTG approved research tests.

Final Study Visit

When you complete the study or if you leave the study early, you will be asked to come in to the clinic for final study evaluations. This study visit will last about 1 hour. You will have about 4 tablespoons of blood drawn.

- You will have a physical exam. The study staff will check your vital signs such as temperature, blood pressure, breathing, and pulse. You may have an evaluation of your injection site if you were receiving injections.
- You will be asked about any medicine changes you have had since your last visit.
- You will have blood drawn for routine blood tests which may include HIV viral load, CD4+ and CD8+, drug levels. You may have an HIV genotype drawn if clinically indicated. You will also have a lipid profile if you are in Step 4.
- You will have blood drawn and stored for future HIV-related ACTG approved research tests.
- You will have a blood draw for dried blood spots (Step 2 only) and will also have the option to provide about 100 strands of hair (obtained within 1 cm of the scalp) collected to measure levels of anti-HIV medications.
- You will be given questionnaires to complete, which may include questions about how you take your medications, pill counts, health and behavior questions, and about your smoking, alcohol and drug use habits.
- You may be asked to give urine specimens.

- If you are a participant who is capable of becoming pregnant, you will be asked to give a urine for a pregnancy test.

You will be given the results of the pregnancy (if done), CD4+ and CD8+ cell counts, viral load, routine blood tests, glucose, cholesterol, triglycerides, hepatitis B and C.

OPTIONAL TESTS

Hair Collection
You have the option to provide about 100 strands of hair (obtained within 1 cm of the scalp) collected to measure levels of anti-HIV medications. Hair collection is not a requirement to participate in the study and you may withdraw your approval for hair collection, at any time.

Please indicate and initial below whether you approve the collection of your hair.

_____YES, I approve the collection of my hair

_____NO, I do not approve the collection of my hair

Other Information
Your research site will collect your contact information including your address in order to keep in touch with you. In addition, in order to get a better understanding of the impact of your surrounding environment on your health, we are asking that we collect ONLY the first 3 digits of your zip code for a future analysis. Collection of this information is not a requirement to participate in the study.

Please indicate and initial below whether you approve the collection of the first 3 digits of your zip code.

_____YES, I approve the collection of the first 3 digits of my zip code.

_____NO, I do not approve the collection of the first 3 digits of my zip code.

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

Some of your blood will be stored and used for study-required pharmacologic, metabolic, immunologic, and virologic testing. Hair and dried blood spots will be stored for current and future research.

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.

Please refer to the "CONSENT FOR USE OF SAMPLES IN OTHER STUDIES" for use of your samples in other studies.

HOW MANY PEOPLE WILL TAKE PART IN THIS STUDY?

A maximum of 640 people will take part in this study

HOW LONG WILL I BE IN THIS STUDY?

You will be in this study between 24 weeks and 180 weeks depending on if you successfully complete each step of the study, and if the long-acting study drug is not available at the end of Step 3.

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

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

- The study is stopped or cancelled by the ACTG, the US Food and Drug Administration (FDA), the Office for Human Research Protections (OHRP), National Institutes of Health (NIH), other government agencies, the drug companies supporting this study, or the site's Institutional Review Board (IRB). (An IRB is a committee that watches over the safety and rights of research participants.)
- A Data Safety Monitoring Board (DSMB) recommends that the study be stopped early (a DSMB is an outside group of experts who monitor the study).
- You are not able to attend the study visits as required by the study.
- You become imprisoned or involuntarily incarcerated in a medical facility and miss too many study visits and/or are unable to take your study drugs.
- Request of your regular doctor if s/he thinks the study is no longer in your best interest.

- If the study doctor feels that you may not be able to complete all of the necessary steps of the study or if continuing on the study may be harmful to you.

The study doctor may also need to take you off the study drug(s) without your permission if:

- Continuing the study drug(s) may be harmful to you
- You need a treatment that you may not take while on the study
- You are not able to take the study drug(s) as required by the study
- You become pregnant or are breast-feeding.

If you must stop taking the study drug(s) before the study is over, the study doctor may ask you to continue to be part of the study and return for some study visits and procedures.

IF I HAVE TO PERMANENTLY STOP TAKING STUDY-PROVIDED DRUGS OR ONCE I LEAVE THE STUDY, HOW WOULD THESE MEDICATIONS BE PROVIDED?

During the study:

If you must permanently stop taking study-provided drugs before your study participation is over, the study staff will discuss other options that may be of benefit to you.

After the study:

After the completion of the study, it is important that you continue treatment for your HIV infection. The study staff will discuss with you what your best options are for continuing treatment. This may be long-acting injectable drugs, if they are available or oral anti-HIV therapy. This will be determined in conjunction with your study and regular doctors.

WHAT ARE THE RISKS OF THE STUDY?

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 study drugs. These lists include the more serious or common side effects with a known or possible relationship. If you have questions concerning the 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 study nurse before enrolling in any other clinical trials while on this study.

Risks of the Questionnaires
You may feel embarrassed or uncomfortable answering the questions in the questionnaires, which will ask mental health questions related to depression, anxiety, suicidal thoughts, as well as substance use and alcohol use.

If you are having suicidal thoughts call the study doctor at the telephone number listed on the first page of this form. 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).

If your answers reveal that you are having suicidal thoughts you will be seen by a study doctor before you leave the clinic and you may be referred for psychiatric care. If your answers reveal a substance use problem to study staff, you may be referred for drug abuse treatment if you agree with being referred.

Risks of Drawing Blood
Taking blood may cause discomfort, bleeding, and bruising where the blood is drawn. Occasionally, there is swelling in the area where the needle enters the body and there is a small risk of infection. There is also a risk of lightheadedness, fainting, and blood clots.

Risks of Hair Collection
For participants who consent to the hair collection, we will collect about 100 strands of your hair. To do this, we will obtain a hair sample from the back of your head and cut close to the scalp with scissors. A noticeable place on the scalp where hair was cut may be visible. Cutting hair will not cause any pain. We will try to cut hair from underneath hair on top of it to hide where the hair was cut from.

Risks of Fasting
Some individuals find fasting to be bothersome. It may make some individuals feel anxious, irritable, light-headed, weak, or hungry. Participants who are required to take their morning medications with food should wait until after the study visit has been completed to take their medications.

Risks of Standard of Care Medications
NOTE: For more information about the side effects and risks of the drugs prescribed to you, ask your study doctor or pharmacist for the package insert.

Risks of Combination Antiretroviral Therapy
Immune Reconstitution Inflammatory Syndrome (IRIS): In some people with advanced HIV infection, signs and symptoms of inflammation from other infections may occur soon after anti-HIV treatment is started.

Some people may develop resistance to the anti-HIV medications. This is more likely to happen if you do not take your medications regularly, but it can also happen if you do. We do not know if the risk of resistance is higher in people who take injectable anti-HIV medications compared to

oral medications. **We also do not know if not being able to obtain a resistance test prior to starting this treatment increases the risk of resistance.**

The use of potent anti-HIV 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 with the Use of Nucleoside Analogues: Emtricitabine (FTC, Emtriva™), Tenofovir alafenamide fumarate (TAF, a component of Genvoya™, Odefsey™ and Descovy™), Abacavir (ABC, Ziagen™), Lamivudine (3TC, Epivir™), Abacavir+Lamivudine (ABC/3TC, Epzicom™ and a component of Triumeq™)

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 antiretroviral nucleoside analogues alone or in combination. The liver complications and death have been seen more often in **individuals assigned female sex at birth**on these drug regimens. Some nonspecific symptoms that might indicate lactic acidosis include: unexplained weight loss, stomach discomfort, nausea, vomiting, fatigue (feeling tired), cramps, muscle pain, weakness, dizziness, and shortness of breath.

In addition, the following side effects have been associated with the use of Nucleoside Analogues:

- Upset stomach, vomiting, gas, loose or watery stools
- Generalized weakness
- Vague overall feeling of discomfort
- Decrease in appetite
- Hypersensitivity reaction (overreaction of the immune system)
- 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, itching, which sometimes can be a sign of an allergic reaction
- Muscle pain and muscle weakness
- Numbness, tingling, and pain in the hands or feet
- Bronchitis
- Pain (not specific)
- Allergic reaction: symptoms may include fever, rash, upset stomach, vomiting, loose or watery stools, abdominal pain, achiness, shortness of breath, a general feeling of illness or 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
- Headache
- Dizziness
- Tiredness
- Inability to sleep, unusual dreams
- Increased cough
- Runny nose
- Abnormal liver function tests, which could mean liver damage
- Increases in pancreatic enzyme (substances in the blood), which could mean a problem with the pancreas
- Increased triglycerides
- Increased creatine phosphokinase (CPK), which could mean muscle damage
- Low cells counts such as anemia, low white count and/or low platelets

NOTE: If you **have** hepatitis B, you are not eligible for the study. Before starting abacavir, your study doctor should test you to determine if you are at risk of developing a severe allergy to abacavir.

Risks with the Use of Protease Inhibitors: Darunavir (DRV, Prezista™) and Cobicistat (COBI, Prezcobix™)

The use of protease inhibitors may be associated with the following:

- Increases in the amount of triglycerides and/or cholesterol in the blood
- Development of diabetes or the worsening of high blood sugar
- There have been reports of increased bleeding in people with HIV with hemophilia who were treated with protease inhibitors. It is not known if protease inhibitors were the cause of these bleeding episodes.

The risks of DRV or DRV/COBI include:

- Severe liver problems, which may be life-threatening. People who have increased liver function tests before starting DRV and people with liver diseases such as hepatitis B or C have an increased risk of worsening liver disease. If you are developing liver problems, you may have one or more of the following symptoms:
  - Yellowing of the skin or of the whites of your eyes
  - Dark urine
  - Pain on the right side of your stomach
  - Loss of appetite
  - Upset stomach or vomiting
  - Pale colored stools
- Itchy skin
- Rash, which may be severe or life-threatening. Contact your study doctor if you develop a rash. If you develop any skin changes with the following symptoms, stop using the DRV/COBI combination and contact your study doctor right away:
  - Fever

  - Tiredness
  - Muscle or joint pain
  - Blisters
  - Mouth sores
  - Red or inflamed eyes
- Changes in blood test results that may show problems with the liver, kidneys and cholesterol levels
- Inflammation of the pancreas. When the pancreas becomes inflamed, it can cause pain in the stomach, nausea, vomiting
- Joint stiffness and bone pains may occur, rarely death of bone tissue and collapse of the bone may occur

Additional side effects include:
- Diarrhea
- Nausea
- Stomach pain
- Vomiting
- Headache

Before starting DRV, you should inform your study doctor if you are allergic to sulfa medicines.

DRV/COBI (Prezcobix®) when taken with some other drugs, like tenofovir, can cause new or worsening kidney problems, which can lead to kidney failure.

NOTE: Your study doctor can provide more complete information about the side effects of protease inhibitors. Before starting darunavir (DRV, Prezista™ and a component of Prezcobix™), you should inform your study doctor if you are allergic to sulfa drugs.

Risks with Use of Integrase Inhibitors: Dolutegravir (DTG, Tivicay™ and a component of Triumeq™) and Elvitegravir/Cobicistat (EVG/COBI, a component of Stribild™ and Genvoya™)

The following side effects have been associated with the use of Integrase Inhibitors:
- Upset stomach
- Headache
- Tiredness
- Weakness
- Trouble sleeping
- Vertigo (feeling dizzy and off balance)
- Rash, which may be severe
- Feeling anxious
- Depression, suicidal thoughts and actions
- Paranoia (an abnormal sense of fear)
- Low blood platelet count
- Muscle pain, tenderness, or weakness, which can be serious and lead to kidney damage

- Abnormal liver function tests
- Changes in body fat
- Abnormal heart rhythm if receiving certain antiarrhythmics such as dofetilide.
- Participants with underlying hepatitis B or C may be at increased risk for worsening or development of transaminase elevations with use of dolutegravir.
- Cancers have been seen in people who took raltegravir with other HIV drugs. The types of cancers seen are typical for people with very sick immune systems. It is unknown if the cancers were related to raltegravir use.
- Contact your study doctor right away if you develop a rash while taking dolutegravir, especially if it is associated with any of the following symptoms:
  - Fever;
  - Blisters or sores in your mouth;
  - Blisters or peeling skin;
  - Redness or swelling of your eyes;
  - Swelling of your mouth, face, lips, or tongue;
  - Trouble breathing
- Contact your study doctor right away if you have any of the following symptoms that could be signs of liver problems:
  - Yellowing of your skin or whites of your eyes (jaundice);
  - Dark or tea-colored urine;
  - Pale-colored bowel movements;
  - Nausea or vomiting;
  - Loss of appetite;
  - Pain, aching, or tenderness on your right side below your ribs

<u>Risks with Use of Rilpivirine (RPV, Edurant™ and a component of Complera™ and Odefsey™) and RPV Long-Acting injections</u>

More than 500 people have received RPV LA injections in clinical trials**,** and this study drug was approved by the Food and Drug Administration on January 21, 2021, for use in people with HIV who are well-controlled (consistently less than 50 copies/mL) on a stable oral anti-HIV regimen, who have never changed anti-HIV medications because they stopped working, and who do not have a history of resistance to CAB or RPV**.** The following side effects have been seen with rilpivirine in people with HIV in clinical trials. Note that oral rilpivirine (Edurant) is an approved drug that may be prescribed by your regular doctor.

The following serious side effects have been associated with the use of rilpivirine:

- Depression or mood changes. Be sure to contact your study doctor immediately if you are feeling sad or hopeless, feeling anxious or restless, or having thoughts of hurting yourself (suicide) or have tried to hurt yourself.
- Rash, which may be severe or life-threatening. Contact your study doctor if you develop a rash or other skin changes, especially if either is associated with any of the following:
  - Fever
  - Blistering on the skin or ulcers in the mouth
  - Eye redness or swelling of the face, moth, or other parts of the body

- Liver problems can happen. People who have abnormal liver tests before starting rilpivirine and people with liver diseases like hepatitis B or C have an increased risk of worsening liver disease. If you are developing problems, you may have one or more of the following symptoms:
  - Yellowing of the skin or of the whites of your eyes
  - Dark urine
  - Pain on the right side of your stomach
  - Loss of appetite
  - Upset stomach or vomiting
  - Pale colored stools
  - Itchy skin

- Additional side effects include:
  - Headache
  - Trouble sleeping
  - Abdominal pain
  - Fatigue (feeling tired)

NOTE: Some people taking rilpivirine have had liver problems. People with a history of hepatitis B virus (HBV) or hepatitis C virus (HCV) infection or who have elevated results on liver function tests may have an increased risk of developing new or worsening liver problems while taking rilpivirine.

In healthy participants, there was no clinically relevant effect on QTc interval (one of the measurements of the electrical activity of the heart as recorded on the electrocardiogram [ECG], and related to heart rate) at a dose of RPV 25 mg once daily. A modest increase in the QTc interval (change in electrical activity) has been observed with RPV at a dose of 75 mg once daily or higher (for example, higher than used in this study). In participants **with HIV** treated with RPV once daily, the change in electrical activity was similar with RPV as in the control group in the phase IIb study after 240 weeks as well as in the phase III study after 96 weeks There is a very small chance this change in electrical activity may lead to more serious heart problems such as abnormal heart rhythms (arrhythmias) and very rarely this could lead to sudden death. These risks may be higher when RPV is combined with certain other drugs with a known risk for such abnormal heart rhythms. However, to date, no such heart rhythm irregularities or sudden deaths have been observed in clinical studies with RPV. Your study doctor will check for these drugs prior to starting the study.

Cabotegravir (CAB) Tablets and CAB Long-Acting Injections
As of December 2017, an estimated 2169 people (including people with HIV, people who do not have HIV and who are taking PrEP, and people who do not have HIV and are not taking PrEP) have received CAB in studies sponsored by ViiV Healthcare. These included blinded studies (where people did not know what treatment they were receiving). In these studies, 1269 of the estimated 2169 people took the long acting (LA) formulation**.** Both the CAB tablets and CAB injections were approved by the Food and Drug Administration on January 21, 2021, for use in people with HIV who are well-controlled (consistently less than 50 copies/mL) on a stable oral

anti-HIV regimen, who have never changed anti-HIV medications because they stopped working, and who do not have a history of resistance to CAB or RPV.

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 study doctor 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 study doctor 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 study doctor right away.
- 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 (feeling tired)
- 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)

General Side Effects of Injections Long-Acting Medications
The injections you receive in this study are long acting, meaning they stay in your body for a long time. Following an injection of CAB-LA or RPV-LA, the study drugs stay in your body for months. In some people, low levels of CAB and RPV may be present in your body for more than a year. If you develop a side effect to CAB-LA or RPV-LA after the injection there will be no way to remove the study drug from your body. You may be taking these study drugs as tablets first, which stay in the body for a shorter amount of time. This will help the study staff understand if you would have problems with the study drugs when received as an injection.

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

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

Injection Site Reactions:
Side effects at the location where you received injections (termed Injection Site Reactions) been seen with both CAB-LA and RPV-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 buttocks (gluteal muscle).

Other Possible Injection Complications:
The injections will be given in the muscles of your buttocks (“bottom” or “cheeks”). 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 study drug may not work against your HIV virus. The risks of having high levels of CAB in your body are not well known. The risk of having high levels of RPV in your body are not well known, but one possible risk could include a change in your heart beat, which in severe cases can be life-threatening. In rare cases, symptoms such as feeling lightheaded, numbness or tingling, difficulty breathing, chest or stomach discomfort, sweating, nausea, and/or feeling

anxious have occurred after an injection with RPV-LA. In these cases, high blood levels of RPV have been observed, which may be due to an accidental injection of part of the drug into a blood vessel instead of the muscle. Not all people in whom an accidental injection in a blood vessel was suspected reported such symptoms. Most of the symptoms resolved within minutes. Your study doctor may need to administer treatment to help resolve these symptoms. Every precaution will be taken to ensure that the correct size needle and injection technique is used to reduce these risks. You will also be monitored for safety events during the study. If your study doctor is concerned that the injection was not given correctly, he or she may ask you to stay in the clinic up to 2 hours after the injection to monitor how you are doing and may order tests to monitor your safety. If you are concerned about this risk, speak to your study doctor.

After receiving RPV-LA injectable, the study drug may be found in the body for longer than a year (longer than 12 months). This means you also may have study drug in your body for longer than a year after the last injection. No safety issues are expected with this. We don't know when all of the study drug will completely leave your body. We do know that levels of the study drug in your body slowly decrease over time and we know that some people still have low levels of study drug in their body a year or longer after receiving the last injection. You have to keep taking the study treatment to avoid that the virus becomes resistant to RPV due to low RPV plasma concentrations, and other types of HIV medications would have to be used to treat your HIV infection.

Receiving injections can cause some people to feel lightheaded or feel like they might pass out. Fainting can also occur. This reaction, called a "vasovagal reaction", has been reported with other injectable medicines, and resolves quickly.

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 4 years. Mothers should not breastfeed a baby while on this study. The drugs used in this study may be unsafe for unborn babies. If you are having sex that could lead to pregnancy, you must agree not to become pregnant. If you are a participant who can get pregnant, you must talk to your study doctor about birth control and use it all of the time. You must continue to use birth control until 30 days after stopping your oral anti-HIV study drugs and 52 weeks after stopping your injectable anti-HIV study drugs (for example, 52 weeks after receiving the last dose of injectable anti-HIV study drug).

You must choose one of the birth control methods listed below:

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

If you can become pregnant, you must have a pregnancy test before you enter this study. The test must show that you are not pregnant. If you think you may be pregnant at any time during the study, tell your study staff right away. If you become pregnant while on study, the study staff will talk to you about your choices.

If you become pregnant at any time during the study, tell your study staff right away. You may need to change your study treatment, but continue your study visits. If you choose to continue on in the study you will need to sign and date the pregnancy informed consent attached to this main consent. Pregnancies will be reported to the antiretroviral pregnancy registry at http://www.apregistry.com.

ARE THERE BENEFITS TO TAKING PART IN THIS STUDY?

If you take part in this study, there may be a direct benefit to you, but no guarantee can be made. It is also possible that you may receive no benefit from being in this study. Information learned from this study may help others who have HIV.

WHAT OTHER CHOICES DO I HAVE BESIDES THIS STUDY?

Instead of being in this study you have the choice of:
- Treatment with other prescription drugs available to you
- Treatment with experimental drugs, if you qualify
- No treatment

On January 21, 2021, oral CAB used in combination with oral RPV for 1 month followed by monthly injectable CAB and RPV were approved by the US Food and Drug Administration for use in people with HIV who are well-controlled (consistently less than 50 copies/mL) on an oral anti-HIV regimen, and who have never changed anti-HIV medications because they stopped working. **On March 24, 2022, the oral CAB and oral RPV 1-month lead-in was made optional.**

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.

WHAT ABOUT CONFIDENTIALITY?

We will do everything we can to protect your privacy. Some of the questionnaires you will complete while in this study reveal very personal information about your mental health and substance use. Study staff will do all they can to keep your information private, but if you want referral for treatment or study staff feel referral to other providers for treatment of these conditions is necessary, some of the information may need to be shared with these other providers. In addition to the efforts of the study staff to help keep your personal information

private, we have gotten a Certificate of Confidentiality from the US 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.

People who may review your records include the ACTG, Office for Human Research Protections (OHRP) or other local, US, and international regulatory entities as part of their duties, Food and Drug Administration (FDA), (insert name of site) institutional review board (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 including a clinical provider if indicated.

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

WHAT ARE THE COSTS TO ME?

Taking part in this study may lead to added costs to you and your insurance company. In some cases, it is possible that your insurance company will not pay for these costs because you are taking part in a research study. The anti-HIV study drugs (oral and injectable) will be provided to you by the study.

WILL I RECEIVE ANY PAYMENT?

You will be compensated for taking part in this study. You will be compensated *(insert amount of site specific visit compensation)* for attending each one of your study visits. During the induction phase (first 20 weeks) you will be compensated additionally if you achieve certain VL "milestones" as follows:

Compensation

Step 1, Week	Milestone	Incentive
2	**Completed visit (in person or virtual during the COVID-19 pandemic restrictions)**	**$75.00**
4	**If you have a ten-fold decrease (for example from 1000 copies to 100 copies) in your HIV VL from entry visit or HIV VL less than or equal to 200**	**$75.00**

Step 1, Week	Milestone	Incentive
	copies/mL or completed a virtual visit during the COVID-19 pandemic restrictions	
8 (if needed)	**If you have a 100-fold decrease in your HIV-1 VL from entry visit (for example from 10,000 copies to 100 copies) or HIV-1 VL less than or equal to 200 copies/mL or completed virtual visit during the COVID-19 pandemic restrictions**	**$75.00**
12 (if needed)	**HIV-1 RNA less than or equal to 200 copies/mL or completed virtual visit during the COVID-19 pandemic restrictions**	**$150.00***
16 (if needed)	**HIV-1 RNA less than or equal to 200 copies/mL or completed virtual visit during the COVID-19 pandemic restrictions**	**$150.00***
20 (if needed) or Confirmation Viral load after week 20 (but prior to week 24)	**HIV-1 RNA less than or equal to 200 copies/mL**	**$150.00**
Additional Continuity Visits during the COVID-19 pandemic (only applicable if in person visits are not permitted by your research site)	**HIV-1 RNA less than or equal to 200 copies/mL or completed virtual visit**	**$150.00**

***** NOTE: If you are virally suppressed (less than or equal to 200 copies/mL) at **week 4, 8**, 12 or week 16, you will be eligible for randomization into Step 2 and will not continue further visits in Step 1. You will additionally receive the CEI that would have been distributed at the later Step 1 visits. For example, if your HIV VL is less than or equal to 200 copies/mL at Step 1, week 12, the CEI for week 12+16+20 ($450) will be disbursed at that time and you will proceed to Step 2 randomization; or if you meet the HIV VL criteria at Step 1, week 16, the CEI for week 16+20 ($300) will be disbursed at that time and you will proceed to Step 2 randomization.

If you do not achieve the milestones, you will not receive conditional economic incentives (you will still receive the usual compensation given for attending your study visit) but you will be allowed to continue on the study and you may be eligible for the next financial compensation (for example, you may not qualify to compensation at Step 1, week 4, but you could still receive conditional economic incentives at Step 1, weeks 8, 12, 16, and/or 20, based on these milestones). The conditional economic incentives will stop once you achieved HIV VL equal to or less than 200 copies/mL.

The total financial reimbursement (compensation for completing all study visits and conditional economic incentives for reaching all “milestones” during the first 20 weeks) of the study is *(insert sum of site specific visit compensations + $675).*

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 will be charged to you or your insurance company.

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

- ***There is no program for compensation through the US National Institutes of Health, but this site has clinical trials insurance. This insurance will allow the site to provide you with monetary compensation if you suffer harm as a result of participating in this research study.***

OR

- ***There is no program for compensation either through this institution or the US National Institutes of Health.]***

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

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.

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 participants. 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: Pro00041207.

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 and date your name below.

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

WITNESS SIGNATURE FOR PARTICIPANTS WHO CANNOT READ
The study subject has indicated that he/she is unable to read. The consent document has been read to the subject by a member of the study staff, discussed with the subject by a member of the study staff, and the subject has been given an opportunity to ask questions of the study staff.

Witness's Name (print) (As appropriate)	Witness's Signature and Date

ATTACHMENT A: CONSENT FOR USE OF SAMPLES IN OTHER STUDIES

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

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

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

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

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

You will not be paid for your samples. Also, a researcher may make a new scientific discovery or product based on the use of your samples. If this happens, there is no plan to share any money with you. Your samples will never be used for commercial profit.

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

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

Research without Human Genetic Testing

If you agree, your extra samples 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 samples

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

Research with Human Genetic Testing

Your extra samples will not be used for human genetic testing.

The ACTG has another study that collects samples for genetic testing. If you live in the US, this study is called ACTG A5128, Plan for Obtaining Informed Consent to Use Stored Human Biological Materials (HBM) for Currently Unspecified Analyses.

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

APPENDIX II: INFORMED CONSENT FOR PARTICIPANTS WHO BECOME PREGNANT WHILE ON STUDY

INTRODUCTION

Because you are now pregnant, you are being asked if you want to continue taking part in this research study. This study was designed so that participants who were pregnant could not join the study. However, because you were already in the study when you became pregnant, you will be allowed to stay in the study and come for the same study visits whether or not you continue study treatment during your pregnancy.

This is a consent form. It gives you more information about how continuing on this study may affect your pregnancy and your baby. The research staff will talk with you about this information. You may also talk with your own doctor about what is best for you and your baby, if you should remain on study-provided anti-HIV drugs, or choose other anti-HIV drugs. If you agree to stay in this study, you will be asked to sign and date this consent form. You will get a copy to keep. You are free to ask questions of the study staff at any time.

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

If you stay in this study, you will continue to be followed as described above. You may choose to stay on the anti-HIV study drugs provided through the study, or you may receive a different anti-HIV regimen from your own doctor. You will continue to come for regularly scheduled study visits, however, you will not be required to fast for any visits.

If you become and remain pregnant during Step 1, you will be followed on study until Step 1, **w**eek 24, but will not be eligible to enroll into Step 2.

If you become pregnant during Step 2 Study Group A or Step 3 and already received at least one dose of RPV-LA + CAB-LA injection, you will be able to continue study treatment if you choose after discussing with your study doctor. If you decide to continue, you will be permitted to move onto the next study **s**tep upon completion of your current **s**tep.

If you are in Step 2 Study Group A or Step 3 and become pregnant while receiving oral CAB + RPV but have not received yet any CAB-LA/RPV-LA injection, you will discontinue study treatment and will need a new regimen. You can remain on study but will not enroll into the next study **s**tep.

If you become pregnant while in Step 2 Study Group B, you can remain on study until Step 2, **w**eek 52, but will complete the study at that time. You will not be eligible to start Step 3 if you are pregnant at the time of your Step 3 registration visit.

This study will not provide care related to your pregnancy, the delivery of your baby, or the care of your baby. You must arrange care for yourself and your baby outside of this 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 **people** taking anti-HIV drugs. This report will not use your name or other information that could be used to identify you.

Study visits may be conducted remotely (for example, telephone, telehealth) if you are unable to attend a visit because of illness, inability to travel, concerns for potential exposure to COVID-19, or the clinic is temporarily unable to conduct non-essential visits in the clinic.

Stored whole blood and plasma will not be collected for participants who become and remain pregnant during the study.

WHAT ARE THE RISKS RELATED TO STAYING IN THE STUDY?

Now that you are pregnant, there are some possible risks you should know. These possible risks to you and your baby are in addition to the risks that are described above.

Risks to You if You Stay on Anti-HIV Drugs
All HIV treatment guidelines recommend that pregnant individuals with HIV should take HIV drugs during pregnancy for their own health and to prevent **perinatal** transmission of HIV. Different side effects or more severe side effects may occur in pregnant individuals taking anti-HIV drugs. This may make it more difficult for the drugs to work on the HIV in your blood. The amount of anti-HIV drugs in the blood may change during pregnancy. This means that the amounts of anti-HIV drugs in your blood may decrease and not work as well or cause the HIV to become resistant to the drugs. It will be important to follow up closely with your doctor to ensure your virus is still under control.

You and your study doctor will decide whether you will stay on your study treatment or whether you will change to a different drug provided by the study doctor.

We do not know if the use of injectable cabotegravir (CAB) or injectable rilpivirine (RPV) will increase the risk of birth defects, stillbirth, or miscarriage. 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 milligram 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. In another study, CAB was administered orally to pregnant rabbits at 0, 30, 500, or 2000 mg/kg/day from Gestation Days 7 to 19. No drug-related fetal toxicities were 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.

Based on reports to a registry collecting outcomes of 390 **participants of child-bearing potential** exposed to oral (pill-version) RPV during the first trimester of pregnancy, and over 170 during second/third trimester of pregnancy, the rate of birth defects was lower than

compared to the expected rate of birth defects in the US (1.3% versus 2.27%).

Breastfeeding
It is unknown whether the study drug passes through breast-milk and may cause harm to your infant. You must not breast-feed if you are in this study.

ARE THERE BENEFITS TO STAYING IN THIS STUDY?

Use of combination anti-HIV drugs during pregnancy significantly decreases the chance that the baby will **get HIV** during pregnancy. However, you can also continue to receive anti-HIV drugs from your provider. If you continue to take part in this study, no guarantee can be made of a benefit to you or your baby. It is possible that you and your baby will receive no benefit from continuing in this study. Information learned from this study may help others who have HIV.

WHAT OTHER CHOICES DO I HAVE BESIDES STAYING ON STUDY DRUGS?

Instead of staying on the study drugs you have the choice of:

- Treatment with prescription medicines available to you
- Treatment with experimental drugs being studied for use during pregnancy, if you qualify
- No treatment

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.

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 received a Certificate of Confidentiality from the US 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.

People who may review your records include the ACTG, FDA, (insert name of site) IRB, OHRP, National Institutes of Health (NIH), study staff, study monitors, drug companies supporting this study and their designees, and other local, US, and international regulatory entities. 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.

WHAT ARE THE COSTS TO ME?

In addition to any costs that are described above, this study will not cover any cost related to your pregnancy, delivery of your baby, or care of your baby.

WILL I RECEIVE ANY PAYMENT?

If you continue your study visits, you will continue to be compensated for study visits as outlined above.

WHAT HAPPENS IF MY BABY OR I AM INJURED?

If your baby or you are injured as a result of being in this study, you will both be given immediate treatment for your injuries. The cost for this treatment will be charged to you or your insurance company.

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

- ***There is no program for compensation through the US National Institutes of Health, but this site has clinical trials insurance. This insurance will allow the site to provide you with monetary compensation if you suffer harm as a result of participating in this research study.***

OR

- ***There is no program for compensation either through this institution or the US National Institutes of Health.]***

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

WHAT ARE MY RIGHTS AS A RESEARCH PARTICIPANT?

Continuing to take part in this study after you become pregnant (and at any time) is completely voluntary. You may choose not to continue 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 be treated the same no matter what you decide.

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.

SIGNATURE PAGE

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

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

WITNESS SIGNATURE FOR PARTICIPANTS WHO CANNOT READ
The study participant has indicated that he/she is unable to read. The consent document has been read to the participant by a member of the study staff, discussed with the participant by a member of the study staff, and the participant has been given an opportunity to ask questions of the study staff.

Witness's Name (print) (As appropriate)	Witness's Signature and Date