IMPAACT 2040

Phase I/II Study of the Pharmacokinetics and Safety of Long-Acting Injectable Cabotegravir and Rilpivirine in Pregnant and Postpartum Adults with HIV-1

CREATE - Cabotegravir & **R**ilpivirin**e A**ntiretroviral **T**h**e**rapy in Pregnancy

A Study of the International Maternal Pediatric Adolescent AIDS Clinical Trials Network

Sponsored by:
National Institute of Allergy and Infectious Diseases
Eunice Kennedy Shriver
National Institute of Child Health and Human Development
National Institute of Mental Health

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DAIDS Study ID #38953
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Version 1.0
PROTOCOL SIGNATURE PAGE

I will conduct this 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 Council for Harmonisation Guideline for Good Clinical Practice (ICH E6); Institutional Review Board/Ethics Committee determinations; all applicable in-country, state, and local laws and regulations; and other applicable requirements (e.g., US National Institutes of Health, Division of AIDS) and institutional policies.

_____ _____
Signature of Investigator of Record Date

_____
Name of Investigator of Record
(printed)

ABBREVIATIONS AND ACRONYMS

AE	Adverse Event
AESI	Adverse Events of Special Interest
ALP	Alkaline Phosphatase
ALT	Alanine Aminotransferase
Anti-HCV ab	Anti-Hepatitis C Virus Antibody
ART	Antiretroviral Therapies
ARV	Antiretroviral
AST	Aspartate Aminotransferase
AUC	Area under the Plasma Concentration-time Curve
BUD	Beyond-Use-Date
BUN	Blood Urea Nitrogen
C-SSRS	Columbia-Suicide Severity Rating Scale
CAB	Cabotegravir
CAB LA	Long-Acting Injectable Cabotegravir
CAR	Current Antiretroviral Regimen
cART	Combination Antiretroviral Therapy
CBC	Complete Blood Count
CD4	Cluster of Differentiation 4
CFR	Code of Federal Regulations
CI	Confidence Interval
CL	Clearance
CLIA	Clinical Laboratory Improvement Amendments
CMC	Clinical Management Committee
COVID-19	Coronavirus Disease 2019
CPK	Creatinine Phosphokinase
CrCl	Creatinine Clearance
CREATE	Cabotegravir & Rilpivirine Antiretroviral Therapy in Pregnancy
CRM	Clinical Research Manager
CRPMC	Clinical Research Products Management Center
DAERS	DAIDS Adverse Experience Reporting System
DAIDS	Division of Acquired Immunodeficiency Syndrome
DAIDS OCSO	DAIDS Office of Clinical Site Oversight
DAIDS PRO	DAIDS Protocol Registration Office
DAIDS RSC	DAIDS Regulatory Support Center
DDI	Drug-Drug Interactions
DILI	Drug Induced Liver Injury
DMC	Data Management Center
DMPK	Drug Metabolism and Pharmacokinetics
DVT	Deep Vein Thrombosis
EAE	Expedited Adverse Event
EC	Ethics Committee
ECG	Electrocardiogram
eCRF	Electronic Case Report Forms
EDD	Estimated Delivery Date

EGA	Estimated Gestational Age
EIA	Enzyme Immunoassay
EU	European Union
FDA	Food and Drug Administration
GCLP	Good Clinical Laboratory Practice
HBsAg	Hepatitis B Surface Antigen
HBcAb	Hepatitis B Core Antibody
HBsAb	Hepatitis B Surface Antibody
HELLP	Hemolysis, Elevated Liver Enzymes and Low Platelets
HIPAA	Health Insurance Portability and Accountability Act
HIV-1	Human Immunodeficiency Virus
HSR	Hypersensitivity Reactions
IB	Investigator's Brochure
ICH	International Council for Harmonisation
IM	Intramuscular
IMPAACT	International Maternal Pediatric Adolescent AIDS Clinical Trials Network
INSTI	Integrase Strand Transfer Inhibitor
IoR	Investigator of Record
IRB	Institutional Review Board
ISR	Injection Site Reaction
ITT-E	Intent-to-Treat-efficacy
IV	Intravenous
LBW	Low Birth Weight
LDMS	Laboratory Data Management System
LMP	Last Menstrual Period
LPC	Laboratory Processing Chart
MACDP	Metropolitan Atlanta Congenital Defects Program
MOP	Manual of Procedures
MRHD	Maximum Recommended Human Dose
NAT	Nucleic Acid Test
NIAID	National Institute of Allergy and Infectious Diseases
NICHD	National Institute of Child Health and Human Development
NIH	National Institutes of Health
NIMH	National Institute of Mental Health
NNRTI	Non-nucleoside Reverse Transcriptase Inhibitor
OHRP	US Office for Human Research Protection
OLI	Oral Lead-in
PCR	Polymerase Chain Reaction
PE	Pulmonary Embolism
PID	Participant Identification Number
PK	Pharmacokinetics
RNA	Ribonucleic Acid
RPV	Rilpivirine
RPV LA	Long-acting Injectable Rilpivirine
Q4W	Every four weeks
Q8W	Every eight weeks
QTcB	Corrected Q-T interval Bazett
QTcF	Corrected Q-T interval Fridericia
SAE	Serious Adverse Events
SAP	Statistical Analysis Plan
SCORE	Site Clinical Operations and Research Essentials Manual

SD	Standard Deviation
SID	Study Identification Number
sIRB	Single Institutional Review Board
SMC	Study Monitoring Committee
SPDSMP	Study Progress, Data, and Safety Monitoring Plan
SOP	Standard Operating Procedures
SUSAR	Suspected, Unexpected Serious Adverse Reactions
TAF	Tenofovir Alafenamide
TdP	Torsade de Pointes
ULN	Upper Limit of Normal
US	United States
VQA	Virology Quality Assurance
WB	Western Blot
WHO	World Health Organization

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IMPAACT 2040/CREATE
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SCHEMA

Purpose: To characterize the pharmacokinetics (PK) and safety of long-acting injectable cabotegravir and rilpivirine (CAB LA + RPV LA) in people with HIV-1 viral suppression, during pregnancy and postpartum.

Design: Phase I/II, multicenter, open-label, non-randomized study with four groups:

Group	Description	Estimated Gestational Age (EGA) at Entry
Q4W Switch	Pregnant people with HIV-1 viral suppression on oral antiretroviral therapy willing to switch to an every four week (Q4W) CAB LA + RPV LA regimen.	Between 10 0/7 and 19 4/7 weeks (inclusive)
Q8W Switch	Pregnant people with HIV-1 viral suppression on oral antiretroviral therapy willing to switch to an every eight week (Q8W) CAB LA + RPV LA regimen.	Between 10 0/7 and 19 4/7 weeks (inclusive)
Q4W Continuation	Pregnant people with HIV-1 viral suppression who were using CAB LA + RPV LA at and since conception and are willing to continue their current CAB LA + RPV LA regimen.	Less than or equal to 19 4/7 weeks
Q8W Continuation		

The study will start with concurrent accrual into the Q4W Continuation, Q8W Continuation, and Q4W Switch Groups. An interim analysis will be conducted with all available data once there are at least 10 evaluable Q4W Switch Group participants. If data from the interim analysis shows acceptable PK, safety, and virologic outcomes, accrual into the Q8W Switch Group will open.

Study Population: Pregnant people with HIV-1 viral suppression age 18 years and older, and in their first or second trimester at time of entry, and their infants.

Note: The term "adult-participant" is used to refer to the adult (pregnant or postpartum) participant. Infants are referred to as "infant-participants."

Sample Size: Approximately 45 pregnant people and their infants, with a target of 10 across the Q4W and Q8W Continuation Groups and 35 across the Q4W and Q8W Switch Groups.

Study Treatment: Adult-participants will receive CAB LA and RPV LA intramuscular (IM) injections Q4W or Q8W, administered as two separate IM injections, starting at entry and continuing throughout follow-up, as follows:

Group	IM Injection Dosing	
	Loading Dose	**Maintenance Dose**
Q4W Switch	CAB LA 600 mg (3mL) + RPV LA 900 mg (3 mL); at **Entry**	CAB LA 400 mg (2 mL) + RPV 600 LA mg (2 mL); at **Week 4** and **every four weeks**
Q8W Switch	CAB LA 600 mg (3mL) + RPV LA 900 mg (3 mL); at **Entry** and again at **Week 4**	CAB LA 600 mg (3mL) + RPV LA 900 mg (3 mL); at **Week 12** and **every eight weeks**
Q4W Continuation	N/A	CAB LA 400 mg (2 mL) + RPV LA 600 mg (2 mL); at **Entry** and **every four weeks**
Q8W Continuation	N/A	CAB LA 600 mg (3mL) + RPV LA 900 mg (3 mL); at **Entry** and **every eight weeks**

Study Duration: Approximately 27 months, from enrollment of first participant to study exit of last participant enrolled. Accrual is expected to require approximately 15 months. Adult-participants will be followed for approximately six to 12 months, which will include the duration of their pregnancy and approximately 7-10 weeks postpartum (Q4W) and approximately 11-18 weeks postpartum (Q8W). Infant-participants will be followed from birth and for the same duration as adult-participants.

Primary Objectives

- To describe the pharmacokinetics (PK) of CAB LA and RPV LA during pregnancy and postpartum in people with HIV-1 viral suppression switching to or continuing CAB LA + RPV LA
- To describe safety of CAB LA + RPV LA during pregnancy and postpartum in people with HIV-1 viral suppression switching to or continuing CAB LA + RPV LA

Secondary Objectives

- To compare CAB and RPV PK parameters following treatment with CAB LA + RPV LA during pregnancy to both intraparticipant postpartum PK data and historical PK data from non-pregnant people
- To assess the maintenance of virologic suppression in people with HIV-1 on CAB LA + RPV LA during pregnancy and postpartum and describe HIV-1 drug resistance in those who experience virologic failure during study treatment
- To characterize the frequency of HIV-1 transmission in infants of people with HIV-1 on CAB LA + RPV LA in pregnancy/postpartum
- To evaluate pregnancy outcomes in adults with HIV-1 on CAB LA + RPV LA during pregnancy and early post-natal safety outcomes of their infants
- To characterize CAB and RPV plasma concentrations in infants exposed to CAB LA + RPV LA during pregnancy and via chest/breastfeeding
- To describe the tolerability and acceptability of Q4W and Q8W CAB LA + RPV LA in people with HIV-1 during pregnancy/postpartum

Other Objectives

- To characterize the cord blood and chest/breastmilk concentrations of CAB and RPV after CAB LA + RPV LA use during pregnancy/postpartum
- To apply CAB and RPV population PK models to determine individual and population estimates of CAB and RPV exposure parameters during pregnancy and postpartum

- To characterize concentrations of unbound drug for CAB and RPV during pregnancy/postpartum and association with viral response

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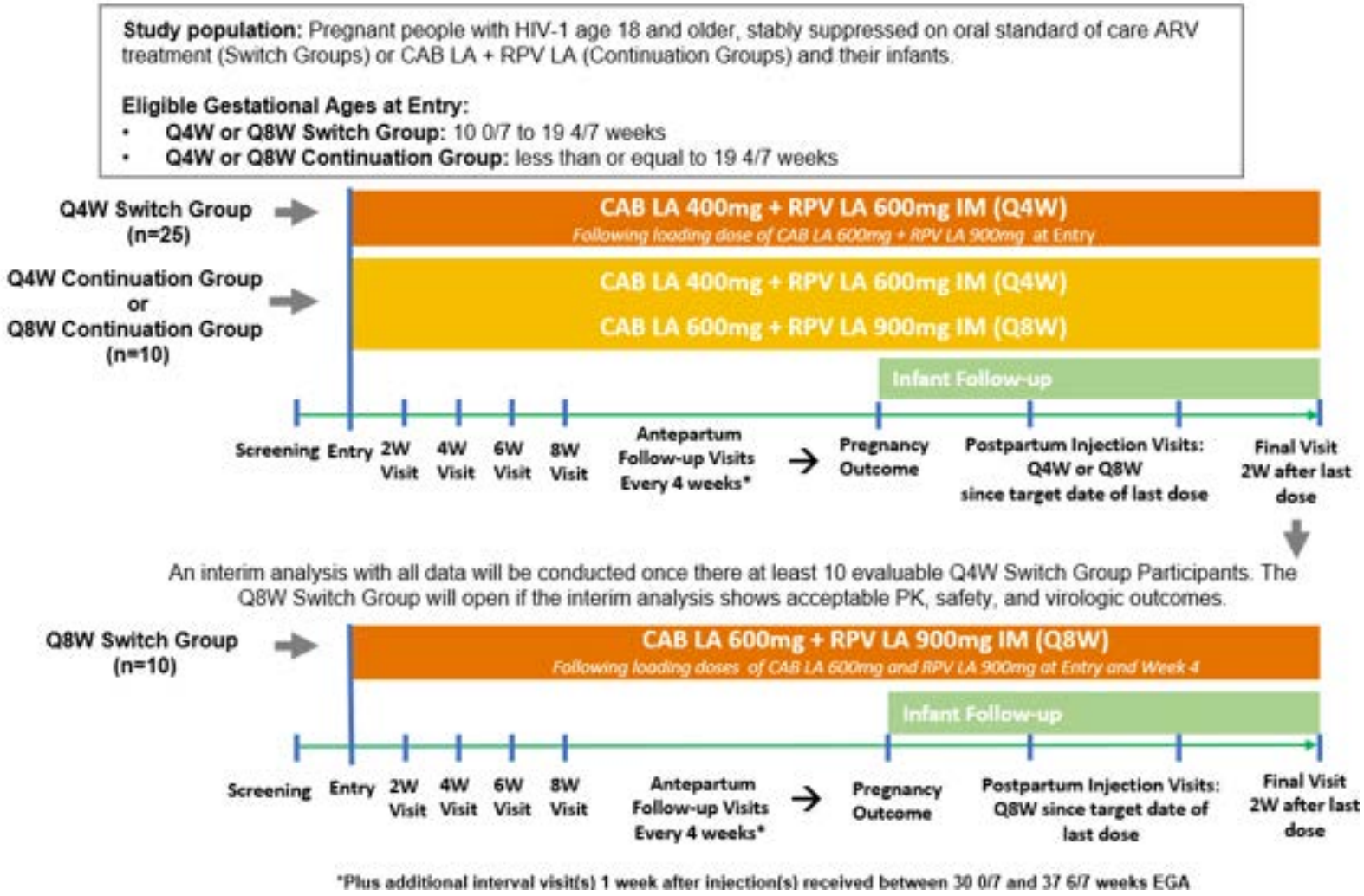
Figure 1. Overview of Study Design



1 INTRODUCTION

1.1 Background

Antiretroviral therapies (ART) that are long-acting have the potential to significantly and sustainably prevent human immunodeficiency virus (HIV) infection and improve treatment outcomes for individuals with HIV-1, including during pregnancy (1). Long-acting injectable (LA) ART, such as cabotegravir (CAB) co-administered with rilpivirine (RPV), offer monthly or every two months alternatives to once or twice daily administration of oral ART, obviating notable barriers of pill burden, daily adherence, and stigma related to disclosure of HIV-1. Pill burden is especially important in pregnancy where nausea and vomiting can complicate tolerance of oral regimens (1). Additionally, viral suppression and optimization of adherence during pregnancy is especially critical, not only for maternal/parental health, but also for prevention of perinatal HIV-1 transmission.

CAB is a potent integrase strand transfer inhibitor (INSTI) with attributes allowing formulation and delivery as a LA parenteral product. RPV, also formulated as a LA product, is a diaryl pyrimidine derivative and a potent non-nucleoside reverse transcriptase inhibitor (NNRTI) with in vitro activity against wild type HIV-1 and select NNRTI-resistant mutants. The combination of CAB LA plus RPV LA has an acceptable safety profile and is well-tolerated and efficacious as a dual injectable ART among adults and adolescents living with HIV-1 (2). Limited drug exposure data are available for these formulations during pregnancy with pregnancy potentially altering the pharmacokinetics (PK) of CAB LA + RPV LA, as well as the maternal/parental and fetal/neonatal safety in this period. Pregnant people experience unique physiological changes that may result in clinically significant alterations in drug PK. These changes begin early in gestation and include: (a) increased gastrointestinal transit time that can alter the rate and extent of oral drug absorption; (b) large changes in total body water and fat, increasing drug distribution volume; (c) decreased albumin and increased alpha-1 acid glycoprotein (AAG) concentrations that may cause clinically relevant changes in drug protein binding; (d) increased cardiac output, ventilation, and hepatic and renal blood flow which may impact drug metabolism and elimination; and (e) increased concentrations of endogenous glucocorticoids that may affect the activity of hepatic enzyme systems that regulate drug metabolism (3-7).

Placental drug transport is another critical aspect of perinatal pharmacology for which few data exist for many antiretrovirals (ARVs). Transport of ARV agents from pregnant parent to fetus may provide protection for the fetus against HIV-1 infection across the placenta and at the time of birth, but may also expose the fetus to the risk of toxic drug effects. Human placental drug transfer studies are limited to comparisons of the ratio of maternal/parental drug concentrations, at the time of delivery, to those in cord blood. While this ratio provides information about only a single point in time, it is the only practical technique currently available for humans and, for now, is the most useful (8).

No studies to date have been conducted on the PK or safety of on-going intramuscular (IM) injectable CAB LA + RPV LA during pregnancy and postpartum and acceptability and tolerability of this regimen has not been evaluated in this population. Published PK and safety for CAB LA + RPV LA in pregnancy are limited to small numbers of continuing pregnancies with early drug exposures, specifically individuals who were receiving injections of CAB LA + RPV LA or CAB LA, became pregnant, and were subsequently switched to oral ART regimen upon confirmation of pregnancy (9-12). In addition, there are PK and safety data in animal models for both drugs, as well as in humans for oral RPV in pregnancy. All are reviewed in Section 1.2.1.

Based upon existing PK and modeling data (9, 10, 12, 13), decreased exposure to CAB and RPV due to increased metabolic enzyme induction in the second and third trimesters of pregnancy is predicted, however it is anticipated that CAB LA + RPV LA exposure at currently licensed monthly doses and every two months doses in the second and third trimesters will allow for maintained viral suppression during pregnancy. Increases in viral load or associated perinatal transmission of HIV-1 is not anticipated. Adverse birth outcomes (for mother/parent or fetus/infant) and safety signals associated with exposure to CAB LA + RPV LA in utero or through chest/breastfeeding are also not anticipated. It is anticipated that CAB LA + RPV LA will be both acceptable and tolerable for the pregnant parent and safe for both parent and fetus. Additionally, cord blood and infant PK sampling will provide key insight into both fetal exposure in utero and the neonatal metabolism of CAB LA + RPV LA, which can, in turn, inform dose development in this key population.

1.2 Prior Research

1.2.1 Cabotegravir

CAB is a HIV-1 INSTI. CAB 30-mg once daily (oral tablet) is approved in multiple countries and regions for the short-term treatment of HIV-1 in adults who are virologically stable and suppressed (plasma viral load less than 50 HIV-1 RNA copies/mL) in combination with oral RPV. This indication for oral CAB is limited to use as either an oral lead-in (OLI) prior to CAB LA + RPV LA to assess individual tolerability prior to receipt of injections or as oral bridging therapy for planned interruptions in CAB LA + RPV LA injection dosing. The CAB oral tablet and a parenteral long-acting formulation of CAB (CAB LA) have been approved for use in combination with oral RPV and RPV LA in a number of countries as a dual regimen to treat HIV-1 in virologically stable and suppressed adults (HIV-1 RNA less than 50 copies/mL).

Summary of Cabotegravir Drug Metabolism and Pharmacokinetics (DMPK):

CAB is rapidly absorbed following oral administration of the micronized tablet formulation, with median time to maximum plasma concentration (T_{max}) observed two to three hours post-dose in the fasted state. CAB LA is a 200 mg/mL suspension that has been administered as an IM and a subcutaneous injection of single doses of 100 to 800 mg and repeat doses from 200 to 800 mg. CAB LA exhibits absorption-limited (flip-flop) kinetics, and CAB has been detected in plasma up to 52 weeks or longer after administration of a single IM injection of CAB LA.

Following administration in humans, CAB is primarily eliminated through metabolism by UGT1A1, with no cytochrome P450 (CYP)-mediated metabolism. Renal elimination of unchanged CAB represents less than 1% of the total dose administered. CAB is the predominant circulating compound in plasma, representing greater than 90% of plasma total radiocarbon. Fifty-eight percent of the total oral dose is excreted as unchanged CAB in the feces, and 26.8% of the total oral dose is excreted in the urine, primarily as a glucuronide metabolite (14).

DMPK Pregnancy:

As noted in Section 1.1, clinical trial and PK data reported to date are limited to pregnant individuals who stopped receiving CAB LA injections for treatment (or CAB LA for prevention) of HIV-1 once pregnancy was recognized and began an alternative oral ARV regimen throughout the remainder of their pregnancies.

Through 31 March 2021, plasma CAB and RPV concentrations were available for seven women who became pregnant in ViiV-sponsored Phase IIb/III/IIIb clinical studies and within the compassionate use program with live birth outcomes. CAB LA + RPV LA was discontinued

following confirmation of pregnancy and an alternative ART regimen was initiated. All seven women remained virologically suppressed from conception through pregnancy and postpartum or last available viral load assessment following switch to alternative ART or during continued LA dosing.

Among individuals exposed to CAB LA + RPV LA in early pregnancy, the CAB LA PK tail data in pregnancy were within the observed range for non-pregnant women, taking into account the alternative ARV regimen to which they switched. Tail concentrations observed for specific participants may have been impacted by metabolic induction or the inhibition propensity of the subsequent alternative ART regimen to which participants were switched after LA discontinuation. For example, CAB + RPV PK levels may have been decreased by induction from EFV (9).

In HPTN 084 (Evaluating the Safety and Efficacy of Long-Acting Injectable Cabotegravir Compared to Daily Oral TDF/FTC for Pre-Exposure Prophylaxis in HIV-Uninfected Women), PK data are available for 18 participants who received at least one dose of CAB prior to confirmation of pregnancy and subsequent discontinuation of CAB. The apparent terminal phase half-life ($t_{1/2app}$) in pregnant participants was comparable to non-pregnant people (62.0 and 64.3 days respectively), with age, race and pregnancy not having a significant impact, although body mass index greater than 27.2 kg/m^2 was associated with longer CAB $t_{1/2app}$ (11).

Placental and Chest/Breast Milk Passage:

Median (interquartile range 25–75) CAB maternal/parental-to-fetal concentration ratio assessed using an *ex vivo,* dually perfused human cotyledon model was 10% (6-12, 15-19), suggesting low placental transfer (8). No data are available describing chest/breastmilk passage of CAB in humans.

Teratogenicity, Safety, and Adverse Pregnancy Outcomes

There are no data in humans on the effects of CAB on fertility; animal studies do not indicate effects of CAB on fertility. CAB when administered orally to male and female rats at exposures, areas under the plasma concentration-time curve (AUC), greater than 20 times the exposure at the Maximum Recommended Human Dose (MRHD) of 30 mg dosed orally or 400 mg IM injection did not cause adverse effects on male or female reproductive organs or spermatogenesis, and no functional effects on mating or fertility were observed (20).

Reproductive toxicity studies in pregnant rats showed that CAB crosses the placenta and can be detected in fetal tissue. CAB was not teratogenic when studied in pregnant rats and rabbits but in rats caused decreased fetal weight, a delay in the onset of parturition and increased stillbirths and neonatal deaths at exposures higher than for therapeutic doses. The relevance to human pregnancy is unknown. In an embryo-fetal development study, there were no adverse developmental outcomes following oral administration of CAB to pregnant rabbits at doses with exposures up to 0.66 times the exposure at the MRHD of 30 mg. In rats, alterations in fetal growth (decreased body weights) were observed at exposures that were 28 times the exposure at the MRHD. In rat pre- and post-natal studies with exposures 28 times the exposures at the MRHD of 30 mg oral or 400 mg IM dose, CAB was associated with delayed onset of parturition, and increased number of stillbirths and neonatal mortalities immediately after birth. In a cross-fostering study, similar incidences of stillbirths and early postnatal deaths were observed when rat pups born to CAB-treated mothers were nursed from birth by control mothers. There was no effect on neonatal survival of control pups nursed from birth by CAB-treated mothers. A lower dose of CAB (at exposures greater than 10 times the exposure at the MRHD of 30 mg oral or 400 mg IM dose) was not associated with delayed parturition or neonatal mortality in rats. In rabbit

and rat studies there was no effect on survival when fetuses were delivered by caesarean section (20).

As of 31 March 2021, 25 pregnancies following CAB + RPV exposure at conception were reported (five oral, 20 LA) in people who became pregnant and had been exposed to one or more doses of CAB + RPV (oral/LA) from ViiV Healthcare-sponsored phase IIb/III/IIIb clinical trials and the compassionate use program. In the clinical trials, CAB + RPV was discontinued upon confirmation of pregnancy and in the compassionate use program, CAB + RPV continuation or alternative ARV initiation was decided upon by the participants and their treating physicians.

Of the 25 pregnancies, four conceived during PK washout following treatment discontinuation. There were eight elective abortions, six miscarriages (five in first trimester), one ectopic pregnancy, and 10 live births (one oral, nine LA), including one infant born with congenital ptosis whose mother was receiving CAB + RPV LA through the compassionate use program. The congenital ptosis was considered to be a random congenital anomaly by the treating physician and not associated with CAB + RPV LA therapy. Among participants exposed to CAB + RPV LA at conception with live births, plasma CAB and RPV washout concentrations during pregnancy were within the range of those observed in non-pregnant women (21).

In the HPTN 084 study, as of 31 December 2021, there have been 31 live births, 10 pregnancy losses and no congenital abnormalities observed (22).

There were more participants who experienced pregnancy-associated adverse events (AEs) (Grades 1-3) in the CAB arm of HPTN 084 compared to the TDF/FTC arm (six participants vs. one participant respectively), but these AEs were deemed unrelated to study drug. The incidence of Grade 2 or higher AEs in the CAB arm was 113 per 100 person years for CAB and 166 per 100 person years for TDF/FTC (12).

The remainder of what is known about safety, teratogenicity, and pregnancy outcomes is from animal models and extrapolated from the structural similarities between CAB and dolutegravir (DTG). Animal studies in pregnant rats demonstrated that while CAB crosses the placenta and can be detected in fetal tissue, there were no effects on fetal viability. There was a minor decrease in fetal weight with exposures 28 times those in humans at the recommended doses of CAB, however this decrease in fetal weight was no longer observed at 13 times the recommended exposure for humans (20).

1.2.2 Rilpivirine

RPV is a NNRTI with *in vitro* activity against wild-type and select NNRTI-resistant HIV-1. RPV 25 mg once daily (oral tablet) in combination with other ARVs has already been approved to treat HIV-1 infection in ART-naive patients age12 years and older in multiple countries and regions. RPV (dose 25 mg) has also been approved as part of once-daily single-tablet oral regimens as FTC/RPV/TDF, FTC/RPV/tenofovir alafenamide (TAF) and DTG/RPV (23).

A parenteral long-acting RPV (RPV LA) formulation (300 mg/mL) has been approved for use in combination with CAB LA in the United States (US), the European Union (EU) and multiple countries/regions. Oral RPV in combination with oral CAB is also approved in multiple other countries and regions, for the short-term treatment of HIV-1 in adults who are virologically stable and suppressed (plasma viral load less than 50 HIV-1 RNA copies/mL), to assess tolerability prior to receipt of injections, or to replace missed injections.

Summary of DMPK:

After oral administration, RPV is absorbed with a T_{max} of about four to five hours. Oral RPV must be taken with a meal for optimal absorption (10). The elimination half-life after oral administration is 45-50 hours. RPV LA has been administered IM to healthy adults and adults living with HIV-1 at 300 mg to 1200 mg. After IM injection of RPV LA, RPV is slowly absorbed from the injection site, exhibiting flip-flop PK with an apparent half-life of 200 days in adults (24).

RPV is primarily metabolised, via CYP3A, and eliminated by the liver. No dose adjustment is required in patients with mild or moderate hepatic impairment (23). Exposure to oral RPV can be affected by drugs that increase gastric pH. Drugs that induce CYP3A4 activity can reduce RPV exposure (both oral and LA) and strong inducers should not be co-administered. Drugs that inhibit CYP3A4 activity can increase RPV exposure (both oral and LA) but do not require dose adjustments (23). Renal elimination of RPV is negligible. Therefore, no dose adjustment of RPV is required in patients with renal impairment (23).

DMPK in Pregnancy:

With oral RPV, there is a pregnancy-associated 20-50% decrease in total RPV exposure in the second and third trimesters of pregnancy, likely attributable to changes in albumin plasma concentrations during pregnancy and pregnancy-related CYP3A4 induction. There were three clinical studies evaluating the pharmacokinetics, safety, and antiviral effects with use of oral RPV 25 mg during pregnancy and postpartum (15, 18, 19). PK and safety data from 32 pregnant people with HIV-1 found that median RPV area under the curve concentration (AUC) and trough concentration (C_{trough}) were approximately 20% to 30% lower in the second and third trimesters than postpartum (18). Plasma HIV-1 RNA at delivery was less than or equal to 50 c/mL in 21 of 30 participants (70%) and less than or equal to 400 c/mL in 27 of 30 participants (90%). All infants with determinate HIV-1 infection status were uninfected (n=25). Median RPV C_{trough} were significantly lower at 14 visits where the participants had detectable HIV-1 RNA (30 ng/mL) than at 62 visits where they had undetectable HIV-1 RNA (63 ng/mL). Ninety percent of participants had C_{trough} above the protein-adjusted 90% maximal effective concentration (EC_{90}) for RPV. PK parameters between participants were highly variable in this study (18). A second study in 16 pregnant people with HIV-1 similarly found that third trimester exposure was approximately 50% lower than postpartum, with four of the 16 individuals having C_{trough} below the target levels for that study during pregnancy. Plasma HIV-1 RNA was less than or equal to 50 c/mL in all (100%) women during pregnancy as well as at delivery. All infants were HIV-1 uninfected and no birth defects were reported (14). A third study reported that total RPV exposure decreased by approximately 30%, and unbound RPV levels decreased by 22% to 25% during pregnancy in 15 individuals compared with the RPV exposures seen in the same individuals postpartum. Despite the decrease in exposure during pregnancy, the once daily RPV 25 mg ARV regimen was effective in preventing perinatal transmission and in suppressing HIV-1 in pregnant women (19). This decrease in RPV exposures with maintained viral suppression and no viral transmission led the US perinatal guidelines (25) to recommend frequent monitoring of viral load with oral RPV-based regimens used during pregnancy but no dose adjustment.

Placental and Chest/Breast Milk Passage:

The three above mentioned PK studies demonstrated placental transfer of RPV for individuals on oral RPV at time of delivery. The first, which included delivery data from 21 mother/parent–infant pairs, found a median cord blood RPV plasma concentration of 29.2 ng/mL (range, less than 10.0 to 101.5 ng/mL), a median maternal/parental delivery plasma RPV concentration of 55.2 ng/mL (range, less than 10.0 to 233.8 ng/mL), and a median cord blood-to-maternal/parental-plasma ratio of 0.55 (range, 0.3–0.8) (18). Osiyemi et al. found that the median

ratio of cord blood-to-maternal/parental-plasma concentration of total RPV in eight participants was 0.55 (range, 0.43–0.98) (19). Similarly, Schalkwijk et al. found a median cord blood-to-maternal/parental-plasma ratio of 0.5 (range, 0.35–0.81) in five participants (15). Lastly, an *ex vivo* human cotyledon perfusion model also showed that RPV crosses the placenta, with fetal transfer rates ranging from 17% to 37% (26, 27). There are limited data on transfer of oral RPV via chest/breastfeeding; among two mother/parent-child pairs in the Swiss Mother and Child HIV Cohort Study the median milk/plasma ratio was 1.08 and the median estimated infant daily dose was 0.02 mg/kg (28). RPV has also been found in rat milk (20).

Teratogenicity, Safety, and Adverse Pregnancy Outcomes

There are no human data on the effects of RPV on fertility; animal studies do not indicate effects of RPV on fertility. In rats, there were no effects on mating or fertility with RPV at exposures greater than 28 times the exposure at the MRHD of 25 mg orally once daily or 600 mg IM injection monthly (20).

No significant toxicological effects were observed in embryo-fetal toxicity studies performed with RPV in rats and rabbits at exposures greater than or equal to 12 (rats) and greater than or equal to 57 (rabbits) times the exposure at the MRHD of 25 mg orally once daily or 600 mg IM injection monthly dose of RPV in people with HIV-1. In a rat pre- and post-natal development study, no adverse effects were noted in the offspring at maternal/parental exposures greater than or equal to 51 times the exposure at the MRHD of 25 mg orally once daily or 600 mg IM injection monthly dose of RPV in HIV-1 infected patients.

No congenital anomalies, preterm birth, or drug-related maternal/parental or neonatal AEs have been reported to date in the live births of infants from people who conceived while receiving IM injections of RPV. The Antiretroviral Pregnancy Registry (APR) has monitored sufficient numbers of first-trimester exposures to oral RPV to detect at least a twofold increase in the risk of overall birth defects and has not detected any such increase (29).

QTc Changes in Adults Receiving Supratherapeutic Doses

While there is no evidence of therapeutic doses of RPV causing QTc prolongation, supratherapeutic doses of 75 mg or 300 mg daily have been shown to prolong the QTc interval in healthy adults (23).

1.2.3 Clinical Trial Experience Using Cabotegravir plus Rilpivirine as a Dual AART in Non-Pregnant Adults

No prospective studies have been conducted on the PKs of CAB and RPV with ongoing IM injections during pregnancy; data are limited to PK and safety data summarized in Section 1.2.1.

Phase III/IIIb studies including First Long-Acting Injectable Regimen (FLAIR) (2), Antiretroviral Therapy as Long Acting Suppression (ATLAS) (30), and Antiretroviral Therapy as Long Acting Suppression every 2 Months (ATLAS-2M) (21) and Phase IIb studies, including Long-Acting Antiretroviral Treatment Enabling Trial (LATTE) (31) and Long-Acting Antiretroviral Treatment Enabling Trial 2 (LATTE-2) (31), have been conducted with oral CAB plus oral RPV and/or CAB LA plus RPV LA.

FLAIR Trial

In the FLAIR Trial (32), which included 63 women on CAB LA + RPV LA, data indicate that CAB LA + RPV LA every four weeks (Q4W) effectively maintains the suppression of plasma

HIV-1 RNA (less than 50 c/mL) following induction of viral suppression with oral dolutegravir-abacavir-lamivudine in HIV-1 ART-naive adults and is non-inferior to continued oral dolutegravir-abacavir-lamivudine at Week 48. Overall, in the intent-to-treat efficacy (ITT-E) population, 2.1% of participants in the CAB LA + RPV LA group and 2.5% of participants in the dolutegravir-abacavir-lamivudine group met the 'snapshot virologic failure' primary efficacy endpoint of plasma HIV-1 RNA greater than 50 c/mL at Week 48 based upon the standardized FDA snapshot algorithm.

The FLAIR 96-week results reaffirm the 48-week results, showing CAB LA and RPV LA continued to be non-inferior compared with continuing a standard of care regimen in adults with HIV-1 for the maintenance of viral suppression. These results support the durability of CAB LA and RPV LA, over an almost two-year-long period, as a therapeutic option for virally suppressed adults with HIV-1.

The FLAIR 124-week Extension Phase results, in which participants originally on oral standard of care could switch to CAB LA + RPV LA after Week 96, show that after 24 weeks of treatment with CAB LA + RPV LA, switching to LA treatment with or without an OLI phase had similar safety, tolerability, and efficacy, supporting future evaluation of the simpler direct-to-injection approach. The week 124 results for participants randomly assigned at study baseline to the long-acting therapy show CAB LA plus RPV LA remains a durable maintenance therapy with a favorable safety profile.

ATLAS Trial

In the ATLAS Trial (30), of which 99/308 on CAB + RPV were women, data indicate that CAB LA + RPV LA effectively maintain the suppression of plasma HIV-1 RNA (less than 50 c/mL) and was non-inferior to combination ART (cART) at Week 48 among participants with virologic suppression. Study participants were randomized to once-daily OLI CAB + RPV followed by Q4W injections of CAB LA + RPV LA versus continuation of their baseline oral current ART regimen (CAR). Overall, in the ITT-E population, 1.6% of participants in the CAB + RPV group (15) and 1.0% of participants in the CAR group (7) met the 'snapshot virologic failure' primary efficacy endpoint of plasma HIV-1 RNA greater than 50 c/mL at Week 48 based upon the standardized FDA snapshot algorithm. The results in women are consistent with the overall ITT-E population with 2% (2/99) of female participants in the CAB+RPV group and none of 104 female participants in CAR group meeting 'snapshot virologic failure' at Week 48 based upon the standardized FDA snapshot algorithm.

ATLAS-2M

In ATLAS-2M (30), 1045 participants (280 women) in the intention to treat population-initiated treatment and were randomly assigned to every eight week (Q8W) or Q4W CAB LA + RPV LA dosing. Data from this study indicate that Q8W dosing with CAB LA + RPV LA is effective in maintaining the suppression of plasma HIV-1 RNA (less than 50 c/mL) and non-inferior to Q4W CAB LA + RPV LA at Week 48. In the ITT-E population, 1.7% of participants in the Q8W group (3) and 1.0% of participants in the Q4W group (7) met the primary efficacy endpoint snapshot virologic failure plasma HIV-1 RNA greater than or equal to 50 c/mL at Week 48 based upon the standardized FDA snapshot algorithm (30). Specifically, 12 (2.3%) participants in the Q8W arm and 2 (0.4%) in the Q4W arm had CVF. There were numerically more virologic failures in the Q8W arm (2% [n=12/522]), including 2 participants since week 96 [18], than in the Q4W arm (<1% {n=2/523; no new CVF since week 48).

CAB LA + RPV LA Q8W dosing had non-inferior efficacy compared with Q4W dosing through the 96-week analysis, with both regimens maintaining high levels of virological suppression. These results show the durable safety, efficacy, and acceptability of dosing CAB LA and RPV LA monthly and every two months as maintenance therapy for people with HIV-1 (33).

Week 152 efficacy endpoints assessed secondary and exploratory efficacy endpoints which demonstrated long-term efficacy of CAB LA + RPV LA up to Week 152. Overall efficacy results at the Week 152 analysis were similar to those reported for the Week 96 analysis (21).

LATTE

In the LATTE trial (34), of which 10/243 were women, antiretroviral-naive participants were randomized in a partially-blinded fashion to either one of three different doses of oral CAB or to efavirenz, in addition to a dual NRTI. At Week 24, participants with virologic suppression in the CAB group were transitioned to the same oral CAB (10, 30 or 60mg) + oral RPV (25 mg) dose, while participants in the efavirenz group remained on the same regimen. At Week 96, 79% (CAB 10 mg group), 85% (CAB 30 mg group), 93% (CAB 60 mg group) and 83% (EFV 600 mg group) of participants maintained virologic suppression (HIV-1 RNA less than 50 c/mL). The study was unblinded at this timepoint, with efavirenz participants considered to have completed the study. CAB participants switched to the Sponsor's selected regimen of open label CAB 30 mg + RPV 25 mg once daily. At Week 312, 52% (31/60; CAB 10 mg arm), 52% (31/60; CAB 30 mg arm) and 70% (43/61; CAB 60 mg arm) of participants randomized to oral CAB dosing maintained virologic suppression (HIV-1 less than 50 c/mL). The LATTE trial provided the rationale for the selected CAB oral dose of 30 mg for adults and was supportive of the efficacy and durability of the dual CAB + RPV regimen.

LATTE-2 Trial (Study 200056)

In LATTE-2 (6), of which 24/246 were women, antiretroviral-naive participants underwent induction with oral CAB+ABC/3TC for 20 weeks with the addition of oral RPV for the final 4 weeks prior to randomization to CAB LA + RPV LA Q4W or Q8W or continued oral CAB 30 mg + dual NRTI treatment. At Week 160, 83% of participants receiving CAB LA + RPV LA Q4W dosing and 90% Q8W dosing maintained virologic suppression (HIV-1 RNA less than 50 c/mL). The difference in virologic success was primarily due to non-virologic reasons. Of the 44 participants in the oral treatment group who opted to switch to CAB LA + RPV LA (Q4W or Q8W) at Week 100 (beginning of the Extension phase), 100% (Q4W) and 97% (Q8W) maintained virologic suppression (HIV-1 RNA less than 50 c/mL) at Week 160.

1.2.4 Summary of Safety Data of CAB LA + RPV LA Combination Therapy

Over 3000 participants have been exposed to oral and/or injectable CAB + RPV through ViiV Healthcare-sponsored HIV-1 treatment clinical studies in Phase II/IIb and Phase III/IIIb (as of March 2022).

The integrated analysis of safety data across the Phase III clinical studies (FLAIR and ATLAS), in combination with Phase I and Phase II data, supports an acceptable CAB + RPV safety profile. The following safety conclusions were drawn:

- The incidence of SAEs reported at the Week 48 analysis in pooled studies FLAIR and ATLAS were comparable between CAB + RPV and the CAR. Thirty-one (5%) participants in the CAB + RPV group and 26 (4%) participants in the CAR group had non-injection site reaction SAEs. The most frequently reported serious adverse events (SAE) with CAB + RPV occurring in more than one participant was hepatitis A (n=4). A single SAE in the CAB +

RPV treatment group was considered study drug-related by the site investigator: an SAE of right knee monoarthritis.

- At the time of the pooled analysis, no fatalities were reported for participants receiving CAB + RPV during FLAIR and ATLAS. During Phase II studies, there were five fatalities. Only one death (myocardial infarction) was considered study drug-related (CAB + RPV) by the site investigator. The participant had been on treatment for approximately three years and had several risk factors for cardiovascular disease.
- There were no cases of serious reactions such as drug-induced liver injury (DILI) or hypersensitivity reactions (HSR) in FLAIR and ATLAS with CAB + RPV. During Phase I and Phase II, DILI was identified in five participants receiving oral CAB (incidence was less than 1%). In FLAIR and ATLAS, there was a higher incidence of Grade 3/4 Alanine Aminotransferase (ALT) and participants who met liver stopping criteria in the CAB + RPV treatment regimen, which was due to the higher incidence of acute viral hepatitis occurring on the regimen.
- AEs of special interest (AESI) have been determined for CAB + RPV (oral and IM) based on: non-clinical and/or clinical safety data for CAB and RPV (oral and IM); labelling and/or regulatory authority interest for approved INSTIs; and/or regulatory authority requirements. Results from the Phase III studies indicated that CAB + RPV appears to have no clinically relevant effect on safety related to the following AESI: QT prolongation, seizures, rhabdomyolysis, pancreatitis, or impact on creatinine.
- The rate of discontinuation was low overall for FLAIR and ATLAS. Twenty-two (4%) participants in the CAB + RPV group and nine (2%) participants in the CAR group had AEs leading to withdrawal/permanent discontinuation of study drug during the maintenance phase. The most common AEs leading to withdrawal with CAB + RPV were acute viral hepatitis (n=9) and ISRs (n=5). All individual AEs leading to withdrawal had an incidence of less than 1%.
- The most frequently reported AEs in the Phase III program were injection site reactions (ISRs), mainly ISR pain. ISRs were generally mild or moderate with no Grade 4 or Grade 5 or serious ISRs. Twenty-two (4%) participants had Grade 3 ISRs, suggesting that ISRs generally did not interfere with daily activities. Most ISRs resolved within seven days. The percentage of participants reporting ISRs at each visit decreased over time. Few ISRs led to withdrawal.
- Other common AEs that were reported more frequently during treatment with CAB + RPV in FLAIR and ATLAS were hemorrhoids, pyrexia, headache, dizziness, fatigue, and back pain. Except for headache, the incidence of these AEs in the CAB + RPV group was less than 10%. Drug-related AEs, as identified by the site investigator, were reported with a higher incidence with CAB + RPV compared with CAR in FLAIR and ATLAS. The most common drug-related non-ISR AEs were headache, pyrexia, nausea, fatigue, asthenia, increased body temperature, myalgia, and dizziness. Most drug-related AEs were Grade 1, although a few Grade 3 and 4 AEs occurred. The most frequent drug-related Grade 3 and 4 AEs were pyrexia (4%), fatigue (3%), and asthenia (2%). Different frequencies of non-ISR, drug-related AEs between treatment groups may be expected for an open-label switch study where the comparator CAR group's participants had been on a stable and tolerable ART regimen.
- The incidence of neuropsychiatric events was low overall for suicidal ideation/behaviour, depression, and anxiety. Events occurred with similar frequency between treatment groups.
- The incidence of sleep disorder events (including drug-related events), particularly insomnia, was higher in the CAB + RPV group than that of the CAR group during the Phase III studies.
- No dose adjustment in CAB (oral or IM) or RPV (oral or IM) is required for patients with mild or moderate hepatic or renal impairment.

- Studies of co-administered oral RPV-25 mg and oral CAB-30 mg revealed no relevant drug interactions.
- The majority (74.7% CAB + RPV, 80.2% CAR) of the maximum post-baseline emergent clinical chemistry abnormalities were Grade 1 or Grade 2 in intensity in pooled FLAIR and ATLAS. With the exception of creatine kinase and lipase, there were similar frequencies of Grade 3/4 clinical chemistry abnormalities between the treatment groups. No clinically relevant differences were observed overall in Grade 3 and Grade 4 post-baseline emergent abnormalities between the CAB + RPV and CAR groups.
- Results from FLAIR and ATLAS do not suggest any effect of age, sex, or race on the safety profile of CAB + RPV.
- Data from Study 207966 (ATLAS-2M) at the Week 48 analysis, showed the safety data from this randomized, open-label Phase III study of participants switching to Q8W CAB LA+ RPV is favorable and consistent with prior Phase II and III trials examining the Q4W and Q8W regimens.

Summary of Risks/Side Effects Observed and/or Monitored for Among Participants on Cabotegravir + Rilpivirine

The following risks have primarily been identified either during routine preclinical testing and/or from clinical trial experience in adults to date receiving CAB + RPV and are considered of potential relevance to clinical usage in the context of this protocol. Additional comprehensive information about clinical experience to date and possible risks/adverse reactions associated with treatment using CAB and/or RPV can be found in the 'Summary of Data and Guidance for the Investigator' sections of the respective IBs for CAB and RPV (14).

Drug Induced Liver Injury (DILI) associated with CAB

A small proportion of participants in the CAB program to date have developed transaminitis (elevated liver transaminases characterised by predominant ALT elevation). In most participants, transient transaminitis was explained by acute viral hepatitis infection. In a small number of participants, there was not an alternative explanation, suggesting a mild form of DILI without hepatic dysfunction, which resolved upon withdrawal of treatment with CAB (19).

Injection Site Reactions (ISRs)

Clinical experience to date has demonstrated that for adults, ISRs occur in the majority of exposed participants treated with CAB LA and RPV LA but are generally mild (Grade 1) or moderate (Grade 2) and include events of pain, tenderness, erythema, or nodule formation of several days' duration (median duration for individual events less than one week) (20).

ISRs may occur more than once in an individual participant receiving multiple injections. Although some Grade 3 ISRs were reported, overall ISRs have been well-tolerated in adult participants and have not to date been associated with excessive participant study withdrawals.

Hypersensitivity Reactions (HSR) CAB

HSR have been reported as uncommon occurrences with this class of INSTIs, including the closely related compound dolutegravir, and were characterized by rash, constitutional findings, and sometimes, organ dysfunction, including liver injury (14).
While there have been no severe clinical cases of HSR with or without hepatic symptoms associated with use of CAB LA (14), the long exposures anticipated after CAB LA injection may complicate the management of a drug HSR, were it to occur.

Rash (RPV)
Some observations of rash with oral RPV have been reported in clinical studies executed to date (the majority are Grade 1 or 2) (35).

Risk of HIV-1 resistance following discontinuation of CAB LA or RPV LA
Residual concentrations of CAB LA and RPV LA can remain in the systemic circulation for prolonged periods (more than one year in some cases) in participants who stop CAB LA or RPV LA treatment (e.g., for tolerability issues or treatment failure) (20). Participants discontinuing a CAB LA + RPV LA regimen may therefore be at risk for developing HIV-1 resistance to CAB and/or RPV after discontinuing injectable therapy (20).

Drug-Drug Interactions (DDIs)
For a complete listing of permitted and prohibited concurrent medications for CAB/CAB LA or RPV/RPV LA, refer to the International Maternal Pediatric Adolescent AIDS Clinical Trials Network (IMPAACT) 2040 Prohibited and Precautionary Medications listing in Appendix IV.

Inadvertent Intravenous Injection (Accidental Maladministration)
As with any IM injection, it is possible that CAB LA or RPV LA can be inadvertently administered intravenously instead of intramuscularly possibly resulting in higher-than-expected concentrations of CAB or RPV shortly after injection and lower concentrations thereafter. This could be due to administrator error, improper injection technique and/or improper needle length used based on body type.

Post-injection reactions (RPV LA)
In clinical trials in adults, there have been occurrences of serious and non-serious post-injection reactions which were reported within minutes after the injection of RPV LA. Some of these events may have been associated with accidental partial intravenous (IV) administration of RPV during the IM injection procedure, as suggested by PK assessments showing unexpectedly high plasma RPV concentrations post-dose. Symptoms ranged from mild to severe, with some participants receiving supportive care. These events have included symptoms such as dyspnea, bronchospasm, agitation, abdominal cramping, rash/urticaria, dizziness, flushing, sweating, oral numbness, changes in blood pressure, and pain (e.g., back and chest). Symptoms typically began to resolve within a few minutes after the injection. These participants made a full recovery after the event resolved (35).

These events are infrequent and occurred in less than 0.5% of participants receiving repeat doses of RPV LA in clinical trials in adults. Of the symptomatic patients who had confirmed RPV PK elevations consistent with accidental partial IV administration, no patients had loss of virological control within weeks after the event (35).

Neuropsychiatric Reactions
Suicidal ideation and suicide attempt, particularly in patients with a pre-existing history of depression or psychiatric illness, has been observed uncommonly in post marketing experience. Depression, anxiety, abnormal dreams and insomnia are considered common adverse drug reactions based on data from Phase 3 clinical trial data from HIV treatment studies (please refer to the current IB for the most up to date information). See Section 8.11 for participant management of psychiatric disorders and suicidal ideation and attempt (20).

Risk of Virologic Failure

This study employs a relatively novel two drug LA ART maintenance regimen for the treatment of HIV-1 infection. CAB LA + RPV LA have demonstrated antiviral activity in large clinical studies in adults and the two-drug combination has demonstrated sustained antiviral activity in the LATTE, LATTE-2, FLAIR, ATLAS and ATLAS-2M studies (20).

Standard doses of CAB LA and RPV LA have been selected for this study to achieve exposures that are expected to maintain virologic suppression on the basis of available data with the oral and LA formulations in adults. Due to administration error, it is possible that a participant could receive an inadequate dose of CAB LA or RPV LA. Sub-therapeutic concentrations of either CAB LA or RPV LA could lead to virologic failure and possibly infant-participant HIV-1 infection or the development of ARV resistance (20).

1.3 Rationale

Long-acting ART, such as CAB LA + RPV LA, has the potential to improve treatment outcomes for individuals living with HIV-1, including during pregnancy. CAB LA + RPV LA offers a monthly or every two month alternative to daily oral ART and obviates the clinically significant barriers of pill burden, daily adherence, and disclosure of HIV-1 status. To date, there has been no prospective evaluation of CAB LA + RPV LA in pregnancy; there is a timely and urgent need to understand how pregnancy potentially alters the PK of CAB LA + RPV LA, as well as to evaluate for any maternal/parental and fetal/neonatal safety signals in this period.

Note: Throughout this document, the term "adult-participant" will be used to refer to the pregnant participant and "infant-participant" will be used in reference to their infants.

1.3.1 Rationale for Duration of Study Participation

Adult-participants will be followed until two CAB LA + RPV LA postpartum injections have been administered and for an additional two weeks following the last doses of CAB LA + RPV LA (resulting in adult-participants on a Q4W injection schedule having approximately 7-10 weeks of postpartum follow-up and those on a Q8W injection schedule having approximately 11-18 weeks of postpartum follow-up). This will allow for a minimum of two postpartum trough PK samples for all adult-participants, a "random" PK sample from the adult-participant's final scheduled visit, and intra-participant comparison of CAB and RPV exposure, as the physiologic changes of pregnancy that alter PK parameters are presumed to have resolved by three to four weeks postpartum. It will also allow for adequate time to evaluate any adverse reactions from the final study-provided doses of CAB LA + RPV LA. Physiologically, the risk of adverse reactions after six weeks postpartum is presumed to be (1) very low and (2) the same as non-pregnant adults and thus the additional two weeks post-injection visit to observe adult-participants on study is only incorporated out of an abundance of caution. Monitoring postpartum adult participants for potential adverse events or safety findings for two weeks after the last study treatment is felt to be adequate.

Infant-participants will be followed for the same duration after birth as adult-participants. All infant participants will be followed for toxicity and to collect HIV-1 status data from birth until two weeks after the last postpartum injection. For non-chest/breastfed infants, there would be no subsequent exposure to CAB LA + RPV LA and drug levels are expected to be below the level of quantification within days after birth. For chest/breastfed infants, low-level drug exposure through chest/breastmilk will likely be relatively consistent until at least 6-12 months of life. Thus, monitoring of the infant through the first 7-18 weeks of life is adequate to evaluate neonatal

safety and PK from chest/breastfeeding exposure and prolonged monitoring is unlikely to yield new or different data.

1.3.2 Rationale for the Gestational Age at Time of Study Entry for the Switch Group

Switch Group adult-participants will enroll into the study with a gestational age between 10 weeks 0 days and 19 weeks and 4 days at time of first injection. By selecting this lower limit (10 weeks and 0 days), risk of early pregnancy losses associated with the first trimester will be minimized while also allowing for early recruitment and maximizing enrollment and first injection prior to the more significant physiologic changes of pregnancy anticipated in the later part of the second trimester and in the third trimester.

There are currently no safety signals from HPTN 084 from CAB LA in early pregnancy (12) and APR data from structurally similar INSTIs DTG and RAL are reassuring (29). There are no published data from the HPTN 084 open label extension. Oral RPV has extensive reported safety data in early pregnancy without safety signal (29). A lower end of 10 weeks EGA was selected, as the most critical portion of organogenesis is completed by 10 weeks (36) and to balance the risk of spontaneous pregnancy loss which is increased at earlier gestational ages. By shifting to enrollment to an earlier EGA, higher CAB and RPV trough plasma levels may be obtained in the second and third trimester where the most impact of lowered exposure during pregnancy is expected.

Numerous mitigating actions have been added to the protocol to allow observation of potential safety signals, including frequent viral load assessments around the time of CAB LA + RPV LA initiation (at two, four, six, and eight weeks, followed by Q4W viral loads for the duration of the study), triggered Study Monitoring Committee (SMC) reviews for safety monitoring (see Section 9.4.2), and a planned interim analysis with data from at least 10 evaluable Q4W Switch Group adult-participants and their infants prior to opening enrollment to the Q8W Switch Group (see Section 9.4.2.2).

The upper limit (19 weeks 4 days) allows for a minimum of two CAB LA + RPV LA injections and one PK study visit with a trough concentration in the second trimester for all adult-participants, including those on a Q8W dosing schedule.

1.3.3 Rationale for the Interim Analysis and Related Components of the Study Design

- Q4W and Q8W Switch Groups: Given the potential for lower CAB and RPV trough concentrations during pregnancy, enrollment into the Q4W and Q8W Switch Groups will be staggered to ensure an interim analysis of safety, PK, and virologic data from the first 10 evaluable Q4W Switch Group participants can be conducted before making a decision about opening the Q8W Switch Group to accrual. The Q4W Switch Group will be opened concurrently with the two Continuation Groups. Lower trough concentrations are of particular concern after the first CAB LA + RPV LA dose before accumulation has occurred and during the second and third trimesters due to metabolic enzyme induction effects. The second CAB LA + RPV LA dose will be administered 21-28 days following the first dose. Results of the interim analysis will also determine the appropriateness of a dosing window of +/- 7 days, as licensed, for Switch Groups at the Week 4 dose visit. An interim analysis of safety, PK, and virologic data will be conducted with all available data once there are at least 10 evaluable Q4W Switch Group adult-participants. The SMC will provide guidance regarding the opening Q8W Switch Group accrual.

The interim analysis will allow for evaluation of PK during pregnancy, including in the second and third trimesters, any increases in viral load, and safety signals of the Q4W dosing schedule. Additionally, PK data from any adult-participant in the Q4W Switch Group and both Continuation Groups will be used to perform population PK modeling and simulate (1) utilization of the standard dosing window after the first injection to 4 weeks +/- 7 days for individuals in these three groups (to reflect the dosing interval in the US Food and Drug Administration [FDA] approval), and (2) Q8W dosing and estimated PK parameters. Data from the interim analysis will be evaluated by the CMC and the SMC to determine whether or not to open recruitment into the Q8W Switch Group. They will also determine if the PK data support an expansion of the administration window around the target date for the Week 4 injections for the Q4W and Q8W Switch Groups (from -7 days to -7 days/+7 days).

Q4W and Q8W Continuation Groups: Modeling does not suggest potential inadequate exposure of CAB or RPV in individuals continuing on CAB LA + RPV LA who have received at least two doses prior to pregnancy, independent of whether CAB LA + RPV LA is administered Q4W or Q8W. Thus, the two Continuation Groups (Q4W and Q8W) will open in parallel within the initial stage of the study, rather than sequentially. As Q8W dosing is FDA approved, adult-participants on Q8W dosing prior to pregnancy will be able to enroll and to continue their currently prescribed CAB LA + RPV LA dosing schedule. Additional details of some of the PK modeling that was done to support the study design is available in Section 10710.3 and Appendix VII.

Individual-level safety decisions are not expected based on PK analyses alone; virologic response will be closely monitored on an individual basis throughout study participation. Furthermore, given the long-acting nature of the study product formulation and as a PK relationship between virologic failure and observed concentrations has not been established in adults using CAB LA + RPV LA, individual dose adjustments are not supported (37, 38).

1.3.4 Rationale for Not Including an Optional Oral Lead-in (OLI) Period for Switch Group Adult-Participants

Week 124 data from the FLAIR study assessed participants who were randomized to a DTG based regimen (control arm) at Day 1 and then proceeded to CAB LA + RPV LA with or without an OLI at W100 (extension phase) and demonstrated similar efficacy and safety profile within both groups with or without an OLI (20, 39). In IMPAACT 2040, all Switch Group adult-participants will initiate use of injectable study products upon entering the study. The decision not to include an optional OLI period was based upon the following:

- The safety and efficacy profile of the CAB + RPV regimen is similar with and without an OLI period (2).
- Earlier injections will allow for the accumulation of CAB/RPV concentrations as early as possible to minimize the impact of the metabolic enzyme induction effects that are expected to occur later in the second trimester and in the third trimester. OLI has minimal impact on accumulation. After the first two injections, the metabolic induction effects are predicted to be mitigated due to accumulation of the drug within the body.
- Eliminating the OLI period will help avoid challenges related to ingestion of an oral medication for adult-participants who are experiencing nausea or vomiting of pregnancy. Concerns about DDIs will also be lessened (e.g., with proton pump inhibitors potentially used as part of treatment).
- Alignment with FDA labeling where an optional OLI is allowed (20).

1.4 Hypotheses

The use of CAB LA + RPV LA in pregnant people with HIV-1, switching to or continuing CAB LA + RPV LA:

- will achieve adequate PK concentrations in the second and third trimester when compared to postpartum PK and established historical PK exposures in non-pregnant people with HIV-1
- will have an acceptable safety profile

2 OBJECTIVES, VARIABLES, OUTCOME MEASURES AND ESTIMANDS

2.1 Primary Objectives and Outcome Measures

	Primary Objectives	Primary Outcome Measures
2.1.1	To describe the pharmacokinetics (PK) of CAB LA and RPV LA during pregnancy and postpartum in people with HIV-1 viral suppression switching to or continuing CAB LA + RPV LA	• PK trough of CAB LA measured in plasma in pregnancy and postpartum • PK trough of RPV LA measured in plasma in pregnancy and postpartum
2.1.2	To describe safety of CAB LA + RPV LA during pregnancy and postpartum in people with HIV-1 viral suppression switching to or continuing CAB LA + RPV LA	• For adult-participants: at least one Grade 3 or higher adverse event or serious adverse event in pregnancy and through 18 weeks postpartum

Note: Throughout the protocol, outcome measures that reference postpartum and post-birth timeframes capture the maximum anticipated follow-up duration possible in the study. However, as described further in Section 3.1, the duration of follow-up for adult-participants and infant-participants will vary based upon the adult-participant's EGA at Entry and their injection schedule.

2.2 Secondary Objectives and Outcome Measures

	Secondary Objectives	Secondary Outcome Measures
2.2.1	To compare CAB and RPV PK parameters following treatment with CAB LA + RPV LA during pregnancy to both intraparticipant postpartum PK data and historical PK data from non-pregnant people	• PK trough of CAB LA measured in plasma in pregnancy and postpartum • PK trough of RPV LA measured in plasma in pregnancy and postpartum
2.2.2	To assess the maintenance of virologic suppression in people with HIV-1 on CAB LA + RPV LA during pregnancy and postpartum and describe HIV-1 drug resistance in those who experience	• HIV-1 RNA less than 50 copies/mL at delivery • HIV-1 RNA less than 50 copies/mL at delivery using the standardized FDA snapshot algorithm

	virologic failure during study treatment	• Virologic escape (single measurement of greater than or equal to 200 copies/mL) from study entry through pregnancy and through 18 weeks postpartum • Confirmed virologic failure, as defined in Section 8.13, through 18 weeks postpartum • HIV-1 resistance to CAB and/or RPV using IAS-USA in a participant who experiences confirmed virologic failure, assessed at entry and time of failure
2.2.3	To characterize the frequency of HIV-1 transmission in infants of people with HIV-1 on CAB LA + RPV LA in pregnancy/postpartum	• Perinatal transmission, assessed at birth and through 18 weeks post-birth
2.2.4	To evaluate pregnancy outcomes in adult-participants with HIV-1 on CAB LA + RPV LA during pregnancy and early post-natal safety outcomes of their infants	• For infant-participants: at least one Grade 3 or higher adverse event or serious adverse event through 18 weeks post-birth • For infant-participants: congenital anomaly consistent with the Metropolitan Atlanta Congenital Defects Program (MACDP) definition of defect (38). • Infant death through 18 weeks post-birth • Spontaneous abortion (less than 20 weeks gestation) • Fetal demise/stillbirth (greater than or equal to 20 weeks gestation) • Neonatal death (within 28 days of life) • Small for gestational age (SGA) at < 10th percentile • Low birth weight < 2500 g • Preterm delivery < 37 weeks gestation • Occurrence of any adverse pregnancy outcome of spontaneous abortion, fetal demise/stillbirth, neonatal death, SGA < 10th percentile, or preterm delivery < 37 weeks
2.2.5	To characterize CAB and RPV plasma concentrations in infants exposed to CAB LA + RPV LA during pregnancy and via chest/breastfeeding	• CAB LA and RPV LA infant-participant post-birth plasma concentrations
2.2.6	To describe the tolerability and acceptability of Q4W and Q8W CAB LA + RPV LA in people with HIV-1 during pregnancy/postpartum	• Tolerability: Discontinuation of injections prior to receiving the full course of injections due to intolerability of injection, frequency of injections received, and responses to questionnaires about tolerability of CAB LA + RPV LA, including side effects, pain associated with injections, and injection site reactions. • Acceptability: Reported attitudes about CAB

	LA or RPV LA, including willingness to continue CAB LA + RPV LA postpartum and/or in future pregnancies

2.3 Other Objectives and Outcome Measures

Other Objectives		Other Outcome Measures
2.3.1	To characterize the cord blood and chest/breastmilk concentrations of CAB and RPV after CAB LA + RPV LA use during pregnancy/postpartum	• CAB LA and RPV LA cord blood concentrations at delivery • CAB LA and RPV LA chest/breastmilk concentrations collected at follow-up postpartum assessment
2.3.2	To apply CAB and RPV population PK models to determine individual and population estimates of CAB and RPV exposure parameters during pregnancy and postpartum	• PK parameter estimates (where available) in second trimester, third trimester, and postpartum
2.3.3	To characterize concentrations of unbound drug for CAB and RPV during pregnancy/postpartum and association with viral response	• Fraction of unbound CAB in plasma in pregnancy and postpartum • Fraction of unbound PK concentrations of RPV in plasma in pregnancy and postpartum

2.4 Estimands

The clinical question of interest for the primary PK objective is: What is the mean trough of CAB LA + RPV LA in pregnancy and postpartum among people with controlled HIV who switch to or continue CAB LA + RPV LA during pregnancy? Table 1 shows attributes describing the estimands for the primary PK objective.

Table 1. Primary PK Estimand

Estimand Attribute	Switch Group	Continuation Group
Treatment	CAB LA + RPV LA with either Q4W or Q8W dosing	
Target population	Pregnant people with controlled HIV-1 who switch from oral standard of care and initiate CAB LA + RPV LA between 10 and 19 4/7 weeks of pregnancy, and continue to receive CAB LA + RPV LA	Pregnant people with controlled HIV-1 who continue CAB LA + RPV LA during pregnancy, and continue to receive CAB LA + RPV LA
Endpoint(s)/Variable(s)	Trough of CAB LA and RPV LA in plasma while pregnant every 4 or 8 weeks after initiating CAB LA + RPV LA and postpartum	Trough of CAB LA and RPV LA in plasma every 4 or 8 weeks while pregnant and postpartum

Handling of intercurrent events	1. Early pregnancy outcome 2. Discontinue treatment for toxicity or non-toxicity reasons 3. Death 4. Oral bridging 5. Use of prohibited medications or other medications that would alter the PK of CAB LA + RPV LA 6. Missed or delayed injections 7. Injection administration error Intercurrent events listed above will be handled using a "while" strategy: 1) while pregnant (or after pregnancy, as applicable), 2) while on treatment, 3) while alive, 4) while no oral bridging, 5) while not using prohibited medications or other medications that would alter the PK of CAB LA + RPV LA, 6) while receiving injections as indicated in the protocol, and 7) while on treatment. For intercurrent events handled using the "while on treatment" or "while alive" strategies (#2, #3, and #7), only observations before the intercurrent event will be used to determine the variable. All other strategies will use observations before and after the intercurrent event is ongoing.
Population-level summary	Geometric mean of CAB LA and RPV LA trough during pregnancy and postpartum

The clinical question of interest for the primary safety objective is: What is the probability of having at least one severe, potentially life-threatening, or fatal adverse event through 18 weeks postpartum and separately the probability of having at least one serious adverse event through 18 weeks postpartum among pregnant persons with controlled HIV-1 who switch to or continue CAB LA + RPV during pregnancy? Attributes describing the estimands for the primary safety objective are displayed in Table 2.

Table 2. Primary Safety Estimand

Estimand Attribute	Switch Group	Continuation Group
Treatment	CAB LA + RPV LA with either Q4W or Q8W dosing	
Target population	Pregnant people with controlled HIV-1 who switch from oral standard of care ART and initiate CAB LA + RPV LA between 10 and 19 4/7 weeks of pregnancy	Pregnant people with controlled HIV-1 who tolerate CAB LA + RPV LA, and continue CAB LA + RPV LA during pregnancy
Endpoint(s)/Variable(s)	• Occurrence of severe, potentially life-threatening, or fatal adverse event through 18 weeks postpartum • Occurrence of serious adverse event through 18 weeks postpartum	
Handling of intercurrent events	1. CAB LA + RPV LA discontinuation not due to Grade 3 or higher adverse event or serious adverse event	

	All observations from first study-provided injection through 18 weeks postpartum will be used to determine the variable (treatment policy strategy) 2. Oral bridging *All observations from first study-provided injection through 18 weeks postpartum will be used to determine the variable (treatment policy strategy)*
Population-level summary	• Probability of having at least one severe, potentially life-threatening, or fatal adverse event through 18 weeks postpartum • Probability of having at least one serious adverse event through 18 weeks postpartum

3 STUDY DESIGN

3.1 Overview

This is a Phase I/II, multicenter, open-label, non-randomized study with four groups to characterize the pharmacokinetics and safety of CAB LA + RPV LA during pregnancy and postpartum among people with HIV-1 viral suppression and their infants.

The study will be conducted in the US and South Africa among approximately 45 pregnant people ("adult-participants") who will enroll into the study in their first or second trimester along with their infants ("infant-participants"). Infant-participant enrollment will occur at the same time as adult-participant enrollment, though data collection for infant-participants will begin at birth, as noted in Section 11.1. Refer to Section 4 for the study eligibility criteria and a description of the study recruitment, screening, and enrollment process. Adult-participants will receive CAB LA + RPV LA as part of their study participation; refer to Section 5 for more detailed information on study drug considerations. Adult-participants will be followed throughout pregnancy, during the early postpartum period, and for two weeks after the last CAB LA + RPV LA injections have been administered. Infant participants will be followed after birth.

Adult-participants will be assigned to one of four groups. Adult-participants who were receiving oral ART prior to entry and will switch to CAB LA + RPV LA upon entering the study will join the Q4W Switch Group or Q8W Switch Group (see Section 3.2 for more information on both Switch Groups). Adult-participants who were already receiving CAB LA + RPV LA prior to entry will be assigned to either the Q4W Continuation Group or Q8W Continuation group based on their current dosing frequency (see Section 3.3 for more information on both Continuation Groups).

Initially, the study will start with concurrent accrual into the Q4W Switch Group, Q4W Continuation Group, and Q8W Continuation Group. Once there are at least 10 evaluable Q4W Switch Group participants, an interim analysis will be conducted with all available data (from both adult-participants and infant-participants) to determine if the Q8W Switch Group will open to accrual. Accrual into the first three groups will continue during the interim analysis.

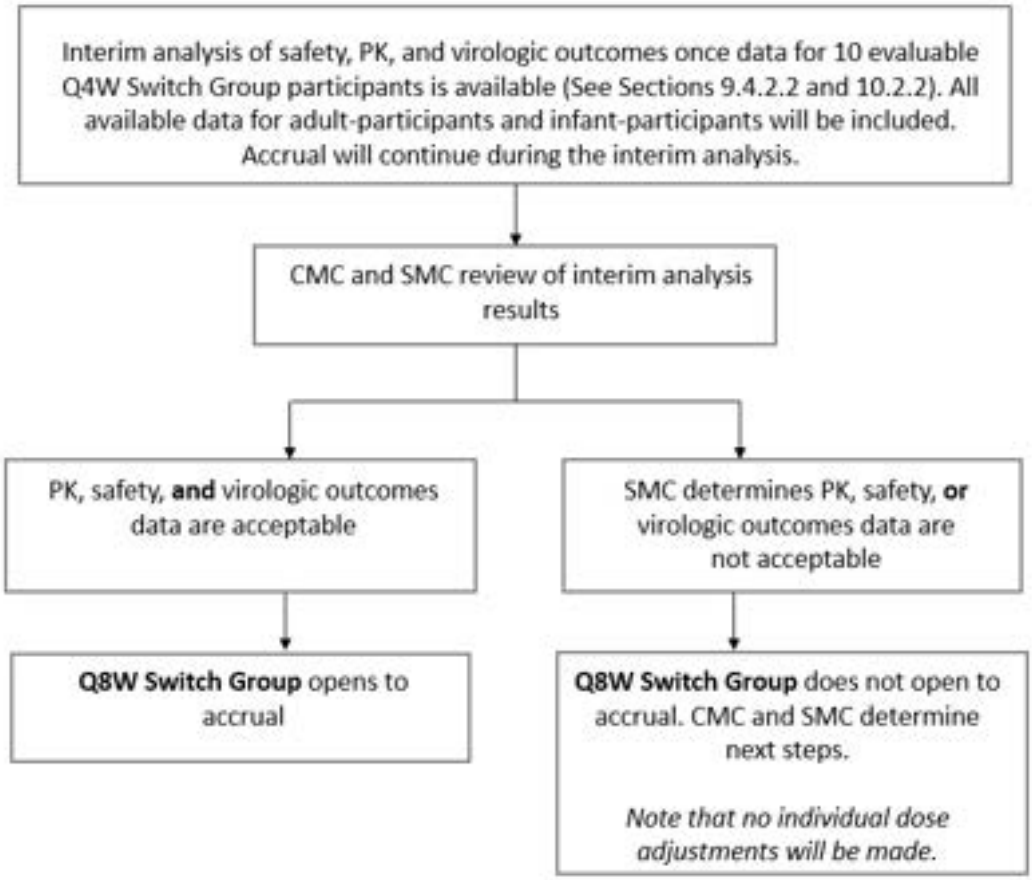
Q4W Switch Group adult-participants will be considered evaluable for the interim analysis if they:

- Complete follow-up visits through the Final Scheduled Visit and

- Receive the expected number of CAB + RPV injections, with no oral bridging (see Section 5.2) and
- Have no more than one missing PK sample for each agent through the Final Scheduled Visit

Recruitment into the Q8W Switch Group will open if the CMC and the SMC determine that PK, safety, and virologic outcomes from the interim analysis are acceptable, as outlined in Section 9.4.2 and Section 10.2.2 and in Figure 2 below.

Figure 2. Interim Analysis



Monthly study visits during pregnancy will be conducted for PK sampling and for dosing of the Q4W or Q8W CAB LA + RPV LA, as applicable. All adult-participants will have an additional visit at two weeks and six weeks after enrollment for viral load monitoring and PK sampling. One or two (depending on dosing regimen) additional PK study visits will be conducted approximately one week after the injection(s) received between 30 0/7 - 37 6/7 weeks EGA. At time of delivery, adult-participant plasma, chest/breastmilk (from those intending to chest/breastfeed), and cord blood will be collected, as well as infant-participant blood draws for CAB and RPV concentrations. Chest/breastmilk sample collection will continue during follow-up for adult-participants who are chest/breastfeeding. Infant-participant PK samples will be drawn depending on chest/breastfeeding status and visit timing to characterize infant-participant concentrations and infant-participant wash-out (See Section 6.4). An additional infant-participant visit will take place within 1-5 days of life.

Two postpartum study visits will be conducted to collect PK samples and to administer the first two CAB LA + RPV LA doses due postpartum. The timing of these visits will be determined by each participant's injection schedule. These postpartum injection visits will be followed by a final postpartum visit two weeks after the last set of injections. Based on this, adult-participants on a Q4W injection schedule will have approximately 7-10 weeks of postpartum follow-up while those on a Q8W injection schedule will have approximately 11-18 weeks of postpartum follow-up. Infant-participants will have corresponding visits at these timepoints as well and will complete scheduled follow-up at the same time as the adult-participant. Safety will be monitored in adult-participants and infant-participants for the duration of the study. Acceptability and tolerability of the LA injections will be assessed at baseline, Week 16, and at the final postpartum study visit. Contraceptive counseling for adult-participants will begin at the first antepartum interval visit and continue throughout the remaining antepartum and postpartum study visits.

Adult-participants will be transitioned into care and treatment outside of the study and provided post-trial access to study drugs at the end of their study participation as outlined in Section 6.8 and Section 13.11.

3.2 Switch Groups

The two Switch Groups (Q4W and Q8W) together comprise the primary analysis group for the study. Approximately 35 adult-participants will be enrolled into the two Switch Groups; final accrual targets for the Q4W Switch Group and Q8W Switch Group will be determined following the interim analysis. If enrollment into the Q4W Switch Group reaches 25 participants before the interim analysis is complete, accrual into the Q4W Switch Group will be paused pending the results of the interim analysis. If accrual into the Q8W Switch Group opens, the overall accrual targets for the Switch Groups will be split, with approximately 25 adult-participants in the Q4W Switch Group and approximately 10 adult-participants in the Q8W Switch Group. If the Q8W Switch Group is not opened to accrual, all 35 adult-participants may enroll in the Q4W Switch Group. In the event that the Q4W Switch Group and Q8W Switch Group have overlapping accrual, newly enrolling adult-participants may join either group until these targets are met.

Both Switch Groups will enroll pregnant people on oral ART, with HIV-1 virologic suppression, and willing to switch to Q4W or Q8W CAB LA + RPV LA. Switch Group adult-participants will enroll between 10 0/7 to 19 4/7 weeks (inclusive) EGA and receive their first injection/loading dose at the time of entry into the study. Loading and maintenance doses for the Switch Groups are described in Section 5.1.

3.3 Continuation Groups

Approximately 10 adult-participants will be enrolled into the two Continuation Groups, without set targets for the Q4W Continuation Group or Q8W Continuation Group.

The Continuation Groups will enroll pregnant people with virally suppressed HIV-1, exposed to CAB LA + RPV LA at the time of conception, and willing to continue receiving CAB LA + RPV LA (Q4W or Q8W dosing) during pregnancy/postpartum. Adult-participants who enroll in the Continuation Groups will maintain the same dosing regimen they were on prior to entry for the duration of the study. Adult-participants in the Continuation Groups may enroll at any gestational age less than or equal to 19 weeks 4/7 days. There is no lower limit on the gestational age enrolling in the Continuation Groups, however ultrasound evidence of a viable, intrauterine, singleton pregnancy must be available prior to entry as outlined in Inclusion Criterion 4.1.3. Continuous use of CAB LA + RPV LA at and since the time of conception is defined further

under Inclusion Criterion 4.1.13Adult-participants in the Continuation Groups will receive their first on-study injection at the time of enrollment, so their Entry Visit must be scheduled to occur within the administration window for their next dose of CAB LA + RPV LA, as outlined in Appendix II. Maintenance doses for the Continuation Groups are described in Section 5.1.

4 STUDY POPULATION

This study will be conducted among approximately 45 adult-participants and their infants. ("infant-participants"). Adult-participants will be selected according to the criteria in Sections 4.1 and 4.2. Infant-participants are enrolled at the same time as adult-participants and without set inclusion or exclusion criteria. The study-specific approach to recruitment, screening, and enrollment is described in Section 4.4. Considerations related to participant retention and withdrawal from the study are provided in Sections 4.5 and 4.6, respectively.

4.1 Inclusion Criteria

Potential adult-participants must meet all of the criteria specified below to be included in this study; in these criteria, "at entry" is used to refer to the day of enrollment in the study.

4.1.1 Willing and able to provide written informed consent for study participation for self and infant.

Note: All sites must follow all applicable IRB/EC policies and procedures; for US sites, this includes single IRB (sIRB) policies and procedures.

4.1.2 At screening, age 18 years or older.

4.1.3 At entry, evidence of a viable, intrauterine, singleton pregnancy with fetal ultrasound performed per Section 6.13 and within the following estimated gestational age (EGA) ranges per Section 6.13.1:

- **Switch Group:** EGA between 10 0/7 and 19 4/7 weeks (inclusive) at entry.
- **Continuation Group:** EGA less than or equal to 19 4/7 weeks at entry.

Note: If adequate ultrasound results are not available from medical records at screening per Section 6.13, an ultrasound must be performed prior to study entry.

4.1.4 At entry, intending to deliver at a study-associated medical facility, remain in the geographic area of the study for the duration of anticipated follow-up, and attend regularly scheduled study visits.

4.1.5 Confirmed HIV-1 infection based on documented testing of two samples collected from two separate blood collection tubes per Sample #1 and Sample #2 requirements. Test results may be obtained from medical records or from testing performed at screening (i.e., from specimens collected within 28 days prior to entry):

- For results obtained from medical records, adequate source documentation, including the date of specimen collection, date of testing or date of test result, name of test/assay performed, and test result, must be available in study records prior to study entry. Requirements related to laboratory operations (e.g., Good Clinical Laboratory Practice [GCLP], Clinical Laboratory Improvement Amendments [CLIA], Virology

Quality Assurance [VQA]) and related to regulatory authority approvals (e.g., FDA) do not apply to results obtained from medical records.

- If adequate source documentation is not available, Sample #1 and/or Sample #2 should be collected during the study screening period and tested in the site's designated testing laboratory. If both samples are tested using antibody tests, at least one of the samples must be tested in a laboratory that operates according to CLIA or equivalent (for US sites) or GCLP (for South African sites) guidelines and participates in an appropriate external quality assurance program. If nucleic acid testing (NAT) is used, at least one test must be performed in the site's CLIA-certified or equivalent (for US sites) or VQA-certified (for South African sites) laboratory.

Sample #1 may be tested using any of the following:

- Two rapid antibody-based tests from different manufacturers or based on different principles and epitopes (combination antigen-antibody-based rapid tests may be used)
- One enzyme immunoassay (EIA) or Western blot (WB) or immunofluorescence assay or chemiluminescence assay
- One HIV-1 DNA polymerase chain reaction (PCR)
- One quantitative HIV-1 RNA PCR (above the limit of detection of the assay)
- One qualitative HIV-1 RNA PCR
- One HIV-1 total NAT

Sample #2 may be tested using any of the following:

- Rapid antibody-based test. If this option is used in combination with two rapid tests for Sample #1, at least one of the three rapid tests must be FDA-approved and the third rapid test must be from a third manufacturer or based on a third principle or epitope. Combination antigen-antibody based rapid tests may be used.
- One EIA or WB or immunofluorescence assay or chemiluminescence assay
- One HIV-1 DNA PCR
- One quantitative HIV-1 RNA PCR (above the limit of detection of the assay)
- One qualitative HIV-1 RNA PCR
- One HIV-1 total NAT

All study-specific samples tested to determine HIV-1 status must be whole blood, serum, or plasma. HIV-1 testing methods and algorithms must be approved for each site by the IMPAACT Laboratory Center (for NIAID-funded sites) or Westat (for NICHD-funded sites). Testing methods should be FDA-approved, if available.

4.1.6 Has at least one documented plasma HIV-1 RNA result less than 50 copies/mL or less than the lower limit of detection from the assay, from a specimen collected in the three to nine months (defined as 90-270 days) prior to entry.

Note: See Exclusion Criterion 4.2.1 for additional criterion that must be evaluated to confirm adequate viral suppression prior to entry.

4.1.7 Documented plasma HIV-1 RNA result less than 50 copies/mL at screening (i.e., from a specimen collected within 28 days prior to entry).

Note: HIV-1 RNA laboratory tests may be repeated if the result is greater than or equal to 50 copies/mL but less than 200 copies/mL during the study screening period, with the latest result used for eligibility determination. The repeat viral load testing should be conducted within two weeks (14 days) of the initial sample collection.

4.1.8 Has no evidence of chronic hepatitis B infection based on hepatitis B surface antigen (HBsAg), hepatitis B core antibody (HbcAb), and hepatitis B surface antibody (HbsAb) testing at screening (i.e., from a specimen collected within 28 days prior to entry); any of the following three combinations of test results are acceptable for inclusion:

- HbsAg negative, HbcAb negative, HbsAb negative
- HbsAg negative, HbcAb negative, HbsAb positive
- HbsAg negative, HbcAb positive, HbsAb positive

4.1.9 Negative hepatitis C antibody (anti-HCV ab) test result at screening (i.e., from a specimen collected within 28 days prior to entry).

4.1.10 Has the following laboratory test results at screening (i.e., from a specimen collected within 28 days prior to entry) based on grading per Section 7.3.3:

4.1.10.1 Grade 2 or lower platelets (greater than or equal to 50,000 cells/mm^3 or greater than or equal to 50.00 x 10^9 cells/L)

4.1.10.2 Grade 2 or lower creatinine (less than or equal to 1.8 x upper limit of normal [ULN])

4.1.10.3 Grade 2 or lower total bilirubin (less than 2.6 x ULN)

4.1.10.4 Grade 1 or lower ALT (less than 2.5 x ULN)

4.1.10.5 Grade 1 or lower aspartate aminotransferase (AST) (less than 2.5 x ULN)

4.1.10.6 Grade 1 or lower absolute neutrophil count (ANC) (greater than or equal to 800 cells/mm^3)

4.1.10.7 Grade 2 or lower hemoglobin (greater than or equal to 8.5 g/dL)

4.1.10.8 Grade 2 or lower lipase (less than 3 x ULN)

Note: Laboratory tests may be repeated during the study screening period (i.e., within 28 days prior to entry), with the latest result used for eligibility determination.

4.1.11 Has a Grade 1 or lower QT interval corrected by the Fridericia formula (QTcF) (mean interval value less than or equal to 470 milliseconds, on ECG performed in triplicate) at screening.

4.1.12 *For Switch Group,* on a stable (i.e., unchanged) oral ART regimen for at least 90 consecutive days prior to entry, as determined by the site investigator based on participant report and available medical records.

Note: Changes of formulation (e.g., from a single agent to fixed dose combination tables) and of boosting agents (e.g., from cobicistat to ritonavir) are permitted.

4.1.13 *For Continuation Group,* received first dose of CAB LA + RPV LA on or before the date of conception of the current pregnancy based on guidelines in Section 6.13.1, has not changed regimens since the time of conception, and is on the appropriate maintenance doses for Q4W or Q8W dosing at screening, as determined by the site investigator based on participant report and available medical records.

4.2 Exclusion Criteria

Potential adult-participants must be excluded from the study if any of the conditions specified below are identified during the screening period. The screening period begins when informed

consent is obtained and ends immediately prior to enrollment. For criteria involving a potential adult-participant's medical history, it is expected that each exclusionary condition will be assessed at screening and subsequently reviewed and confirmed on the day of study entry, prior to enrollment.

4.2.1 Within nine months (270 days) prior to entry, any plasma HIV-1 RNA measurement greater than or equal to 200 copies/mL or two or more detectable plasma HIV-1 RNA measurements greater than or equal to 50 copies/mL at least 14 days apart.

4.2.2 History of treatment/virologic failure associated with documented or presumed viral resistance to NNRTI or INSTI, defined as two consecutive plasma HIV-1 RNA measurements greater than or equal to 200 copies/mL after initial suppression to less than 50 copies/mL.

4.2.3 Has any of the following, as determined by the site investigator based on participant report, clinical evidence, and/or available antenatal/medical care records:

4.2.3.1 Contraindication to CAB or RPV (e.g., historical or suspected resistance to NNRTI and INSTI classes based on available records at screening, HSR, or known or suspected allergy to study product components).

Note: If there are questions regarding suspected resistance, the site investigator should consult with CMC prior to enrolling the participant.

4.2.3.2 Contraindication to IM injection such as a current inflammatory skin condition that compromises the safety of IM injections or a dermatological condition which, may interfere with the interpretation of ISRs (including but not limited to gluteal implants).

Note: Use of the proper needle length based on participant body size and shape is essential to ensure correct IM injection technique. See Section 5.4.1 for more information. High body mass index (BMI) is not considered exclusionary.

4.2.3.3 Known ARV treatment interruption (greater than 30 consecutive days) in the 24 months prior to entry.

4.2.3.4 For participants on EFV, known treatment interruption (greater than seven consecutive days) in the 24 months prior to entry.

4.2.3.5 Any use of Nevirapine (ever), including, but not limited to a short course regimen to prevent perinatal transmission.

4.2.3.6 At entry, current use or anticipated need of therapeutic anticoagulation (e.g., low molecular weight heparin, coumadin, heparin, or enoxaparin).

4.2.3.7 History of known or suspected bleeding disorder.

4.2.3.8 Current severe hepatic impairment (Class C) as determined by Child-Pugh classification.

4.2.3.9 Suicidal ideation or attempt within six months of entry, based on completion of the Columbia-Suicide Severity Rating Scale (C-SSRS).

4.2.3.10 Unstable or poorly controlled seizure disorder.

4.2.3.11 Known tuberculosis infection.

4.2.3.12 Ongoing malignancy other than Kaposi's sarcoma, basal cell carcinoma, or resected, non-invasive cutaneous squamous cell carcinoma, or cervical intraepithelial neoplasia.

4.2.3.13 Symptoms suggestive of active coronavirus disease 2019 (COVID-19) or test results or contacts that require isolation or quarantine per local clinical practice, public health, and/or infection control guidelines.

Note: Potential participants with symptoms suggestive of active COVID-19, test results, and/or contacts that require quarantine may resume screening (or be re-screened) after symptoms have resolved and applicable quarantine requirements have been completed.

4.2.4 Known to have any of the following during the current pregnancy as determined by the site investigator based upon participant report, clinical evidence, and/or available antenatal/medical care records:

4.2.4.1 Multiple gestation

4.2.4.2 Abnormal placentation, including placenta previa (complete) and placenta accreta/increta/percreta

4.2.4.3 Cervical cerclage/cervical incompetence

4.2.4.4 Abnormal fetal anatomy (in the opinion of the site investigator)

4.2.5 Known to have had any of the following in a previous pregnancy as determined by the site investigator based upon participant report, clinical evidence, and/or available antenatal/medical care records:

4.2.5.1 Eclampsia/Hemolysis, Elevated Liver enzymes and Low Platelets (HELLP) syndrome

4.2.5.2 Intrauterine fetal demise (EGA greater than 20 weeks) without known non-recurrent etiology

4.2.5.3 Spontaneous very preterm delivery (less than 32 weeks)

4.2.5.4 Very low birth weight (LBW) (less than 1500 g)

4.2.5.5 Cervical or abdominal cerclage due to cervical incompetence

4.2.6 At entry, has uncontrolled pregnancy-related comorbidities (e.g., diabetes with fasting blood glucose greater than 200, hypertension with recurrent systolic greater than or equal to 160 or diastolic greater than 100) per the discretion of the site investigator.

4.2.7 Receipt of any prohibited medication within seven days prior to entry, with the exception of antiviral agents that are part of the participant's ART regimen, as determined by the site investigator based on participant report and available medical records, see Appendix IV.

Note: Medications and vaccines approved for emergency use (e.g., COVID vaccines) that do not appear in the IMPAACT 2040 Prohibited and Precautionary Medications listing are not exclusionary and may be administered as per standard of care.

4.2.8 Enrolled in another clinical trial of an investigational agent, device, or vaccine.

4.2.9 Receipt of an investigational agent or chemotherapy (active malignancy) within 30 days prior to study entry.

4.2.10 Adult-participant or fetus has any condition that, in the opinion of the site investigator or designee, would make participation in the study unsafe, complicate interpretation of study outcome data, or otherwise interfere with achieving the study objectives.

4.3 Co-Enrollment Considerations

Co-enrollment in observational or other studies not involving an investigational agent, device, or vaccine may be permitted, although careful consideration must be given to visit burden, blood draw volumes, and interpretation of outcome data across studies. Given these considerations, requests for co-enrollment must be approved in advance by the Protocol Teams of both studies. Requests for such approval should be emailed to the IMPAACT 2040 CMC (see Section 7.1.2 for more information regarding the role of the CMC for this study).

4.4 Recruitment, Screening, and Enrollment Process

Participant recruitment methods for this study may vary across sites. In general, recruitment of adult-participants is expected to rely on current patients being seen at a study clinic or from active identification and referral of pregnant people living with HIV-1 from nearby clinics or other medical facilities. Any study advertising materials must undergo approval by the sIRB (for US sites) or site institutional review boards (IRBs)/ethics committees (ECs) (for South African sites). Sites are encouraged to solicit input and feedback on recruitment materials from their local Community Advisory Board.

As part of participant outreach and recruitment strategies, study staff may pre-screen potential study participants either on-site or at off-site locations. Study staff will consult with their local IRBs/ECs regarding pre-screening potential adult-participants. If deemed acceptable, during pre-screening interactions study staff may explain the study to potential participants and ascertain elements of presumptive eligibility, to be confirmed at clinic screening visits. A key element of presumptive eligibility, gestational age, will be confirmed by ultrasound conducted prior to enrollment. Ultrasounds may occur during pre-screening as part of standard of care. Process information (e.g., number of potential participants contacted, number presumptively eligible) may be recorded in the absence of written informed consent from potential participants, provided the information is collected in such a manner that it cannot be linked to potential participant identifiers. Whenever de-identified process information is recorded, it will be stored at the study site. At each site, procedures and documentation will comply with local IRB/EC requirements.

Upon identification of a potentially eligible adult-participant, study staff will provide information about the study to the potential participant. Each potential adult-participant who expresses interest in learning more about the study will be provided additional information, education, and counseling as part of the study informed consent process. The process will include detailed review of the study informed consent forms, time to address any questions or concerns the potential adult-participant may have, and an assessment of understanding, before proceeding to informed consent decisions. Informed consent processes will be fully documented, consistent with the Division of Acquired Immunodeficiency Syndrome (DAIDS) policies referenced in Section 13.3.

Eligibility screening will be initiated after written informed consent is provided. Screening evaluations must be completed prior to enrollment; re-screening is permitted. Screening evaluations may be performed up to and on the day of enrollment; however, all required screening outcomes, including confirmation of HIV-1 infection status, must be available prior to enrollment.

Each site must establish Standard Operating Procedures (SOPs) for eligibility determination that describe where and when screening procedures will be performed; roles and responsibilities for performing the required procedures; roles and responsibilities for assessing and confirming eligibility; and procedures for documenting the process, taking into consideration the required timing of entry. Sites are encouraged to minimize the time from screening to enrollment.

Adult-participants who are found to meet the study eligibility criteria will be enrolled in the study with infant-participants. The IMPAACT Data Management Center (DMC) Stars system will be used to assist with tracking the screening and enrollment process, within and across study groups. When informed consent is obtained, participant identification numbers (PIDs) will be assigned to the adult-participant and infant-participant, and a study-specific screening number will be obtained for the pair through Stars. For adult-participants found to be eligible, enrollment will occur upon successful entry of required eligibility data into Stars. Successful entry into Stars will generate study identification numbers (SIDs) for the adult-participant and infant-participant and study product prescribing information for the adult-participant study product regimen. For people found to be ineligible for the study, or who do not enroll in the study for any reason, limited demographic information and reasons for non-enrollment will be entered into electronic case report forms (eCRFs). Refer to Section 9.4.1 for more information on monitoring participant accrual in this study.

4.5 Participant Retention

Once an adult-participant or infant-participant is enrolled in this study, study staff will make every effort to retain them in follow-up for the protocol-specified duration of follow-up, thereby minimizing potential biases and loss of precision associated with loss-to-follow-up in estimating PK parameters and the risk of experiencing adverse events. Refer to Section 9.4.1 for more information on monitoring participant retention in this study.

4.6 Participant Withdrawal or Termination from the Study

Adult-participants may voluntarily withdraw themselves or their infants from the study at any time. Adult-participants or infant-participants may also be terminated from the study by the site investigator or designee under the following circumstances:

- Adult-participant and/or infant-participant relocates away from the study site (with no options to transfer to another site) or is otherwise determined to be lost-to-follow-up.
- Site investigator/designee determines that continued participation in the study would be unsafe or otherwise not in the best interest of the adult-participant and/or infant-participant.
- The study is stopped or canceled by the sponsors or government or regulatory authorities.
- Site participation in the study is canceled by the sponsors, government or regulatory authorities, the sIRB (for US sites), or site IRBs/ECs (for South African sites).
- Adult-participant and/or infant-participant fails to comply with study requirements so as to cause harm to self or seriously interfere with the validity of the study results.

In each of the circumstances listed above, except the study being stopped or cancelled, the CMC should be consulted before terminating the adult-participant and/or infant-participant from follow-up. Withdrawal and termination decisions can be made on an individual basis (e.g., the adult-participant or infant-participant may withdraw or be terminated early from the study without impacting the participation of the other).

For any participant who withdraws/is withdrawn or is terminated from the study prior to scheduled completion of follow-up, study staff will document the reason for the withdrawal or termination in detail and will make every effort complete final evaluations as described in Section 6.8. If the circumstances that led to a participant's withdrawal or termination change (e.g., they return to the study site area after having re-located previously), the site investigator or designee should contact the protocol team to discuss options for resuming follow-up.

Should the consenting parent of an enrolled infant-participant die or no longer be available for any reason, no further study-specific evaluations should be performed until informed consent for continued study participation is obtained from a legally authorized representative, as defined locally. Refer to Section 13.3 for further guidance on guardian consent for study participation.

5 STUDY PRODUCT

Site pharmacists should consult the *Pharmacy Guidelines and Instructions for DAIDS Clinical Trials Networks* for standard pharmacy operations. For this study, the term study product refers to injectable CAB LA and injectable RPV LA administered to pregnant and postpartum women, as well as oral CAB (tablet formulation) and oral RPV (tablet formulation) that may be used for oral bridging (see Section 5.2). Refer to the Investigator's Brochures (IB) or the package insert for oral CAB, CAB LA, oral RPV and RPV LA for further information about these study product formulations.

Adult-participants will be exposed to study product through IM injections or direct ingestion (if oral bridging administration is needed); infant-participants may be exposed to study product *in utero* and through chest/breastfeeding.

5.1 Study Product Regimen

All adult-participants will receive CAB LA + RPV LA IM injections Q4W or Q8W from study entry until the Final Scheduled Visit.

Adult-participants in the Switch Groups will discontinue their pre-study oral ART regimen at their study Entry Visit prior to initiating treatment with CAB LA + RPV LA (the final dose of pre-study ARTs should be taken the same day as and prior to the first CAB and RPV injections). Adult-participants in the Switch Groups will receive a loading dose of both CAB LA and RPV LA at their Entry Visit (Day 0). Q4W Switch Group adult-participants will receive maintenance doses thereafter while Q8W Switch Group adult-participants will receive a second loading dose at Week 4 followed by maintenance doses thereafter.

Adult-participants in the Continuation Groups will continue CAB LA + RPV LA, with the first on-study injections administered at the Entry Visit (Day 0). See Section 6.2 for guidance on Entry Visit scheduling considerations for the Continuation Groups. Adult-participants in the Continuation Groups will receive maintenance doses of both CAB LA and RPV LA at the Entry Visit and thereafter.

Adult-participants will receive CAB LA + RPV LA as shown in Table 3. Target dates and allowable windows for administration of injections are outlined in Appendix II.

Note: For Switch Group adult-participants, the administration window for injections given at the Week 4 Visit will be limited 21-28 days after the Entry visit loading dose. This dosing window

may be expanded to 21-35 days if supported by the interim analysis.

Table 3. Dosing Regimens

Group	IM Injection Dosing	
	Loading Dose	**Maintenance Dose**
Q4W Switch	CAB LA 600 mg (3 mL) + RPV LA 900 mg (3 mL); at **Entry**	CAB LA 400 mg (2 mL) + RPV 600 LA mg (2 mL); at **Week 4** and **every four weeks**
Q8W Switch	CAB LA 600 mg (3 mL) + RPV LA 900 mg (3 mL); at **Entry** and again at **Week 4**	CAB LA 600 mg (3 mL) + RPV LA 900 mg (3 mL); at **Week 12** and **every eight weeks**
Q4W Continuation	N/A	CAB LA 400 mg (2 mL) + RPV LA 600 mg (2 mL); at **Entry** and **every four weeks**
Q8W Continuation	N/A	CAB LA 600 mg (3 mL) + RPV LA 900 mg (3 mL); at **Entry** and **every eight weeks**

5.2 Oral Bridging for Adult-Participants Receiving Long-Acting Injectables

In exceptional circumstances and following consultation with the CMC, sites may provide daily oral CAB 30 mg + RPV 25 mg as a bridging strategy for adult-participants who will miss a scheduled injection. Prior to dispensing oral study product, the site pharmacists must receive a new prescription(s) from an authorized prescriber that documents the dosing regimen. The pharmacist must place a participant-specific label directly on the prepared study product in accordance with local regulations and by following instructions provided in the *Pharmacy Guidelines and Instructions for DAIDS Clinical Trials Networks.*

Oral study product may be dispensed to study staff for providing to an adult-participant off-site or shipped from the site directly to the adult-participant (if allowable per local laws and regulations). If applicable, the pharmacist should refer to the *Pharmacy Guidelines and Instructions for DAIDS Clinical Trials Networks* for detailed procedures regarding shipping study product.

When supplying oral bridging for adult-participants on long-acting injectables, the site should ensure sufficient coverage for daily use until the adult-participant can resume study product injections. Adult-participants will be instructed to return all oral study product to the site clinic at the visit when study product injections resume.

Adult-participants are to ideally begin the oral bridging regimen on the same target visit date (or within the same target visit window) as that of the missed injection visit. The last dose of the short-term oral bridging regimen should be taken on the same day as and prior to resuming injectable study product. The CMC must be consulted prior to resuming study product injections. Adult-participants may be required to have an interim injection visit upon resuming the study product injections to appropriately reinitiate the dosing regimen or to realign to the original injection visit dosing schedule.

See Section 6 for required procedures prior to dispensing oral study products or administering study project injections. See Section 6.5 for guidance pertaining to interim injection visits.

5.3 Study Product Formulation and Storage

Injectable CAB LA

CAB LA is formulated as a sterile white to slightly pink suspension containing 200 mg/mL of cabotegravir free acid for administration by IM injection. The product is packaged in a glass vial with a stopper and an aluminium seal with a plastic flip-off lid. Each vial is for single use and contains a nominal fill volume of 2 mL (400 mg of CAB LA) or 3 mL (600 mg of CAB LA). Dilution is not required prior to administration. In the study site pharmacy, vials should be stored up to 30° C (86° F) and must not be frozen.

Injectable RPV LA

RPV LA is formulated as a sterile white to off-white suspension containing 300 mg/mL of RPV free base for administration by IM injection. The product is packaged in single-use vials, containing a nominal fill volume of 2 mL (600 mg of RPV LA) or 3 mL (900 mg of RPV LA). Dilution is not required prior to administration. In the study site pharmacy, vials should be stored refrigerated at 2° to 8° C (36° to 46° F); should be protected from light and must not be frozen.

Oral CAB (Tablets) labeled as VOCABRIA®

Cabotegravir 30 mg tablets are formulated as white to almost white oval-shaped film-coated tablets for oral administration. The tablets are debossed with the code "SV CTV" on one face. The tablets are packaged in high density polyethylene bottles with child resistant closures that include induction seal liners. The bottles contain 30 tablets and a desiccant. The tablets should be stored up to 30° C (86° F), in the original container with the desiccant, and protected from moisture. Further information on the study product is available in the VOCABRIA® package insert.

Oral RPV (Tablets) labeled as EDURANT®

RPV 25 mg tablets are formulated as white to off-white, film-coated, round, biconvex tablets for oral administration. Each tablet is debossed with "TMC" on one side and "25" on the other side. The tablets are packaged in bottles containing 30 tablets. Tablets should be stored in their original bottles to protect from light. The tablets should be stored at 25° C (77° F) with excursions permitted to 15°-30° C (59°-86° F). Further information on the study product is available in the EDURANT® package insert.

5.4 Study Product Preparation, Dispensation, and Administration

See Section 6.3 for required study procedures to be performed prior to administering the study product injections.

For each visit where study product is dispensed, the site pharmacists must receive a new prescription(s) from an authorized prescriber that documents the dosing regimen prior to dispensing study products. The prescription, at a minimum, must include the name and strength of each individual study product to be prepared, dispensed, and administered to the adult-participant along with the specific dose, quantity or volume, and directions for administration in addition to any in country and/or institutional requirements.

For injectable study product prescriptions, if the pharmacy needs to attach a needle for administration prior to dispensation (versus a syringe cap) per institutional policy, the prescription should also include the size and gauge of the needle to be attached to each prepared study product.

Protocol Section 6 and Appendix II have additional information for the administration window for study products.

5.4.1 Injectable Study Product

Preparation and Dispensing

The site pharmacist must be proficient in the preparation of products requiring aseptic technique under a pharmacy biological safety cabinet/isolator. Local regulations and site institutional policies and procedures for use of personal protective equipment, such as gloves, gowns, masks, and safety glasses, must be followed. Refer to Appendix VI for detailed instructions on the preparation of injectable study products.

After preparation, injectable study product should be dispensed to authorized study staff for IM administration to the adult-participant.

Administration and Observation

All injections will be administered using standard IM injection technique in the gluteus medius. Administration within the ventrogluteal or dorsogluteal muscle is acceptable, though a ventrogluteal administration is recommended. Injectable study product must be administered within the respective study visit windows or per CMC guidance (for participants requiring an interim injection visit); see Appendix II. visit window requirements.

The following information must be source documented and entered into eCRFs for each injection:

- Adult-participant height and weight at time of injection
- Date and time of administration
- Location of administration
- Volume of each injectable study product administered
- Needle length and needle gauge used
    - *Note:* BMI is not a risk factor for virologic failure and, as such, is not a criterion for study participation (see Sections 4.1-4.2 (38). Body size and shape should be considered in selecting the proper needle length to ensure intramuscular administration of CAB LA + RPV LA to avoid inadvertent injection into adipose tissue.
- Participant-reported injection pain assessed using a visual analog and/or pictorial scale, as specified in the IMPAACT 2040 MOP

It is recommended that CAB LA and RPV LA be administered bilaterally in the contralateral gluteus medius muscles. Unilateral injections at least two cm apart may be considered if clinically indicated (e.g., need to administer Bicillin® LA simultaneously) or if an adult-participant refuses bilateral injections.

Persons administering injections should carefully follow the instructions for use to avoid accidental IV administration. It is important that the prepared study product in a syringe is at room temperature prior to administration and is injected slowly.

To monitor for any post-injection reaction, adult-participants should be observed for at least 15 minutes after the injections are administered, with confirmation of the observation recorded in source documents. See Section 8.4 for guidance on suspected IM maladministration.

5.4.2 Oral Study Product

Dispensing

CAB + RPV oral study products may be dispensed as needed for the purposes of oral bridging. Otherwise, no routine provision of oral CAB + RPV is planned for this study. Prior to dispensing oral study product, the site pharmacists must receive a new prescription(s) from an authorized prescriber that documents the dosing regimen. The pharmacist must place a participant-specific label directly on the prepared study product in accordance with local regulations and by following instructions provided in the *Pharmacy Guidelines and Instructions for DAIDS Clinical Trials Networks.*

CAB + RPV Tablet Administration

Oral CAB 30 mg tablets + oral RPV 25 mg tablets are to be taken at the same time, once daily with a meal. Refer to the IMPAACT 2040 MOP for additional instructions and guidance on the administration of these doses.

Redosing

If the adult-participant vomits within the first 30 minutes after administration (of either oral formulation), the dose should be repeated for the specific oral study product (CAB and/or RPV).

5.5 Study Product Supply

CAB (tablet, and LA injectable) will be manufactured and supplied by ViiV Healthcare Ltd.

RPV (tablet, and LA injectable) will be manufactured by Janssen Pharmaceutical, Inc. and supplied by ViiV Healthcare Ltd.

All the above-listed study products will be made available to study sites through the NIAID Clinical Research Products Management Center (CRPMC). Upon successful completion of protocol registration procedures, these study products may be obtained by the site pharmacist following instructions provided in the *Pharmacy Guidelines and Instructions for DAIDS Clinical Trials Networks*.

All ancillary supplies such as needles and syringes should be obtained locally by the site. Should supplies not be available locally (e.g., due to stock outs), sites should contact the protocol team to determine if they are able to assist with procurement.

5.6 Study Product Accountability

Site pharmacists must maintain complete records of all study products received from the CRPMC and subsequently dispensed to adult-participants. All study products must be stored in the pharmacy.

5.7 Final Disposition of Study Product

Any unused study product remaining at US sites after the study is completed or terminated will be returned to the CRPMC (unless otherwise directed by the sponsor). At South African sites, any remaining unused study products will be quarantined for destruction. Study products may also be returned to the CRPMC for other reasons, as requested by the sponsor. Site pharmacists will follow the relevant instructions for return or destruction of unused study products provided in the

Pharmacy Guidelines and Instructions for DAIDS Clinical Trials Networks.

5.8 Study Product Adherence Counseling

Adherence counseling will be provided to all adult-participants throughout study participation at specified study visits, and as needed based on site investigator discretion.

Counseling may be provided by clinic and/or pharmacy staff consistent with local standards of care and site SOPs. Counseling should be provided in a client-centered manner, tailored as needed to the information, skills building, and support needs of each participant. As needed for oral bridging, information on correct use of oral study products will be provided. Counseling will also address challenges to consistent use of oral study product (if oral bridging is needed) or attending injectable study visits over time, with the aim of supporting participants in identifying strategies to address any such challenges.

During postpartum period, adherence counseling should also include planning for post-trial access to CAB LA + RPV LA or transition to another SOC treatment option. See Section 6.8 and Section 13.11 for more information.

5.9 Concomitant Medications

The term "concomitant medications" is used in this study to refer to medications other than the study products listed in Section 5. This includes prescription and non-prescription (over-the-counter) medications; vaccines, and other preventive medications; nutritional supplements; and alternative, complementary, and traditional medications and preparations. All concomitant medications received by adult-participants and infant-participants must be source documented as part of the medical and medication histories obtained at each study visit and will be entered into eCRFs as specified in Section 6.10.

Precautionary and Prohibited Concomitant Medications

For a list of medications that should be used with caution and prohibited medications while on study product, refer to Appendix IV.

Upon identification of the need for a prohibited medication, the site investigator/designee should consult the CMC for further guidance on determining next steps for clinical management, study product management, and per Section 8. Any adult-participant who requires a medication considered prohibited while on study product must have the study product held or permanently discontinued, as described in Section 8.15 and Section 8.16.

6 STUDY VISITS AND PROCEDURES

An overview of adult-participant and infant-participant study visits, evaluation schedules, and blood draw volumes are provided in Appendix I-A, Appendix I-B, and Appendix I-C. Presented in this section is additional information on visit-specific study procedures.

In addition to the protocol-specified procedures listed in this section, study staff may complete other tasks consistent with site SOPs, including but not limited to collecting, reviewing, and updating demographic and locator information; reviewing elements of informed consent; scheduling visits; providing instructions for contacting study staff between visits; providing visit reminders; and following up on missed visits. All such tasks should be documented consistent

with site SOPs. Study staff should inform adult-participants of clinically meaningful physical exam findings and laboratory test results when available.

All visits should be conducted as close as possible to specified target visit dates and within specified visit windows. Target visit dates, visit windows, and minimum/maximum days between injections are summarized in Appendix II.

For study product injection visits, target visit dates and target visit windows are based on the adult-participant's first study product injection at Entry. In addition, study product injections must be administered within the minimum and maximum ranges from the previous injection. Scheduled injection visits that do not occur within the target window and satisfy minimum/maximum requirements are considered missed, and the CMC must be consulted regarding clinical considerations and study product management in instances when the scheduled injection visit does not occur within these timeframes.

For applicable study visits, the following procedures must be performed on the same day as and prior to dispensing oral study product (for oral bridging) or administering a study product injection, to assess for any adverse events indication that a study product hold or permanent discontinuation should be initiated:

- Clinical evaluations per the respective scheduled study visit
- Laboratory test results from the previous study visit obtained and reviewed for indication of study product hold or permanent discontinuation (see Section 8.15 and Section 8.16)

See Section 8 for details regarding participant management, including additional details related to deferring study product due to managing adverse events and other indications.

Following the pregnancy outcome, there will be both adult-participant and infant-participant visits. When possible, procedures for both individuals should be completed at the same visit. However, procedures for the adult-participant and infant-participant may also be done during separate visits scheduled within the visit window, if needed. When visits are combined, efforts should be made to collect the chest/breastmilk and infant-participant PK samples in close proximity to one another. As noted in Section 4, there are no set inclusion or exclusion criteria for infant-participants; however, prior to performing any study-related procedures, the site investigator should confirm that they can be safely conducted. Infant-participant PK specimens should not be collected if the infant-participant's birth weight is less than 1000 grams. Blood draws and other clinical procedures may also be omitted if the site investigator identifies congenital anomalies or other medical conditions that may put the infant-participant at undue risk if the procedure is conducted.

Unscheduled study visits may be performed at participant request or as deemed necessary by the site investigator at any time during the study. Visits at which no data are collected should be source documented but not entered into eCRFs. When contacts or visits are completed in response to participant reports of adverse events, study staff will assess the reported event clinically, enter the event into eCRFs and provide or refer the participant to appropriate medical care. See Section 8 for participant management and specified AE management. For adult-participants initiating oral bridging, an unscheduled visit may be conducted to dispense oral study products and conduct required procedures per Section 5.2 or when resuming injections. Section 6.5 provides additional information on interim injection visits.

If a scheduled visit is missed (i.e., no procedures for a given visit type are completed within the applicable window), the missed safety, PK, and virologic evaluations should be completed as

soon as possible as an unscheduled visit or at the next scheduled visit. If any study procedures are conducted at an unscheduled visit (e.g., safety evaluations, PK collection, provision of study product), this information will be entered into eCRFs.

If a participant relocates away from the study site, options for transfer to another site should be explored; when a transfer is possible, procedures for transferring and receiving sites should be carried out consistent with guidance provided in the IMPAACT MOP.

All visits and procedures must be documented in accordance with the DAIDS requirements for source documentation; refer to Section 11 for more information on documentation requirements and entry of eCRFs. Refer to Section 7.3 for information on expedited adverse event (EAE) reporting, which may be required at any time during follow-up.

All injections and blood draws must be performed at the approved clinical research site or approved associated facilities, unless otherwise noted. Other study visit procedures may be conducted off-site at an agreed upon location or telephonically, with written informed consent.

For sites that experience operational disruptions from disasters or public health emergencies, such that participant accrual (screening and enrollment) or conduct of protocol-specific procedures must be paused, the site should notify the CMC for additional guidance. Protocol teams, in consultation with the study sponsor, may provide additional guidance to sites following FDA guidance (40).

6.1 Screening Visit[s]:

Refer to Section 4.4 for a description of the participant recruitment, screening, and enrollment process.

Written informed consent must be obtained before screening procedures are performed. All screening procedures must be performed within 28 days prior to study entry. Multiple visits may be conducted within the 28-day time frame to complete all required procedures and to repeat laboratory tests for confirmation, if necessary. When scheduling a potential Continuation Group adult-participant's Screening Visit, consideration should be given not only to the screening and enrollment window and EGA, but also to the timing of the adult-participant's next CAB LA + RPV LA dose (which must align with the Entry Visit). See Appendix II for additional information on timing of study entry relative the last non-study CAB LA + RPV LA injections. Adult-participants in the Switch Groups will be advised to continue their non-study oral ARTs between the Screening and Entry Visits. For potential adult-participants who do not meet the eligibility criteria, screening is expected to be discontinued once ineligibility is determined.

Screening Visit Procedures (up to 28 days prior to enrollment)		
Administrative and Regulatory		• Obtain written informed consent • Assign PIDs to adult-participant and infant-participant • Obtain screening number from Stars • Collect demographic and locator information • Obtain antenatal care provider information and planned location for delivery
Clinical		• Obtain available medical records and medical and medications history • Assess documentation of HIV-1 infection and of current pregnancy in relation to study requirements • Assess ARV history in relation to study requirements • Assess HIV-1 RNA test result history • Assess available historical resistance data • Perform fetal ultrasound *(if not performed prior to the study screening period)* • Assess current gestational age based on best available method • Perform complete physical examination • Perform ECG (in triplicate) • Administer Columbia-Suicide Severity Rating Scale (C-SSRS) Screening Version
Laboratory	**Blood**	Collect blood for: • Confirmatory HIV-1 testing *(if needed per criterion 4.1.5)* • Chemistries: Creatinine, bilirubin (total and direct), AST, ALT, lipase • Hematology: Complete blood count (CBC- RBC, hemoglobin, hematocrit, MCHC, MCV, WBC) with differential with platelets • Hepatitis B testing: HBcAb, HBsAg, HBsAb • Hepatitis C testing: anti-HCV Ab • HIV-1 RNA

Adult-participants may rescreen provided that adequate time remains to permit enrollment within the allowable gestational age range. If any participant is rescreened, all screening procedures listed above must be repeated, with the following exceptions:

- A new PID should not be assigned (Note: Obtain new screening number from Stars for second screening attempt)
- Confirmatory HIV-1 testing, if conducted during first screening attempt, need not be repeated, unless required to meet eligibility criteria
- Fetal ultrasound need not be repeated
- Previously documented medical and medications history information should be reviewed and updated through the date of re-screening (it is not necessary to re-record history information that was previously documented)

6.2 Entry Visit:

Entry may occur between 10 0/7 and 19 4/7 weeks (inclusive) EGA for adult-participants enrolling in the Switch Group. Adult-participants enrolling in the Continuation Group may enroll at any EGA less than or equal to 19 4/7 weeks and the study Entry Visit must align with the adult-participant's pre-study injection schedule. See Appendix II for additional information on visit windows.

All Entry Visit procedures are expected to be performed on the day of enrollment. Procedures that may provide information relevant to eligibility for the study (e.g., medical history, physical examination), should be performed first, prior to final eligibility determination. In the event that an adult-participant is found ineligible on the day of the scheduled day of enrollment, enrollment should not occur.

Additional requirements for sequencing of procedures at this visit are as follows:

- Final eligibility determination and confirmation must precede enrollment
- Enrollment must precede prescribing of study product
- Prescribing must precede dispensing of study product
- Blood collection must precede injection of study product

Entry Visit Procedures *(Day 0)*		
Administrative and Regulatory		• Complete final eligibility determination and confirmation* • Complete paper-based eligibility checklist*, enter checklist data into Stars to enroll the participants, print and file a copy of the confirmation file
Behavioral and Counseling		• Provide adherence counseling • Administer acceptability/tolerability assessment
Clinical		• Update medical and medications history since last visit* • Perform targeted physical exam* • Perform fetal ultrasound* *if not done previously* • Assess ARV history* • *If applicable,* ascertain gender identity
Laboratory	**Blood**	Collect blood for: • CD4 count and percentage • HIV-1 RNA • Chemistries: albumin, alkaline phosphatase (ALP), ALT, AST, bilirubin (total and direct), blood urea nitrogen (BUN), calcium, CO_2, chloride, creatinine, glucose (non-fasting glucose permitted), potassium, total protein, and sodium, plus lipase • Hematology: CBC (RBC, hemoglobin, hematocrit, MCHC, MCV, WBC) with differential with platelets • Stored whole blood for HIV-1 resistance testing • PK evaluation: Single pre-injection sample
Study Product		• Prescribe, prepare, and administer injectable study products • Provide information on potential study product side effects

*Perform prior to enrollment

Gender identity should be ascertained; however, this procedure should not be performed at sites that have formally opted out of collection of gender identity data, in accordance with policies specified in the IMPAACT MOP. Gender identity data should be collected from adult-participants in private.

6.3 Antepartum Follow-Up Visits:

After study entry, adult-participants will complete scheduled follow-up visits every four weeks (28 days) until their pregnancy outcome. Additional visits will occur at Study Week 2 and Week 6 for close monitoring of adult-participants following study product initiation and will include HIV-1 RNA and PK evaluation. Between scheduled visits, particularly in the first month of study participation, study site staff are encouraged to contact adult-participants to address any issues or questions about their study participation, clarify instructions for follow-up, and/or provide adherence counseling as needed.

Adult-participants will be enrolled over a range of gestational ages less than or equal to 19 4/7 weeks, and the number of antepartum follow-up visits will be dependent on the gestational age at entry and the gestational age at delivery. For example, an adult-participant who enrolls at 14 weeks gestation and delivers at 40 weeks gestation would be expected to complete antepartum visits at 16, 18, 20, 22, 26, 30, 34, and 38 weeks gestation; the corresponding study weeks for these visits would be Antepartum Study Weeks 2, 4, 6, 8, 12, 16, 20, and 24. The number of antepartum follow-up visits may be more or less than this example. The target dates for all antepartum follow-up visits are counted from the date of Entry as Day 0; a full listing of visit target dates, visit windows and administration windows is available in Appendix II.

6.3.1 Antepartum Visits - Study Week 2 and 6:

All adult-participants will complete a Study Week 2 and Week 6 visit for close monitoring of HIV-1 RNA and PK evaluations. The Study Week 2 visit will be scheduled approximately 14 days after entry. The Study Week 6 visits will be scheduled approximately 42 days after entry. The allowable window for Study Week 2 is -7 days/+6 days and for Study Week 6 is -6 days/+6 days from the target dates.

Antepartum Study Week 2 and 6 Visit Procedures		
Clinical		• Obtain interval medical and medications history • Identify/review/update adverse events • Perform additional evaluations per Section 8 and/or if clinically indicated (consult CMC if indicated)
Laboratory	**Blood**	Collect blood for: • HIV-1 RNA • PK evaluation: single PK sample

6.3.2 Antepartum Visits - Study Week 4, 8, 12, 16, 20, 24, 28, 32:

In addition to the Study Week 2 and Week 6 visits, all adult-participants will complete antepartum follow-up visits every four weeks until their pregnancy outcome (note that depending on the EGA at enrollment and timing of the pregnancy outcome, not all participants will complete antepartum visits through Study Week 32). Scheduling of the antepartum follow-up visits will need to consider the allowable visit window as well as the administration window based on the last injection received. Lower trough concentrations are of particular concern after the first CAB LA + RPV LA dose before accumulation has occurred and during the second and third trimesters due to metabolic enzyme induction effects.

Note: For Switch Group adult-participants, the administration window for injections given at the Week 4 Visit will be limited to 21-28 days after the Entry visit loading dose.

This dosing window for Q4W and Q8W Switch Group participants may subsequently be expanded to 21-35 days if supported by the interim analysis.

Required sequencing of procedures at these visits are as follows:

- Samples for PK evaluation should be collected prior to receiving any injections
- Procedures in Section 6 must be performed prior to receiving any injections

Antepartum Study Week 4, 8, 12, 16, 20, 24, 28, 32 Visit Procedures (± 7 days)		
Behavioral and Counseling		• Provide adherence counseling • Administer acceptability/tolerability assessment *at Week 16*
Clinical		• Obtain interval medical and medications history • Perform targeted physical exam • Identify/review/update adverse events • Perform additional evaluations per Section 8 and/or if clinically indicated (consult CMC if indicated)
Laboratory	**Blood**	Collect blood for: • Hematology: CBC (RBC, hemoglobin, hematocrit, MCHC, MCV, WBC) with differential with platelets • Chemistries: Creatinine, bilirubin (total and direct), AST, ALT, lipase • Albumin *at Week 8 and Week 16* • HIV-1 RNA • PK evaluation: Single pre-injection sample • CD4 count and percentage *at Week 12 and Week 24*
Study Product		Prescribe, prepare, and administer injectable study products *as needed based on group dosing schedule*

The schedule of injections at the antepartum study visits depends on the adult-participant's dosing regimen (Q4W or Q8W) and whether they are enrolling in one of the Switch or Continuation Groups:

- Adult-participants enrolling in the Q4W Switch Group or the Q4W Continuation Group will receive injections at antepartum visits every four weeks (Study Weeks 4, 8, 12, 16, 20, 24, 28, 32)
- Adult-participants enrolling in the Q8W Continuation Group will receive injections at antepartum visits every eight weeks (Study Weeks 8, 16, 24, 32)
- Adult-participants enrolling in the Q8W Switch Group will receive injections at the Week 4 antepartum visit, followed by every eight weeks (Study Weeks 4, 12, 20, 28)

6.3.3 Antepartum Interval Visits:

Additional antepartum study visits to assess additional PK levels will be scheduled approximately seven days after the injection(s) received between 30 0/7 - 37 6/7 weeks EGA. The allowable window on the antepartum interval visits is -2 days/+14 days from the target date. Adult-participants on a Q4W dosing regimen will have up to two antepartum interval visits, adult-participants on a Q8W dosing regimen will have one antepartum interval visit.

Antepartum Interval Visits		
Behavioral and Counseling		• Provide contraceptive counseling
Clinical		• Obtain interval medical and medications history • Identify/review/update adverse events • Perform additional evaluations per Section 8 and/or if clinically indicated (consult CMC if indicated)
Laboratory	**Blood**	Collect blood for: • PK evaluation: single PK sample

6.4 Postpartum Adult-Participant and Infant-Participant Visits:

6.4.1 Adult-Participant Pregnancy Outcome Visit

The Pregnancy Outcome Visit should be targeted for the day of the pregnancy outcome, with an allowable window of +5 days from the pregnancy outcome. If the visit cannot be completed on the day of the pregnancy outcome, if the pregnancy does not result in a live birth, or if there are circumstances that prohibit collection (i.e., delivery at a non-study facility, delivery during non-business hours), the cord blood PK sample will be omitted.

In the event that an enrolled adult-participant does not deliver a live born infant, or that a live born infant dies soon after delivery, the adult-participant should still complete the Pregnancy Outcome Visit and all subsequent postpartum visits if they are willing to do so.

Pregnancy Outcome Visit Procedures – *(Day of PO + 5 days)*		
Behavioral and Counseling		• Provide contraceptive counseling
Clinical		• Obtain interval medical and medications history • Perform targeted physical exam • Identify/review/update adverse events • Perform additional evaluations per Section 8 and/or if clinically indicated (consult CMC if indicated)
Laboratory	**Blood**	Collect blood for: • HIV-1 RNA • Single PK sample (delivery) • Cord blood PK sample *if live birth and visit is completed on day of delivery*
	Other	Chest/breastmilk PK sample, *if intending to chest/breastfeed*
Study product		Prescribe, prepare, and administer injectable study products *as needed based on group dosing schedule*

6.4.2 Infant-Participant Birth Visit and Five-Day Post-Birth Visit

The Infant-Participant Birth Visit will be targeted for the day of birth. If this visit does not occur on the day of birth, it will be missed. Regardless of whether the Birth Visit occurs, a separate visit will be targeted for all infant-participants with an allowable window of +1-5 days after birth to collect an additional PK blood sample.

Additional requirements for PK sample collections at these visits are as follows:

- If the Infant-Participant Birth Visit occurs and the cord blood has been collected as part of the adult-participant's Pregnancy Outcome Visit: The PK sample at the Infant-Participant Birth Visit should be omitted. In this case, infant-participant blood collection for PK evaluation will begin at the Five-Day Post-Birth Visit.

- If the Infant-Participant Birth Visit occurs, and no cord blood has been collected as part of the adult-participant's Pregnancy Outcome Visit: A single infant-participant PK sample should be taken as part of the Infant-Participant Birth Visit and again at the Five-Day Post-Birth Visit.
- If the Infant-Participant Birth Visit does not occur: All procedures listed for the Infant-Participant Birth Visit should be completed at the Five-Day Post-Birth Visit. A single infant-participant PK sample will be taken at this visit.

Infant-Participant Birth Visit Procedures *(Day of Birth)*		
Clinical		• Obtain birth history, medical and medications history since birth, and feeding history since birth • Perform complete physical exam • Identify/review/update adverse events • Perform additional evaluations per Section 8 and/or if clinically indicated (consult CMC if indicated)
Laboratory	**Blood**	Collect blood for: • HIV NAT (*documented HIV NAT results obtained as part of standard of care, external to the study, may be used if the sample was collected prior to the visit)* • PK evaluation: Single PK sample (*if cord blood is not collected and if birth weight greater than or equal to 1000 grams)*
Infant-Participant Five-Day Post Birth Visit Procedures *(+1-5 days after birth)*		
Clinical		• Obtain/review/update birth history, medical and medications history since birth, and feeding history • Perform complete physical exam *(if Infant-Participant Birth Visit not done)* • Identify/review/update adverse events Perform additional evaluations per Section 8 and/or if clinically indicated (consult CMC if indicated)
Laboratory	**Blood**	Collect blood for: • Bilirubin (total and direct) • HIV NAT *(if Infant-Participant Birth Visit not done; documented HIV NAT results obtained as part of standard of care, external to the study, may be used if the sample was collected prior to the visit)* • PK evaluation: Single PK sample *(if birth weight greater than or equal to 1000 grams)*

In the event that the infant-participant HIV NAT is positive, the infant-participant should be recalled to the clinic as soon as possible for confirmatory HIV NAT testing. See also Section 6.7.

6.4.3 Postpartum Injection Visits (Adult-Participant and Infant-Participant):

All adult-participants and infant-participants will have two Postpartum Injection Visits to collect PK samples and for adult-participants to receive their postpartum study product injection. Adult-participants who received CAB LA + RPV LA as part of their Pregnancy Outcome Visit will still complete both Postpartum Injection Visits. As noted in Section 5.8, starting at the first Postpartum Injection Visit, adherence counseling should include planning for post-trial access to CAB LA + RPV LA or transition to another SOC treatment option.

The target dates for this visit type for both adult-participants and infant-participants will be based on the target date of the adult-participant's last dose, i.e., for adult-participants on Q4W dosing, 28 days since their last targeted dose and for adult-participants on Q8W dosing, 56 days since their last targeted dose. The visit window will be +/- 7 days from the target date. Note that the

target dates and visit windows for these visits are fixed and should not shift based on the actual date of the previous injection administration; as with other injection visits, the minimum/maximum injection administration window must also be considered when scheduling these visits.

In the event that an enrolled adult-participant does not continue to receive CAB LA + RPV LA during the postpartum period, they should remain on study together with the infant-participant for the duration of their originally planned follow-up schedule. See Section 8.16 for additional guidance on participant management following premature permanent discontinuation of study product.

Postpartum Injection Visit Procedures		
Behavioral and Counseling		• Provide adherence counseling • Provide contraceptive counseling
Clinical		• Obtain interval medical and medications history • Perform targeted physical exam • Identify/review/update adverse events • Perform additional evaluations per Section 8 and/or if clinically indicated (consult CMC if indicated)
Laboratory	**Blood**	Collect blood for: • Hematology: CBC (RBC, hemoglobin, hematocrit, MCHC, MCV, WBC) with differential with platelets • Chemistries: Creatinine, Bilirubin (total and direct), AST, ALT, Lipase • Albumin • HIV-1 RNA • PK evaluation: Single pre-injection sample
	Other	• Chest/breastmilk PK sample, *if currently chest/breastfeeding*
	Urine	• Offer pregnancy testing, *if clinically indicated*
Study Product		Prescribe, prepare, and administer injectable study products *as needed based on group dosing schedule*

Infant-Participant Procedures		
Clinical		• Obtain interval medical, medications, and feeding history • Perform targeted physical exam • Identify/review/update adverse events • Perform additional evaluations per Section 8 and/or if clinically indicated (consult CMC if indicated)
Laboratory	**Blood**	Collect blood for: • HIV NAT (*documented HIV NAT results obtained as part of standard of care, external to the study, may be used if the sample was collected within seven days prior to the visit)* • Infant-participant PK sampling, *for all infant-participants if adult-participant is chest/breastfeeding and ideally concurrent with chest/breastmilk collection. If infant-participant is not chest/breastfeeding, only collect at the first postpartum visit if adult-participant is on Q4W dosing and infant-participant visit is conducted within 28 days since the adult-participant's last injection. In all cases, only collect if birth weight was greater than or equal to 1000 grams.* • Chemistries: Creatinine, Bilirubin (total and direct), AST, ALT, Lipase *Collect only if visit is conducted 14 days or more after birth and 14 days or more in advance of the next scheduled visit's target date.*

All infant-participants will undergo HIV NAT testing at these visits, regardless of feeding method. In the event of any positive test, the infant-participant should be recalled to the clinic as soon as possible for confirmatory testing. See Section 6.7.

6.4.4 Final Scheduled Visit (Adult-Participant and Infant-Participant) / Early Termination Visits

The Final Postpartum Visit is the last scheduled study visit for adult-participants and infant-participants. This visit will be conducted 14 days after the second Postpartum Injection Visit (+/- 7 days).

Any participant withdrawing or terminating from the study prior to this timepoint is considered as prematurely terminating from the study and the Final Postpartum Visit procedures for the adult-participant and/or infant-participant will be conducted as an Early Termination Visit. This final series of evaluations should replace the participant's regularly scheduled study visit. If the adult-participant is terminating before their pregnancy outcome the following procedures will be omitted:

- Chest/breastmilk sample
- All infant-participant procedures

Final Scheduled Visit Procedures/ Early Termination Visit		
Behavioral and Counseling		• Administer acceptability/tolerability assessment • Provide contraceptive counseling
Clinical		• Obtain interval medical and medications history • Perform targeted physical exam • Identify/review/update adverse events • Perform additional evaluations per Section 8 and/or if clinically indicated (consult CMC if indicated) • Provide information, counseling, and/or referrals (as needed) in relation to study exit at this visit, including post-trial access of study product • Administer Columbia-Suicide Severity Rating Scale (C-SSRS) Screening Version
Laboratory	**Blood**	• HIV-1 RNA • PK evaluation: Single PK sample • Hematology: CBC (RBC, hemoglobin, hematocrit, MCHC, MCV, WBC) with differential with platelets • Chemistries: Creatinine, Bilirubin (total and direct), AST, ALT, Lipase • Albumin
	Other	Chest/breastmilk PK sample, *if currently chest/breastfeeding*
	Urine	Offer pregnancy testing, *if clinically indicated*
Study Product		Prescribe, prepare, and administer injectable study products *if within administration window based on group dosing schedule and continuing on injections*

Infant-Participant Final Scheduled Visit Procedures / Early Termination Visit		
Clinical		• Obtain interval medical, medications, and feeding history • Perform targeted physical exam with growth evaluation • Identify/review/update adverse events • Perform additional evaluations per Section 8 and/or if clinically indicated (consult CMC if indicated)
Laboratory	**Blood**	Collect blood for: • HIV NAT *(Documented HIV NAT results obtained as part of standard of care, external to the study, may be used if the sample was collected within seven days prior to the visit)* • Infant-participant PK sample, *if postpartum participant is chest/breastfeeding and ideally concurrent with postpartum chest/breastmilk collection. Only collect if birth weight greater than or equal to 1000 grams.* • Chemistries: Creatinine, Bilirubin (total and direct), AST, ALT, Lipase

6.5 Interim Injection Visit

For adult-participants resuming injectable study products following oral bridging or in other rare circumstances, one or more interim visits may be required to appropriately reinitiate an adult-participant on the dosing regimen or realign to the original injection visit schedule or dose. The CMC must be consulted prior to initiating oral bridging and prior to conducting an interim injection visit regarding clinical considerations, and injectable study product management and scheduling. Additional guidance on resuming injectable study products following oral bridging is provided in the IMPAACT 2040 MOP.

Interim Injection Visit procedures are provided below, and study data will be entered into eCRFs. Further details and guidance on scheduling and conducting study injection visits, including Interim Injection Visits, are provided in the IMPAACT 2040 MOP.

Interim Injection Visit Procedures		
Behavioral and Counseling		• Provide adherence counseling*
Clinical		• Update medical and medications history since last visit* • Perform targeted physical exam* • Identify/review/update adverse events*
Laboratory	**Blood**	Collect blood for: • Hematology: CBC (RBC, hemoglobin, hematocrit, MCHC, MCV, WBC) with differential with platelets • Chemistries: Creatinine, Bilirubin (total and direct), AST, ALT, Lipase • HIV-1 RNA* • PK evaluation: Single pre-dose sample*
Study product		• Prescribe, prepare, and administer injectable study products *based on group dosing schedule*

***** Perform prior to administration of injectable study products.

6.6 Viral Load Assessment Visit

Any adult-participant with a plasma HIV-1 RNA level greater than or equal to 50 copies/mL after enrollment should be recalled to the clinic as soon as possible to complete a Viral Load Assessment Visit for additional clinical management, as outlined in Section 8.13. Adult-participants should return for additional Viral Load Assessment Visits based on viral load results as outlined in Appendix III.

Scheduling of this visit type within the timeframes specified in Appendix III should also take into consideration any potential causes for virologic failure such as intercurrent illness, recent immunizations, inadequate adherence, interruptions of study product, or other extenuating circumstances. For adult-participants receiving injectable study product, confirmatory test results should ideally be obtained and reviewed prior to the next scheduled administration of injectable study product. While injection study visits for these adult-participants may be delayed within the respective target visit window, injectable study product must not be withheld for pending confirmatory testing or results.

See Section 5.8 for additional details on adherence counseling.

Viral Load Assessment Visit procedures may be combined with regularly scheduled visit procedures if they are performed within the target window of a regularly scheduled visit (i.e., all procedures for both visit types performed once during a single visit). Viral load results should be provided to adult-participants and may be used to guide adherence counseling. In addition to the protocol-specific procedures listed in this section, study staff may complete other tasks and assessments consistent with local standards of care and site SOPs.

Viral Load Assessment Visit Procedures		
Behavioral and Counseling		• Provide adherence counseling
Clinical		• Obtain interval medical and medications history • Perform targeted physical exam • Identify/review/update adverse events • Perform additional evaluations per Section 8 and/or if clinically indicated (consult CMC if indicated)
Laboratory	**Blood**	Collect blood for: • HIV-1 RNA • Plasma for HIV-1 resistance testing • PK evaluation: single sample

6.7 Modified Procedures for Infant-Participants with Suspected or Confirmed HIV Infection

Any infant-participant with a positive HIV NAT result should be recalled to the clinic for a confirmatory HIV NAT and ARV resistance testing **as soon as possible** and within 14 days of specimen collection for the initial test. A total blood volume of approximately 6 mL should be collected for the repeat HIV NAT test, including resistance testing.

In the event that the second HIV NAT test does not confirm the initial result, a third test should be done to make a final determination (the CMC may be consulted for guidance on next steps to clarify the infant-participant's HIV status). Pending confirmatory testing, infant-participant ARVs should be managed consistent with local standards of care.

All infant-participants identified with HIV-1 infection will remain in study follow-up but will be referred to non-study HIV-1 care for ARV treatment as soon as possible. Study visits will be conducted as originally scheduled with the exception that no further HIV-1 tests will be performed. Study sites may perform additional laboratory testing as needed to facilitate rapid initiation of ART for infant-participants with HIV.

6.8 Study Exit

All participants will exit the study at the completion of the Final Scheduled Visit.

Any adult-participant or infant-participant withdrawing or terminating from the study prior to this timepoint is considered as prematurely terminating from the study and the Final Scheduled Visit procedures should be conducted as an Early Termination Visit, instead of their regularly scheduled study visit, for a final series of evaluations.

Prior to exiting any adult-participant or infant-participant from the study, results for all laboratory evaluations should be assessed to determine if the study exit should be postponed. See Section 6.8.1 for additional information on reasons to postpone study exit. At any study exit visit (scheduled completion of follow-up or an early termination visit), arrangements should be made to provide all clinically meaningful results to the participant. Results of IMPAACT 2040 evaluations that are significant for clinical management should also be provided to non-study care providers for further follow-up and all such communications should be documented in the participant's study records. The adult-participant or the infant-participant parent/caregiver should be provided information on how to remain in contact with study staff (if desired) and how to learn about the results of the study when available. The adult-participant or infant-participant parent/caregiver should also be provided information, counseling, and referrals to non-study sources of care and treatment, as applicable. See Section 8.1 regarding management of adverse events at study exit, and Section 4.6 for additional considerations regarding participant withdrawal or termination.

Planning for transition to non-study care and treatment for adult-participants exiting the study should begin prior to the adult-participant's scheduled study exit visit, and the transition should be implemented at the adult-participant's scheduled study exit visit. Study staff will complete a final study contact with the adult-participant within four weeks of the adult-participant's study exit visit to confirm the transition and the contact should be documented in each adult-participant's study chart. These contacts are not expected to be entered into eCRFs.

6.8.1 Reasons to Postpone Study Exit

In the following circumstances, an adult-participant's or infant-participant's early termination or planned study exit may need to be postponed to allow for additional participant management and/or eCRF data collection:

- If an adult-participant withdraws consent or stops the study prior to their pregnancy outcome, the site should confirm if the adult-participant is willing to be contacted one final time following the pregnancy outcome to ascertain the outcome and enter the outcome on relevant eCRFs. The infant-participant should remain in follow-up or be exited from the study as well, per the adult-participant's request (See Section 4.6).

- If an adult-participant experiences a subsequent pregnancy, follow-up visits will conclude at the originally scheduled Final Scheduled Visit, but study exit should be postponed to allow for eCRF data collection on the pregnancy outcome and concomitant medication use during

the subsequent pregnancy. See Section 8.14 for additional guidance on participants who experience a subsequent pregnancy. Adult-participants will exit after their pregnancy outcome has been obtained (no additional pregnancies that may occur will be followed on-study).

- If an adult-participant's confirmation of virologic failure is pending: A Viral Load Assessment Visit should be conducted (refer to Section 6.6) with all relevant eCRFs entered prior to study exit.

- If an infant participant's HIV NAT testing is not complete or is inconclusive at the Final Study Visit: A repeat HIV NAT test should be done, up to 24 weeks of life. For infant-participants who have received a positive HIV NAT result, all testing specified in Section 6.7 should be complete prior to study exit.

- If the adult-participant or infant-participant has any Grade 3 or higher adverse event: See protocol Section 8.1 for requirements regarding extended follow-up of these participants. Note that all eCRFs must be completed prior to study exit.

6.9 Performing an Electrocardiogram (ECG)

For all ECG readings, a 12-lead ECG should be performed with the adult-participant in a semi-supine position. An ECG machine that automatically calculates the heart rate and measures QTcF intervals is preferred, and the automated calculations can be used for reporting purposes. The site investigator can review the ECG reading and a cardiologist reading is not required. The Fridericia QT correction formula must be used in this study for all adults who have protocol-required ECG readings.

At the Screening Visit, the ECG reading should be done in triplicate such that three, single automated QTc readings will be done, each separated by at least 2 minutes, with the mean value establishing baseline. Results from the ECG will be source documented and entered into eCRFs.

During study treatment, routine ECGs will not be required, but should be performed as needed for evaluation of cardiac complaints. A QTcF interval result of greater than or equal to 500 msec or a greater than 60 msec increase from baseline requires two repeat readings (each separated by at least two minutes, for a total of three readings). See Section 7.3.3.1 for Protocol-Specific Grading of ECG results and Section 8.12 for Management of QTcF. ECG AEs should be source documented and entered in appropriate eCRFs.

6.10 Adult-Participant Medical and Medication History

Collection of medical and medication history is required at each scheduled visit. A baseline history is established at the Screening and Entry Visits and interval (since the last visit) histories are obtained at follow-up visits. All history information may be obtained based on adult-participant report, but available medical records should also be obtained, when possible, to supplement reported information. Where feasible, additional effort should be made to obtain medical records related to HIV-1 resistance and prior ARV treatments to confirm adult-participant reports.

Documented medical conditions will be assessed for severity as described in Section 7.3.3 and new conditions occurring during follow-up will be assessed for relationship to study product as described in Section 8.1. Relevant dates will be recorded for all conditions and medications; refer to Section 5.9 for more information on concomitant medications. Table 4 specifies the baseline and interval medical and medications history elements that must be source documented, as well as associated eCRF entry requirements.

Table 4. Documentation Requirements for Medical and Medication Histories

Assess for and Source Document	Enter into eCRFs or Stars
Baseline Medical and Medication History Elements	
Date of birth, sex at birth, race, ethnicity	Yes
Gender identity	Yes
Date of HIV-1 diagnosis and current World Health Organization (WHO) clinical stage	Yes
Documented resistance to CAB, RPV, or any INSTIs or NNRTIs (ever)	Yes
All documented HIV-1 RNA test results within the nine months (270 days) prior to enrollment	Yes
Any documented HIV-1 test results used for confirmation of HIV-1 status for eligibility determination	Yes
History of allergy and/or hypersensitivity (including to ARVs)	Yes
Smoking status	Yes
Medical conditions occurring within the current pregnancy or ongoing at the time of enrollment and any other medical condition occurring prior to the first study-provided injection and deemed clinically significant by the site investigator	Yes, with the exception of specific pregnancy-related conditions meeting criteria outlined in Section 7.2.1.
All medications (other than ARVs), taken or administered during the current pregnancy and continuing through scheduled study completion of follow-up or subsequent pregnancy outcome (if applicable), that meet the following criteria: • All prescription medications • Blood products and transfusions • Prenatal vitamins • Cation-containing antacids, acid suppressants, and iron supplements	Yes
ARVs taken within the 24 months prior to enrollment and any treatment interruptions	Yes
Reproductive and obstetrical history: • Dates and outcomes of all prior pregnancies • Intrapartum ARVs taken at time of last delivery, if applicable • Other targeted conditions specified in Section 4.2.5 from previous pregnancies • Date of LMP prior to the current pregnancy	Yes
Any other information needed to determine eligibility for the study	No
Interval Medical and Medication History Elements	
Current status of conditions that were ongoing at the previous visit	Any updates of previous entries (e.g., resolution dates)

Assess for and Source Document	Enter into eCRFs or Stars
Occurrence of any new conditions since the last visit	All newly identified adverse events, with exception of conditions that meet criteria outlined in Section 7.2.1.
Current status of medications that were ongoing at the previous visit	Any updates of previous entries (e.g., stop dates)
Use of any new medications since the last visit (see Section 5.9 for more information on concomitant medications)	• All ARVs taken from time of enrollment through scheduled study completion of follow-up or subsequent pregnancy outcome for a (if applicable) • All vaccines received from time of enrollment through scheduled study completion of follow-up or subsequent pregnancy outcome for a (if applicable)All medications taken at onset of or in response to adverse events that are specified to be entered into eCRFs per Section 7.2. Note: eCRFs will also capture whether corticosteroids were taken for fetal lung maturity at any time during pregnancy.
All ARV resistance test results obtained after enrollment	Transferred electronically to DMC using data submission utilities (not entered into eCRFs)
Smoking status at visits with PK sample collection	Yes
Pregnancy Outcome information, including: • Complications of pregnancy identified following enrollment and before delivery, regardless of severity grade • Other targeted conditions potentially associated with adverse pregnancy outcomes identified following enrollment and before delivery, regardless of severity grade • Date and time of onset of labor • Type of labor (spontaneous or induced) • Mode of delivery • Complications of delivery • Outcome of delivery	Yes

6.11 Adult-Participant Physical Examinations During Pregnancy/Postpartum

A physical examination is required during pregnancy and postpartum according to the schedule outlined in Appendix I-A. Complete exams are required at the Screening Visit; targeted exams are required at all other visits.

Complete exams should include the following:

- Height measurement
- Weight measurement
- Vitals (temperature, heart rate, blood pressure)
- Obstetric exam (at antepartum visits)
- Auscultation of chest (heart and lung exam)

- Examination of:
  - Skin
  - Head
  - Mouth
  - Neck
  - Abdomen
  - Extremities

Targeted exams should include the following:

- Weight measurement
- Vitals (temperature, heart rate, blood pressure)
- Obstetric exam (including fundal height and fetal heartrate at antepartum visits)
- Examination of body systems driven by prior and new signs, symptoms, and diagnoses

At all visits, additional assessments may be performed at the discretion of the examining clinician.

All exam findings should be source documented and the following should be entered into eCRFs: height, weight, blood pressure, fundal height and fetal heartrate (only at antepartum exams). Abnormal findings identified prior to enrollment will be entered into medical history eCRFs. Abnormal findings identified after enrollment will be entered into adverse events eCRFs as specified in Section 7.2.

6.12 Pregnancy Testing, Contraceptive Counseling, and Contraceptive Use

Adult-participants enrolled in this study will be provided with contraceptive counseling throughout follow-up as specified in Sections 6.3-6.4. Adult-participants will be informed of available contraceptive methods and counseled on initiation of effective contraception after delivery. External and internal condom use will be recommended with all contraceptive methods for dual protection against pregnancy and to avoid transmission of sexually transmitted infections; the importance of condom use will be emphasized during the early postpartum period prior to initiation of effective contraception.

Contraceptive counseling will be provided per site SOPs, which should reflect study-specific requirements, locally available contraceptive methods, and site-specific plans for provision of contraceptive methods to study participants, when possible.

Study staff should actively facilitate access to contraceptive services and, to the extent possible, should provide these services to adult-participants on-site. At sites where full-service provision is not possible, study staff should actively refer adult-participants to local service providers for methods that cannot be provided on site. Access to effective contraception should be provided or facilitated for all adult-participants, regardless of group.

Regardless of the contraceptive counseling and access to effective contraception provided or facilitated by study staff, some participants may decline or stop use of effective contraception. This is acceptable and will have no impact on study participation or continued study product use.

Pregnancy testing should be offered if clinically indicated during the postpartum period beginning at the Postpartum Injection Visit (or earlier, per clinical discretion). Study participants should be instructed to contact study staff as soon as possible if they suspect they may be pregnant at any

time during postpartum follow-up, so that an interim pregnancy test can be performed between scheduled visits.

6.13 Fetal Ultrasound

A fetal ultrasound scan is required to permit more accurate calculation of gestational age at entry into the study and gestational age at delivery. Scans should be performed prior to study entry. Results must be used to estimate gestational age and assess for evidence of multiple gestation and fetal anomalies for purposes of eligibility determination.

Ultrasound scans may be performed at the study site or at off-site facilities. In the event that a scan is performed prior to the study screening period, and an ultrasound report meeting all requirements specified below is available, it is not necessary to perform another scan for study purposes.

An ultrasound report that minimally documents the following must be obtained for filing in participant study charts and entry into eCRFs; if more than one ultrasound report that meets these requirements is available, the earliest available results should be entered into eCRFs for estimation of gestational age:

- Date of scan
- Intrauterine gestation
- Number of fetuses
- Biometry measures
  - If less than 14 weeks gestation:
    - Crown-rump length
  - If 14 or more weeks gestation:
    - Femur length
    - Abdominal circumference
    - Biparietal diameter
    - Head circumference
- Ultrasound-based gestational age on the date of the scan or ultrasound-based estimated date of delivery
- Estimated delivery date (EDD)

If any fetal anomalies are identified, these should also be documented in the result report.

6.13.1 Calculation of Gestational Age

The best obstetric estimate should be used as the measure for gestational age, rather than estimates based on the LMP alone. Ultrasound measurement of the fetus in the first trimester (up to and including 13 6/7 weeks of gestation) is the most accurate method to establish or confirm gestational age. Gestational age assessment based on measurement of the crown–rump length has an accuracy of ±5–7 days in the first trimester. However, it may not be possible to ensure that adult-participants have a first-trimester ultrasound. The range of second-trimester gestational ages (14 0/7 weeks to 27 6/7 weeks of gestation) introduces greater variability and complexity, which can affect revision of LMP dating and assignment of a final EDD. Table 5 includes guidelines for redating based on ultrasonography.

Table 5. Guidelines for Redating based on Ultrasonography

Gestational Age Range	Discrepancy between Ultrasound Dating and LMP that Supports Redating
Less than or equal to 8 6/7 weeks	More than 5 days
9 0/7 weeks to 15 6/7 weeks	More than 7 days
16 0/7 weeks to 21 6/7 weeks	More than 10 days

If the EGA by the adult-participant's LMP differs from the ultrasound estimate by more than these accepted variations, the ultrasound estimate of gestational age should be used instead of the adult-participant's LMP estimate.

6.14 Infant-Participant Medical and Medication History

Collection of medical and medication history information is required at each scheduled infant-participant visit. A baseline history is established at the first study visit after birth and interval (since the last visit) histories are obtained at subsequent follow-up visits. Infant-participant birth details should ideally be obtained from available medical records. If birth details are not available, indicate as such on the eCRF. Thereafter, history information may be obtained based on parent/caregiver report and/or chart abstraction.

6.15 Infant-Participant Physical Exam

A physical examination is required at each scheduled infant-participant visit. A complete exam is required at the Infant-Participant Birth Visit (or at the Five-Day Post-Birth Visit if the Infant-Participant Birth Visit is missed); targeted exams are required at all other scheduled visits.

Complete exams should include the following:

- Newborn step-wise surface examination of:
  - Physical appearance
  - Length
  - Weight
  - Skin
  - Head (including fontanels and circumference)
  - Face (including mouth)
  - Neck
  - Chest
  - Abdomen and anus
  - Hips and genitalia
  - Arms, legs, fingers, and toes
  - Spine
- Auscultation of chest
- Neurologic assessment

The newborn step-wise surface examination will be performed consistent with World Health Organization (WHO) guidelines (available on the study-specific website: https://www.impaactnetwork.org/studies/impaact2040). The purpose of this examination is to establish each infant-participant's physical condition at the Infant-Participant Birth Visit and to complete a systematic and standardized assessment for congenital anomalies. All elements of the surface examination should be performed for purposes of assessing for congenital anomalies in all infant-participants, with the exception of the intra-oral, cardiac, and genitourinary systems (which will be included in the general examination but will not be

routinely assessed for presence of congenital anomalies). If any potential congenital anomalies are identified on examination of any body system, these should be photographed by the examining clinician and a site pediatrician should ideally examine the infant-participant as soon as possible.

Targeted exams should include the following:

- Length measurement
- Weight measurement
- Head circumference measurement
- Assessment of fontanel closure
- Auscultation of chest
- Examination of body systems driven by prior and new signs, symptoms, and diagnoses

At all visits, additional assessments may be performed at the discretion of the examining clinician. Also at all visits, the measurements listed above will be used to determine weight-for-length z-scores, which will be assessed in relation to WHO growth standards; measurements may also be charted on standard infant growth charts.

All exam findings should be source documented and the following should be entered into eCRFs: length, weight, head circumference, fontanel closure. Abnormal findings — including congenital anomalies in any body system meeting the MACDP criteria as a defect — will be entered into adverse events eCRFs as specified in Section 7.2; photographs of abnormal findings may be securely uploaded to the DMC upon request to permit review and evaluation of findings by the CMC (41).

6.16 Infant-Participant Feeding History

An infant-participant feeding history is required at each scheduled visit. At the Birth Visit, feeding history since birth (including date and time of first chest/breastfeeding, if applicable) will be collected. Thereafter, interval (since the last visit) histories will be collected. At each time point, data will be collected (source documented and entered into eCRFs) on feeding method, including whether the infant-participant has been chest/breastfed, formula fed, or mixed, and date of last exposure to chest/breastmilk.

Table 6 summarizes the data that should be collected, source documented and entered into eCRFs for each of the infant-participant visits.

Table 6 Documentation Requirements for Infant-Participant Medical and Medication Histories

Assess for and Source Document	Enter into eCRFs or Stars
Baseline Medical and Medication History Elements	
Date and time of birth	Yes
Sex	Yes
EGA at birth (by best available method)	Yes
Head circumference, birth length and weight	Yes
Any medical conditions identified since birth that meet the criteria in Section 7.2.	Yes
All prescription medications taken or administered since birth	• All ARVs

Assess for and Source Document	Enter into eCRFs or Stars
	• All medications taken at onset of or in response to adverse events that are specified to be entered into eCRFs per Section 7.2
Laboratory results (conducted per protocol or available in medical records) • All HIV-1 test results • Hematology: All Grade 2 or higher results for CBC with differential and platelets; first and last results at each reportable grade and first normal result afterward • Chemistries: All Grade 2 or higher glucose, AST, and ALT results • For infant-participants with HIV-1 only: Grade 2 or higher electrolytes, blood urea nitrogen (BUN), creatinine, total and direct bilirubin, lipase, albumin, total protein, triglycerides, cholesterol, creatinine phosphokinase (CPK), and amylase results	Yes
Feeding History: • Feeding method: formula, chest/breastmilk, or mixed • Date and time of first chest/breastfeeding, if applicable • Date and time of last exposure to chest/breastmilk, if applicable	Yes
Interval Medical and Medication History Elements	
Current status of conditions that were ongoing at the previous visit	Any updates of previous entries (e.g., resolution dates)
Occurrence of any new conditions since the last visit	All newly identified adverse events
Current status of medications that were ongoing at the previous visit	Any updates of previous entries (e.g., stop dates)
Use of any new medications since the last visit	• All ARVs • All medications taken at onset of or in response to adverse events that are specified to be entered into eCRFs per Section 7.2
Laboratory results available in medical records since the last study visit	

6.17 Questionnaire Evaluations

Questionnaires to assess acceptability and tolerability of the study products will be administered by site staff to adult-participants at study visits specified in Appendix I-A, and data will be entered into eCRFs. Questionnaires will also be triggered for administration in the event of premature permanent study product discontinuation. The questionnaires may be administered in-clinic or, where necessary, telephonically and will cover topics such as perceptions of the study product injections, satisfaction with treatment, quality of life, and treatment preferences. Questionnaire topics may vary based on when each is administered during follow-up and based on participant Group. Following completion of the questionnaires, study staff should review the responses and refer any participant with potential adverse events to a study clinician to be assessed. Further guidance and considerations for conducting and reviewing the acceptability and tolerability assessments, the timing of administering the assessments relative to other visit procedures, as well as guidance regarding the appropriate site staff to administer specified assessments are provided in the IMPAACT 2040 MOP.

In addition to the acceptability and tolerability questionnaires, the Columbia-Suicide Severity Rating Scale (C-SSRS) Screening Version will be administered by site staff to adult-participants once at the Screening Visit and then again at the Final Scheduled Visit, with data entered into eCRFs. Per exclusion criterion 4.2.3.9, any adult-participant with suicidal ideation or attempt within six months of entry will be excluded from the study and should be referred to non-study care providers, as needed. See Section 8.11 for adult-participant management of psychiatric disorder and/or suicidal ideation or attempt occurring after entry.

6.18 Additional Considerations for Laboratory Procedures

Each study site and laboratory involved in this study will comply with the DAIDS policy on Requirements for DAIDS Funded and/or Sponsored Laboratories in Clinical Trials Policy, which is available at:
https://www.niaid.nih.gov/research/daids-clinical-research-laboratory-specimens-management

6.18.1 Specimen Collection

Specimens will be collected for this study as indicated in the Schedule of Evaluations and per detailed guidance provided in the Laboratory Processing Chart (LPC), which will be available on the study-specific website: https://www.impaactnetwork.org/studies/impaact2040

Consistent with US National Institutes of Health (NIH) Guidelines for Limits of Blood Drawn for Research Purposes at the NIH Clinical Center, adult blood collection will not exceed 10.5 mL/kg or 550 mL, whichever is smaller, over any eight-week period. Pediatric (infant) blood collection will not exceed 5 mL/kg in a single day or 9.5 mL/kg over any eight-week period.

In the event that blood collection must be limited, available specimens should be prioritized for use in the following order: (1) safety (chemistries, hematology), (2) HIV-1 viral load, (3) HIV NAT, (4) resistance testing, and (5) PK. This prioritization applies to both adult-participants and infant-participants.

The date and time of collection should be source documented for all samples collected for laboratory evaluations. All pre-dose PK sample collections should be performed on the same day as, but prior to, administration of the specified study product. The date and time of each PK sample collection timepoint must be source documented and entered into laboratory eCRFs or transferred electronically to the DMC through the Laboratory Data Management System (LDMS).

Site staff collecting specimens for PK evaluations must prepare workspace and supplies with regards to protecting all PK specimens from light. The PK sample collection must be sufficient for the number of aliquots specified in the LPC for CAB and for RPV. See Appendix I for required blood volumes.

6.18.2 Specimen Preparation, Testing, Storage, and Shipping

All specimens collected for this study will be labeled, transported, processed, tested, stored and/or shipped in accordance with the DAIDS policy referenced in Section 6.18, site and local laboratory SOPs, and the LPC. The frequency of specimen collection and testing will be directed by the Schedule of Evaluations and specifications for clinical management provided in Section 8. The LDMS will be used to document specimen collection, testing, storage, and shipping. Any

specimens stored at the Screening Visit for participants who do not subsequently enroll in the study will be destroyed. Similarly, any specimens from enrolled participants that are leftover once all protocol-required testing is complete will be destroyed.

All HIV-1 RNA assays must be performed in a laboratory that is CLIA-certified or equivalent (for US sites) or VQA-certified (for South African sites) for the assay performed and have a lower limit of quantification of less than 50 copies/mL using standard manufacturers' protocols. Sample dilution for HIV RNA assays should not occur. If an adequate sample volume cannot be collected at a given study visit, the participant should return to the clinic on a different day within the allowable visit window for a repeat specimen collection attempt. CD4+ cell counts must be performed in a CLIA-certified (US) or equivalent or VQA-certified (South African) laboratory.

HIV-1 resistance samples collected at the Viral Load Assessment Visit(s) must be processed and retained at the site laboratory pending HIV-1 RNA test results to confirm virologic failure. If virologic failure is confirmed, samples from the Viral Load Assessment Visit(s) will be shipped to the designated testing laboratory (residual aliquots will be stored at the site laboratory) and resistance testing will be performed in real time. If virologic failure is not confirmed, all aliquots will remain stored at the site laboratory. Testing of baseline samples collected at the Entry Visit for archived resistance will be directed by the CMC.

Specimens collected, processed, and stored at site laboratories for plasma PK evaluations are expected to be shipped to the designated testing laboratory in real time, defined as within two to four weeks of specimen collection, and will be tested upon receipt, which is expected to take approximately 10 business days. Additional details will be specified in the LPC. Chest/breastmilk and cord blood samples will be batch shipped approximately every six months. Samples may be requested for more rapid shipment prior to the interim analysis and at the end of the study.

6.18.3 Biohazard Containment

As the transmission of HIV-1 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 US Centers for Disease Control and Prevention, NIH, and other applicable agencies. All specimens will be shipped using packaging that meets requirements specified by the International Air Transport Association Dangerous Goods Regulations for UN 3373, Biological Substance, Category B, and Packing Instruction 650. Culture isolates, if obtained in this study, are to be shipped as specified for UN 2814 Category A Infectious Substances.

7 SAFETY ASSESSMENT, MONITORING, AND REPORTING

Participant safety will be carefully assessed, monitored, and reported at multiple levels throughout this study. Sections 7.1-7.3 describe safety-related roles, responsibilities, and procedures for site investigators. The safety monitoring roles of the Clinical Management Committee (CMC) and the IMPAACT SMC are briefly referenced in Section 7.1 and described in greater detail in Section 9.4.1 and 9.4.2.

7.1 Safety-Related Roles and Responsibilities

7.1.1 Site Investigators

Site investigators are responsible for continuous monitoring of all study participants and for alerting the CMC if unexpected concerns arise. Site investigators will enter safety-related data into eCRFs as indicated in Section 7.2 and complete EAE reporting as indicated in Section 7.3.

Site investigators are also responsible for prompt reporting of any unanticipated problems involving risks to participants or others to all applicable IRBs/ECs and other applicable review bodies, per the procedures of each applicable review body.

7.1.2 Clinical Management Committee (CMC)

The following protocol team members comprise the CMC: Chair, Vice Chair, Medical Officers, Pharmacologists, Virologist, Statisticians, Data Managers, Clinical Research Managers (CRM), Laboratory Center representatives, and pharmaceutical company representatives. The CMC will provide guidance as needed to site investigators regarding all aspects of participant management, including but not limited to questions of participant eligibility and management of adverse events, study product regimens, and concomitant medications. Refer to Section 8 for more information on participant management.

On behalf of the full Protocol Team, the CMC will monitor participant safety through routine review of study data reports as described in Section 9.4.1.

7.1.3 Study Monitoring Committee (SMC)

An independent IMPAACT SMC will monitor participant safety through routine and as needed reviews of study data, including the planned interim analysis. Refer to Section 9.4.2 for more information on the role of the SMC in monitoring this study.

7.2 Safety-Related Data Collection

This section describes eCRF data collection for pre-existing conditions and adverse events. As part of this description, reference is made to severity grading and criteria for EAE reporting; refer to Section 7.3.2 and 7.3.3, respectively, for detailed information on these topics.

The definition of the term adverse event provided in Version 2.0 of the Manual for Expedited Reporting of Adverse Events to DAIDS (DAIDS EAE Manual) will be used in this study. This definition will be applied to each adult-participant and their infant-participant beginning at the time of the adult-participant's first study-provided injection, regardless of subsequent exposure to study product. Any untoward medical conditions identified prior to first study-provided injection will be considered pre-existing conditions. Refer to Section 4.4 for more information on defining the effective point of enrollment in the study.

Pre-existing conditions and adverse events will be entered into eCRFs as specified below.

7.2.1 Safety-Related Data Collection for Adult-Participants

Adult-Participant Pre-Existing Conditions

The following adult-participant pre-existing conditions will be entered into medical history eCRFs:

- All conditions (i.e., Grade 1 or higher) identified during the current pregnancy or ongoing at study entry prior to the first study-provided injection, with the exception of Grade 2 or lower pregnancy/postpartum conditions listed below under Adult-Participant Adverse Events
- Any other medical condition (i.e., Grade 1 or higher) experienced prior to the first study-provided injection and deemed clinically significant by the site investigator, including, but not limited to, significant central nervous system disorders (including seizures and migraines/headaches), mood disorders (such as depression), and significant liver disease resulting in hospitalization or interfering with daily activities

Adult-Participant Adverse Events

All laboratory and clinical adverse events (i.e., all Grade 1 or higher) will be entered into adverse event eCRFs except for the pregnancy-related events listed below.

All adverse events assessed as related to the study product and all serious adverse events (SAEs) and all other adverse events that meet criteria for EAE reporting will be entered on eCRFs, regardless of whether they are common during pregnancy.

Unless assessed as related to study product or determined to be SAEs or EAEs, the following pregnancy-related adverse events will not be entered on eCRFs:

- Any of the following pregnancy/postpartum conditions if Grade 2 or lower:
  - Bilateral, painless, lower extremity edema
  - Physiologic discharge associated with pregnancy
  - Nausea/vomiting of pregnancy (not requiring anti-emetics/treatment)
  - Gastroesophageal reflex disease/heart burn
  - Lower back pain
  - Urinary frequency not associated with a urinary tract infection
  - Sleep disturbances
  - Constipation
  - Hemorrhoids
  - Stretch marks
  - Abdominal pain due to round ligament pain
  - Carpal tunnel syndrome
  - Varicose veins
  - Chest/breast growth/discomfort
  - Shortness of breath (dyspnea)
    - Note: Dyspnea out of proportion to what is expected should be evaluated for hypoxia. Dyspnea with hypoxia should be reported as an adverse event on eCRFs, regardless of relatedness assessment.
  - Uterine cramping or perineal pain post-delivery
  - Lochia or vaginal bleeding during the postpartum period
- Decreased fetal movement; however, other adverse events identified during clinical evaluation of decreased fetal movement will be captured on eCRFs.
- Findings on electronic fetal monitoring strips.

7.2.2 Safety-Related Data Collection for Infant-Participants

Infant-Participant Pre-Existing Conditions

Because infant-participants will be exposed to study product in utero, all abnormal conditions identified during and after birth will be considered adverse events. No pre-existing conditions will be entered into eCRFs.

Infant-Participant Adverse Events

The following adverse events, inclusive of abnormal laboratory test results and clinical signs, symptoms, and diagnoses, will be entered into infant-participant adverse event eCRFs:

- All Grade 2 or higher adverse events
- All congenital anomalies that meet the MACDP defect criteria
- All SAEs as defined in Version 2.0 of the DAIDS EAE Manual and all other adverse events that meet criteria for EAE reporting

7.2.3 Laboratory Test Results for Adult-Participants and Infant-Participants

All safety-related laboratory test results for adult-participants and infant-participants will be entered into laboratory eCRFs, regardless of severity grade and regardless of whether the test was protocol-specified or ordered by the site investigator for clinical purposes. All pregnancy test results, hepatitis B and hepatitis C test results, and CD4 cell counts and percentages will also be entered into laboratory eCRFs. HIV-1 RNA and infant-participant HIV NAT results will be entered into laboratory eCRFs or transferred electronically to the DMC through the LDMS. ARV resistance test results will be transferred electronically to DMC using data submission utilities.

7.3 Expedited Adverse Event (EAE) Reporting

7.3.1 EAE Reporting to DAIDS

Requirements, definitions and methods for expedited reporting of adverse events are outlined in Version 2.0 of the DAIDS EAE Manual, which is available 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 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

Queries may also be sent from within the DAERS application itself.

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

7.3.2 EAE Reporting Requirements for this Study

The SAE Reporting Category, as defined in Version 2.0 of the DAIDS EAE Manual, will be used

for adult-participants and infant-participants in this study.

In addition, the following adult-participant events must also be reported in an expedited manner (i.e., as EAEs), regardless of relationship to study product:

- Grade 2 or higher ALT or AST with total bilirubin greater than or equal to 2x ULN and direct bilirubin greater than 35% of total bilirubin
- Grade 2 or higher ALT or AST with signs/symptoms of clinical hepatitis
- Grade 3 ALT or AST that persists greater than two weeks
- Grade 4 ALT or AST
- Grade 3 or higher hypersensitivity/allergic reactions deemed related to study product
- Grade 3 or higher post-injection reaction (i.e., within minutes after the injection dyspnea, bronchospasm, agitation, abdominal cramping, rash/urticaria, dizziness, flushing, sweating, oral numbness, changes in blood pressure, and pain (e.g., back and chest))
- Any seizure event
- Grade 3 or higher psychiatric disorders
- Grade 2 or higher suicidal ideation or attempt
- Pregnancy complications that result in medically indicated and/or elective termination of the pregnancy
- Spontaneous abortions and fetal deaths
- Grade 3 or higher QTcF

The study products for which expedited reporting are required are oral cabotegravir (CAB), long-acting injectable cabotegravir (CAB LA), oral rilpivirine (RPV), and long-acting injectable rilpivirine (RPV LA).

7.3.3 Grading Severity of Events (applies to EAEs and all other adverse events)

The Division of AIDS Table for Grading the Severity of Adult and Pediatric Adverse Events (DAIDS AE Grading Table), Corrected Version 2.1, dated July 2017, will be used in this study, except where otherwise noted below. This table is available on the RSC website at https://rsc.niaid.nih.gov/clinical-research-sites/daids-adverse-event-grading-tables.

7.3.3.1 Protocol-Specific Grading for Participants

QTcF Intervals

The DAIDS AE Grading Table provides grading for prolonged QTc interval assessed per Bazett's formula (QTcB); in IMPAACT 2040, prolonged QTc interval should be assessed using the DAIDS-indicated parameters for prolonged QTc interval but corrected per Fridericia's formula (QTcF).

Creatinine and eGFR

The Division of AIDS Table for Grading the Severity of Adult and Pediatric Adverse Events provides severity grading for Creatinine based on both absolute value and change from baseline. Because participants are pregnant at study entry and experience physiologic changes during pregnancy that affect these parameters, changes from baseline do not provide a valid measure of renal function over time (antepartum and postpartum). Therefore, grading for Creatinine will be based on absolute values, only.

Although creatinine clearance (CrCl) is not a required study procedure, if the site receives CrCl reports from the testing laboratory, site staff should assess the result and grade according to the

Division of AIDS Table for Grading the Severity of Adult and Pediatric Adverse Events, using the absolute value, only. When assessing the grade for a CrCl result, site staff should confirm the result utilizing the 2021 CKD-EPI equation, as provided in the IMPAACT 2040 MOP.

7.3.3.2 Protocol-Specific Definitions and Grading for Infant-Participants

Fever

When temperatures are collected, clinical discretion should be used to determine if an axillary or non-axillary temperature is most appropriate with the below specified grading used for participant safety management:

Table 7. 2040 protocol-specific grading table for infant-participants - fever

	Grade 1	Grade 2	Grade 3	Grade 4
Fever (axillary temperature)	37.4 to <38.0°C	38.0 to <38.7°C	38.7 to <39.4°C	≥39.4°C
Fever (non-axillary temperature)	38.0 to < 38.6°C or 100.4 to < 101.5°F	≥ 38.6 to < 39.3°C or ≥ 101.5 to < 102.7°F	≥ 39.3 to < 40.0°C or ≥ 102.7 to < 104.0°F	≥ 40.0°C or ≥ 104.0°F

Creatinine and Creatinine Clearance

The DAIDS AE Grading Table provides grading for creatinine and CrCl values based on both absolute value and change from baseline. For this study, only the grading based on absolute value should be used.

7.3.4 EAE Reporting Period

The EAE reporting period for this study begins at the time of first study-provided injection and continues through the date of the last regularly scheduled follow-up visit.

After the above-specified EAE reporting period, unless otherwise noted, only Suspected, Unexpected Serious Adverse Reactions (SUSARs) as defined in Version 2.0 of the DAIDS EAE Manual will be reported to DAIDS if the study staff become aware of the events on a passive basis (from publicly available information).

8 PARTICIPANT MANAGEMENT

8.1 Adult-Participant and Infant-Participant Adverse Events

All adult-participant and infant-participant adverse events identified in this study will be source documented in participant research records, consistent with the requirements referenced in Section 11. Among other details, source documentation will include the severity of each event (graded as described in Section 7.3.3) and its relationship to study products, assessed by the site investigator or designee according to the following categories and definitions:

Related There is a reasonable possibility that the adverse event may be related to the study product(s)

Not related There is not a reasonable possibility that the adverse event may be related to the study product(s)

Further standardized guidance on determining whether there is a reasonable possibility of a relationship is available in the DAIDS EAE Manual, referenced in Section 7.3.1 above.

For adult-participants, relationship should be assessed for each study product received (ingested or injected).

For infant-participants, relationship should be assessed for study products received by the adult-participant to which the infant-participant may have been exposed in utero or through chest/breastfeeding.

Individual dose adjustments or reductions of study products for management of toxicity-related AEs are not allowed. In the event of a temporary study product hold or a permanent discontinuation of study product, both study products that are part of the adult-participant's current study regimen will be held (or discontinued). See Section 8.15 regarding temporary product holds and Section 8.16 regarding permanent discontinuation of study product and considerations for adult-participants resuming (non-study provided) oral ART.

All adverse events must be followed to resolution (return to baseline) or stabilization, with the frequency of repeat evaluations determined by the clinical significance of each event. Additional evaluations beyond those listed in Appendix I-A, Appendix I-B, and Appendix I-C may be performed at the discretion of the site investigator to determine the etiology of a given event and/or further assess its severity or relationship to study product. Clinical management of all adverse events should be provided consistent with the best medical judgment of the site investigator and local clinical practice standards.

Adult-participants and infant-participants with Grade 3 or higher adverse events at their last regularly scheduled study visit should remain on study for up to 28 days or until resolution or stabilization, whichever is sooner. The frequency of any additional adverse event follow-up visits is determined by the site investigator in consultation with the CMC. If the site investigator feels that additional PK evaluations would be of benefit during these follow-up visits, testing may be performed in consultation with the CMC. Once AE stabilization is established, the site investigator should actively facilitate referral to local non-study sources of appropriate medical care and treatment.

Unless otherwise specified, when an adverse event requires consultation with the CMC, the CMC should be contacted as soon as possible and within two business days of site awareness of the event.

8.2 Management of Participant Adverse Events

Sections 8.2-8.17 provide detailed participant and study product management on specified adult-participant and infant-participant adverse events including specified abnormal laboratory test result values. If an observed adverse event or abnormal laboratory test result value is not specifically listed in the sections below, the guidance in this section (Section 8.2) should be followed.

Site investigators are encouraged to register included adult-participants with the APR prospectively as soon as possible after the adult-participant starts treatment as part of the study on Day 1, and before the pregnancy outcome (otherwise there is less likelihood of the adult-participant being included in the APR) by calling the following number in the US: +1-800-258-

4263. Outside of the US, please see the APR website (www.apregistry.com) for additional toll-free numbers, copies of applicable CRFs, and fax.

In general, the site investigator has the discretion to temporarily hold study product at any time if they feel that continued product use would be harmful to the adult-participant or interfere with treatment deemed clinically necessary. The CMC should be notified within 48 hours when study product holds are required. See Sections 8.3 and 8.4 below.

- **Grade 1 or Grade 2, regardless of relationship to study product:** Continue study product and manage adult-participant according to standard of care practice at the site.
- **Grade 3 assessed as not related:** Continue study product and re-evaluate adult-participant at least weekly until improvement to Grade 2 or lower. If improvement to Grade 2 or lower cannot be documented in two weeks, consult the CMC.
- **Grade 3 assessed as related:** Temporarily hold study product use, notify the CMC within 48 hours, and re-evaluate the adult-participant at least weekly until improvement to Grade 2 or lower. If within two weeks the AE has improved to Grade 2 or lower, study product may be resumed. Consult the CMC if improvement to Grade 2 or lower cannot be documented within two weeks.
    - If study product use is resumed and the same Grade 3 AE deemed related to study product recurs at any time, the site investigator must temporarily hold study product and consult the CMC for further guidance.
- **Grade 4 regardless of relationship to study product:** Temporarily hold study product, re-evaluate the adult-participant as soon as possible or within 48 hours, and consult the CMC. Continue the temporary product hold until a recommendation is obtained from the CMC.

8.3 Injection Site Reactions (ISRs)

An ISR is defined as an adverse event which, in the opinion of the IoR or designee, results in pain, tenderness, erythema, redness, induration or swelling, or pruritis. ISRs should be assessed and reported per the Site Reactions to Injections and Infusions section of the DAIDS toxicity tables.

Adult-participants with ISRs should be managed as follows, regardless of relationship to study product:

- **Grade 1 or Grade 2:** Continue study product, and manage the adult-participant symptomatically (e.g., cold/warm compress, acetaminophen, ibuprofen).
- **Grade 3 or 4:** Consult the CMC to determine etiology and study product management.

8.4 Suspected IM Maladministration and/or Post-Injection Reaction

In the event that an adult-participant experiences a serious post-injection reaction or IM maladministration is suspected at any time (e.g., suspected under or overdose or inadvertent IV dosing), the site investigator should request that the adult-participant stay onsite for approximately two to three hours post-dose for safety monitoring. If inadvertent intravenous administration is suspected, an ECG should be obtained within two to three hours, along with any other supportive testing needed at the discretion of the site investigator. Additionally, PK samples should be drawn approximately two hours post-dosing for evaluation of CAB and RPV plasma concentrations. The CMC should be notified immediately and no later than 24 hours after a suspected maladministration event. Additional safety labs or PK samples may be requested by the CMC or collected per site investigator discretion.

8.5 Lipase Elevations and Pancreatitis

Adult-participants with asymptomatic elevations in lipase should be managed as follows, regardless of relationship to study product:

- **Grade 1 or 2:** Continue study product, and be followed for development of symptoms (i.e., pancreatitis) according to standard of care practice at the site.
- **Grade 3 or higher:** Temporarily hold study product and repeat testing on a newly obtained sample within two weeks. If the repeat test result is Grade 2 or lower, resume study product. If upon resuming study product lipase elevation is Grade 3 or higher, permanently discontinue study product. If the repeat test result is Grade 3 or higher, and in the absence of other diagnoses, permanently discontinue study product.

Adult-participants with a confirmed diagnosis of clinical pancreatitis (i.e., symptomatic elevations in lipase) should be managed as follows:

- **Grade 2 or higher assessed as not related:** Temporarily hold study product, notify the CMC within 48 hours, and re-evaluate the adult-participant weekly until complete resolution (i.e., return to baseline). Return to baseline and CMC approval to resume study product must be documented before lifting the temporary study product hold. Upon returning to baseline, re-evaluate the participant every two weeks for at least six weeks. If after resuming study product, any elevation of lipase of Grade 2 or higher, or any recurrence of symptoms, then permanently discontinue study product.
- **Grade 2 or higher assessed as related:** Permanently discontinue study product and notify the CMC.

8.6 Elevations in ALT or AST, Bilirubin

ALT, AST, and bilirubin (total and direct) will be routinely monitored for adult-participants in this study.

In all cases of elevated ALT, AST, and/or elevated bilirubin (total and direct), possible alternative etiology should be assessed, and the underlying illness treated, or the likely causative agent removed. Sites should counsel adult-participants about signs and symptoms of hepatotoxicity. Adult-participants should be advised to notify the study site immediately if they develop any concerning signs or symptoms: new or worsening nausea, vomiting, unexplained loss of appetite; yellowing of the skin or eyes; increased weakness or fatigue; pain in the upper abdomen (liver tenderness or hepatomegaly); pale or clay-colored stools; itchy palms and/or soles of the feet; tea-colored urine; and/or unexplained weight loss.

Elevated bilirubin in the absence of elevated ALT or AST should be managed per Section 8.2. In the event total bilirubin is greater than 1.5xULN, reflex testing for fractionated bilirubin should be conducted.

ALT or AST results of severity Grade 1 or 2 — other than the Grade 2 results specified in the first two bullet points below — require no additional action. Study product should be continued with routine monitoring per the Schedule of Evaluations unless more frequent monitoring is considered clinically indicated in the opinion of the site investigator. If any results of severity Grade 3 or higher are obtained, all four tests (i.e., ALT, AST, and bilirubin [total and direct]) should be repeated as soon as possible and within three business days. Re-evaluation should continue at least weekly until improvement to Grade 2 or lower or until stabilized and no longer in need of frequent monitoring, as determined by the site investigator and in consultation with the CMC.

Study product must be held in the following scenarios (See Section 7.3.2 for EAE reporting requirements):

- **Grade 2 or higher ALT or AST** with total bilirubin greater than two times the upper limit of normal (greater than 2xULN). In this case, study product should be permanently discontinued, and the CMC should be notified.
- **Grade 2 or higher ALT or AST** with signs or symptoms of clinical hepatitis (e.g., fatigue, nausea, vomiting, right upper quadrant pain, jaundice) or hypersensitivity (e.g., rash, fever, facial edema, eosinophilia, difficulty breathing). In this case, if another cause of the ALT or AST elevation is identified, consideration may be given to resuming study product with approval from the CMC.
- **Grade 3 ALT or AST** for more than two weeks (with total bilirubin less than or equal to 2xULN and no signs or symptoms of clinical hepatitis or hypersensitivity). In this case, if another cause of the ALT or AST elevation is identified, consideration may be given to resuming study product, with approval from the CMC.
- **Grade 4 ALT or AST**. Hold study product upon first identification of the Grade 4 result, i.e., pending receipt of the repeat test result; inform the CMC of the initial result and the repeat result. In the case of a confirmed Grade 4 result, if another cause of the ALT or AST elevation is identified, consideration may be given to resuming study product, with approval from the CMC.

8.7 Hypersensitivity Reaction

Hypersensitivity includes a constellation of symptoms, which may include but are not limited to severe rash, or rash accompanied by fever, general malaise, fatigue, muscle or joint aches, blisters, oral lesions, conjunctivitis, facial oedema, hepatitis, eosinophilia or angioedema, difficulty breathing.

If the site investigator suspects HSR deemed related to the study product, the participant should be managed as follows:

- Temporarily hold study product, and within 24 hours of site awareness repeat hematology and chemistries testing on newly obtained samples and notify the CMC within 24 hours.
- Continue to re-evaluate the adult-participant and repeat testing on newly obtained samples at least twice weekly until any abnormal laboratory test results return to baseline values or stabilize.
- Refer adult-participant to a specialist or hepatology consultation, at the discretion of the site investigator, and in consultation with the CMC.

8.8 Allergic Reaction

Adult-participants with allergic reactions should be managed as follows:

- **Grade 1 or higher assessed as not related, and Grades 1 or 2 assessed as related:** Continue study product, and antihistamines, topical corticosteroids, or antipruritic agents may be prescribed at the discretion of the site investigator. The adult-participant should be advised to contact the site immediately if there is any worsening of symptoms or if further systemic signs or symptoms develop.

- **Grade 3 or higher assessed as related:** Permanently discontinue study product and notify the CMC within 24 hours. Manage as clinically appropriate including antihistamines, topical corticosteroids, or antipruritic agents. Admission to hospital may be required for severe allergic reactions. Following clinical stabilization, re-evaluate the adult-participant weekly, and manage according to standard of care practice at the site until resolution to baseline.

8.9 Skin Rash

All adult-participants experiencing a rash should be assessed for systemic symptoms, laboratory abnormalities, or mucosal involvement.

Adult-participants with skin rash should be managed as follows, regardless of relationship to study product:

- **Grade 1 or Grade 2:** Continue study product use at the discretion of the site investigator.
- **Grade 3 or higher:** permanently discontinue study product and consult the CMC within 48 hours. Re-evaluate daily for at least five days for systemic symptoms, laboratory abnormalities, mucosal involvement, and for any progression of the rash or increase in severity. Adult-participants may be referred to a dermatologist, at the discretion of the site investigator.

8.10 Deep Vein Thrombosis (DVT) and Pulmonary Embolism (PE)

Adult-participants who develop DVT and/or PE should be managed clinically per standard of care and would be discontinued from study product as per Section 8.16 presuming need for systemic therapeutic anticoagulation.

8.11 Psychiatric Disorders and Suicidal Ideation or Attempt

All potential adult-participants will be screened for suicidal ideation or attempt using the C-SSRS and excluded from the study if they experienced suicidal ideation or attempt within six months prior to entry. Enrolled adult-participants will complete the C-SSRS again during the postpartum period at the Final Scheduled Visit. Adult-participants may also report symptoms of depression, other psychiatric disorders, and/or suicidal ideation or attempt at any time during follow-up outside of the formal screening. Participants who report any such symptoms, regardless of relationship to study product, will be managed by the site investigator consistent with site SOPs, which should reflect local standards of care. Referrals for specialist evaluation and treatment should be made when clinically indicated. Adult-participants will also be instructed to contact study staff immediately if symptoms of severe acute depression (including threats of harm to self or others) develop. Site SOPs must include procedures for managing participant reports of psychiatric symptoms and risk of suicide. The severity of psychiatric disorders and suicidal ideation or attempt will be graded according to the DAIDS AE Grading Table. The CMC must be consulted within 24 hours regarding the management of any grade 3 or higher psychiatric disorder or suicidal ideation or attempt; consultation is available but not required for Grade 1 and Grade 2 events.

8.12 Management of QTcF Prolongation

ECGs will be performed in triplicate at screening and if clinically indicated to evaluate a cardiac complaint during study follow-up. See Section 6.9 for the specifics concerning QTcF prolongation requiring repeat ECG readings. If any one of the repeated readings confirm a QTcF interval greater than or equal to 500 msec, or a greater than 60 msec increase from baseline,

temporarily hold study product and assess adult-participant for concomitant medications known to cause prolonged QT or Torsades de pointes. Study product may be resumed in consultation with the CMC, and if the prolonged QTcF is assessed as not related to study product. If the prolonged QTcF is assessed as related, or no other likely cause identified, permanently discontinue study product.

For any other adverse cardiac signs or symptoms experienced by the adult-participant or for any abnormality or irregularity reported by the automated read during follow-up that is considered clinically significant by the site investigator or designee, a cardiologist should be consulted, and the CMC notified.

8.13 Monitoring and Management of Adult-Participant HIV-1 Viral Load

Monitoring

HIV-1 RNA (viral load) will be monitored closely with frequent testing as specified in the Schedules of Evaluations in Appendix I-A, Appendix I-B, and Appendix I-C. All HIV-1 RNA assays must be performed in a CLIA-certified or equivalent (US sites) or VQA-certified (South African) laboratory using the testing platform specified in the LPC.

Site investigators should review the results of each test as well as trends over time and consult with the CMC regarding any individual test results or trends of concern. Viral load results should be provided to participants and may be used to guide adherence counseling.

Definition and Confirmation of Virologic Failure

Any adult-participant with a plasma HIV-1 RNA level greater than or equal to 50 copies/mL after enrollment should be recalled to the clinic as soon as possible for completion of the Viral Load Assessment Visit for additional clinical management, see Section 6.6. Notify the CMC of any adult-participant with HIV-1 RNA level greater than or equal to 50 copies/mL. Note that study enrollment may continue during the CMC review. Refer to Section 6.6 and Appendix III for details regarding the Viral Load Assessment Visit.

Any adult-participant with a plasma HIV-1 RNA level greater than or equal to 200 copies/mL will be classified as having suspected virologic failure. The adult-participant needs to have two successive plasma HIV-1 RNA test results greater than or equal to 200 copies/mL from separate specimens collected at least two weeks apart to be classified as having confirmed virologic failure.

Management of Adult-Participants with Confirmed Virologic Failure

The CMC should be consulted regarding any adult-participant with confirmed virologic failure. All adult-participants with confirmed virologic failure will be permanently discontinued from study product. Refer to Section 8.16 for adult-participant management regarding permanent discontinuation of study product.

HIV-1 resistance samples will be processed and stored per Section 6.18.2 and the LPC. Upon confirmation of virologic failure, shipping and testing of resistance samples will be performed, per Section 6.18.2 and the LPC. These resistance test results will be reviewed by the site investigator, and used to inform a recommended cART regimen, in consultation with the CMC. Adult-participants should resume the recommended non-study provided oral cART as soon as possible and within four weeks.

For adult-participants in their third trimester, consideration should be given to mode and timing of delivery and adult-participant and infant-participant prophylaxis. In the case of sustained elevated participant viral load, timing, and mode of delivery as well as participant prophylaxis with IV AZT, should be per local standard of care (e.g., cesarean delivery prior to onset of labor at 38 weeks EGA). Adult-participant prophylaxis with IV AZT and infant-participant prophylaxis should also be administered per local standard of care.

8.14 Management of Adult-Participants who Experience Subsequent Pregnancies on Study

Site clinicians should consult with the CMC regarding any adult-participants who conceive during the study. The CMC should be notified immediately and no later than 24 hours following receipt of a positive pregnancy test result; study product use may continue during CMC consultation. A confirmatory pregnancy test should be conducted as soon as possible and within 48 hours.

Sites should actively refer participants who experience subsequent pregnancies following the study pregnancy outcome to non-study care following local standard of care and encourage them to engage in care as soon as possible.

Follow-up visits for adult-participants with subsequent pregnancies will conclude at the originally scheduled Final Scheduled Visit, but study exit will be postponed until delivery or other pregnancy outcome; see Section 6.8.1.

Study sites are strongly encouraged to prospectively register adult-participants with subsequent pregnancies in the APR prior to pregnancy outcome.

8.15 Criteria for Deferring Study Product and Temporary Hold of Study Product

At each study product administration time point, the site investigator must confirm adult-participant eligibility to receive study product (see Section 6). Study product administration must be deferred consistent with the guidance provided in this section.

For any other significant medical condition that, in the opinion of the site investigator, would make it unsafe to administer study product or make it difficult to assess for subsequent study product related adverse events, if present on the scheduled day of study product administration, administration must be deferred, and the CMC should be consulted within 48 hours on next steps and continued study product management.

For all temporary holds, both CAB and RPV formulations that make up the adult-participant's current regimen should be held, and the CMC should be consulted as soon as possible and within 48 hours. In the event of a hold on CAB LA and RPV LA, no new injections should be administered during the hold period. A hold should be put in place if/when conditions requiring a hold are met, even if injections are not immediately due for administration. The AE should be managed in accordance with the specifications detailed in the applicable protocol section and with consideration given to the long-acting nature of the injectable treatment regimen. In the event of a hold on oral CAB and oral RPV, no new oral study product should be dispensed while the hold is in place. For both injectable and oral formulations, when a temporary hold is no longer required, the temporary hold is effectively lifted, and study product is considered resumed.

In the case of a temporary hold, the CMC may recommend resuming a (non-study provided) cART regimen. For adult-participants resuming a cART regimen for the duration of a temporary

study product hold, site staff should provide the adult-participant with referrals to non-study sources of treatment, as applicable. See the IMPAACT 2040 MOP for operational consideration and guidance.

Study product will be temporarily held from an adult-participant for any of the following reasons:

- Meeting the condition-specific criteria for holding study product as outlined in Sections 8.1-8.14.
- Report of use of prohibited concomitant medications (see Section 5.9). Study product use may resume upon consultation with the CMC and when the participant reports that they are no longer taking the prohibited medication, provided other reasons for temporary study product hold/permanent discontinuation do not apply. The CMC should be consulted in all cases of an adult-participant reporting taking a prohibited concomitant medication during the course of the study.
- The adult-participant is unable or unwilling to comply with required study procedures, such as protocol-required laboratory assessments or injectable study product visits, or otherwise might be put at undue risk to their safety and well-being by continuing study product use, according to the judgment of the site investigator. The site investigator must consult the CMC on all temporary study product holds instituted for this reason, for further guidance on resuming study product use, continuing the temporary hold, or progressing to permanent discontinuation.

8.16 Criteria for Premature Permanent Discontinuation of Study Product

See Section 4.6 for guidance regarding participant management in the event of early termination or withdrawal from study participation. Administration of study product will be permanently discontinued in the following circumstances:

- Adult-participant intention to discontinue study product
- Sustained non-adherence to injection visit schedule that, in the opinion of the site investigator and in consultation with the CMC, warrants early study product discontinuation (per site investigator discretion, a temporary product hold may be initially implemented; see Section 8.15).
- The adult-participant requires treatment with prohibited medications (see Section 5.9)
- The adult-participant experiences an adverse event that requires discontinuation as defined in Section 8.2.
- Virologic failure as described in Section 8.13.
- The site investigator determines that further administration of virologic product would be detrimental to the participant's health or well-being.
- New data become available that indicate study products should be discontinued as determined by the CMC.

Adult-participants who permanently discontinue study product should resume (non-study provided) oral ART as follows:

- All adult-participants on a Q4W dosing regimen: within four weeks of their last study product injection.
- All adult-participants on a Q8W dosing regimen: within eight weeks of their last study product injections.

Adult-participants who have received at least one CAB LA + RPV LA injection while on study and subsequently permanently discontinue injectable study product will remain on study together with their infant-participant for the duration of their originally planned follow-up schedule. All visit procedures should be conducted, with the exception of:

- Adherence counseling and prescribing, preparing, and administering injectable study products will be discontinued
- Acceptability/tolerability assessments will be administered once (at point of discontinuation) and then omitted at subsequent visits

8.17 Infant-Participant Management

Infant-participants should receive ARV prophylaxis and other standard interventions such as childhood immunizations consistent with local standards of care from non-study sources. Likewise, infant-participants diagnosed with HIV-1 infection should receive ART consistent with local standards of care from non-study sources.

In the event that an adult-participant needs to interrupt study product (e.g., due to an adverse event), information and counseling will be provided regarding locally available options for reducing the risk of perinatal HIV-1 transmission. Such options may include infant-participant ARV prophylaxis during chest/breastfeeding and replacement feeding if determined to be safe and accessible and if the adult-participant's ART interruption is likely to be prolonged. Any interventions to prevent perinatal transmission per standard of care are allowed and encouraged.

Infant-participant adverse events will be managed consistent with the best medical judgment of the site investigator and local clinical practice standards. It is not expected that adult-participant study product regimens will routinely be modified in response to infant-participant adverse events; the site investigator may modify infant-participant ARV use and other concomitant medications in response to infant-participant adverse events. Consultation with the CMC is available but not required for most infant-participant adverse events. However, should an infant-participant experience a Grade 3 or higher adverse event that is assessed by the site investigator as related to the adult-participant's study product regimen, the CMC should be consulted within two business days.

9 STATISTICAL CONSIDERATIONS

9.1 General Design Issues

This is a Phase I/II, multicenter, open-label, non-randomized, four group study to characterize the PK and safety of CAB LA + RPV LA during pregnancy and postpartum among people with HIV-1 virologic suppression, and their infants. Approximately 45 total pregnant adult-participants will be enrolled to switch to or to continue CAB LA + RPV LA during pregnancy. Adult-participants will be administered CAB LA + RPV LA on a fixed dosing schedule, either every 4 weeks (Q4W) or every 8 weeks (Q8W) throughout study follow-up. The study will first open to adult-participants newly starting the injectable regimen on a Q4W schedule (Q4W Switch Group) as well as adult-participants on both dosing schedules who continue to receive CAB LA + RPV LA (Continuation Groups). If the interim analysis (described in Sections 3.1 and 9.4.2.2) supports opening to the Q8W Switch Group, enrollment will open to this group as well. It is expected the majority of pregnant adult-participants will be in the Q4W Switch Group.

The primary objectives are to describe the PK and safety of CAB LA + RPV LA during

pregnancy and up to 18 weeks postpartum. The primary PK outcome measure is the minimum concentration (trough) of CAB LA + RPV LA, measured before the maintenance injections, in pregnancy/postpartum when initiated or continued in pregnancy. Trough is the main PK parameter of interest since low drug levels may lead to virologic rebound and ARV resistance. Due to accumulation, the troughs are expected to increase from injection to injection, and the main time of risk for virologic rebound is thought to be the first trough measured just before the first maintenance injection; however, this previously observed pattern might be different in pregnancy. The secondary objectives are to describe infant safety and pregnancy clinical outcomes; compare PK parameters of CAB LA + RPV LA in pregnancy and postpartum to historical controls and in pregnancy to postpartum; assess the maintenance of virologic suppression in pregnant people and frequency of perinatal HIV-1 transmission; characterize concentrations of CAB and RPV in infants exposed to CAB LA + RPV LA; and describe tolerability and acceptability of CAB LA + RPV LA. The other objectives are to determine CAB and RPV individual and population estimates during pregnancy and postpartum using PK modeling and characterize concentrations of CAB and RPV in cord blood and chest/breastmilk.

The majority of data will be collected within the Q4W Switch Group. Analyses for the primary PK outcome measure will be summarized within the Q4W and Q8W Switch Groups separately but combined across the Q4W and Q8W Continuation Groups. For all other primary and secondary outcome measures, the main focus of analyses will be on the Switch Group (Q4W and Q8W) and Continuation Group (Q4W and Q8W), to describe safety and efficacy among pregnant adults who either switch to CAB LA + RPV LA or choose to continue CAB LA + RPV LA during pregnancy.

This study's sample size was based on the primary PK analyses for the Q4W Switch Group, and safety analyses for adult-participants in the Switch Group (Q4W and Q8W) and the Continuation Group (Q4W and Q8W). The main limitation of this study is the great amount of uncertainty, due to the small sample size, that will be present to accurately characterize infrequent risks potentially associated with the use of CAB LA + RPV LA. For example, if the probability of virologic failure while taking CAB LA + RPV LA in pregnancy is two or three times larger than what was observed in non-pregnancy (non-pregnancy virologic failure rate was approximately 1%), the probability of not observing a virologic failure on IMPAACT 2040 is 42% or 26% in 45 adult-participants and 62% or 49% in 25 adult-participants of the Q4W Switch Group, respectively. Similarly, the probability of not observing a perinatal transmission is 64% or 51% for a sample size of 45. These high probabilities imply that it will be hard to assess the clinical implications of the use of CAB LA + RPV LA in pregnancy, particularly if the average trough is low and there are no observed clinical events of concern. Based on exclusion criteria, this study is also limited to participants who have not experienced extreme adverse pregnancy events in prior pregnancies, which may result in a selected group of participants where event rates (e.g., pregnancy outcomes) are lower than in the eventual population who will be taking these regimens.

In the combined Continuation Groups the sample size is small, with heterogenous baseline length of exposure to CAB LA + RPV LA. This will make results based on the Continuation Groups difficult to interpret and they may not be generalizable. Selection bias is possible in the Continuation Groups because those who discontinue CAB LA + RPV LA before pregnancy due to tolerability, toxicity, or virologic failure will not be included in IMPAACT 2040. Selection bias may affect estimates across and within the Continuation Groups, and these groups cannot provide adequate comparisons to the Switch Groups. Also, the Continuation Groups do not have a lower limit on gestational age at entry but the Switch Group requires a minimum gestational age of 10 weeks gestation at entry; as a result, the Continuation Groups may have more early pregnancy losses than the Switch Groups and may not be comparable.

9.2 Randomization, Stratification, and Enrollment Limits

There is no randomization or stratification in this study. Approximately10 adult-participants can be enrolled in each of the Continuation Groups and in the Q8W Switch Group. Approximately 45 adult-participants will be enrolled overall, with a minimum of 25 enrolled in the Q4W Switch Group. Enrollment limits were described based on the precision of estimating the trough of CAB LA + RPV LA with the anticipated percentage with data unavailable, and based on the precision of estimating safety in pregnant adults. Adult-participants will not be replaced due to missing data. Enrollment limits may be adjusted as described in Section 3.4.

9.3 Sample Size and Accrual

Approximately 45 pregnant adult-participants will be enrolled with their infant-participant, with a minimum of 25 adult-participants in the Q4W Switch Group. Enrollment targets were selected to address the primary objective of this study to describe PK parameters of CAB LA + RPV LA during pregnancy and up to 18 weeks postpartum. The sample size is based on the precision to estimate the geometric mean of the trough concentrations of CAB LA + RPV LA, since the main concern is that drug exposure in pregnancy might be too low. We assessed precision by comparing the frequency of low PK exposure using a parametric model with parameters set at the lower limit versus the middle of the confidence interval for the geometric mean. Precision for estimating the probability of an adverse event in pregnant persons was also calculated.

The data analyses for the primary PK objective will include descriptive statistics and 90% confidence intervals (CIs) for the PK parameters of CAB LA + RPV LA. The confidence coefficient will be 90% rather than 95% to match the usual practice in the pharmacokinetic literature. Since steady-state for these LA injectables is not achieved until at least 1 (CAB) or 2 (RPV) years after treatment initiation, PK parameters will be described cross-sectionally at each visit and pregnancy time period (second trimester, third trimester, postpartum) in the Switch Groups, and by pregnancy time period in the Continuation Groups (20). PK results will be presented separately between the Q4W and Q8W dosing for the Switch Groups but will be combined across the Q4W and Q8W dosing for the Continuation Groups (see Section 9.5.2).

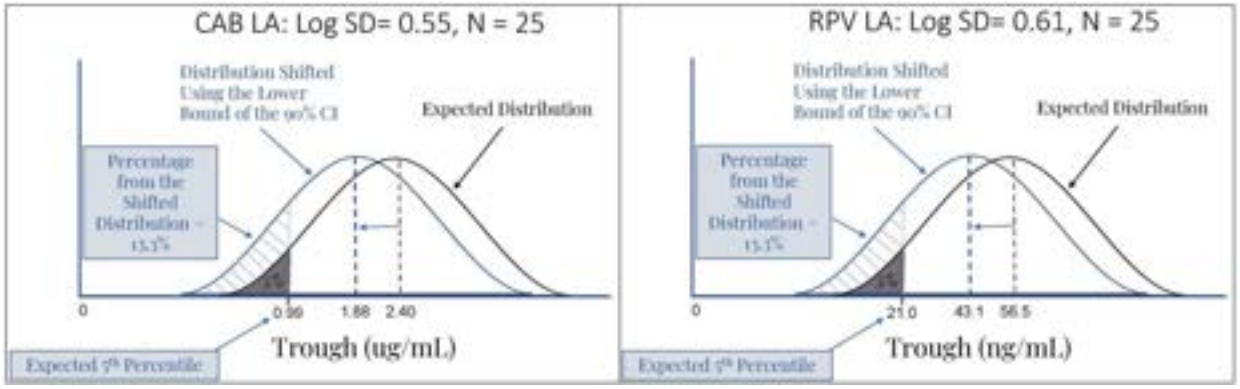
To describe the sample size for the PK primary objective, we considered the precision for estimating the trough of CAB LA + RPV LA with different target sample sizes and standard deviations, as measured by the width of two-sided 90% CIs, and whether the lower bound of the expected CI would exclude trough values potentially of concern. To compute the expected CIs and CI width, a simulation approach was taken. The simulation assumed the troughs were lognormally distributed, a common PK distributional assumption. Parameters for the lognormal distribution were modeled using data on 159 non-pregnant females who took oral CAB + RPV for four weeks and initiated CAB LA + RPV LA thereafter (32, 42). To account for uncertainty present in the previous studies, the mean of the log trough was assumed to follow a normal distribution and the variance was assumed to follow a chi-square distribution, with hyperparameters for these distributions estimated from the previous studies. To account for the possibility of observing increased variability due to a variety of gestational ages at baseline, two standard deviations were considered: 1) the previously observed value, and 2) a standard deviation 25% larger than what was previously observed. Across the Continuation Groups, a third standard deviation is also presented, 100% larger (twice as large) than what was previously observed, since this group includes adult-participants with varying treatment exposure and injection schedules (Q4W and Q8W). The averages of the lower limit and the upper limit of the 100,000 simulated 90% CIs were used to compute the expected 90% CIs of the geometric mean of the trough at a timepoint based on the proposed sample size.

The sample size selection for PK focuses on one key timepoint: Week 16 trough for adult-participants expected to be in the third trimester. The Protocol Team considers 30-32 weeks gestation as a key pregnancy timepoint to evaluate trough, since this timepoint is anticipated to have the largest effect on study product absorption, and in the Q4W Switch Group for the dosing schedule, the Week 16 post study product initiation visit is anticipated to have the most adult-participants within 30-32 weeks gestation. The sample size used to compute the expected confidence intervals was reduced from the number enrolled for three reasons: 1) not all pregnant persons are expected to be in the third trimester at Week 16 (i.e., enrollments early in gestation would not be expected to be in the third trimester by Week 16), 2) some samples might not be present due to lost to follow-up or other reasons for missing data, and 3) some pregnancy outcomes might occur before Week 16. The sample size simulations across the trimesters in the Q4W Switch Group assumed enrollment between 10 and 19 weeks 4 days in gestation were equally likely, 20% of pregnant persons would experience an early pregnancy outcome (<37 weeks), and a conservative estimate of 10% of adult-participants not having PK data due to intercurrent events or missing data (e.g., adult-participant lost to follow-up). For more details on intercurrent events for the primary analysis, see Section 2. Adult-participants in the Continuation Groups were assumed to have received CAB LA + RPV LA for 24 weeks at the time of trough sampling and have 10% of data unavailable due to gestational age, intercurrent events, or missing data. Since the combined Continuation Groups will primarily present PK within trimesters and pooled over visits, more data are expected to be included in analyses than the Switch Group.

The Protocol Team considers the 5th percentile of the trough distribution to be an important level. In this study, the observed percentage of adult-participants below the previously-observed 5th percentile in non-pregnant adults would be unstable due to the relatively small sample size (e.g., with only 20 adult-participants, 1/20 = 0.05 but 2/20 = 0.10; population PK modeling will be used to estimate the percentage below the threshold). For this reason and because the primary PK objective of the study is to estimate trough of CAB LA + RPV LA, the geometric mean trough was considered when setting the sample size. However, the level of geometric mean trough required to ensure viral suppression in the population of pregnant people is unknown. Given the difficulty of pre-specifying a value for the geometric mean that would result in unacceptably low exposure, the precision that is achievable with a given sample size was described using a location shift model (i.e., the whole distribution would shift as the mean changes) such that a lower geometric mean would result in a higher percentage of adult-participants with low CAB LA + RPV LA exposure.

The study team considered the sample size sufficient if there was no more than 10%-15% of adult-participants with trough under the expected 5th percentile when assuming the geometric mean is equal to the lower limit of the 90% confidence interval. See Figure 3 for a graphical description of how a change in the geometric mean would impact the percentage under the expected 5th percentile. The expected 5th percentile was computed using summary statistics from data on non-pregnant female persons at Week 16 (or Week 24 in the Continuation Group) after starting CAB LA + RPV LA, assuming the model described above. The percentage of adult-participants below the expected 5th percentile was computed assuming the geometric mean was shifted to the lower bound of the 90% CI based on the proposed sample size. The lower bound of the 90% CI was considered as the lowest geometric mean compatible with data in non-pregnant persons. As the sample size increases, the CI width for the geometric mean becomes smaller and the percentage of participants under the expected 5th percentile approaches 5%, assuming the lower bound of the CI. Under the same assumption and with a smaller sample size, the percentage of adult-participants under the expected 5th percentile based on the lower bound of the CI would be greater than 5%, since the lower bound of the CI approaches zero.

Figure 3. Example Illustrating the Calculation of the Percentage Under the Expected 5th Percentile



For clarity, trough values, rather than the log transformed trough values, were displayed in the figure above. For the sample size calculation, trough values were assumed to follow a log-normal distribution. The expected 5th percentile was derived from observed mean trough in non-pregnant female participants (32, 42). The geometric mean was shifted to the lower bound of the 90% CI.

Importantly, the lower limit of the 90% CI is not intended to represent a decision rule (i.e., success or failure of either CAB LA or RPV LA) since the true trough distribution may not be a location shift distribution, rather the sample size is presented this way to understand the level of uncertainty that would be present under a scenario in which the results were observed as expected from non-pregnant females.

The percentage under the PK trough threshold at the lower limit of the 90% CI is presented in Table 8 for third trimester Week 16 Q4W Switch Group adult-participants and in Table 9 for third trimester Continuation Group adult-participants.

Assuming the geometric mean trough is the same as in non-pregnant persons and 25 persons enroll in the Q4W Switch Group, the simulated geometric mean trough (90% CI) in the third trimester at Week 16 is 2.40 (1.88, 3.07) ug/mL for CAB LA and 56.5 (43.1, 74.3) ng/mL for RPV LA (Table 8). Assuming these geometric means and the model stated above, the expected 5th percentiles are 0.99 ug/mL for CAB LA and 21.0 ng/mL for RPV LA. If the geometric mean trough was shifted to the lower limit of the CI (1.88 ug/mL for CAB LA and 43.1 ng/mL for RPV LA), 13% of pregnant persons would have a trough under 0.99 ug/mL for CAB LA and 21.0 ng/mL for RPV LA (Figure 3). The precision would be sufficient to conclude that no more than 13% of adult-participants would have a trough below the expected 5th percentile in non-pregnant persons, which is within the study team's acceptable precision range.

In the Continuation Group, adult-participants will have varying exposure time to CAB LA + RPV LA. Since trough levels are dependent on exposure time, the estimation of trough at each study week will be limited and may vary widely. Table 9 presents 90% CIs for CAB LA + RPV LA troughs, assuming adult-participants will have started study product at least 24 weeks before the trough is sampled and 10% of data are not available for the third trimester. At 24 weeks after study product initiation with 10 adult-participants enrolled, the percentage of adult-participants with trough below the expected trough 5th percentile ranges from 13% to 27%, with standard deviations 25% and 100% more than what was observed previously. Thirteen percent would be an acceptable precision range; however, if the standard deviation is larger (e.g., 100%), the precision for trough will be outside of the acceptable range (e.g., 27%).

The sample size will be limited for the Q8W Switch Group. At Week 12 after initiating treatment (eight weeks after receiving the first maintenance dose), if the trough is equivalent to that in non-pregnant persons, the lower limit of the 90% CI of trough ranges from 0.82 to 0.90 ug/mL for CAB LA and 26.1 to 32.3 ng/mL for RPV LA for 10 persons enrolled. The percentage of adult-participants with a trough below the expected trough 5th percentile ranges from 24% to 61%. Due to this, the conclusions drawn about the PK trough level based on the Q8W Switch Group data will be limited; however, the collected data will be useful for inclusion in the PK model (see Section 10.2).

Table 8 Expected Third Trimester Trough Values in Switch Group at Week 16 after Initiating Q4W Study Product

			Third Trimester				
Week after Initiating Study Product	Study Product	Log SD	N‡	n‡	Geometric Mean (90% CI)	CI Half Width	Percentage Below the Expected 5th Percentile Shifting the Geometric Mean to Lower Bound of 90% CI*
16	CAB ug/mL	0.44	20	13	2.40 (1.94, 2.96)	0.51	11.9%
			25	15	2.40 (1.97, 2.92)	0.47	11.2%
			30	19	2.39 (2.01, 2.84)	0.41	10.3%
		0.55	20	13	2.40 (1.84, 3.13)	0.64	14.4%
			25	15	2.40 (1.88, 3.07)	0.59	13.3%
			30	19	2.40 (1.94, 2.98)	0.52	12.0%
	RPV ng/mL	0.49	20	13	56.4 (44.6, 71.5)	13.5	11.8%
			25	15	56.4 (45.4, 70.2)	12.4	11.1%
			30	19	56.3 (46.5, 68.2)	10.9	10.2%
		0.61	20	13	56.5 (42.1, 76.1)	17.0	14.2%
			25	15	56.5 (43.1, 74.3)	15.6	13.3%
			30	19	56.6 (44.6, 72.0)	13.7	11.8%

‡*N represents the number of enrolled adult-participants, with n showing the anticipated number of adult-participants with data in the third trimester. For example, with 25 enrolled in the Q4W Switch Group, approximately 15 would have a third trimester PK value at 16 weeks, 3 would be missing PK data due to non-adherence or lost to follow-up, 2 would be in the second trimester, and 5 would have had a pregnancy outcome.*

**The expected 5th percentiles of 0.99 ug/mL or 21.0 ng/mL were calculated from a trough distribution assuming the estimated (expected) geometric mean of 2.4 ug/mL or 56 ng/mL and the given log SD were the same as what was observed in non-pregnant adults. The percentage below the expected 5th percentile was calculated assuming the true geometric mean is equal to the lower boundary of the 90% confidence interval*

Table 9 Expected Trough Values in Continuation Group at 24 Weeks after Initiating Q4W or Q8W Study Product

Week after Initiating Study Product*	Study Product	Log SD	N‡	n‡	Geometric Mean (90% CI)	CI Half Width	Percentage below the expected 5th Percentile Shifting the Geometric Mean to Lower Bound of 90% CI*
24	CAB ug/mL	0.40	5	4	2.91 (2.05, 4.20)	1.08	20.7%
			10	9	2.88 (2.30, 3.61)	0.66	13.4%
			15	13	2.87 (2.41, 3.44)	0.52	11.1%
		0.50	5	4	2.94 (1.90, 4.67)	1.39	26.5%
			10	9	2.89 (2.19, 3.85)	0.83	16.3%
			15	13	2.88 (2.31, 3.61)	0.65	13.3%
		0.80	5	4	3.05 (1.53, 6.52)	2.50	46.3%
			10	9	2.94 (1.88, 4.66)	1.39	27.1%
			15	13	2.93 (2.05, 4.20)	1.08	20.5%
	RPV ng/mL	0.48	5	4	57.3 (37.8, 89.1)	25.7	20.3%
			10	9	56.5 (43.2, 74.2)	15.5	13.4%
			15	13	56.4 (45.6, 69.9)	12.2	11.1%
		0.60	5	4	57.8 (34.4, 101.0)	33.3	26.2%
			10	9	56.9 (40.7, 80.1)	19.7	16.2%
			15	13	56.6 (43.3, 74.1)	15.4	13.2%
		0.96	5	4	61.7 (27.4, 152.8)	62.7	43.5%
			10	9	59.1 (34.6, 102.8)	34.1	25.8%
			15	13	57.8 (37.8, 89.1)	25.7	20.3%

**Treatment start assumed to occur prior to study enrollment.*

‡N represents the number of enrolled adult-participants, with n showing the anticipated number of adult-participants with data The expected 5th percentile was calculated from a trough distribution assuming the estimated (expected) geometric mean and the given log SD were the same as what was observed in non-pregnant adults. The percentage below the expected 5th percentile was calculated assuming the true geometric mean is equal to the lower boundary of the 90% confidence interval.

For the primary safety objective, we calculated the precision for potential proportions of pregnant adult-participants experiencing at least one Grade 3 or higher adverse events or separately at least one serious adverse event for analysis subgroups: 10 across the Continuation Groups or Q8W Switch Group, 25 in the Q4W Switch Group, and 35 total in the combined Switch Groups (See Section 9.5 for safety analysis details). Table 10 below presents the exact binomial upper and lower 95% confidence limits and confidence interval half width. With a sample size of 35 pregnant adult-participants in the Switch Group, CI half width ranges from 10% to 66% with event rates from 0% to 50%, respectively. Safety conclusions in the combined Continuation Groups will be limited, with CI half widths ranging from 15% to 30%.

Table 10 Precision (exact binomial 95% confidence interval) for estimating the percentage of adult-participants experiencing a primary safety outcome

Sample Size	Number (Percentage) with Adverse Event	95% Exact Confidence Interval	Confidence Interval Half Width
10	0 (0%)	(0%, 31%)	15%
25	0 (0%)	(0%, 14%)	7%
35	0 (0%)	(0%, 10%)	5%
10	1 (10%)	(0%, 45%)	22%
25	3 (12%)	(3%, 31%)	14%
35	4 (11%)	(3%, 27%)	12%
10	2 (20%)	(3%, 56%)	27%
25	5 (20%)	(7%, 41%)	17%
35	7 (20%)	(8%, 37%)	14%
10	3 (30%)	(7%, 65%)	29%
25	8 (32%)	(15%, 54%)	19%
35	10 (29%)	(15%, 46%)	16%
10	5 (50%)	(19%, 81%)	31%
25	13 (52%)	(31%, 72%)	20%
35	18 (51%)	(34%, 69%)	17%

9.3.1 Accrual

The Q4W Continuation, Q8W Continuation, and Q4W Switch Groups will open to accrual first. Once there are at least 10 evaluable Q4W Switch Group participants, an interim analysis will be conducted with all available data (from both adult-participants and infant-participants) to determine if the Q8W Switch Group will open to accrual. If the Q8W Switch Group does not open to accrual, accrual targets designated for this group will be reallocated to the Q4W Switch Group. Accrual of the targeted number of adult-participants is expected to be completed in 15 months from the date of first enrollment. The rate of accrual is expected to be higher in the Switch Groups than the Continuation Groups.

9.4 Monitoring

Implementation of this study will be monitored at multiple levels, consistent with standard IMPAACT procedures. Detailed plans for study monitoring will be outlined in a Study Progress, Data, and Safety Monitoring Plan (SPDSMP) developed by the Statistical and Data Management Center (SDMC). Sections 11 and 12 provide more information on on-site monitoring and quality management at the site level. Further information on monitoring of study progress, quality of study conduct, and participant safety across sites is provided below.

9.4.1 Monitoring by the Protocol Team

Study Progress and Quality of Study Conduct

The Protocol Team is responsible for continuous monitoring of study progress, including timely achievement of key milestones, and quality of study conduct. The Protocol Team will closely monitor total and group study accrual based on reports that will be generated at least monthly by the SDMC. Accrual performance will be reported by the SDMC, by site and across sites, and the team will review and discuss study progress at least monthly.

On behalf of the Protocol Team, the CMC will monitor participant retention and other key indicators of the quality of study conduct (e.g., protocol deviations, adherence to study product regimen, data quality, and data and specimen completeness) based on reports generated by the SDMC and take action with study sites as needed to ensure high quality study conduct throughout the period of study implementation.

Participant Safety

On behalf of the Protocol Team, the CMC will closely monitor participant safety through routine review of safety data reports generated by the SDMC. The CMC will review these reports at least monthly, and reports will include summaries used to monitor safety triggers to either pause participant accrual and/or convene an *ad hoc* SMC review, as described in the remainder of this section. Reports will also include available PK results. The occurrence of adverse events or virologic events meeting criteria to pause accrual and/or convene an *ad hoc* SMC review will be summarized, along with 90% CIs used to monitor safety triggers. At the time of each review, the DAIDS Medical Officer may, when possible, also review any EAEs (defined in Section 7.3.2) reported to the DAIDS Safety Office that are not yet reflected in the data reports. The CMC (and specifically, the clinician members) will continually evaluate the pattern and frequency of reported events and assess for any individual occurrences or trends of concern.

9.4.2 Monitoring by the Study Monitoring Committee (SMC)

An independent IMPAACT Study Monitoring Committee (SMC) will review this study regularly, following policies described in the IMPAACT MOP. SMC reviews will occur at least annually and on a more frequent or *ad hoc* basis if any safety issues or concerns arise. An SMC review will also occur to review the interim analysis and assess whether to open the Q8W Switch Group to enrollment. *Ad hoc* reviews may also be triggered per the safety monitoring guidelines specified below. Based on any of its reviews, the SMC may recommend that the study proceed as currently designed, proceed with design modifications, or be discontinued. The SMC may also provide operational recommendations to help address any study implementation challenges that may be identified during their reviews. The SMC will monitor study progress, quality of study conduct, and participant safety. For *ad hoc* reviews or triggered reviews, more limited data may be reviewed, focusing on the events or other concerns that necessitated the reviews.

Ad hoc SMC reviews will occur in the following scenarios:

(1) One or more adult-participants experience virologic failure (unless participants have discontinued study product or are known to have missed a scheduled dose prior to viral load assessment)
(2) One or more live born infant-participants are diagnosed with HIV infection.
(3) The lower limit of the 90% exact CI is above:
    - 10% for spontaneous abortions (<20 weeks gestation)
    - 2% for fetal demise (≥20 weeks gestation) or neonatal deaths

- 20% for prematurity, small for gestational age, or low birth weight among live born infant-participants

(4) In the event of any fatal or life-threatening adverse event, assessed by the site investigator as related to study product. The CMC will pause accrual into all groups as soon as possible (ideally within three business days of site awareness). An *ad hoc* SMC review will be convened as soon as possible to discuss how the study should proceed.

If the lower limit of the 90% exact CI is greater than 5% for the events listed below, an SMC review will be convened:

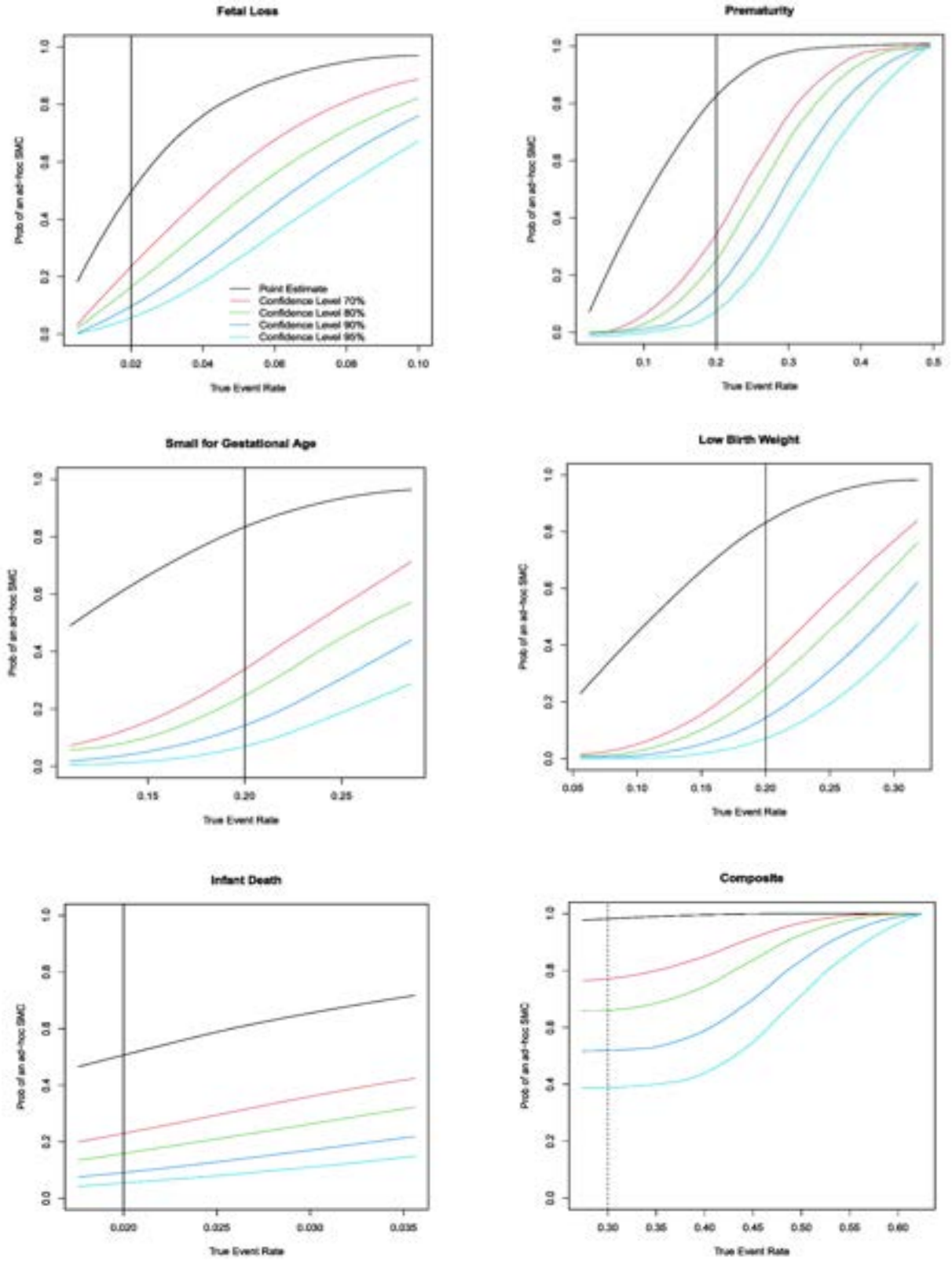
- Grade 3 or higher adverse events assessed by the site investigator as related to study product
- Any adverse event resulting in permanent discontinuation of the study product assessed by the site investigator as related to study product

Confidence intervals will be pooled across all groups within adult-participants or infant-participants. Accrual will only immediately be paused after the occurrence of a fatal or life-threatening adverse event assessed as related to study drug. Following an initial triggered SMC review, if additional adult-participants experience a virologic failure, or fatal/life-threatening adverse event related to study product, or if an infant-participant HIV-1 infection occurs, an additional SMC review will be convened, unless otherwise specified by the SMC. In the event of any infant HIV infection, enrollment will be allowed to continue but an SMC review will be convened.

9.4.2.1 Likelihood of Ad Hoc SMC Review

Figure 4 shows the probability of triggering an *ad hoc* SMC review for all adverse pregnancy outcomes combined across all groups: fetal loss, prematurity, small for gestational age, low birth weight, and infant-participant death. The probability of any adverse pregnancy event triggering an *ad hoc* SMC review is shown in the composite section of Figure 4. A trigger for a composite for all the pregnancy outcomes was not defined, but the composite summary provides an estimate of how likely an *ad hoc* SMC review will occur based on pregnancy outcomes. To estimate the probability of triggering an *ad hoc* SMC review, a simulation approach using chained logistic regression models based on IMPAACT 2010 adverse pregnancy event data was done to account for correlation between adverse pregnancy events (e.g., probability of small for gestational age is correlated with the chance of preterm delivery and low birth weight).

Figure 4. Probability of Triggering an Ad Hoc SMC Review for an Adverse Pregnancy Outcome



The study team considered two tuning parameters to select the optimal *ad hoc* SMC review decision rule: 1) the confidence level of the CI (displayed as different colored lines), and 2) a threshold at the lower bound of the CI (displayed as a vertical line). These two tuning parameters allow the selection of any overall probability to trigger an *ad hoc* SMC review. The study team selected the 90% CI for the decision rule, which is equivalent to a one-sided test with alpha of 5%. As noted in the section above, if the lower limit of the 90% exact CI for the event rate percentage is above a defined threshold (2% for fetal deaths and neonatal deaths, 20% for all other outcomes), an *ad hoc* SMC review will occur. No data were available for spontaneous abortions in IMPAACT 2010 to provide a summary above. For comparison, confidence intervals of 95%, 90%, 80%, and 70% are shown, as well as if we used the observed point estimate for triggering an *ad hoc* SMC review.

Observed rates of adverse pregnancy outcomes in IMPAACT 2010 (gestational age at enrollment of 14-28 weeks) were no spontaneous abortions, 2% fetal demises, 9% preterm deliveries, 20% infants small for gestational age, 9% infants with low birth weight, and 2% neonatal death (42). Adverse pregnancy outcomes were observed more frequently in PROMISE (43). For IMPAACT 2040, we expect higher rates of adverse pregnancy outcomes since adult-participants are enrolling at earlier gestational ages. If the true rate of preterm deliveries and infants with low birth weight in IMPAACT 2040 are 20%, using the 90% CI, there is an approximately 10% chance of an *ad hoc* SMC review. If the rate of infants small for gestational age is as expected, the probability of an *ad hoc* SMC review is small. If the true event rate is 30% for preterm deliveries, low birth weight, or infants small for gestational age, the probability of an *ad hoc* SMC review is approximately 50%. Since fetal demises are expected to be a rare occurrence and the study sample size is small, the true event rate would need to be much higher than 2% to trigger an *ad hoc* SMC review (i.e., true event rate of 7% for approximately a 50% probability of an *ad hoc* SMC review). In IMPAACT 2040, observing at least 2 fetal demises when the sample size is less than 18 pregnant adult-participants, or observing at least 3 fetal demises with a sample size of 18 or more pregnant adult-participants, would trigger an *ad hoc* SMC review. Considering all adverse pregnancy outcomes, if the true event rate of a pregnant person on CAB LA + RPV LA experiencing any adverse pregnancy outcome is 30%, there is approximately a 50% chance an *ad hoc* SMC review will occur. The likelihood of an *ad hoc* SMC review increases as the event rate increases for all pregnancy outcomes.

Table 11 displays the probability of observing an event on IMPAACT 2040 when the true event rate ranges from 1% to 10%, which will be discussed below for other events triggering an *ad hoc* SMC review.

Table 11
Probability of Observing an Event

Sample Size	Probability of an Event*					
	1%	2%	3%	4%	5%	10%
10	9.5%	18.9%	25.9%	33.8%	40.0%	64.4%
25	21.9%	40.3%	53.7%	64.0%	72.8%	93.0%
30	25.7%	44.7%	59.5%	70.4%	78.7%	95.7%
35	29.5%	51.4%	66.4%	76.0%	83.7%	97.3%
40	32.7%	55.3%	70.1%	80.6%	87.8%	98.5%
45	36.9%	59.8%	74.6%	84.3%	89.8%	99.2%

Virologic Failure and Infant HIV Infection

In ATLAS-2M (21), 1% of participants experienced virologic failure ≥200 copies/mL within 60 weeks of follow-up. If pregnant persons on CAB LA + RPV LA have a virologic failure rate that is two, three, or four times higher than non-pregnant persons on CAB LA + RPV LA, there is a 55%, 70%, or 81% chance a virologic failure will be observed, assuming 40 persons will be at risk for the event for all of follow-up.

If the probability of virologic failure is the same in pregnant persons as it is in non-pregnant persons receiving CAB LA + RPV LA, there is a 33% chance a virologic failure will occur on IMPAACT 2040 and an *ad hoc* SMC review will take place. For the interim analysis of 10 persons, it is unlikely an adult-participant will experience virologic failure, unless the true rate of virologic failure is much higher than expected (>5%).

Similar to virologic failure, the probability of observing an infant HIV infection is low (33% assuming a 1% rate of transmission). In IMPAACT 2010 and PROMISE, rates of infant HIV infection were 0.5% for those randomized to an ART regimen. If the true HIV infection rate is 2-3%, there is a 55% or greater chance an *ad hoc* SMC review would occur. An SMC is likely to occur (>80%) if the HIV infection rate is 5% or more.

Fatal or Life-Threatening Adverse Event Related to Study Product

An *ad hoc* SMC review will occur in the event of a fatal or life-threatening adverse event assessed as related to study product for any participant. Not all Grade 4 adverse events will be considered life-threatening, only events meeting life-threatening criteria per ICH guidelines. An *ad hoc* SMC review will be likely to occur if the true rate of having a fatal or life-threatening related adverse event is 5% or higher see Table 11.

9.4.2.2 Interim Review to Open Q8W Switch Group Enrollment

An interim review of PK, safety, and virologic data will occur after data are available for the first 10 evaluable Q4W Switch Group adult-participants (defined in Section 3.1) to determine whether the Q8W Switch Group will open to accrual. PK criteria for this interim review are summarized in Section 10.2.2. Observed PK trough will also be presented using the same analyses described in Section 9.4.2. The safety and virologic outcomes described in ad hoc SMC review Section 9.4.2 will be presented among all enrolled participants, including the Continuation Groups, if data are available. Infant-participant safety data will also be described. There are no pre-specified safety or virologic criteria to open the Q8W Switch Group to enrollment.

As part of the interim review, the CMC will review the safety, virologic, and PK data noted above and, based upon their evaluation, will share their recommendation to the SMC regarding whether to proceed with opening the Q8W Group. The SMC will review the CMC's recommendation as well as all PK, safety, and virologic data and will subsequently provide guidance regarding ongoing participant management and the opening of Q8W Switch Group accrual. If PK, safety, and virologic outcomes are acceptable to the SMC, the Q8W Switch Group will open to accrual.

9.5 Analyses

Final analyses, including primary and secondary analyses, and additional analyses to address regulatory requirements will occur after all participants have completed postpartum follow-up. Interim analyses will be done while follow-up is ongoing.

9.5.1 Analysis Sets

Primary PK analyses will include all adult-participants who continued or switched to and received at least one dose of CAB LA or RPV LA.

Primary and secondary safety analyses will include all adult-participants who received at least one dose of CAB LA or RPV LA, and all live-born infants whose pregnant parent received at least one injection of the study product.

All secondary analyses will include adult-participants who received at least one dose of CAB LA or RPV LA or whose pregnant parent received at least one dose of CAB LA or RPV LA (infant-participants).

9.5.2 Primary Analyses

The data analyses to address PK objectives will include descriptive statistics for the PK trough (concentration prior to receiving study product dose): at each study visit since first CAB LA + RPV LA injection and pregnancy timepoint in the Switch Groups. Pregnancy timepoints are defined as the first, second, and third trimester, and postpartum. Since the Continuation Groups will have varying exposure times to CAB LA + RPV LA, PK trough will be summarized at each pregnancy timepoint. Analyses will be done separately for the Switch Groups and Continuation Groups. Q4W and Q8W dosing will be analyzed separately in the Switch Groups. For the main Continuation Group PK analyses, Q4W and Q8W will be pooled estimates since adult-participants will be closer to steady state when parameters are expected to be similar between Q4W and Q8W dosing. A key supplemental analysis providing separate PK estimates for the Q4W and Q8W doses across the Continuation Groups will also be presented; however, we expect precision to be limited for these estimates. Descriptive statistics will include the mean and median as measures of location and the standard deviation, 90% CI, 25th and 75th percentiles, minimum, maximum, 5^{th} percentile, and 95^{th} percentile as measures of dispersion. An estimate of the geometric mean trough will be summarized by the geometric mean bounded by a 90% confidence interval using the t distribution on the log scale. Missing data will be assumed non-informative for the primary analysis and a complete case analysis will be conducted. The estimands related to the primary PK outcome measures for the Switch Group and Continuation Group are in Section 2.

The primary safety outcome measure of any Grade 3 or higher adverse event and any serious adverse event will be summarized separately within each Group for adult-participants. The probability of participants experiencing each of the events will be estimated using proportions and exact two-sided binomial 95% CIs. Adverse events starting at the time of first study-provided

injection up to 18 weeks postpartum visit will be included for adult-participants. Safety summaries will also be presented separately for Q4W and Q8W dosing as a supplemental analysis since safety may be different by dose; however, precision will be limited in these summaries. To account for truncated follow-up time due to early study discontinuations a supplemental survival analysis that assumes loss to follow-up is non-informative will be conducted in adult-participants to estimate the probability of adverse event rates over the average follow-up time. Estimands related to the primary safety outcome measures are in Section 2.

Adverse events will additionally be described by the worst grade experienced by a participant overall, within MedDRA system organ class and MedDRA preferred term. Adverse events will also be summarized by relationship to study product, as assessed by site investigator. Further details of the analyses will be included in a separate Statistical Analysis Plan (SAP), which will define the content of the primary analysis report, primary study manuscript, and results reported to ClinicalTrials.gov.

9.5.3 Secondary and Other Analyses

For the secondary outcome measure comparing PK trough values in pregnancy versus postpartum, the within-person ratio of the pregnancy to postpartum trough will be calculated and averaged by study week and trimester. A repeated measures analysis using a linear link after log transformation will also be done to estimate the slope of PK trough values while pregnant and while postpartum. In the Switch Group, the geometric mean ratio and 90% CI comparing the observed IMPAACT 2040 trough values (described in primary PK analysis) and the trough in non-pregnant adult females will be computed. Trough within each trimester and study week will be compared to equivalent dose and week since CAB LA + RPV LA injection seen in non-pregnant adults.

Secondary PK outcome measures in infant-participants and the PK outcome measure of the fraction unbound PK concentrations will be analyzed using the same descriptive statistics as the primary PK outcome measure. PK will be described by study visit.

Virologic outcome measures, adverse pregnancy outcome measures, and early post-natal safety outcome measures will be summarized using proportions and exact two-sided binomial 95% confident intervals. Post-natal adverse event summaries in live born infants will include adverse events starting from birth to age 18 weeks. For adult-participants with confirmed virologic failure, a listing of HIV-1 CAB or RPV resistance will be summarized. The estimated probabilities of experiencing a confirmed virologic failure and suspected virologic failure (as defined in Section 8.13) will both be presented.

Virologic outcome measures and perinatal transmission will be summarized in adult- and infant-participants overall, within Group, and within dosing regimen. Adverse pregnancy outcome measures will be analyzed on the adult-participant and infant-participant pair and early post-natal safety outcomes on individual infant-participants. Adverse pregnancy and early post-natal safety outcome measures will be summarized in aggregate. The combined summary of any occurrence of spontaneous abortion, fetal demise/stillbirth, neonatal death, SGA, or preterm delivery is to provide an overall safety statement, estimating the probability of a parent-infant pair having any major adverse pregnancy or neonatal event. Neonatal death will include infant deaths occurring through 28 days after birth. Tolerability and acceptability will be summarized within Group and dosing regimen.

The number and percentage of adult-participants who discontinue CAB LA + RPV LA early due to intolerability, complete all scheduled injections, and intend to continue CAB LA + RPV LA will be calculated and summarized using descriptive statistics. Descriptive statistics of the mean, standard deviation, range, 5th, 25th, 50th, 75th, and 95th percentiles will be used to summarize the number of injections received over study-follow-up and number of injections received for every 4 (Q4W) or 8 (Q8W) weeks on study. Questionnaire responses assessing aspects of acceptability and tolerability will be summarized at Entry, Week 16, and the Final Scheduled Visit. Within each collection timepoint, responses will be described overall and by antepartum and postpartum periods.

9.6 Additional Analyses

Additional analyses and reports may be done to aid in regulatory submissions. Specifications for these additional regulatory deliverables will be specified in a separate document.

10 CLINICAL PHARMACOLOGY PLAN

The primary objective in the IMPAACT 2040 study is to describe the PK of CAB LA + RPV LA during pregnancy and postpartum in people with HIV-1 viral suppression switching to CAB LA + RPV LA (from oral HIV-1 ART) or continuing on CAB LA + RPV LA. Clinical pharmacology objectives and procedures are described in more detail below.

10.1 Clinical Pharmacology Objectives

Clinical pharmacology evaluations will assess CAB LA and RPV LA exposure by measuring drug concentrations during pregnancy and postpartum at study weeks specified in Section 6 and Appendix I-A. These results will be compared to pre-specified 5th percentile trough thresholds after the second injection (as noted below), as well as comparing drug concentrations during pregnancy to drug concentrations postpartum. PK evaluations will include additional samples at two and six weeks after study entry and up to two additional inter-dose concentration measurements at clinic visits in the third trimester (approximately seven days after the injection(s) received between 30 0/7 - 37 6/7 weeks EGA).

A preliminary PK analysis once data are available from the first 10 evaluable Q4W Switch Group participants will be conducted to determine feasibility of opening the Q8W Switch Group to accrual. All available data from the Q4W Switch and both Continuation Groups will be included in the analysis. For PK, the adequacy of predicted and observed trough concentrations collected in the Q4W Switch Group and predicted for Q8W Switch Group will be the primary guide to opening the Q8W Switch Group (5th percentile trough after the second injection CAB greater than 0.65 ug/mL, RPV greater than 17.3 ng/mL). These PK data will be evaluated in conjunction with viral load and safety data prior to deciding on the opening of Q8W Switch Group.

10.2 Clinical Pharmacology Study Design

The study is structured with two dosing regimens, Q4W and Q8W in both Switch and Continuation Groups. The opening of the Q8W Switch Group is conditional on adequacy of CAB LA + RPV LA exposure (in conjunction with viral load and safety data) during pregnancy that will be assessed in an interim analysis after data are available for the first 10 evaluable Q4W Switch Group adult-participants (See Section 3). There will be no dose adjustments made during

the course of the study based on individual or interim PK results. Additional details of the study design are presented in protocol Section 3.

For the primary and secondary PK objectives, drug concentrations will be quantified in plasma. For the secondary PK objectives, drug concentrations will also be quantified in cord blood, infant-participant plasma, and chest/breastmilk. All samples for CAB and RPV measurement will be entered into LDMS and shipped to the IMPAACT Pharmacology Laboratory listed in the IMPAACT 2040 LPC for both CAB and RPV containing specimens. Sample collection, processing, storage, and shipping details are provided in the IMPAACT 2040 LPC.

PK samples from adult-participants and infant-participants will have assays performed, in real time , as designated in the LPC. As noted in Section 6.18.2, samples may be requested for more rapid shipment prior to the interim analysis and at the end of the study. PK samples collected from any Viral Load Assessment Visit will be assayed as requested by the team.

Data from adult-participants receiving oral bridging will be described separately and excluded from descriptive statistics (for duration of oral bridging). Further details on data handling are in the PK analysis plan.

10.2.1 Pharmacokinetic Sampling, Drug Concentration Measurements

Pharmacokinetic blood samples will be collected as noted in Section 6 and further described below. All assay methods will be standardized with a filed Methods Report, under Good Laboratory Practice (GLP) conditions and cross-validated with primary assay providers used for CAB and RPV. The assays will be performed using high-performance liquid chromatography and tandem mass spectrometry (HPLC/MS/MS). Dose administration times and exact sample timing will be recorded on eCRFs.

In all groups, a single pre-injection blood sample will be collected at the Entry Visit. Additional plasma concentration measurements will be made based on blood draws taken every four weeks (pre-injection if coinciding with a dose administration visit) and at two weeks and six weeks after study entry. This sampling schedule will provide multiple inter-dose interval samples that will be informative for the exploratory PK analyses. Additional PK blood draws will be collected approximately seven days after the injection(s) received between 30 0/7 - 37 6/7 weeks EGA.

Adult-participant blood, cord blood or infant-participant blood, and chest/breastmilk samples will be collected at delivery. Infant-participant blood will also be collected within five days from birth. Adult-participant blood will be collected at postpartum injection visits as specified in Section 6. Adult-participant chest/breastmilk samples will be collected at postpartum injection visits. Infant-participant blood samples will be collected at postpartum injection visits if the visit is conducted within 28 days from the adult-participant's last injection. If the visit takes place more than 28 days post-injection, infant-participant blood samples will only be collected if the adult-participant is currently chest/breastfeeding. Ideally blood samples will be collected concurrent with chest/breastmilk collection, if applicable.

10.2.2 Interim analysis to evaluate feasibility of Q8W dosing in the Switch Group and expansion of the Week 4 injection dosing window

A previously developed population PK model for each drug will be used to preliminarily assess the adequacy of Q8W dosing in the Switch Group with all available data once the study has completed at least 10 evaluable Q4W Switch Group adult-participants. The interim analysis will

also determine whether the administration window for injections given to Switch Group adult-participants at the Week 4 Visit may be expanded from 21-28 days to 21-35 days after the Entry visit loading dose.

The PK models will be evaluated and, if needed, updated utilizing data from these adult-participants across pregnancy as well as any data from Q4W and Q8W Continuation Group adult-participants enrolled at that time. Changes will be noted in parameter values by trimester. The updated model will be utilized to simulate the dosage regimen in the proposed Q8W Switch Group. In addition to other factors (safety, virologic failure), guidelines for consideration of the feasibility of the Q8W Switch Group regimen include the proportion of individuals predicted to remain above the thresholds listed below:

- The proportion of individuals in the Q8W Switch Group predicted to maintain trough concentrations of CAB LA and RPV LA above the protein-adjusted inhibitory concentration required for 90% inhibition ($PAIC_{90}$) across all visits.
- CAB LA: Trough drug concentration (Ctrough) after second injection and third injection consistent with typical values observed in non-pregnant adults following the second dose (non-steady state). This is typically a concentration greater than 0.65 ug/mL in approximately 95% of adult-participants after the second injection.
- RPV LA: Ctrough after second injection and third injection consistent with typical values observed in non-pregnant adults following the second dose (non-steady state). This is typically a concentration greater than 17.3 ng/mL in approximately 95% of adult-participants after the second injection.

Based on their evaluation of the above criteria, along with safety and virologic data, as described in Section 9.4.2.2, the CMC will make a recommendation to the SMC for consideration regarding whether to proceed with opening the Q8W Switch Group.

10.3 Pharmacokinetic Sample Size Justification for the Interim Analysis

Two techniques were utilized to determine whether parameters could be effectively estimated given the drug concentration sampling design proposed. The first technique utilized a population optimal design approach as implemented in the POP ED software utilizing the Yu et al model (43). A population PK model for CAB LA was utilized based on the Han et al study (44). Briefly, sampling was permitted to occur at trough and then at one time point for each of the months of treatment. The optimal sampling design suggested samples taken in the inter-dose period (non-trough) would dramatically increase the certainty of the estimation of the key PK parameters of clearance and absorption rate. To further refine the sampling approach and address potential issues related to the practicality of obtaining samples in the inter-dose interval in the third trimester, a simulation estimation pair approach was utilized.

Assessment of Interim Analysis (n=10)

The virtual trial design was simulated for the interim analysis with trough samples allowed and in the third trimester, two additional sample collection times, one to two weeks after the dose. Ka and clearance (CL) were well estimated using this technique. During the initial phase of the study, it is anticipated that 10 Q4W Switch Group adult-participants will provide samples that can be utilized to evaluate the PK parameter changes and the population PK model will be updated to simulate Q8W Switch Group PK. This will be achieved by simulating PK profiles expected based on the updated PK parameters (in particular, the anticipated changes in the absorption rate and clearance). The individual estimates (empirical Bayes Estimates or individual Bayesian estimates depending on the method utilized) will be used for exploratory analysis of other additional regimens or covariates that may affect disposition.

Parameter estimation accuracy when n=10 was tested. The Han et al population pharmacokinetic model for CAB was modified to include a shift in apparent clearance anticipated in the second (20% increase) and third (50% increase) trimesters (44). This model was used to simulate 10 individuals 100 times. Each of the simulated trials (100 trials) was then used to re-estimate the population pharmacokinetic model. The shift in clearance anticipated for the third trimester was captured 100% of the time based on a likelihood ratio test incorporating the trimester effect on apparent clearance with a mean prediction error of 10%. The shift in clearance anticipated for the second trimester was captured 28% of the time, the estimated clearance had a mean bias of 15%. The results showed that the Ka, CL, and CL shift during third trimester could be estimated relatively well for small sample size (n =10) and will be sufficient for informing decision making around the opening of the Q8W Switch Group. Simulating the trial design for the Q4W Switch Group with the Han et al model for a normal body mass index pregnant individual receiving long acting cabotegravir and the anticipated increases in clearance (20% in the second trimester, 50% in the third trimester) represents a conservative case scenario here.

For reference, a separate simulation of virtual individuals (n=1,000) were simulated with anticipated gestational ages at study entry. These simulations resulted in a prediction of 0% of individuals below the $PAIC_{90}$ for all trough levels of CAB, and 11%, 2.7%, and 2.4% below four times the $PAIC_{90}$ after the first, second, and third injections, respectively. The simulations of the Q8W Switch Group resulted in 0% of individuals predicted to have trough concentrations below the $PAIC_{90}$ and 11%, 5.1%, and 0.6% of individuals below four times the $PAIC_{90}$ after the first, second, and third injections, respectively.

Utilizing the long acting rilpivirine population PK model (with parameters provided by Janssen Pharmaceutical, Inc.), with an assumed 43% increase in clearance in both the second and third trimesters (10), this model was used to simulate 10 individuals 100 times. Each of the simulated trials (100 trials) was then used to re-estimate the population pharmacokinetic model slow absorption and elimination rates. The shift in elimination rate (43%) anticipated for the second and third trimester was captured 100% of the time based on a likelihood ratio test incorporating the trimester effect on elimination rate with a mean prediction error of less than 10%. The results showed that the elimination rate shift during the second and third trimesters could be estimated relatively well for a small sample size (n =10), which could support the decision to open the Q8W Switch Group.

For RPV in the Q4W Switch Group, simulations in pregnant individuals (n=1,000) resulted in 0.8%, 0.4%, and 0.2% of individuals below the 12ng/mL and 8.1%, 3.1% and 1.4% of individuals below the 17.3ng/mL concentration after the first, second, and third injections respectively. Simulation of the Q8W Switch Group for RPV resulted in 0.8%, 2.9%, and 0.1% below the $PAIC_{90}$ (12.1ng/mL) and 8.1%, 15.7%, and 1.1% of individuals below the 17.3ng/mL concentration for the troughs after the first, second, and third doses respectively. The shift in clearance for RPV was set to 43% for the second and third trimesters per prior information supplied by Janssen (10).

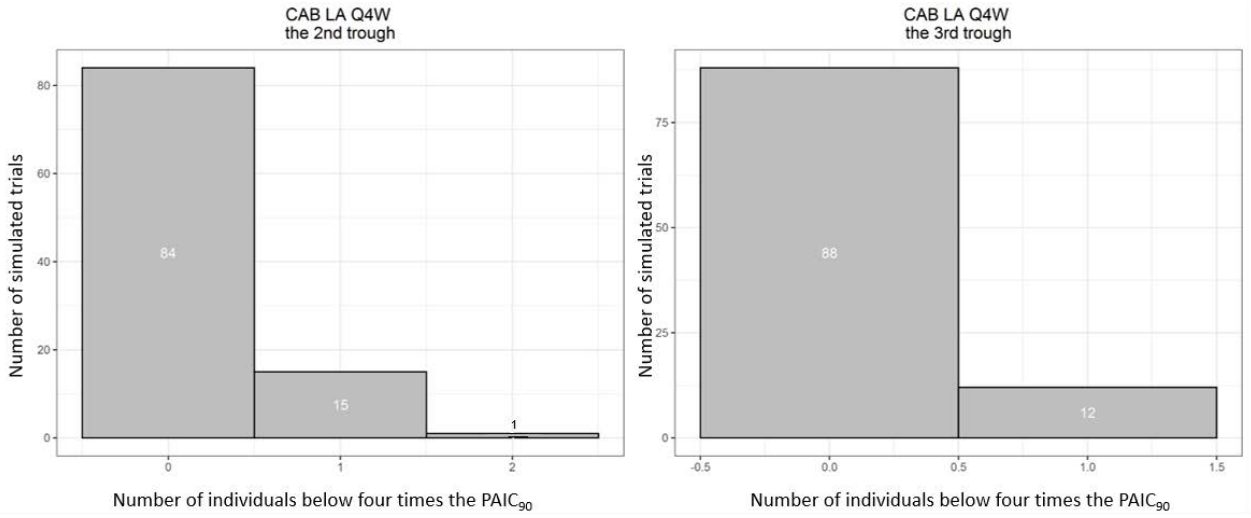
The above simulations that estimate expected proportions of individuals below threshold concentrations reflect an approximation of what is expected in the overall population. Given the interim analysis is based on a sample of 10 individuals, there may be some sensitivity to sampling variability. To further explore the characteristics of the study design and the sample size of 10 for the interim analysis, the sensitivity of the study design to sampling variability was explored by simulating the study design (n=10 individuals) 100 times for CAB and RPV with the same assumptions as the models above. The distributions of the number of studies with trough concentrations below the critical thresholds are shown in Figure 5 and Figure 6 below. Each

histogram shows the number of studies where a particular number of individuals were observed at that study visit (i.e., first, second, third troughs) that were below the specified threshold. Histograms were not presented if all observed troughs were above the $PAIC_{90}$ threshold.

In the simulations, no trials had any CAB trough concentrations below $PAIC_{90}$ in the Q4W Switch Group, which was similar to the simulation of 1,000 persons (0%). With an expected 0.8% of participants below the RPV $PAIC_{90}$ of 12.1ng/mL, concentrations for the first trough in the Q4W Switch Group were below the $PAIC_{90}$ of 12.1ng/mL in at least one participant in four of the study instances (4% of simulated studies). All other simulated $PAIC_{90}$ trough measurements for the Q4W Switch Group for RPV were above the $PAIC_{90}$. During the interim review, if CAB and RPV levels in pregnancy are similar to the above models, there is an estimated 4% chance of observing a participant with a RPV concentration under the $PAIC_{90}$ at the first trough, and an estimated 0% chance of observing any participant with a CAB or RPV concentration under the $PAIC_{90}$ at any other timepoint.

As stated above, the expected number of people (n=1,000) with trough below four times the $PAIC_{90}$ is 2.7% at the second trough and 2.4% at the third trough. In an interim analysis of 10 persons, there is approximately a 16% and 12% chance of observing a participant with a concentration below four times the $PAIC_{90}$ at the second and third trough, respectively (Figure 5).

Figure 5. Number of simulated studies with number of individuals below four times the $PAIC_{90}$ for CAB at the second and third trough for the Q4W Switch Group.

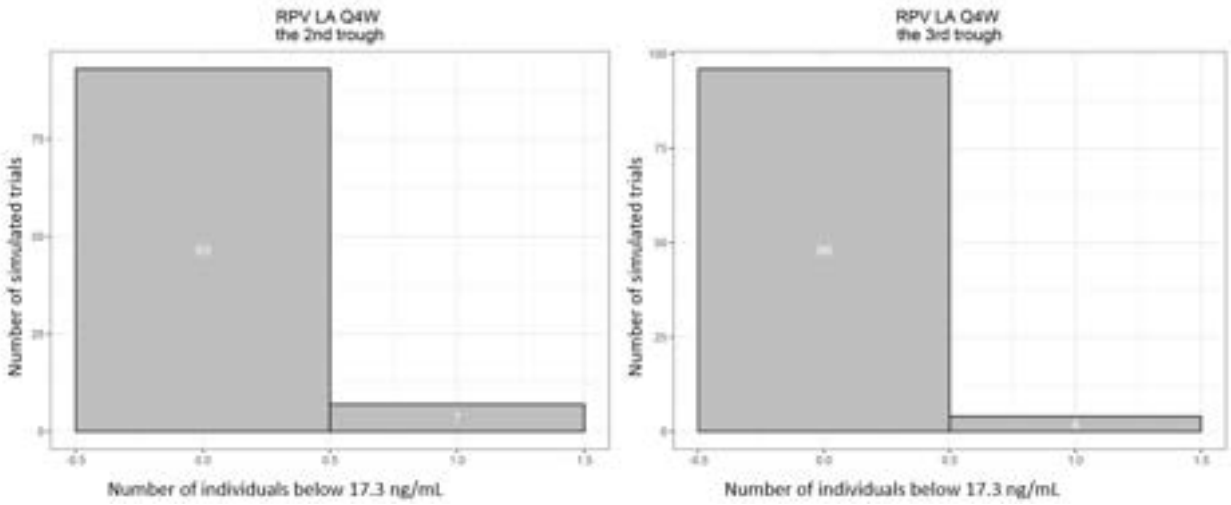


For RPV, there was only one out of one hundred of simulated trials for RPV in the Q8W Switch Group where individuals were simulated with trough concentrations below 12.1 ng/mL for the first trough. All second and third troughs in this group were above this threshold.

Figure 6 shows the number of simulated trials for the RPV Q4W Switch Group where individuals were evaluated for trough concentrations below 17.3 ng/mL. The y-axis shows the number of simulated studies and the x-axis shows the number of individuals below the threshold (each individual can only have a single trough concentration measurement for each visit). With an estimated percentage of persons with RPV below 17.3ng/mL of 3.1% at the second trough and 1.4% at the third trough, the probability of observing at least one person at the interim analysis with a trough below 17.3ng is low (7% at the second trough and 4% at the third trough).

For both CAB and RPV, these simulations in the Q4W Switch Group illustrate the probability of observing extreme events given the model, physiology, and study design assumptions and will be used as a reference when considering the feasibility of the Q8W Switch Group based on the parameters outlined in Section 10.2.2.

Figure 6. Number of simulated studies with number of individuals below 17.3 ng/mL for RPV at the second and third trough for the Q4W Switch Group



10.4 Pharmacokinetic Analyses

Estimation of both population and individual PK parameters based on sparse sampling will be done using an appropriate nonlinear mixed effects modeling or Bayesian implementation. In addition to the 10 adult-participants considered evaluable for the interim analysis to determine opening of the Q8W Switch Group accrual, all study participants who received at least one CAB LA or RPV LA dose with at least one concentration measurement will be included in the population pharmacokinetic model to evaluate the PK across the second and third trimesters of pregnancy and the postpartum period. Upon study completion, all available PK data (from adult-participants with at least one injection and one concentration measurement with recorded time/date of dose and measurement) will be utilized in the development of the final population PK model. Additional information on the implementation will be described in the PK analysis plan.

11 DATA HANDLING AND RECORD KEEPING

11.1 Data Management Responsibilities

As described in Section 4.4, data on screening and enrollment in this study will be collected using the DMC Stars.

Study sites must maintain adequate and accurate research records containing all information pertinent to the study for all screened and enrolled participants, including paper based CRFs (if used), eCRFs, and supporting source data. In maintaining these records, sites must comply with

the standards of source documentation specified in the DAIDS Site Clinical Operations and Research Essentials (SCORE) Manual, which is available at: https://www.niaid.nih.gov/research/daids-clinical-site-implementation-operations

eCRFs and an eCRF completion guide will be made available to study sites by the DMC. Study site staff will enter required data into eCRFs, with system checks applied and data queries generated immediately upon saving the entered data. Data must be entered within timeframes specified by the DMC; queries must also be resolved in a timely manner. For adult-participants, eCRF data entry will begin at study entry. For infant-participants, eCRF data entry will begin at birth. Selected laboratory data will be transferred electronically to the DMC through the LDMS or through other secure mechanisms.

The Protocol Team and/or study oversight bodies (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.

Further information on eCRFs and IMPAACT data management procedures will be provided by the DMC. A User Manual for Stars is available on the DMC portal at: https://www.frontierscience.org

11.2 Essential and Source Documents and Access to Source Data

Study sites must comply with requirements for essential documents and source documentation specified in the DAIDS SCORE Manual. This includes establishing SOPs for maintaining essential and source documents. Site SOPs should be updated and/or supplemented as needed to describe roles, responsibilities, and procedures for this study, and site SOPs should be followed throughout the study.

Per the DAIDS policy on Storage and Retention of Clinical Research Records, study records must be stored in a manner that ensures privacy, confidentiality, security, and accessibility during the conduct of the study and after the study is completed. Records must be retained for a minimum of three years after the completion of the study. Per 21 CFR 312.62, records must be maintained for two years after the date a marketing application is approved for one or more of the study products for the indication for which it is evaluated in this study; or, if no application is filed, or if the application is not approved for this indication, records must be retained two years after the study is discontinued and the FDA is notified.

All study records must be accessible for inspection, monitoring, and/or auditing during and after the conduct of the study by authorized representatives of the study sponsors and their contracted monitors, IMPAACT, the product manufacturer, the US FDA, site drug regulatory authorities, site IRBs/ECs, the sIRB (for US sites), US Office for Human Research Protection (OHRP), and other US, local, and international regulatory entities. Records must be kept on-site throughout the period of study implementation; thereafter, instructions for off-site storage may be provided by NIAID or NICHD. No study records may be removed to an off-site location or destroyed prior to receiving approval from NIAID or NICHD.

11.3 Quality Control and Quality Assurance

Study sites must ensure that essential documents and participant research records are subject to continuous quality control and quality assurance procedures consistent with the DAIDS SCORE Manual.

12 CLINICAL SITE MONITORING

Under contract to NIAID or NICHD, site monitors will inspect study site facilities and review participant study records — including informed consent forms, paper-based CRFs (if used), eCRFs, medical records, laboratory records, and pharmacy records — to ensure protection of study participants, compliance with the IRB/EC approved protocol, and accuracy and completeness of records. Monitors also will review essential document files to ensure compliance with all applicable regulatory requirements. Site investigators will make study facilities and documents available for inspection by monitors.

Remote monitoring may be performed to supplement or reduce the frequency and extent of on-site monitoring (40). Site investigators must make available study documents for site monitors to review utilizing a secure platform that is both 21 CFR Part 11 and Health Insurance Portability and Accountability Act (HIPAA) compliant. The DMC has configured Medidata Remote Source Review (RSR) to be available to all sites. If Medidata RSR is not utilized, other potential platform options include: Veeva SiteVault, Medidata Rave Imaging Solution, site-controlled SharePoint or cloud-based portal, and direct access to electronic medical records. Other secure platforms that are 21 CFR Part 11 and HIPAA compliant may be utilized, as allowed by DAIDS Office of Clinical Site Oversight (OCSO) or NICHD.

13 HUMAN SUBJECTS PROTECTIONS

13.1 Additional Protections for Research Involving Pregnant People, Fetuses, and Children

NIH policy requires that pregnant people and children should be included in clinical research when appropriate (45, 46). This study complies with that mandate and will provide clinical research data to inform treatment guidelines for pregnant individuals.

Additional protections apply to the pregnant people, fetuses, and children who take part in this study per the US Code of Federal Regulations (45 CFR 46 Subpart B, for pregnant people, fetuses, and neonates; and 45 CFR 46 Subpart D, for children). IRBs/ECs must consider the potential risks and benefits to pregnant, fetal, and infant participants; documentation of these determinations is required to complete the DAIDS protocol registration process. Consenting requirements at each site will depend on the IRB/EC risk determination.

With respect to 45 CFR 46 Subpart B, the specifications of 45 CFR 46.204 (d) are generally expected to apply such that adult-participants will be able to provide informed consent for their own and their infant's participation in this study.

With respect to 45 CFR 46 Subpart D, IRBs/ECs must determine the level of risk to children in the categories specified in 45 CFR 46.404-407. Documentation of this determination is required to complete the DAIDS protocol registration process described in Section 14.2. The risk category assigned by the IRB/EC determines the parental permission requirements for the study at each site. Per 45 CFR 46.408 (b), the IRB/EC may find that the permission of one parent is sufficient

for research to be conducted under 46.404 or 46.405. If the IRB/EC finds that the research is covered by 46.406 or 46.407, both parents must give their permission, unless one parent is deceased, unknown, incompetent, or not reasonably available or when only one parent has legal responsibility for the care and custody of the child (as determined locally). IRBs/ECs must document their risk determination, and study sites should adapt the signature pages of their site-specific ICFs, as needed, to accommodate the parental permission requirements associated with the IRB/EC determination.

Study sites must comply with the requirements for enrolling minors in clinical research specified in the DAIDS SCORE Manual. In accordance with these requirements, sites must establish and maintain written procedures describing local standards for identifying who may serve as guardian for a clinical research infant-participant and how guardianship will be recognized. Guardianship will be documented at study entry, including whether the infant-participant's guardian is a parent, other family member or individual, or governmental or non-governmental organization or institution. Should any changes of guardianship occur during study participation, these will be similarly documented.

In addition to the US regulations cited above, sites must also comply with all applicable local and national and international guidelines and regulations. When multiple different sets of requirements apply, the most stringent requirements must be followed.

13.2 Institutional Review Board/Ethics Committee Review and Approval

Prior to study initiation, site investigators must obtain IRB/EC review and approval of this protocol and site-specific informed consent forms in accordance with 45 CFR 46; subsequent to initial review and approval, IRBs/ECs must review the study at least annually. Site investigators must promptly report to the IRBs/ECs any changes in the study and must comply with the requirements of 45 CFR 46.108(a)(4) and 21 CFR 56.108(b) for promptly reporting the following: unanticipated problems involving risks to participants or others; serious or continuing noncompliance with applicable regulations or the requirements or determinations of their IRBs/ECs; and any suspension or termination of IRB approval.

South African sites are frequently overseen by more than one IRB/EC. US sites are overseen by an sIRB, with additional review by local IRBs if required per their agreements with the sIRB. Site investigators are responsible for awareness of and adherence to the policies and procedures of all applicable IRBs/ECs. All such policies and procedures must be followed and complete documentation of all correspondence to and from all applicable IRBs/ECs must be maintained in site essential document files. Sites must submit documentation of both initial review and approval and continuing review to the DAIDS Protocol Registration Office (PRO) in accordance with the DAIDS Protocol Registration Manual (see Section 13.2).

13.3 Informed Consent

Refer to Section 4.4 for further information on informed consent procedures for this study. Refer to Appendix V for sample informed consent forms.

Written informed consent for adult-participant and infant-participant study participation will be obtained before any study-specific procedures are performed (see Appendix V).

As indicated above, it is generally expected that adult-participants will provide informed consent for their own and their infant's participation in this study. However, parental permission

requirements at each site will depend on the IRB/EC risk determination described in Section 13.2; all IRB/EC requirements must be followed.

The informed consent process will include information exchange, detailed discussion, and assessment of understanding of all required elements of informed consent, including the potential risks, benefits, and alternatives to study participation. The process will include a description of what is currently known about the safety of the study products and the context of current local ART standards of care.

Should the consenting parent of an enrolled infant die or no longer be available for any reason, all applicable IRB/EC policies and procedures should be followed. No further study-specific infant-participant evaluations should be performed until permission for continued study participation is obtained from the infant-participant's legally authorized representative, as defined locally. Study sites may continue to provide care for the infant-participant as needed and appropriate (outside of the study), consistent with local standards of care, but no study-specific procedures (outside of the standard of care) may be performed. If a legally authorized representative cannot be identified, or if they do not provide permission for continued study participation, the infant-participant must be withdrawn from the study.

In accordance with DAIDS requirements for enrolling minors in clinical research (as specified in the DAIDS SCORE Manual), all sites must establish and maintain written procedures describing the standards that will be followed to identify who may serve as a legally authorized representative for an enrolled infant-participant, reflective of applicable IRB/EC guidance for conduct of human subjects research within the context of available local law, regulation, or government policy.

13.4 Potential Benefits

There may or may not be direct benefit to adult-participants and infant-participants who take part in this study. Although direct benefit cannot be guaranteed, the study products have been demonstrated as safe, effective, and well-tolerated in adolescents and adults (including through Week 152 of ATLAS 2M and through Week 124 of FLAIR (21, 39). There is a potential benefit for improved understanding of, and engagement in, HIV-1 care and study-specific evaluations may provide beneficial information relevant to participants' health and clinical care. Information learned in this study may benefit participants and others in the future, particularly information that may lead to more treatment options for pregnant and postpartum people with HIV-1.

For adult-participants, there may be potential benefits associated with switching from an oral ART regimen to a long-acting injectable regimen. Adult-participants receiving CAB LA+ RPV LA Q4W or Q8W dosing will not need to take concomitant daily oral therapy. Adherence in these adult-participants is expected to be improved and will be directly observed during IM injections. Reduction in ART, and the discontinuation of NRTIs, may offer long term safety and tolerability benefits in these adult-participants. There may be benefits of a parenteral regimen for adult-participants who are having issues with oral therapy for reasons such as hyperemesis, difficulty swallowing, adherence to oral therapy, psychological issues, etc. Lastly, adult-participants may also appreciate the opportunity to contribute to HIV-1-related research.

13.5 Potential Risks

The potential risks of participation in this study include risks associated with study procedures and, for adult-participants, risks associated with receipt of study product.

Most study procedures for adult-participants and infant-participants are routine medical procedures that are associated with minimal to no risk. It is acknowledged, however, that the frequency at which some procedures will be performed for this study is not routine in clinical practice. As indicated above, the increased frequency of some procedures may be of potential benefit. The increased frequency of blood collection may be of potential risk to adult-participants and/or infant-participants, as blood collection may cause pain, bruising, swelling, or fainting. There is a very small chance of infection where the needle is inserted. Adult-participants may feel uncomfortable or become anxious or embarrassed when responding to questionnaires or answering other questions asked by study staff.

Refer to Section 1.2.4 and the IB for CAB and the IB for TMC278 (RPV, oral and parenteral) for a description of the potential risks to adult-participants associated with the use of these drugs. Although there is robust safety, PK and efficacy data in adults, these drugs have not yet been studied in a pregnant population. The injections may cause pain, swelling, reddening of the skin, and nodule formations where the needle is inserted. There may also be additional unknown risks associated with use of these study products during pregnancy. For virologically suppressed ART-experienced pregnant individuals switching to use of CAB LA + RPV LA, there is a potential additional risk that the study products may not be as well-tolerated as the adult-participant's pre-study ART regimen. For both Switch and Continuation Groups, the effectiveness of CAB LA + RPV LA in maintaining virologic suppression during pregnancy is unknown. If loss of virologic suppression occurs, there is a risk of developing resistance and a potential increased risk of HIV transmission to the fetus or to any sexual partners.

The CAB LA and RPV LA injections are long-acting and may be present in the adult-participant's blood for one year or longer, after a single injection. The amount of drug will decrease over time and will eventually disappear. Infant-participants who chest/breastfeed may have exposure to CAB and RPV through chest/breast milk; the amount of drug that accumulates in human milk and the effects of this exposure are unknown.

Refer to Section 13.7 for further information on privacy and confidentiality. Despite efforts to maintain confidentiality, a participant's involvement in this study could become known to others, possibly leading to unfair treatment, discrimination, or other social impacts (e.g., because participants could become known as having HIV-1). For example, participants could be treated unfairly or discriminated against or could have problems being accepted by their families and/or communities. Every effort will be made to protect a participant's information, but this cannot be guaranteed.

13.6 Reimbursement/Compensation

Pending IRB/EC approval, participants will be reimbursed for costs associated with completing study visits (e.g., transport costs). Reimbursement amounts will be specified in site-specific ICFs and/or other materials per applicable IRB/EC policies and procedures.

13.7 Privacy and Confidentiality

All study procedures will be conducted in private and every effort will be made to protect participant privacy and confidentiality to the extent possible. Participant information will not be released without written permission to do so except as necessary for review, monitoring, and/or auditing as described in Section 11. Data or information from the study may be shared with drug companies who have agreements with IMPAACT and/or NIH, or regulatory entities, but individual participants will not be identified. Individual participant information may be disclosed to relevant authorities if required by law. For example, sites may be required to report any significant risk of harm to participants or others.

All study-related information will be stored securely. Participant research records will be stored in locked areas with access limited to study staff. All laboratory specimens, CRFs, and other documents that may be transmitted off-site (e.g., EAE report forms, photographs of observed reactions) will be identified by PID only. Likewise, communications between study staff and Protocol Team members regarding individual participants will identify participants by PID only.

Study sites are encouraged but not required by DAIDS to store study records that bear participant names or other personal identifiers separately from records identified by PID. All local databases must be secured with password protected access systems. Lists, logbooks, appointment books, and any other documents that link PID numbers to personal identifying information should be stored in a separate, locked location in an area with limited access.

In addition to the above, a Certificate of Confidentiality has been issued for the IMPAACT Network by the US Department of Health and Human Services. This certificate protects study staff from being compelled to disclose study-related information by any US Federal, state, or local civil, criminal, administrative, legislative, or other proceedings. It thus serves to protect the identity and privacy of study participants. Because the certificate cannot be enforced outside of the US, however, it applies only to US sites and participants.

13.8 Communicable Disease Reporting

Study staff will comply with local requirements to report communicable diseases including HIV-1, Hepatitis B, and/or Hepatitis C infection identified among study participants to health authorities. Participants will be made aware of all applicable reporting requirements as part of the study informed consent process.

13.9 Management of Incidental Findings

Site clinicians will inform participants of all clinically meaningful physical exam findings and laboratory test results. When applicable, site clinicians will provide referrals to non-study sources of medical care for further evaluation and/or treatment of these findings.

The results of other tests that may be performed using specimens collected in this study, such as PK test results, are not planned to be provided to participants, as these are considered research tests that are not expected to be relevant to clinical care and management. If, however, new information becomes available indicating that the results of any tests are of clinical relevance, the results will be provided. When applicable, site clinicians will provide referrals to non-study sources of medical care for further evaluation and/or treatment of these findings.

13.10 Management of New Information Pertinent to Study Participation

Study staff will provide participants with any new information learned over the course of the study that may affect their willingness to continue receiving study products and/or remain in follow-up. Participants (or legally authorized representatives, if applicable) will also be provided any new information learned over the course of the study that may affect their willingness to continue in follow-up or their willingness to allow their infant to continue in follow-up.

13.11 Post-Trial Access to Study Product

ViiV Healthcare Ltd and Janssen Research & Development LLC are committed to exploring all options to provide continued access to investigational product to adult-participants deriving therapeutic benefit from CAB LA + RPV LA. Prior to site activation, ViiV will provide confirmation that a suitable option for access has been identified that can be operational at least two months before the anticipated first exit visit at that site. Adult-participants who received CAB LA + RPV LA and who have reached the end of the study follow-up period, will be given the opportunity to continue to receive CAB LA + RPV LA. Additionally, both of the following conditions must be met for the participant to continue to receive CAB LA + RPV LA:

- there is evidence of continued clinical benefit for the participant; and
- such provision of CAB LA + RPV LA is permitted under local laws and regulations.

The site investigator is responsible for ensuring that consideration has been given to the post-study care of the participant and for determining whether all parameters are met for an individual participant's post-study access to CAB LA + RPV LA or whether the participant should transition to local standard HIV care and treatment (see Section 6.8).

Continued access to unapproved CAB LA + RPV LA will cease if the adult-participant no longer exhibits a clinical benefit or if risks of continuing treatment outweigh benefits. Additionally, access will cease if the development of CAB LA + RPV LA is discontinued, or market access is or becomes available.

The mechanism that will be used to provide post-trial access to study product may be country-specific; additional details will be provided in the IMPAACT 2040 MOP.

14 ADMINISTRATIVE PROCEDURES

14.1 Regulatory Oversight

This study is sponsored by the National Institute of Allergy and Infectious Diseases (NIAID), *Eunice Kennedy Shriver* National Institute of Child Health and Human Development (NICHD), and National Institute of Mental Health (NIMH), which are part of the US National Institutes of Health (NIH). ViiV Healthcare Ltd and Janssen Research and Development LLC will provide funding for this study. Study products are provided by ViiV Healthcare Ltd and Janssen Research and Development LLC; however, these organizations are not involved in sponsorship or regulatory oversight of this study.

Within the NIAID, DAIDS is responsible for regulatory oversight of this study. DAIDS will distribute safety-related information pertaining to the study products prior to and during the conduct of the study, in accordance with its sponsor obligations.

NIAID and NICHD provide funding to the clinical research sites at which this study will be conducted. Each institute contracts with an independent clinical site monitoring group to perform clinical site monitoring as described in Section 12. As part of this activity, monitors will inspect study-related documentation to ensure compliance with applicable US, local, and international regulatory requirements.

14.2 Protocol Registration

Prior to implementation of this protocol, and any subsequent full version amendments, each site must have the protocol and the study informed consent forms approved, as appropriate, by applicable IRBs/ECs, and any other applicable regulatory entities; for US sites, this includes the sIRB. Upon receiving final approval, sites will submit all required protocol registration documents to the DAIDS PRO at the RSC. The DAIDS PRO will review the submitted protocol registration packet to ensure that all required documents have been received.

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

For any future protocol amendments, upon receiving final IRB/EC and other applicable regulatory entity approvals, as well as meeting any additional study specific requirements as determined by the Protocol Team, sites should implement the amendment immediately. Sites are required to submit an amendment registration packet to the DAIDS PRO at the RSC. The DAIDS PRO will review the submitted protocol registration packet to ensure that all required documents have been received. Site-specific informed consent forms 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, which is available at: https://www.niaid.nih.gov/research/daids-clinical-site-implementation-operations

14.3 Study Implementation

This study will be conducted in accordance with the protocol, international good clinical practice guidelines, and all applicable US, local, and international regulations. Study implementation will also be guided by the IMPAACT Network MOP, IMPAACT 2040 MOP, LPC, and other study implementation materials, which will be available on the study-specific website: https://www.impaactnetwork.org/studies/impaact2040

Study implementation at each site will also be guided by site-specific SOPs. The DAIDS SCORE Manual specifies the minimum set of SOPs that must be established at sites conducting DAIDS funded and/or sponsored clinical trials. These SOPs should be updated and/or supplemented as needed to describe roles, responsibilities, and procedures for this study.

14.4 Protocol Deviation Reporting

Per the requirements for source documentation specified in the DAIDS SCORE Manual, all protocol deviations must be documented in participant research records. Reasons for the deviations and corrective and preventive actions taken in response to the deviations should also be documented.

Deviations should be reported to applicable IRBs/ECs and other applicable review bodies in accordance with the policies and procedures of these review bodies. Serious deviations that are associated with increased risk to one or more study participants and/or significant impacts on the integrity of study data must also be reported within IMPAACT, following procedures specified in the IMPAACT Network MOP.

14.5 ClinicalTrials.gov

The NIH Policy on Dissemination of NIH-funded Clinical Trial Information establishes the expectation that clinical trials funded in whole or in part by the NIH will be registered and have summary results information submitted to ClinicalTrials.gov for public posting. The Protocol Team will comply with this policy as well as the requirements of 42 CFR 11.

15 PUBLICATIONS

All presentations and publications of data collected in this study are governed by IMPAACT policies, which are available in the IMPAACT MOP.

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Appendix I: Schedule of Evaluations
Appendix I-A: Adult-Participant Schedule of Evaluations (Scheduled Visits)

	Screen	Entry	Antepartum Study Wk 2, 6	Antepartum Study Wk 4, 8, 12, 16, 20, 24, 28, 32	Antepartum Interval[5]	Pregnancy Outcome	First and Second Postpartum Injection Visits	Final Scheduled Visit and Early Termination	Interim Injection Visit	Viral Load Assessment Visit
Behavioral Evaluations										
Acceptability/Tolerability Assessment		X		X – only at Week 16				X		
Clinical Evaluations										
Medical and Medication History	X	X	X	X	X	X	X	X	X	X
Physical Examination[1]	X	X		X		X	X	X	X	X
Fetal Ultrasound	*	*								
ECG	X									
C-SSRS	X							X		
Study Product										
Administer injectable study products		X		X[2]		*	X	*	X	
Laboratory Evaluations										
Chemistries[3]	5 mL	5 mL		5 mL			5 mL	5 mL	5 mL	
Hematology: CBC with differential with platelets[3]	3 mL	3 mL		3 mL			3 mL	3 mL	3 mL	
Albumin				3 mL – Wk 8 and Wk 16			3 mL	3 mL		
Hepatitis C testing: anti-HCV ab	3 mL									
Hepatitis B: HBcAb, HBsAg, HBsAb	6 mL									
CD4 Count and Percentage		3 mL		3 mL – Wk 12 and Wk 24						
Confirmatory HIV-1 Testing	0-6 mL*									
HIV-1 RNA	6 mL	6 mL	6 mL	6 mL		6 mL	6 mL	6 mL	6 mL	6 mL
HIV-1 Resistance Testing		4 mL (whole blood)								6 mL (plasma)
PK Evaluation[4]		2 mL	2 mL	2 mL	2 mL	2 mL	2 mL	2 mL	2 mL	2 mL
Cord blood PK Sample						2 mL[6]				
Chest/Breastmilk sample (if chest/breastfeeding)						X	X	X		

	Screen	Entry	Antepartum Study Wk 2, 6	Antepartum Study Wk 4, 8, 12, 16, 20, 24, 28, 32	Antepartum Interval[5]	Pregnancy Outcome	First and Second Postpartum Injection Visits	Final Scheduled Visit and Early Termination	Interim Injection Visit	Viral Load Assessment Visit
Offer Pregnancy Test							*	*		
Total maximum blood volume per visit	23-29 mL	23 mL	8 mL	16 - 19 mL	2 mL	10 mL	19 mL	19 mL	16 mL	14 mL

Notes: X – required; * - if indicated; Columbia Suicide Severity Rating Scale (C-SSRS)

1. Complete physical exam required at screening, targeted exam at all other visits
2. Adult-participants enrolling the Q4W Switch Group or the Q4W Continuation Group will receive injections at antepartum visits every four weeks (Entry and Study Weeks 4, 8, 12, 16, 20, 24, 28, 32). Adult-participants enrolling in the Q8W Continuation Group will receive injections at antepartum visits every eight weeks (Entry and Study Weeks 8, 16, 24, 32). Adult-participants enrolling in the Q8W Switch Group will receive injections at Entry and the Antepartum Week 4 visit, followed by every eight weeks (Study Weeks 12, 20, 28)
3. See Section 6.1-6.8 for specific analytes included in chemistries and hematology at each visit.
4. See Section 6.1-6.8 for PK sample collection procedures
5. Visit(s) scheduled seven days after the injection(s) received between 30 0/7 - 37 6/7 weeks EGA
6. If a live birth and visit is performed on day of delivery

Appendix I-B: Infant-Participant Schedule of Evaluations (for infants of adult-participants receiving Q4W injections)

Study Visit	Infant-Participant Birth Visit	Infant-Participant Five Day Post Birth Visit[1]	Infant-Participant Procedures at First Adult-Participant Postpartum Injection Visits	Infant-Participant Procedures at Second Adult-Participant Postpartum Injection Visit	Final Scheduled Visit/Early Termination	HIV-1 Confirmation Visit(s)
CLINICAL EVALUATIONS						
Medical, Medication, and Feeding History	X	X	X	X	X	
Complete Physical Examination	X	*				
Targeted Physical Examination			X	X	X	
LABORATORY EVALUATIONS						
Bilirubin (total and direct)		.5 mL				
Chemistries: Creatinine, Bilirubin (total and direct), AST, ALT, Lipase			1.5 mL[4]	1.5 mL[4]	1.5 mL	
PK Evaluation (if birth weight greater than or equal to 1000 grams)	.5 mL[2]	.5 mL	.5 mL[3]	.5 mL[3]	.5 mL[3]	
HIV NAT[5]	0 – 3 mL	*	0 – 3 mL	0 – 3 mL	0 – 3 mL	6 mL[6]
Total Maximum blood volume per visit	.5 – 3.5 mL	1 mL	2 – 5 mL	2 – 5 mL	2 – 5 mL	6 mL

Notes: X – required; * - if indicated

1. If the Infant-Participant Birth Visit does not occur, all procedures listed for the Infant-Participant Birth Visit should be completed at the Five-Day Post-Birth Visit.
2. The at-birth sample may be omitted if cord blood was collected.
3. Collect for all infant-participants who are chest/breastfeeding. If not chest/breastfeeding, only collect at the first postpartum injection visit if visit is conducted within 28 days from adult-participant's last injection.
4. Only collect if visit is conducted 14 days or more after birth and 14 days or more in advance of the next scheduled visit's target date.
5. Documented HIV NAT results obtained as part of standard of care, external to the study, may be used if the sample was collected prior to the Birth or Five-Day Post-Birth Visits or within 7 days of any other visit.
6. When collected for HIV-1 confirmation, will also include resistance testing.

Appendix I-C: Infant-Participant Schedule of Evaluations (for infants of adult-participants receiving Q8W injections)

Study Visit	Infant-Participant Birth Visit	Infant-Participant Five Day Post Birth Visit[1]	Infant-Participant Procedures at First Adult-Participant Postpartum Injection Visits	Infant-Participant Procedures at Second Adult-Participant Postpartum Injection Visit	Final Scheduled Visit/Early Termination	HIV-1 Confirmation Visit(s)
CLINICAL EVALUATIONS						
Medical, Medication, and Feeding History	X	X	X	X	X	
Complete Physical Examination	X	*				
Targeted Physical Examination			X	X	X	
LABORATORY EVALUATIONS						
Bilirubin (total and direct)		.5 mL				
Chemistries: Creatinine, Bilirubin (total and direct), AST, ALT, Lipase			1.5 mL[4]	1.5 mL[4]	1.5 mL	
PK Evaluation (if birth weight greater than or equal to 1000 grams)	.5 mL[2]	.5 mL	.5 mL[3]	.5 mL[3]	.5 mL[3]	
HIV NAT[5]	0 – 3 mL	*	0 – 3 mL	0 – 3 mL	0 – 3 mL	6 mL[6]
Total Maximum blood volume per visit	.5 – 3.5 mL	1 mL	2 – 5 mL	2 – 5 mL	2 – 5 mL	6 mL

Notes: X – required; * - if indicated

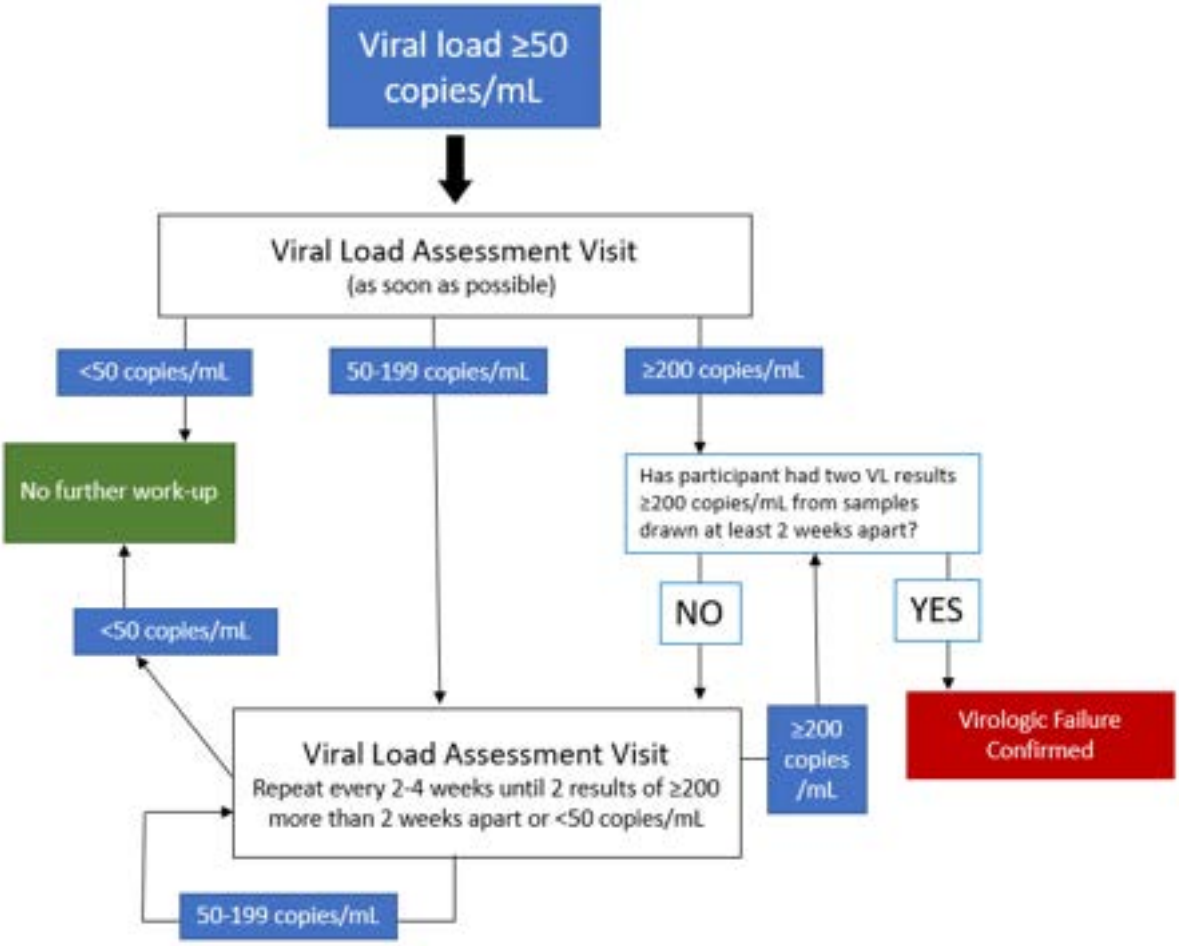
1. If the Infant-Participant Birth Visit does not occur, all procedures listed for the Infant-Participant Birth Visit should be completed at the Five-Day Post-Birth Visit.
2. The at-birth sample may be omitted if cord blood was collected.
3. Collect for all infant-participants who are chest/breastfeeding.
4. Only collect if visit is conducted 14 days or more after birth and 14 days or more in advance of the next scheduled visit's target date.
5. Documented HIV NAT results obtained as part of standard of care, external to the study, may be used if the sample was collected prior to the Birth or Five-Day Post-Birth Visits or within 7 days of any other visit.
6. When collected for HIV-1 confirmation, will also include resistance testing.

Appendix II: Target Visit Dates and Visit Windows

Q4W Dosing			
Study Visit Name	**Target Visit Date**	**Target Visit Window**	**Min/Max Administration Window from last injection**
Antepartum Visit Schedule			
Entry	Within 28 days of screening date		**Switch Group:** N/A **Continuation Group:** 21 to 35 days after previous (non-study) dose
Antepartum Study Week 2	14 days after Entry	-7/+6 days from target visit date	
Antepartum Study Week 4	28 days after Entry	-7/+7 days from target visit date *Note:* The injection administration window for Switch Group participants is more restrictive than the visit window (though may be expanded if supported by the interim analysis). As with all injection visits, injections should be scheduled on a date when the visit window and administration window overlap.	**Switch Group:** 21 to 28 days after loading dose (may be expanded to 21 to 35 days if supported by the interim analysis) **Continuation Group:** 21 to 35 days after previous dose
Antepartum Study Week 6	42 days after Entry	-6/+6 days from target visit date	
Antepartum Study Week 8	56 days after Entry	-7/+7 days from target visit date	21 to 35 days after previous dose
Antepartum Study Week 12	84 days after Entry		
Antepartum Study Week 16	112 days after Entry		
Antepartum Study Week 20	140 days after Entry		
Antepartum Study Week 24	168 days after Entry		
Antepartum Study Week 28	196 days after Entry		
Antepartum Study Week 32	224 days after Entry		
Antepartum Interval Visit(s)	7 days after the injection(s) received between 30 0/7 and 37 6/7 weeks EGA	-2/+14 days from the target visit date	N/A
Postpartum/Infant-Participant Visit Schedule (Adult-Participant and Infant-Participant)			
Pregnancy Outcome Visit (adult-participant)	Day of pregnancy outcome (PO)/birth	+5 days from target visit date	21 to 35 days after previous dose, *if applicable*
Infant-Participant Birth Visit (infant-participant)	Day of birth	N/A	N/A
Infant-Participant Five-Day Post Birth Visit (infant-participant)	+1-5 days after birth	+1-5 days after birth	N/A
Postpartum Injection Visits (adult-participant and infant-participant)	28 days from target date of last dose	-7/+7 days from target visit date	21 to 35 days after previous dose
Final Scheduled Visit (adult-participant and infant-participant)	14 days after previous dose	+7 days from target visit date	N/A

Q8W Dosing			
Study Visit Name	**Target Visit Date**	**Target Visit Window**	**Min/Max Administration Window from last injection**
Antepartum Visit Schedule			
Entry	Within 28 days of screening date		**Switch Group:** N/A **Continuation Group:** 49 to 63 days after previous (off-study) dose
Antepartum Study Week 2	14 days after Entry	-7/+6 days from target visit date	
Antepartum Study Week 4	28 days after Entry	-7/+7 days from target visit date *Note:* The injection administration window for Switch Group participants is more restrictive than the visit window (though may be expanded if supported by the interim analysis). As with all injection visits, injections should be scheduled on a date when the visit window and administration window overlap.	**Switch Group:** 21 to 28 days after loading dose (may be expanded to 21 to 35 days if supported by the interim analysis) **Continuation Group:** N/A
Antepartum Study Week 6	42 days after Entry	-6/+6 days from target visit date	
Antepartum Study Week 8	56 days after Entry	-7/+7 days from target visit date	49 to 63 days after previous dose, *if applicable*
Antepartum Study Week 12	84 days after Entry		
Antepartum Study Week 16	112 days after Entry		
Antepartum Study Week 20	140 days after Entry		
Antepartum Study Week 24	168 days after Entry		
Antepartum Study Week 28	196 days after Entry		
Antepartum Study Week 32	224 days after Entry		
Antepartum Interval Visit(s)	7 days after the injection(s) received between 30 0/7 and 37 6/7 weeks EGA	-2/+14 days from the target visit date	N/A
Postpartum/Infant-Participant Visit Schedule (Adult-Participant and Infant-Participant)			
Pregnancy Outcome Visit (adult-participant)	Day of pregnancy outcome (PO)/birth	+5 days from target visit date	49 to 63 days after previous dose, *if applicable*
Infant-Participant Birth Visit (infant-participant)	Day of birth	N/A	N/A
Infant-Participant Five-Day Post Birth Visit (infant-participant)	+1-5 days after birth	+1-5 days after birth	N/A
Postpartum Injection Visits (adult-participant and infant-participant)	56 days from target date of last dose	-7/+7 days from target visit date	49 to 63 days after previous dose
Final Scheduled Visit (adult-participant and infant-participant)	14 days after previous dose	+7 days from target visit date	N/A

Appendix III: Procedures in the Event of Viral Load Greater Than or Equal to 50 copies/mL



The CMC should be notified within 24 hours of any HIV-1 RNA level ≥50 copies/mL

Appendix IV: Prohibited and Precautionary Medications

The following information may not be all-inclusive. Our understanding of drug interactions continues to grow as new information becomes available. Please refer to the most up-to-date prescribing and drug interaction information in the respective Investigator's Brochures.

Any IMPAACT 2040 participant requiring a prohibited or precautionary medication, refer to protocol Section 8.

Appendix IV-A and Appendix IV-B provides further information on medications considered prohibited or precautionary with concurrent use of each study product. Note that Appendix IV-B contains sub-sections listing prohibited medications for specified participants.

Appendix IV-A: Precautionary Medications

IMPAACT 2040 study participants will receive both CAB LA and RPV LA. During study conduct and prior to prescribing new medications, study investigators should review drug labels, exercise caution, and exert medical judgment (in regard to risk-benefit) when prescribing a medicinal product associated with an increased risk for Torsades de Pointes (TdP), including the below medications. If questions arise when prescribing drugs associated with an increased risk of TdP, please contact the IMPAACT 2040 CMC.

- Anti-arrhythmics:
  - Amiodarone
  - Disopyramide
  - Dofetilide
  - Dronedarone
  - Flecainide
  - Ibutilide
  - Procainamide
  - Quinidine
  - Sotalol
- Antipsychotics:
  - Chlorpromazine
  - Droperidol
  - Haloperidol
  - Levomepromazine
  - Mesoridazine
  - Pimozide
  - Thioridazine
- Anti-infectives:
  - Clarithromycin
  - Erythromycin
  - Roxithromycin
  - Pentamidine
  - Sparfloxacin
- Gastro-intestinal drugs:
  - Cisapride
  - Domperidone
- Opiate agonists:
  - Levomethadyl
  - Methadone
- Antimalarials:
  - Chloroquine
  - Halofantrine
- Other:
  - Arsenic trioxide
  - Bepridil
  - Probucol
  - Paxlovid (nirmatrelvir/ritonavir)

Note: Consider alternatives for anti-infectives, such as azithromycin, which increases rilpivirine concentrations less than other macrolides

Appendix IV-B: Prohibited Medications

The below section contains listings of prohibited medications for **specified participants** at **specified timepoints during study participation** and **within seven days prior to entry (per exclusion criterion 4.2.9)**. If, for any of the below medications, the participant cannot discontinue or change to an allowable alternative, refer to protocol Section 8 for participant management due to prohibited medications.

Prohibited Medications Throughout Study Participation

The following medications may not be administered at any time during study participation:

- HIV-1 immunotherapeutic vaccines.
- Other experimental agents, ARV drugs not otherwise specified in the protocol, cytotoxic chemotherapy, or radiation therapy.
- Chronic use of systemic (oral or parenteral) glucocorticoids 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.
- While 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 are allowed.
- Systemically administered immunomodulators (such as interleukin and interferon agents). This includes topical agents with substantial systemic exposure and systemic effects. Use of topical imiquimod is permitted (see below).

Prohibited Systemically Administered Immunomodulators

The below is a list of examples of immunomodulators prohibited in the study. Please note that the list is not exhaustive and may be updated as needed. The IoR should consider medical history of auto-immune disease and the use of potential immunomodulators not listed below. Use of other immunomodulators that directly affect immune responses will be considered in consultation with the CMC on a case-by-case basis.

- Calcineurin inhibitors:
  - Cyclosporine A
  - Pimecrolimus
  - Tacrolimus
- Fluorouracil (including topical)
- Imiquimod topical (use within 30 days prior to entry requires consultation with the CMC)
- Interferon
- mTOR kinase inhibitors:
  - Everolimus
  - Sirolimus
- Methotrexate purine analogues:
  - Azathioprine
  - 6-Mercaptopurine
- Targeted immune modulators (biological response modifiers):
  - Abatacept
  - Adalimumab
  - Alefacept
  - Anakinra
  - Certolizumab
  - Efalizumab

    - Etanercept
    - Golimumab
    - Infliximab
    - Natalizumab
    - Rituximab
    - Tocilizumab
    - Ustekinumab
- Aminosalicylates:
    - Sulfasalazine
- Aminoquinoline compounds/anti-malarial drugs commonly used to treat auto-immune disorders:
    - Hydroxychloroquine

Prohibited Medications During Study Treatment

For participants receiving any formulation (oral or injectable) of CAB and RPV, the following medications could significantly decrease levels of CAB and/or RPV due to enzyme induction and therefore must not be administered concurrently:

- Carbamazepine
- Oxcarbazepine
- Phenobarbital
- Phenytoin
- Rifabutin
- Rifampicin/Rifampin
- Rifapentine
- Systemic dexamethasone (more than a single dose)
- St. John's wort (Hypericum perforatum)

Additionally,

- Hepatitis C infection therapy is prohibited in conjunction with ongoing study product treatment.

Additional Prohibited Medications During Oral Bridging

In addition, participants must discontinue the following (or change to an allowable alternative) while receiving oral RPV study product:

- Proton pump inhibitors, such as esomeprazole, lansoprazole, omeprazole, pantoprazole, rabeprazole

Additional Prohibited Medications While Receiving Injectables

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 DVT prophylaxis (e.g., postoperative DVT prophylaxis) or the use of low dose acetylsalicylic acid (81 mg). Systemic anticoagulation (including prophylaxis doses) within six hours of an IM injection should be avoided.

Note: Any prohibited medications that decrease CAB or RPV concentrations should be discontinued for a minimum of four 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 two weeks or a minimum of three half-lives (whichever is longer) prior to the first dose.

Appendix V: Sample Informed Consent Forms
Appendix V-A: Sample Informed Consent Form for Q4W and Q8W Continuation Groups

IMPAACT 2040/CREATE
Phase I/II Study of the Pharmacokinetics and Safety of Long-Acting Injectable Cabotegravir and Rilpivirine in Pregnant and Postpartum Adults with HIV-1

CREATE - Cabotegravir & Rilpivirine Antiretroviral Therapy in Pregnancy

Version 1.0, 05 January 2024

Sponsor / Study Title:	**National Institute of Allergy and Infectious Diseases (NIAID) / National Institute of Child Health and Human Development (NICHD)/ National Institute of Mental Health (NIMH) / "CREATE"**
Protocol Number:	**IMPAACT 2040**
Principal Investigator: (Study Doctor)	*<<PI Full Name>>*
Telephone:	*<<Phone Number>>*
Address:	*<<Location>>*

Introduction

You and your baby are being asked to join the research study named above.

This form gives information about the study. Please read it or have it read to you. Ask any questions you may have. We will take as much time as needed for you to fully understand the study. We will ask you questions to see if we have explained the study clearly.

Here is a summary of important information about the study:

- The is the first study testing two anti-HIV drugs, cabotegravir (CAB) and rilpivirine (RPV), given as long-acting injections, to pregnant people aged 18 years and older.
- Both study products are already approved in some countries for use in adolescents or adults, but more information is needed for their use during pregnancy.
- The main purpose of the study is to look at how much CAB and RPV gets into your blood and to see whether the injections are safe for pregnant people.
- You will continue receiving your CAB and RPV injections as part of this study. The study injections will be given every month or every two months. How often you get your study injections will be the same as your current injection schedule. We will explain your study injection schedule before you join.

- Once you join the study, you will have study visits every two weeks for the first two months of the study and about once a month until you finish the study about three to five months after your baby is born (depending on your injection schedule).
- While in the study, you will have clinic visits with physical examinations and blood draws for laboratory tests. Visits will include a review of your medical records and some visits will include an electrocardiogram (ECG), which is a test to look at how well your heart is working. You will answer questions about your health and the drugs being tested. Once your baby is born, we will collect chest/breastmilk samples if you choose to chest/breastfeed your baby.
- Your baby will also have clinical visits with physical examinations and blood draws for laboratory tests.
- At the end of the study, you may be able to continue getting the CAB and RPV injections, if you wish. We will explain all the treatment options available to you and help make sure you have access to continued HIV treatment.
- There are possible risks in the study. Although you have been using the CAB and RPV injections already, one possible risk is that side effects are still possible with continued use of these drugs. The most severe side effects include allergic reactions, liver problems, and mental health problems. Severe side effects are not common. Risks during pregnancy or for the unborn baby are unknown. We do not know if babies who chest/breastfeed will be exposed to CAB and RPV through chest/breastmilk or what the effects may be. If the CAB and RPV stop working as well to control the HIV in your body, it may be possible to pass HIV to your baby or to any sexual partners.
- There may or may not be benefits for you in the study. One possible benefit is being able to continue to receive your injections during pregnancy instead of switching to taking a daily pill. Another possible benefit is that the CAB and RPV injection schedule may be easier to follow than other HIV medicines that require you to take pills every day. If you have nausea and/or vomiting related to your pregnancy, you may find injections easier than taking pills.
- Before you make a decision about joining the study, you should discuss it with your doctor and other important people in your life. Your decision to join in the study will not affect the medical care you or your baby receive. Your access to services, and the benefits and rights you normally have, will not be affected.

More information about the study is given in this form. You should feel that you understand the study before deciding whether you want to join. If you decide that you will join, you will be asked to sign or make your mark on this form. You will be offered a copy to keep.

Your decision to join this study is voluntary. It is completely up to you. You can change your decision and leave the study at any time without giving a reason.

About the study

The International Maternal Pediatric Adolescent AIDS Clinical Trials Network (IMPAACT) and *<<site name>>* are doing this study. The person in charge of the study at *<<site name>>* is the study doctor listed on the first page of this form.

HIV is the virus that can lead to AIDS. The study is testing two anti-HIV drugs in pregnant people age 18 years and older. The study HIV medicines are called cabotegravir (CAB) and rilpivirine (RPV).

The study will include about 45 people from South Africa and the United States. The study will include people who are already receiving CAB + RPV injections to treat their HIV, as well as people who are receiving other HIV medicines and will switch to CAB + RPV injections to treat their HIV during pregnancy. This form is for people who are already receiving CAB + RPV injections.

The United States National Institutes of Health and the companies that make CAB and RPV, ViiV Healthcare and Janssen Pharmaceuticals, are paying for this study.

1. The study is testing long-acting (LA) CAB and RPV in pregnant people.

People with HIV usually take several HIV medicines each day to stay healthy. HIV medicines work by lowering the levels of HIV in your blood (also known as your "viral load"). When at very low levels, your viral load is said to be "undetectable." This study will test CAB LA and RPV LA injections which may be given every month or every two months. How often you receive the injections will be the same as your current injection schedule for CAB LA and RPV LA. We will explain your injection schedule before you join and during follow-up.

Some countries have already approved CAB LA and RPV LA injections for use in adults and in adolescents starting at age 12 years. The approvals were possible because of studies, like this one, that showed CAB LA and RPV LA were safe and worked well to control HIV. While CAB LA and RPV LA have been approved for use in adults and adolescents in some countries, and RPV oral pills are approved for use in pregnant people, there is little information on the use of these injections in pregnant people.

While people in other studies were allowed to continue taking CAB LA and RPV LA injections if they became pregnant, this is the first time that the CAB LA and RPV LA injections are being actively studied in pregnant people for HIV treatment. This study will look at how well the CAB LA and RPV LA injections control the amount of HIV in the pregnant person's blood and how much CAB LA and RPV LA is in their and their baby's blood. The study will also look at whether CAB LA and RPV LA are safe for pregnant people and whether the drugs cause any bad effects for parents and their babies.

2. Only pregnant people and babies who qualify can join the study.

If you decide to join this study with your baby, we will first do some tests to find out if you qualify. More information about the tests is given in #4, below. To qualify for the study, you should be intending to deliver your baby at *<<name of delivery facility>>* and you must agree for your baby to join as well. If you qualify, you and your baby may join the study. If you do not qualify, you and your baby cannot join the study.

3. It is your decision whether or not to join the study.

Deciding to join the study with your baby is voluntary (your choice). You are free to join or not join. You should talk with your doctor and important people in your life about whether the study is a good fit for you or not. If you decide to join, you can change your mind and leave the study at any time. Your decisions will not affect the medical care that you and your baby receive. Your access to services, and the benefits and rights you normally have, will not be affected.

You do not need to join this study to receive medical care and HIV medicine. There are other options to joining the study. For example, you can continue to receive medical care and HIV medicine from outside the study. Even if you join the study and begin to receive your CAB LA and RPV LA injections at the study site, you will need to continue with your regular pregnancy care appointments with your regular doctor. Take your time and make your decision carefully. You may also qualify for other studies. Please ask any questions you may have about these other options. If you wish, you can talk to other people about the study before you decide. You can bring other people here to learn about the study with you.

No matter what you decide about the study, it is important for you to receive medical care and take HIV medicine. Taking HIV medicine is the best way for you to stay healthy and to avoid passing HIV to your baby.

Finding out if you and your baby qualify for this study

4. We will ask questions, examine you, and test your blood.

To find out if you and your baby qualify for the study, we will:

- Look at your medical records.
- Ask about your health, HIV medicines, and other medicines.
- Talk with you about the study requirements.
- Do a physical examination. This will include an exam *<<here and below, sites may use locally appropriate terminology to refer to this exam>>* to check on the progress and health of your pregnancy.
- Give you an electrocardiogram (ECG). This tests how well your heart is working.
- Ask you questions about your mental health. We will ask questions about how you have been feeling (for example, if you have thoughts of harming or killing yourself). Sometimes being pregnant and having HIV can make people feel sadder than normal, and perhaps even have feelings of wanting to harm yourself. If the questions show that you are thinking of harming yourself, we will talk with you about this and we will tell you about other services outside the study that might help you.
- Collect up to 29 mL (almost six teaspoons) of blood for tests. The tests will:
  - Check your blood cells, liver, and kidneys. This includes checking for infections called hepatitis B and C.
  - Confirm you have HIV. If the tests that are required for joining this study are already in your medical records, we may not need to do these tests again.
  - Check how much HIV is in your blood. This is called your "viral load."

- Do an ultrasound scan, if you do not have one already available in your medical records that meets the study requirements.

<< Sites to modify first three sentences as needed >> The scan will be done at *<<site name or location>>*. It will take less than 30 minutes. We will arrange for you to have the scan at a scheduled time. The scan must be done before joining the study.

These procedures will take about *<<X>>* hours. *<<Here and throughout this form, sites should enter the expected visit duration as needed.>>*

Most of the blood tests we do at this visit and any future visits will be processed and analyzed here. Some of the analysis of your blood will be done at other laboratories. We will give you the results of any tests that might affect your or your baby's medical care. Some tests are important for the study, but do not affect your or your baby's medical care, and these results may not be shared with you. Some test results from this visit will be ready quickly. Others may take about two to three weeks. We will ask you to come back when the results are ready. We may ask you to come back for more tests, if needed to find out if you qualify for the study. While waiting for the results, it is important for you to keep taking your regular HIV medicines.

5. We will tell you if you and your baby are eligible.

If you and your baby are not eligible for the study for any reason, we will tell you this. You will not join

the study. You can and should continue to get medical care and treatment outside of the study. We will tell you more about getting this care and treatment and any other services you may need. If you and your baby do not join the study, we will still use some information collected about you (for example, age, sex, and race). We will use this information to look at patterns or common reasons for not joining the study.

If you and your baby are eligible for the study, you can come back for the study Entry Visit.

Joining the study

6. If you and your baby qualify, you will enter the study within four weeks of your first visit

On the day you join the study, we will need to make sure that you qualify. On that day, we will:

- Look at your medical records.
- Ask about your health, HIV medicines, and other medicines.
- Ask you questions about what you think about the study products.
- Talk to you about the importance of getting your HIV medicine on time.
- Do an ultrasound scan, if needed.
- Do a physical examination.
- Collect about 23 mL (almost five teaspoons) of blood for tests. The tests will:
  - Check your blood cells, liver, and kidneys.
  - Check your CD4 cells. These cells help your body fight infections. HIV attacks CD4 cells. The number of CD4 cells should increase over time as you take HIV medicine.
  - Check how much HIV is in your blood (HIV viral load). Your HIV viral load should get lower over time or stay low as you take HIV medicine.
  - Check how much CAB LA and RPV LA is in your blood.
  - Some blood will be saved for later to test if it is resistant to HIV medicine. This test shows whether different HIV medicines may work against the HIV in your blood.

If these procedures show that you and your baby qualify, you and your baby will join the study. You will continue to receive the CAB LA and RPV LA injections:

☐ every month

☐ every two months

We will give you your injections at the study visit.

These procedures will take about <<*X*>> hours.

During the study

The number of visits during pregnancy will depend on when you join the study and when your baby is born. Most visits will take place about a month apart, but visits at the beginning of the study and around the time of delivery will be more often.

7. Injections will be given once a month (every four weeks) or every two months (every eight weeks).

One of the goals of the study is to see how the study injections will work when they are given every month (every four weeks) or every two months (every eight weeks). The visit schedule is mostly the same for both groups; any differences are explained below.

8. After joining the study, you will have a visit every two weeks for the first two months (Week 2, Week 4, Week 6, Week 8).

At the start of the study, you will have more frequent visits to make sure you are healthy, see if you have had any side effects from the HIV medicines, and check how much CAB LA and RPV LA is in your blood. The Week 2 and Week 6 visits will be different from the Week 4 and Week 8 visits.

Week 2 and Week 6

At these visits, we will:

- Look at your medical records.
- Ask about your health, HIV medicines, and other medicines.
- Do a physical exam and perform additional tests, only if necessary for your health.
- Collect about 8 mL (almost two teaspoons) of blood for tests. These tests will check how much HIV is in your blood (HIV viral load) and how much CAB LA and RPV LA is in your blood.

Each visit will take about <<*X*>> hours.

Week 4 and Week 8

At these visits we will:

- Look at your medical records.
- Ask about your health, HIV medicines, and other medicines.
- Talk to you about the importance of getting your HIV medicine on time.
- Do a physical exam.
- Do extra tests, if necessary for your health.
- Collect up to 22 mL (about four and a half teaspoons) of blood for tests to:
    - Check your blood cells, liver, and kidneys.
    - Check your HIV viral load.
    - Check how much CAB LA and RPV LA is in your blood.
- Give you the CAB LA and RPV LA injections*

*Note: those who are on the monthly injection schedule will get their injections at Week 4 and Week 8, and those who are on the every two months injection schedule will get their injections at Week 8 only.

Each visit will take about <<*X*>> hours.

9. You will continue to have study visits every month until you give birth (Week 12, Week 16, Week 20, Week 24, Week 28, Week 32).

At your monthly visits we will check on your health, see if you have had any side effects from the HIV medicines, check how much CAB LA and RPV LA is in your blood, and see how well the drugs are managing your HIV. Each visit will take about <<*X*>> hours.

At these visits we will:

- Look at your medical records.
- Ask about your health, HIV medicines, and other medicines.
- Ask you questions about what you think about the study products (Week 16 only).
- Talk to you about the importance of getting your HIV medicine on time.
- Do a physical exam.
- Do extra tests, if necessary for your health.
- Collect up to 19 mL (almost four teaspoons) of blood for tests to:
    - Check your blood cells, liver, and kidneys.
    - Check your HIV viral load.
    - Check your CD4 cell count (Week 12 and Week 24 only).
    - Check how much CAB LA and RPV LA is in your blood.
- Give you the CAB LA and RPV LA injections*

*Note: Participants with the monthly injection schedule will get their injections at every visit, and participants with the every two months injection schedule will get their injections at every other visit.

10. Extra visits after you are 30 weeks pregnant.

We will schedule special visits after you have reached your 30th week of pregnancy to check how much CAB LA and RPV LA is in your blood. These visits will take place about 1 week after you get your injections. People who are getting monthly injections may have two visits, while people who are getting injections every other month will have one visit. Each visit will take about <<*X*>> hours.

At these visits we will:

- Look at your medical records.
- Ask about your health, HIV medicines, and other medicines.
- Do extra tests, if necessary for your health.
- Collect about 2 mL (almost half a teaspoon) of blood for tests to check how much CAB LA and RPV LA is in your blood.

11. You and your baby will have a visit soon after delivery.

We will stay in contact with you as you get close to your delivery date. We will ask you to contact us when your labor begins and will make plans for you to deliver your baby at <<*delivery facility name*>> if possible. We will arrange for a visit with you as soon as possible after delivery. It is important for this visit to take place as close to the baby's birth as possible, and ideally on the same day. At the latest, the visit must be within 5 days of the baby's birth. This visit will take up to <<*X*>> hours.

For you, the parent, we will:

- Look at your medical records.
- Ask about your health, HIV medicines, and other medicines.
- Do a physical exam.
- Do extra tests, if necessary for your health.
- Collect chest/breastmilk, if you are chest/breastfeeding, to check how much CAB LA and RPV LA is in your milk.
- Collect blood from the umbilical cord to check how much CAB LA and RPV LA is in your baby's blood.
- Collect about 10 mL (two teaspoons) of blood for tests to:
    - Check how much HIV is in your blood (HIV viral load).
    - Check how much CAB LA and RPV LA is in your blood.

- Give you information about ways to prevent pregnancy.
- Give you the CAB LA and RPV LA injections if you have your baby around the time that you are scheduled to have your next injections.

If possible, your baby will have a visit at the same time as you on the day you deliver. At the visit for your baby, we will:

- Look at your baby's medical records.
- Ask about your baby's health, medicines, and feeding.
- Do a physical exam. If anything unusual is seen when your baby is examined, we may take photos of your baby. The photos will help the study doctors and other experts working on the study decide if it is important for your baby's health. We will tell you the doctors' opinion when we have information to share. *<<Here, sites may modify text regarding photographs if IRBs/ECs mandate a separate form for obtaining informed consent for photographs.>>*
- Do extra tests, if necessary for your baby's health.
- Collect up to 3.5 mL (about a teaspoon) of blood for tests to:
    - Check if your baby has HIV. If the tests that are required for the study are already in your baby's medical records, we may not need to do this test again. Some blood may be saved for later to test if it is resistant to HIV medicines. This test shows whether different HIV medicines may work against the HIV in your baby's blood (if your baby has HIV).
    - Check how much CAB LA and RPV LA is in your baby's blood.

<<Here and throughout this form, sites may modify the amount of blood collected for infant-participants based on local regulations.>>

Regardless of whether the visit for your baby happens on the day of their birth, your baby will also have a visit within five days of birth. At this visit we will collect about 1 mL (less than half a teaspoon) of blood to check your baby's liver and check how much CAB LA and RPV LA is in your baby's blood. We will look at your baby's medical records and ask about your baby's health, medicines, and feeding. If your baby was not able to complete a visit on the day of birth, we will complete all of the procedures listed above for the birth visit.

12. Post-Delivery visits.

You and your baby will have three more visits before you finish the study. You will complete two visits where you will receive your final study injections according to your injection schedule. The final study visit will happen two weeks after your last study-provided injections.

Postpartum Injection Visits

For you, the parent, we will:

- Look at your medical records.
- Ask about your health, HIV medicines, and other medicines.
- Talk to you about the importance of getting your HIV medicine on time.
- Do a physical exam.
- Do extra tests, if necessary for your health.
- Collect chest/breastmilk, if you are chest/breastfeeding.
- Give you information about ways to prevent pregnancy.
- Collect urine for a pregnancy test, if needed.
- Collect about 19 mL (almost four teaspoons) of blood for tests to:

    - Check your blood cells, liver, and kidneys.
    - Check how much HIV is in your blood (HIV viral load).
    - Check how much CAB LA and RPV LA is in your blood.
- Give you the CAB LA and RPV LA injections.

For your baby, we will:

- Look at your baby's medical records.
- Ask about your baby's health, medicines, and feeding.
- Do a physical exam.
- Do extra tests, if necessary for your baby's health.
- Collect up to 5 mL (one teaspoon) of blood for tests to:
    - Check if your baby has HIV. If the tests that are required for the study are already in your baby's medical records, we may not need to do this test again. Some blood may be saved for later to test if it is resistant to HIV medicines. This test shows whether different HIV medicines may work against the HIV in your baby's blood (if they have HIV).
    - Check your baby's liver and kidneys
    - Check how much CAB LA and RPV LA is in your baby's blood

Final Study Visit - Two weeks after the last study-provided injections

For you, the parent, we will:

- Look at your medical records.
- Ask about your health, HIV medicines, and other medicines.
- Ask some questions about what you think about the study products.
- Do a physical exam.
- Do extra tests, if necessary for your health.
- Collect chest/breastmilk, if you are chest/breastfeeding.
- Give you information about ways to prevent pregnancy.
- Collect urine for a pregnancy test, if needed.
- Collect about 19 mL (almost four teaspoons) of blood for tests to:
    - Check your blood cells, liver, and kidneys.
    - Check your HIV viral load.
    - Check how much CAB LA and RPV LA is in your blood.
- Ask you questions about your mental health.
- Talk about your HIV medicine options.

For your baby, we will:

- Look at your baby's medical records.
- Ask about your baby's health, medicines, and feeding.
- Do a physical exam.
- Do extra tests, if necessary for your baby's health.
- Collect up to 5 mL (one teaspoon) of blood for tests to:
    - Check if your baby has HIV. Some blood may be saved for later to test if it is resistant to HIV medicines. This test shows whether different HIV medicines may work against the HIV in your baby's blood, (if your baby has HIV).
    - Check your baby's liver and kidneys
    - Check how much CAB LA and RPV LA is in your baby's blood

At your final study visit we will give you the results of the tests that will help you manage your health and tell you where you can go for any care or treatment you or your baby may need. It is very important for you to keep taking HIV medicine after leaving the study. We will talk with you about your options and help make sure you can get HIV medicine from outside the study. We will answer any questions you may have and tell you how to contact us in the future, if you wish.

13. If you do not receive a scheduled injection, you may need to use oral pills until you can get back on your injection schedule.

If you miss an injection visit or cannot receive your CAB LA and RPV LA injections for any reason, your study doctor may give you the oral pill version of CAB and RPV to use. Your study doctor will also talk to you about when you can start the injections again.

You may need to have an extra visit in order to restart the CAB LA and RPV LA injections and get back on your original injection schedule. At this extra visit, we will:

- Look at your medical records.
- Ask about your health, HIV medicines, and other medicines.
- Talk to you about the importance of getting your HIV medicine on time.
- Do a physical examination.
- Do extra tests, if necessary for your health.
- Collect about 16 mL (about three and a half teaspoons) of blood for tests to:
    - Check your blood cells, liver, and kidneys.
    - Check how much HIV is in your blood (HIV viral load).
    - Check how much CAB LA and RPV LA is in your blood.
- Give you the CAB LA and RPV LA injections.

14. You may have an extra visit if your HIV is not controlled.

While receiving the study products, the amount of HIV in your blood (HIV viral load) should stay low. If tests show that your viral load is higher than expected, you will have an extra visit. At this visit we will:

- Look your medical records.
- Ask about your health, HIV medicines, and other medicines.
- Talk to you about the importance of getting your HIV medicine on time.
- Do a physical examination.
- Do extra tests, if necessary for your health.
- Collect about 14 mL (about three teaspoons) of blood for tests. The tests will re-check your viral load and the amount of CAB LA and RPV LA in your blood.
- If your viral load is still high, we will test for resistance.

We will give you the results of these tests and explain them to you. If the results show that your HIV medicine may need to be changed, we will discuss that with you.

15. Your baby may have an extra visit if your baby tests positive for HIV.

While getting the study products, the amount of HIV in your blood (HIV viral load) should stay low. This makes it harder for your baby to get HIV. If we receive a positive HIV test result for your baby, you will have to bring in your baby for an extra visit. At this visit we will:

- Collect about 6 mL (about one and a half teaspoons) of blood from your baby for tests. The tests will re-check your baby for HIV and test for HIV resistance.
- Talk to you about starting HIV medicine for your baby and the care available locally

We will give you the results of these tests and explain them to you. If the extra tests confirm that your baby has HIV, we will talk to you about care options for your baby.

16. You may choose to leave the study at any time or we may need to take you off the study early.

You are free to leave the study, or take your baby off the study, at any time for any reason. Leaving the study will not affect the care you and your baby receive, but it is important that you tell us before you or your baby leave the study.

Some people may have to stop the study products or stop the study early. This could happen if:
- You are not able to come to the study visits or meet other study requirements.
- You need to take medication that is not allowed in this study.
- The study is stopped for any reason.
- The study doctor decides that being in the study would be unsafe or otherwise not in the best interest for you or your baby.

If you leave the study early, we will ask you to come back for one last clinic visit.

For you, the parent, we will:

- Look at your medical records.
- Ask about your health, HIV medicines, and other medicines.
- Do a physical exam.
- Do extra tests, if necessary for your health.
- Collect chest/breastmilk, if you are chest/breastfeeding.
- Collect urine for a pregnancy test, if needed
- Give you information about ways to prevent pregnancy.
- Collect about 19 mL (almost four teaspoons) of blood for tests to:
    - Check your blood cells, liver, and kidneys.
    - Check how much HIV is in your blood (HIV viral load).
    - Check how much CAB LA and RPV LA is in your blood.
- Ask some questions about what you think about the study products.
- Ask you questions about your mental health.
- Give you the CAB LA and RPV LA injections, if required based on your injection schedule
- Talk about your HIV medicine options.

For your baby, we will:
- Look at your baby's medical records.
- Ask about your baby's health, medicines, and feeding.
- Do a physical exam.
- Do extra tests, if necessary for your baby's health.
- Collect about 5 mL (one teaspoon) of blood for tests to:
    - Check if your baby has HIV. Some blood may be saved for later to test if it is resistant to HIV medicines. This test shows whether different HIV medicines may work against the HIV in your baby's blood (if your baby has HIV).
    - Check your baby's liver and kidneys

- Check how much CAB LA and RPV LA is in your baby's blood, if you are chest/breastfeeding.

If you leave the study early for any reason, we will tell you where you can go for any care or treatment you or your baby may need. It is very important for you to keep taking HIV medicine after leaving the study. We will talk with you about your options and help make sure you can get HIV medicine from outside the study. We will answer any questions you may have and tell you how to contact us in the future, if you wish.

Risks of the study

17. There are several possible risks of the study.

Being in this study may involve some risks and discomfort. Most procedures done in this study are routine medical procedures, with little risk to you or your baby. Collecting chest/breastmilk could be uncomfortable. There is no risk from ultrasound. Study risks include risks from collecting blood, risks from getting injections, risks from the study products, and risks to your privacy. You may feel nervous or embarrassed when answering questions for the study.

Your baby will be tested for HIV while in this study. You may become worried or anxious about your baby's test results. We will explain all tests to you and give you counseling to help with feelings you may have about the tests and your baby's results.

18. There are risks from collecting blood and getting injections.

Giving blood. Collecting blood can cause pain, swelling, bruising, or bleeding where the needle is inserted. Rarely, collecting blood can cause fainting or infection.

Feeling faint after injection. Getting injections can cause some people to feel light-headed or feel like they might faint. This reaction, also called a 'vasovagal reaction', can happen with many medical procedures. This reaction usually improves quickly and is generally not a bad sign regarding your health.

Injection site reactions. CAB and RPV injections can cause the following reactions where the needle is inserted:

- pain and discomfort, or a hardened lump (very common)
- swelling, redness, itching, bruising, warmth or discoloration, which may include a collection of blood under the skin (common)
- cellulitis (heat, swelling or redness), abscess (collection of pus), numbness, minor bleeding, or discoloration (uncommon)

Some reactions may happen quickly, but others may happen a day or two later. Most reactions go away in a week or less, but sometimes they can last longer. Most people who have reactions can continue the study injections.

Post-injection reaction. Some people experience reactions soon after receiving their RPV injection. Most reactions resolved within a few minutes after the injection. Reactions may include: difficulty breathing, stomach cramps, rash, sweating, numbness of the mouth, blood pressure changes, and pain (back and chest), feeling anxious, feeling warm, or feeling lightheaded or faint. These cases may be due to an accidental injection of part of the medication into a blood vessel instead of the muscle. Not all people who may have received an injection into a blood vessel by mistake had these reactions. Most of the reactions

resolved in a few minutes. Your study doctor may need to give you treatment to help with these reactions. You will be observed (approximately 15 minutes) after each injection.

Other possible side effects from the injection procedure. Another risk is that the injection could be given too deeply, not deeply enough, or part of the injection may be injected into a blood vessel, a nerve, or into the skin only instead of a muscle by mistake. The risks of getting an injection the wrong way are not well understood, but it could make the amount of CAB or RPV in your body too high or too low. If too low, the medicines may not work against your HIV. If the RPV levels are too high, there could be a change in your heart beat due to a change in the electrical activity in your body. Very rarely, in severe cases this can be life-threatening and could lead to sudden death; however, no such severe changes in electrical activity or sudden deaths have been seen in clinical studies with RPV. If your study doctor thinks that the injection was not given in the right way, we may need you to stay in the clinic for extra time for observation or for additional treatment and tests to make sure you are safe.

19. There are risks from the study HIV medicines

All HIV medicines can cause side effects. This includes the HIV medicines you are taking right now and any other HIV medicines you would receive outside the study. A side effect is a bad effect that may be caused by the drugs you are taking. Some side effects are minor, others can be severe. Some side effects are common, others are rare. Some people have some of the side effects. Other people have no side effects.

The known side effects for CAB and RPV are listed in the tables below, but there may be other side effects that we do not know about at this moment. This may be especially true for pregnant people, because this is the first study of the CAB and RPV combination for HIV treatment in pregnant people. It is possible that new and previously unknown side effects for the pregnant person as well as the unborn baby could be serious or even life-threatening. It is also possible that the CAB and RPV injections might not work as well to treat HIV during pregnancy as they did before you were pregnant. This is why we will closely monitor the amount of HIV in your blood (HIV viral load) several times during the study and schedule extra visits if your HIV is not well controlled (see #13 above). If the CAB LA and RPV LA do not control the HIV in your body very well, there may be a higher chance that you can give HIV to your baby or to any sexual partners.

If you join the study, we will tell you more about the study products you will be taking. At each study visit, we will check on whether the study products are causing any side effects. We will also tell you what to do if you have side effects. If you have questions or concerns at any time, please tell us.

20. Side effects from the CAB injection.

Many adults and a small number of adolescents have received CAB injections in other studies. The table below lists side effects from other studies of CAB in people who have HIV. Note that these side effects have been seen in people taking CAB together with RPV.

Side Effects of CAB (when taken together with RPV)*

Very Common (may affect at least 1 in 10 people)	**Common** (may affect up to 1 in 10 people)	**Uncommon** (may affect up to 1 in 100 people)
• Injection site reaction • Headache • Pyrexia (fever)	• Rash • Diarrhea or loose stools • Nausea (feeling sick to the stomach) • Flatulence (passing gas or wind) • Vomiting (being sick) • Abdominal pain (stomach pain and discomfort) • Insomnia (problems sleeping) • Abnormal dreams/nightmares • Feeling light-headed (dizziness) • Anxiety (feeling anxious) • Depression (feelings of deep sadness and unworthiness) • Myalgia (muscle pain) • Fatigue (lack of energy) • Asthenia (feeling weak) • Malaise (feeling generally unwell) • Weight increase • Hemorrhoids	• Hypersensitivity (allergic reaction) (including angioedema (swelling), urticaria/hives (raised and itchy rash)). • Somnolence (Sleepiness or drowsiness) • Vasovagal reactions (lightheadedness or fainting, during or following an injection) • Hepatotoxicity (liver problems) • Transaminase increase (blood test may show increase in the level of liver enzymes) • Suicidal thoughts and actions (suicidal ideation and suicide attempt)* *Mainly in people who had depression or mental health conditions before.

*In addition to risks from receiving injections, as described in Section 17.

More details on the side effects of CAB are described below:

Hypersensitivity. Some people have had hypersensitivity reactions (also known as allergic reactions) when using CAB. These reactions have mostly included signs and symptoms of swelling and/or a raised and itchy rash (hives).

Hypersensitivity reactions for other medicines similar to CAB also included a general feeling of being sick, a high temperature, lack of energy, blisters, mouth ulcers, conjunctivitis (also known as pink eye), muscle or joint aches and swelling (sometimes of the face or mouth which caused difficulty breathing).

While more serious allergic reactions have not yet been seen for CAB, it is possible that you may have one of these reactions. If you have any of these symptoms during the study, you must call your study doctor immediately. The study doctor may decide to do tests on your liver, kidneys or blood, and may tell you to stop taking CAB LA + RPV LA.

Abnormal liver tests. A small number of people in CAB research studies had abnormal liver tests and had to stop CAB treatments. For some people, the abnormal liver tests were explained by other causes (such as an illness). A smaller number of people (less than 1% of all people in the studies) did not have other causes that could explain the abnormal test, so it is possible that a mild form of liver damage happened from taking CAB. The liver tests got better after stopping CAB, suggesting that the damage was temporary.

Blood tests to check the health of your liver will be done during the study. Your study doctor will tell you if you need to stop taking the study products or if other actions are needed. If you stop taking the study product, you may be able to re-start the study product or may need to change to a non-study HIV medicine.

If you have a history of seizures, please let your study doctor know.

21. Side effects from the RPV pills and RPV injection

Oral RPV is a drug that many people throughout the world take to treat HIV, so we know a lot about it. In addition, many adults and a small number of adolescents get RPV injections in other studies. The following side effects have been seen in people with HIV taking RPV.

Side Effects of RPV*

Very Common (may affect at least 1 in 10 people)	**Common** (may affect up to 1 in 10 people)	**Uncommon** (may affect up to 1 in 100 people)
• Headache • Fever (pyrexia), feeling hot, body temperature increase	• Feeling less hungry (decreased appetite) • Sleep disorders, insomnia (sleeplessness) • Abnormal dreams • Dizziness • Fatigue (lack of energy) • Asthenia • Malaise • Myalgia (muscle pain) • Rash • Depression • Diarrhea • Nausea, vomiting abdominal pain or discomfort (belly ache)	• Immune reconstitution syndrome (this can be an overreaction of the body's recovering defense system to a previously present infection, or problems in the immune system) • Depressed mood • Sleepiness (somnolence) • Abdominal (belly) discomfort • Dry mouth • Transaminases increased (increased levels in the blood of certain liver function tests)

Very Common (may affect at least 1 in 10 people)	**Common** (may affect up to 1 in 10 people)	**Uncommon** (may affect up to 1 in 100 people)
	• Upper abdominal (belly) pain	

*In addition to risks from receiving injections, as described in Section 17.

More information on the side effects of RPV are listed below:

Liver problems. Changes in blood tests have been seen. People with Hepatitis B or C, or who have possible liver damage before starting RPV, may have worse liver tests while taking RPV. A few cases of liver problems were found in people taking RPV who did not already have any liver problems.

Sometimes allergic reactions can affect body organs. For example, an allergic reaction can cause liver problems which can lead to liver failure. Contact your study doctor right away if you have any of the following signs or symptoms of liver problems:

- Yellowing of the skin or whites of the eyes
- Dark or tea colored urine
- Pale colored stools/bowel movements
- Nausea/vomiting
- Loss of appetite
- Pain, aching or tenderness on the right side below the ribs
- Itchy skin
- Unexplained weight loss

Skin rash. Most rashes were mild or moderate, and happened within the first four weeks of taking RPV. Most rashes got better after one week, and the people did not need to stop taking RPV. However, the study HIV medicines will need to be stopped for some types of moderate rash and all types of severe rash, which can be life-threatening. If this happens to you, you will need to come for extra study visits to monitor your health. Some people with rash may also have other signs and symptoms of allergic reaction.

If you have any type of rash or other skin problems during the study you must tell your study doctor right away, and the doctor may tell you to stop taking the study products.

22. There may be other possible risks.

Risk of your HIV becoming resistant. With any drug used to treat HIV, there is a risk that the virus in your body will become resistant, meaning that the drug will not work as well or not work at all against your HIV.

Even though you will continue to take your current HIV medicine if you join the study, resistance could develop if the HIV medicine stops working as well to control the amount of HIV in your blood. The risk of your HIV becoming resistant is unknown. It will depend on how well the study products work against your virus and how well you are able to follow the injection schedule. To prevent resistance, it is important that you get your study injections as instructed, and do not miss any injections.

Talk to your study doctor any time you miss or if you think you will be late or early for getting injections—this includes vacations or work-related travel that may affect your scheduled visits.

Do not change or skip of any of your study injections unless your study doctor tells you to do so.

Possible effects on pregnancy, unborn babies, and chest/breastfeeding babies. Taking HIV medicine is the best known way for you to maintain your health and to avoid passing HIV to your baby during pregnancy and chest/breastfeeding. HIV and HIV medicine may lead to some pregnancy complications, like early delivery or a low birth weight for the baby. We do not yet know if CAB is safe or works well to treat HIV in pregnancy or prevent pregnant parents from giving HIV to their babies. There is little information from people on the effects of CAB in pregnancy, but CAB LA and RPV LA have been found in the body for up to 12 months or longer after an injection and the effects of the drugs on an unborn baby are currently unknown. Most of the information we have is from studies on animal. RPV does not seem to have bad effects on pregnancy and the baby from what we know now, but more information is still being collected.

Babies who chest/breastfeed may get the HIV medicine taken by their parents through chest/breastmilk. We do not know how much of the HIV medicine goes into chest/breastmilk, how long after an injection the HIV medicine may be in the chest/breastmilk or what effects getting CAB LA and RPV LA through chest/breastfeeding may have on babies. Your study doctor and health care provider(s) outside the study can tell you about the possible benefits and risks of different infant feeding options you may be considering.

We are doing this study to learn more about safety of CAB LA and RPV LA for pregnant people and their babies. We will also learn how much of this HIV medicine is passed to babies and what effects this may have.

Mental illness or depression. Some people with chronic health conditions, including HIV, sometimes have feelings of depression or may feel sad or hopeless, feel anxious or restless, or may have thoughts of hurting or killing themselves (suicide). A small number of people being treated with CAB and RPV have had thoughts of killing themselves and have tried to do so, particularly people with a history of depression or mental health illness.

Tell the study doctor if you have a history of mental health illness. If you are worrying more often, feeling low or sad, having sleep problems, have thoughts of hurting or killing yourself, or have any other unusual or uncomfortable thoughts during this study, you should tell the study doctor or go to the nearest hospital right away.

Immune reconstitution syndrome. In some people with advanced HIV, signs and symptoms from other infections or certain diseases (for example a liver condition called autoimmune hepatitis) may start soon after starting HIV medicine or later into treatment. Some of these symptoms may be life threatening. This would be very rare, but if you start having new symptoms, or if you notice that any existing symptoms are getting worse, tell your doctor immediately.

Abnormal distribution of body fat and wasting. The use of strong HIV medicine may cause some types of body changes, especially related to where fat is in your body. Body changes could include more fat around the waist and stomach area or on the back of the neck. Other body changes include bigger chest/breast and/or less fat in the face, legs, and arms.

General side effects of CAB LA and RPV LA injections:

The study injections stay in your body for a long time. The injections you get in this study are long-acting, meaning they stay in the body for a long time. In most people, the drugs will no longer be in the body one year after an injection, but in some people, low levels of CAB and RPV may still be in the body after one year.

If you develop a side effect to the study product after the injection, there will be no way to remove the drug from your body. If you develop a symptom from these drugs while the drugs are still in your body, every effort will be made to treat the side effects. The amount of drug in your body will decrease overtime and will eventually disappear.

If you stop getting the study injections, the study products will stop working to treat HIV, as the amount of drug in the body decreases slowly over time. When stopping these drugs, it will be very important for you to start taking other HIV medications, as directed by your doctor.

Risks of disclosure of your information. In addition to the risks of study procedures and the study products, there is a risk of that someone may learn about your and your baby's information. We will make every effort to keep your and your baby's information private and confidential. Study records and blood and chest/breastmilk samples will be kept in secure locations. All samples and most records will be labeled only with a code number. However, your and your baby's name will be written on some records.

<<To be included at US sites>> U.S. Federal laws protect the privacy of your and your baby's protected health information ("personal/private information"). However, there are exceptions to these laws. The Researchers will ask you to sign a form ("HIPAA Authorization") to give your permission for certain uses and sharing of your and your baby's personal (private) information for the study. That form provides more details about the types of information that may be used and shared, and how it will be protected.

<<To be included at South African sites>> In addition, the Protection of Personal Information Act (POPIA) ensures that all South African institutions conduct themselves in a responsible manner when collecting, processing, storing and sharing your and your baby's personal information by holding them accountable should they abuse or compromise your personal information in any way.

<<All sites to include any other relevant country-specific data-sharing requirements, as applicable>>

<<To be included at US sites>> You and your baby's privacy may also be protected by a Certificate of Confidentiality that helps us avoid being forced to release information that may identify you or your baby, such as by the courts or police. The certificate cannot be used in all situations, but it can be used to resist demands for information that would identify you or your baby. The certificate does not protect against requests for information from the United States federal government or from the United States Food and Drug Administration. Regardless of the certificate, you can release information about your or your baby's participation in the study to others, if you wish.

Samples collected from you and your baby will be used for study testing only, as described in this form. None of the testing involves whole genome sequencing. The samples will not be used for other research now or in the future. The samples will not be sold or used for commercial profit. For example, the samples will not be used to make a new product that could be sold.

The information we collect about you and your baby for this study will be combined with information collected about all other participants in the study. This will be done at an organization called a statistical and data management center. The IMPAACT Network statistical and data management center is in the United States. We will send your and your baby's information to this center, but your and your baby's name and other information that could personally identify you will not be sent. The information will be sent securely, following applicable laws and policies.

Information collected for this study may be used for other research in the future. For example, researchers may use information from this study to try to answer different questions about pregnant people with HIV. Any future research done with the information from this study must be approved by the IMPAACT Network. If any future research is done, information about you or your baby may be used without additional informed consent. Your and your baby's information will be labeled with a code number, and the only link between the code number and your and your baby's name will be kept here at this clinic.

We will try our best to keep your and your baby's information private. However, it is still possible for someone who should not have your or your baby's information to get it. If this happens, you or your baby could be treated badly or unfairly.

Benefits of the study

23. There may or may not be benefits to you from joining the study.

By joining the study, you will be part of the search for new treatments for pregnant people with HIV. There may be a direct benefit to you by joining the study, but we cannot guarantee that being in the study will benefit you or your baby in any way. There may also be benefit if the information from this study lead to a safe and effective dose of the study products for pregnant people. One possible benefit is that you might prefer getting CAB and RPV as a monthly (or every two months) injection instead of taking pills every day. If you have pregnancy nausea and/or vomiting, you may find injections easier than taking pills. If you like the injections, and they are working well, you may be able to continue getting them after the study is over. Information learned from this study may help other pregnant people who have HIV.

You and your baby will have regular visits here and frequent checks on your health, including checking how much HIV is in your blood (HIV viral load). It is possible the study HIV medicine will slow the progress of HIV for you.

Other information about the study

24. There are no costs to you for joining the study.

There are no costs to you or your baby for study visits or procedures, or the study products.

<<Sites insert information about compensation/reimbursement here.>> You will be reimbursed for the cost of travel to study visits and your time spent here. For each visit, you will be given *<<specify amount>>*.

25. Your and your baby's records may be looked at by study staff and groups that oversee the study.

Groups that oversee the study include:

- *<<U.S. sites insert sIRB>>*
- *<<Sites insert local IRBs/ECs as applicable>>*
- *<<Sites insert applicable drug regulatory authorities and other regulatory entities>>*
- The United States National Institutes of Health and its study monitors
- The United States Food and Drug Administration
- The United States Office for Human Research Protections
- Other United States, local, and international regulatory entities
- The IMPAACT Network that is coordinating the study
- The companies that make the study products, ViiV Healthcare and Janssen Research and Development

Like the study staff, these groups are required to make efforts to keep study records private and confidential.

The results of the study may be presented publicly or published. However, no presentation or publication will use your baby's name or identify your baby personally.

A description of this clinical trial will be available on https://www.clinicaltrials.gov/, as required by U.S. 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.
Your or your baby's study information may be given to other authorities if required by law. *<<Sites may add more specific detail here describing local laws that may be applicable.>>*

26. If you or your baby gets sick or injured, contact us immediately.

Your and your baby's health is important to us. We will make every effort to protect your and your baby's well-being and lower risks. It is possible, however, that you or your baby could have an illness or injury that is study-related. This means that the illness or injury occurred as a direct result of being in the study.

<<Sites may modify this paragraph to reflect local institutional policies; information regarding coverage available through clinical trial insurance obtained by the site should be included if applicable; the statement regarding no program for compensation through the NIH may not be removed.>> If a study-related illness or injury occurs, we will treat you or your baby or tell you where you can get the treatment you need. The cost for this treatment may be charged to you or your health insurance. There is no program to pay money or give other forms of compensation for study-related illness or injury through *<<site name>>* or the United States National Institutes of Health.

Who to contact

27. If you have questions, concerns, or problems at any time, use these contacts.

If you have questions, concerns, or problems at any time, use these contacts.

- If you have questions about the study or your or your baby's health, or if you want to leave the study:
  <<Name, phone number, and other relevant contact details of investigator or other study staff>>

- If you have questions about your or your baby's rights as a study participant, or problems or concerns about how you or your baby is being treated in the study:
  <<Name, phone number, and other relevant contact details of IRB contact person or other appropriate person or organization; US sites to include sIRB contact information>>

Permission for Off-Site Visits

On rare occasions, members of the research team may be able to schedule visit activities off-site at your home or at another location. Before any visits take place off-site, the study staff will discuss the location and time so that the visit is at a convenient time and place where you feel comfortable and confidentiality can be maintained. To have visits outside of the clinic, you will need to give us written permission to do so.

Please read the following statements carefully and write your initials or make your mark next to the option you prefer.

_____ I do agree to have study visits at a location other than the study clinic, when necessary.

_____ I do not agree to have study visits at a location other than the study clinic, when necessary.

Signatures

If you decide to have you and your baby join this study, please sign or make your mark below.

Before deciding whether to have you and your baby join this study, make sure you have read this form or had it read to you. Make sure all your questions have been answered. You should feel that you understand the study, its risks and benefits, and what is expected of you and your baby.

We will tell you any new information from this study or other studies that may affect your willingness to keep you and your baby in the study. You are welcome to ask questions or request more information at any time.

You do not give up any rights by signing this form.

<<Sites insert signature blocks as required by IRB and institutional policies.>>

Name of Participant (print)	Participant Signature	Date
Name of Witness (if applicable, print)	Witness Signature	Date
Study Staff Conducting Permission Process Name (print)	Study Staff Signature	Date

Appendix V-B: Sample Informed Consent Form for Q4W and Q8W Switch Groups

IMPAACT 2040/CREATE
Phase I/II Study of the Pharmacokinetics and Safety of Long-Acting Injectable Cabotegravir and Rilpivirine in Pregnant and Postpartum Adults with HIV-1

CREATE - Cabotegravir & Rilpivirine Antiretroviral Therapy in Pregnancy

Version 1.0, 05 January 2024

Sponsor / Study Title:	**National Institute of Allergy and Infectious Diseases (NIAID) / National Institute of Child Health and Human Development (NICHD)/ National Institute of Mental Health (NIMH) / "CREATE"**
Protocol Number:	**IMPAACT 2040**
Principal Investigator: (Study Doctor)	*<<PI Full Name>>*
Telephone:	*<<Phone Number>>*
Address:	*<<Location>>*

Introduction

You and your baby are being asked to join the research study named above.

This form gives information about the study. Please read it or have it read to you. Ask any questions you may have. We will take as much time as needed for you to fully understand the study. We will ask you questions to see if we have explained the study clearly.

Here is a summary of important information about the study:

- The is the first study testing two anti-HIV drugs, cabotegravir (CAB) and rilpivirine (RPV), given as long-acting injections, to pregnant people aged 18 years and older.
- Both study products are already approved in some countries for use in adolescents or adults, but more information is needed for their use during pregnancy.
- The main purpose of the study is to look at how much CAB and RPV gets into your blood and to see whether the injections are safe for pregnant people.
- Once you qualify for the study, your will stop taking your anti-HIV drugs on the day when your study doctor starts your CAB and RPV injections. The study injections will be given every month or every two months until six weeks after you have your baby (for those taking monthly injections) or 10 weeks after you have your baby (for those getting injections every two months). How often you get the injections will be based on when you join the study and which injection schedule is being studied at that time. We will explain your injection schedule before you join.

- Once you join the study, you will have study visits every two weeks for the first two months of the study and about once a month until you finish the study about three to five months after your baby is born (depending on your injection schedule).
- While in the study, you will have clinic visits with physical examinations and blood draws for laboratory tests. Visits will include a review of your medical records and some visits will include an electrocardiogram (ECG), which is a test to look at your heart. You will answer questions about your health and the drugs being tested. Once your baby is born, we will collect chest/breastmilk samples if you choose to chest/breastfeed your baby.
- Your baby will also have clinical visits with physical examinations and blood draws for laboratory tests.
- At the end of the study, you may be able to continue getting the CAB and RPV injections, if you wish. We will explain all the treatment options available to you and help make sure you have access to continued HIV treatment.
- There are possible risks in the study. One possible risk is that the drugs being tested could cause side effects. The most severe side effects include allergic reactions, liver problems, and mental health problems. Severe side effects are not common. Risks during pregnancy or for the unborn baby are unknown. We do not know if babies who chest/breastfeed will be exposed to CAB and RPV through chest/breastmilk or what the effects may be. If the CAB and RPV do not work well to control the HIV in your body, it may be possible to pass HIV to your baby or to any sexual partners.
- There may be benefits for you in the study. One possible benefit is that the CAB and RPV injection schedule may be easier to follow than other HIV medicines that require you to take pills every day. If you have pregnancy nausea and/or vomiting, you may find injections easier than taking pills.
- Before you make a decision about joining the study, including changing your usual HIV medicine to CAB and RPV injections, you should discuss it with your doctor and other important people in your life. Your decision to join the study will have not affect the medical care you or your baby receive. Your access to services, and the benefits and rights you normally have, will not be affected.

More information about the study is given in this form. You should feel that you understand the study before deciding whether you want to join. If you decide that you will join, you will be asked to sign or make your mark on this form. You will be offered a copy to keep.

Your decision to join this study is voluntary. It is completely up to you. You can change your decision and leave the study at any time without giving a reason.

About the study

The International Maternal Pediatric Adolescent AIDS Clinical Trials Network (IMPAACT) and *<<site name>>* are doing this study. The person in charge of the study at *<<site name>>* is the study doctor listed on the first page of this form.

HIV is the virus that can lead to AIDS. The study is testing two anti-HIV drugs in pregnant people age 18 years and older. The study HIV medicines are called cabotegravir (CAB) and rilpivirine (RPV).

The study will include about 45 people from South Africa and the United States. The study will include people who are already receiving CAB + RPV injections to treat their HIV, as well as people who are receiving other HIV medicines and will switch to CAB + RPV injections to treat their HIV during pregnancy. This form is for people who will be switching to CAB + RPV injections.

The United States National Institutes of Health and the companies that make CAB and RPV, ViiV Healthcare and Janssen Pharmaceuticals, are paying for this study.

1. The study is testing long-acting (LA) CAB and RPV in pregnant people.

People with HIV usually take several HIV medicines each day to stay healthy. HIV medicines work by lowering the levels of HIV in your blood (also known as your "viral load"). When at very low levels your viral load is said to be "undetectable." This study will test CAB LA and RPV LA injections which may be given every month or every two months. How often you get the injections will be based on when you join the study and which injection schedule is being studied when you join. We will explain your injection schedule before you join and during follow-up.

Some countries have already approved CAB LA and RPV LA injections for use in adults and in adolescents starting at age 12 years. The approvals were possible because of studies, like this one, that showed CAB LA and RPV LA were safe and worked well to control HIV. While CAB LA and RPV LA have been approved for use in adults and adolescents in some countries, and RPV oral pills are approved for use in pregnant people, there is little information on the use of these injections in pregnant people.

While people in other studies were allowed to continue taking CAB LA and RPV LA injections if they became pregnant, this is the first time that the CAB LA and RPV LA injections are being actively studied in pregnant people for HIV treatment. When people with HIV become pregnant, their doctor usually continues the same HIV medicines, if those medicines have been working well to control the HIV levels in the blood. Pregnant persons who switch from their oral HIV medicine to the injections of CAB LA and RPV LA in this study may or may not find that the injections work better for them during pregnancy. This study will look at how well CAB LA and RPV LA injections control the amount of HIV in the pregnant person's blood and how much CAB LA and RPV LA is in their and their baby's blood. If the injections do not work well to control the amount of HIV in the pregnant person's blood, there may be risks to them and their baby, including additional side effects and an increased risk of their baby getting HIV.

The study will also look at whether CAB LA and RPV LA are safe for pregnant people and whether the drugs cause any bad effects for parents and their babies.

2. Only pregnant people and babies who qualify can join the study.

If you decide to join this study with your baby, we will first do some tests to find out if you qualify. More information about the tests is given in #4, below. To qualify for the study, you should be intending to deliver your baby at <<name of delivery facility>> and you must agree for your baby to join as well. If you qualify, you and your baby may join the study. If you do not qualify, you and your baby cannot join the study.

3. It is your decision whether or not to join the study.

Deciding to join the study with your baby is voluntary (your choice). You are free to join or not join. You should talk with your doctor and important people in your life about whether the study is a good fit for you or not. If you decide to join, you can change your mind and leave the study at any time. Your decisions will not affect the medical care that you and your baby receive. Your access to services, and the benefits and rights you normally have, will not be affected.

You do not need to join this study to receive medical care and HIV medicine. There are other options to joining the study. For example, you can continue to receive medical care and HIV medicine from outside the study. Even if you join the study and begin to receive your CAB LA and RPV LA injections at the

study site, you will need to continue with your regular pregnancy care appointments with your regular doctor. Take your time and make your decision carefully. You may also qualify for other studies. Please ask any questions you may have about these other options. If you wish, you can talk to other people about the study before you decide. You can bring other people here to learn about the study with you.

No matter what you decide about the study, it is important for you to receive medical care and take HIV medicine. Taking HIV medicine is the best way for you to stay healthy and to avoid passing HIV to your baby.

Finding out if you and your baby qualify for this study

4. We will ask questions, examine you, and test your blood.

To find out if you and your baby qualify for the study, we will:

- Look at your medical records.
- Ask about your health, HIV medicines, and other medicines.
- Talk with you about the study requirements.
- Do a physical examination. This will include an exam *<<here and below, sites may use locally appropriate terminology to refer to this exam>>* to check on the progress and health of your pregnancy.
- Give you an electrocardiogram (ECG). This tests how well your heart is working.
- Ask you questions about your mental health. We will ask questions about how you have been feeling (for example, if you have thoughts of harming or killing yourself). Sometimes being pregnant and having HIV can make people feel sadder than normal, and perhaps even have feelings of wanting to harm yourself. If the questions show that you are thinking of harming yourself, we will talk with you about this and we will tell you about other services outside the study that might help you.
- Collect up to 29 mL (almost six teaspoons) of blood for tests. The tests will:
  - Check your blood cells, liver, and kidneys. This includes checking for infections called hepatitis B and C.
  - Confirm you have HIV. If the tests that are required for joining this study are already in your medical records, we may not need to do these tests again.
  - Check how much HIV is in your blood. This is called your "viral load."

- Do an ultrasound scan, if you do not have one already available in your medical records that meets the study requirements.

<< Sites to modify first three sentences as needed >> The scan will be done at *<<site name or location>>*. It will take less than 30 minutes. We will arrange for you to have the scan at a scheduled time. The scan must be done before joining the study.

These procedures will take about *<<X>>* hours. *<<Here and throughout this form, sites should enter the expected visit duration as needed.>>*

Most of the blood tests we do at this visit and any future visits will be processed and analyzed here. Some of the analysis of your blood will be done at other laboratories. We will give you the results of any tests that might affect your or your baby's medical care. Some tests are important for the study, but do not affect your or your baby's medical care, and these results may not be shared with you. Some test results from this visit will be ready quickly. Others may take about two to three weeks. We will ask you to come back when the results are ready. We may ask you to come back for more tests, if needed to find out if you

qualify for the study. While waiting for the results, it is important for you to keep taking your regular HIV medicines.

5. We will tell you if you and your baby are eligible.

If you and your baby are not eligible for the study for any reason, we will tell you this. You will not join the study. You can and should continue to get medical care and treatment outside of the study. We will tell you more about getting this care and treatment and any other services you may need. If you and your baby do not join the study, we will still use some information collected about you (for example, age, sex, and race). We will use this information to look at patterns or common reasons for not joining the study.

If you and your baby are eligible for the study, you can come back for the study Entry Visit.

Joining the study

6. If you and your baby qualify, you will enter the study within four weeks of your first visit

On the day you join the study, we will need to make sure that you qualify. On that day, we will:

- Look at your medical records.
- Ask about your health, HIV medicines, and other medicines.
- Ask you questions about what you think about the study products.
- Talk to you about the importance of getting your HIV medicine on time.
- Do an ultrasound scan, if needed.
- Do a physical examination.
- Collect about 23 mL (almost five teaspoons) of blood for tests. The tests will:
  - Check your blood cells, liver, and kidneys.
  - Check your CD4 cells. These cells help your body fight infections. HIV attacks CD4 cells. The number of CD4 cells should increase over time as you take HIV medicine.
  - Check how much HIV is in your blood (HIV viral load). Your HIV viral load should get lower over time or stay low as you take HIV medicine.
  - Check how much CAB LA and RPV LA is in your blood.
  - Some blood will be saved for later to test if it is resistant to HIV medicine. This test shows whether different HIV medicines may work against the HIV in your blood.

If these procedures show that you and your baby qualify, you and your baby will join the study. You will receive CAB LA and RPV LA injections:

☐ every month

☐ every two months

You will stop taking your usual HIV medicine on the day that your study doctor starts your CAB LA and RPV LA injections.

These procedures will take about <<*X*>> hours.

During the study

The number of visits during pregnancy will depend on when you join the study and when your baby is born. Most visits will take place about a month apart, but visits at the beginning of the study and around the time of delivery will be more often.

7. Injections will be given once a month (every four weeks) or every two months (every eight weeks).

One of the goals of the study is to see how the study injections will work when they are given every month (every four weeks) or every two months (every eight weeks). To make this decision, we first need to see how the injections work in pregnant people when given monthly. Participants who enroll early in this study will get the injections every four weeks. When we have enough information, we will see if the injections are safe and how well the injections are working in these people. Based on this information we will decide if the injections can be spaced out to every two months. If you are receiving injections every two months, you will still have follow-up visits every month.

8. After joining the study, you will have a visit every two weeks for the first two months (Week 2, Week 4, Week 6, Week 8).

At the start of the study, you will have more frequent visits to make sure you are healthy, see if you have had any side effects from the HIV medicine, and check how much CAB LA and RPV LA is in your blood. The Week 2 and Week 6 visits will be different from the Week 4 and Week 8 visits.

Week 2 and Week 6

At these visits, we will:

- Look at your medical records.
- Ask about your health, HIV medicines, and other medicines.
- Do a physical exam and perform additional tests, only if necessary for your health.
- Collect about 8 mL (almost two teaspoons) of blood for tests. These tests will check how much HIV is in your blood (HIV viral load) and how much CAB LA and RPV LA is in your blood.

Each visit will take about <<*X*>> hours.

Week 4 and Week 8

At these visits we will:

- Look at your medical records.
- Ask about your health, HIV medicines, and other medicines.
- Talk to you about the importance of getting your HIV medicine on time.
- Do a physical exam.
- Do extra tests, if necessary for your health.
- Collect up to 22 mL (about four and a half teaspoons) of blood for tests to:
    - Check your blood cells, liver, and kidneys.
    - Check your HIV viral load.
    - Check how much CAB LA and RPV LA is in your blood.
- Give you the CAB LA and RPV LA injections*

*Note: those who are on the monthly injection schedule will get their injections at Week 4 and Week 8, and those who are on the every two month injection schedule will get their injections at Week 4 only.

Each visit will take about <<*X*>> hours.

9. You will continue to have study visits every month until you give birth (Week 12, Week 16, Week 20, Week 24, Week 28, Week 32).

At your monthly visits we will check on your health, see if you have had any side effects from the HIV medicines, check how much CAB LA and RPV LA is in your blood, and see how well the drugs are managing your HIV. Each visit will take about <<*X*>> hours.

At these visits we will:

- Look at your medical records.
- Ask about your health, HIV medicines, and other medicines.
- Ask you questions about what you think about the study products (Week 16 only).
- Talk to you about the importance of getting your HIV medicine on time.
- Do a physical exam.
- Do extra tests, if necessary for your health.
- Collect up to 19 mL (almost four teaspoons) of blood for tests to:
    - Check your blood cells, liver, and kidneys.
    - Check your HIV viral load.
    - Check your CD4 cell count (Week 12 and Week 24 only).
    - Check how much CAB LA and RPV LA is in your blood.
- Give you the CAB LA and RPV LA injections*

*Note: Participants with the monthly injection schedule will get their injections at every visit, and participants with the every two months injection schedule will get their injections at every other visit.

10. Extra visits after you are 30 weeks pregnant.

We will schedule special visits after you have reached your 30th week of pregnancy to check how much CAB LA and RPV LA is in your blood. These visits will take place about one week after you get your injections. People who are getting monthly injections may have two visits, while people who are getting injections every other month will have one visit. Each visit will take about <<*X*>> hours.

At these visits we will:

- Look at your medical records.
- Ask about your health, HIV medicines, and other medicines.
- Do extra tests, if necessary for your health.
- Collect about 2 mL (about half a teaspoon) of blood for tests to check how much CAB LA and RPV LA is in your blood.

11. You and your baby will have a visit soon after delivery.

We will stay in contact with you as you get close to your delivery date. We will ask you to contact us when your labor begins and will make plans for you to deliver your baby at <<*delivery facility name*>> if possible. We will arrange for a visit with you as soon as possible after delivery. It is important for this visit to take place as close to the baby's birth as possible, and ideally on the same day. At the latest, the visit must be within five days of the baby's birth. This visit will take up to <<*X*>> hours.

For you, the parent, we will:

- Look at your medical records.
- Ask about your health, HIV medicines, and other medicines.
- Do a physical exam.
- Do extra tests, if necessary for your health.
- Collect chest/breastmilk, if you are chest/breastfeeding, to check how much CAB LA and RPV LA is in your milk.
- Collect blood from the umbilical cord to check how much CAB LA and RPV LA is in your baby's blood.
- Collect about 10 mL (two teaspoons) of blood for tests to:
    - Check how much HIV is in your blood (HIV viral load).
    - Check how much CAB LA and RPV LA is in your blood.
- Give you information about ways to prevent pregnancy.
- Give you the CAB LA and RPV LA injections if you have your baby around the time that you are scheduled to have your next injections.

If possible, your baby will have a visit at the same time as you on the day you deliver. At the visit for your baby, we will:

- Look at your baby's medical records.
- Ask about your baby's health, medicines, and feeding.
- Do a physical exam. If anything unusual is seen when your baby is examined, we may take photos of or your baby. The photos will help the study doctors and other experts working on the study decide if it is important for your baby's health. We will tell you the doctors' opinion when we have information to share. *<<Here, sites may modify text regarding photographs if IRBs/ECs mandate a separate form for obtaining informed consent for photographs.>>*
- Do extra tests, if necessary for your baby's health.
- Collect up to 3.5 mL (about a teaspoon) of blood for tests to:
    - Check if your baby has HIV. If the tests that are required for the study are already in your baby's medical records, we may not need to do this test again. Some blood may be saved for later to test if it is resistant to HIV medicines. This test shows whether different HIV medicines may work against the HIV in your baby's blood (if your baby has HIV).
    - Check how much CAB LA and RPV LA is in your baby's blood.

<<Here and throughout this form, sites may modify the amount of blood collected for infant-participants based on local regulations.>>

Regardless of whether the visit for your baby happens on the day of their birth, your baby will also have a visit within five days of birth. At this visit we will collect about 1 mL (less than half a teaspoon) of blood to check your baby's liver and check how much CAB LA and RPV LA is in your baby's blood. We will look at your baby's medical records and ask about your baby's health, medicines, and feeding. If your baby was not able to complete a visit on the day of birth, we will complete all of the procedures listed above for the birth visit.

12. Post-Delivery visits.

You and your baby will have three more visits before you finish the study. You will complete two visits where you will receive your final study injections according to your injection schedule. The final study visit will happen two weeks after your last study-provided injections.

Postpartum Injection Visits

For you, the parent, we will:

- Look at your medical records.
- Ask about your health, HIV medicines, and other medicines.
- Talk to you about the importance of getting your HIV medicine on time.
- Do a physical exam.
- Do extra tests, if necessary for your health.
- Collect chest/breastmilk, if you are chest/breastfeeding.
- Give you information about ways to prevent pregnancy.
- Collect urine for a pregnancy test, if needed.
- Collect about 19 mL (almost four teaspoons) of blood for tests to:
    - Check your blood cells, liver, and kidneys.
    - Check how much HIV is in your blood (HIV viral load).
    - Check how much CAB LA and RPV LA is in your blood.
- Give you the CAB LA and RPV LA injections.

For your baby, we will:

- Look at your baby's medical records.
- Ask about your baby's health, medicines, and feeding.
- Do a physical exam.
- Do extra tests, if necessary for your baby's health.
- Collect up to 5 mL (one teaspoon) of blood for tests to:
    - Check if your baby has HIV. If the tests that are required for the study are already in your baby's medical records, we may not need to do this test again. Some blood may be saved for later to test if it is resistant to HIV medicines. This test shows whether different HIV medicines may work against the HIV in your baby's blood (if they have HIV).
    - Check your baby's liver and kidneys
    - Check how much CAB LA and RPV LA is in your baby's blood

Final Study Visit - Two weeks after the last study-provided injections

For you, the parent, we will:

- Look at your medical records.
- Ask about your health, HIV medicines, and other medicines.
- Ask some questions about what you think about the study products.
- Do a physical exam.
- Do extra tests, if necessary for your health.
- Collect chest/breastmilk, if you are chest/breastfeeding.
- Give you information about ways to prevent pregnancy.
- Collect urine for a pregnancy test, if needed.
- Collect about 19 mL (almost four teaspoons) of blood for tests to:
    - Check your blood cells, liver, and kidneys.
    - Check your HIV viral load.
    - Check how much CAB LA and RPV LA is in your blood.
- Ask you questions about your mental health.
- Talk about your HIV medicine options.

For your baby, we will:

- Look at your baby's medical records.
- Ask about your baby's health, medicines, and feeding.
- Do a physical exam.
- Do extra tests, if necessary for your baby's health.
- Collect up to 5 mL (one teaspoon) of blood for tests to:
    - Check if your baby has HIV. Some blood may be saved for later to test if it is resistant to HIV medicines. This test shows whether different HIV medicines may work against the HIV in your baby's blood (if they have HIV).
    - Check your baby's liver and kidneys
    - Check how much CAB LA and RPV LA is in your baby's blood

At your final study visit we will give you the results of the tests that will help you manage your health and tell you where you can go for any care or treatment you or your baby may need. It is very important for you to keep taking HIV medicine after leaving the study. We will talk with you about your options and help make sure you can get HIV medicine from outside the study. We will answer any questions you may have and tell you how to contact us in the future, if you wish.

13. If you do not receive a scheduled injection, you may need to use oral pills until you can get back on your injection schedule.

If you miss an injection visit or cannot receive your CAB LA and RPV LA injections for any reason, your study doctor may give you the oral pill version of CAB and RPV to use. Your study doctor will also talk to you about when you can start the injections again.

You may need to have an extra visit in order to restart the CAB LA and RPV LA injections and get back on your original injection schedule. At this extra visit, we will:

- Look at your medical records.
- Ask about your health, HIV medicines, and other medicines.
- Talk to you about the importance of getting your HIV medicine on time.
- Do a physical examination.
- Do extra tests, if necessary for your health.
- Collect about 16 mL (about three and a half teaspoons) of blood for tests to:
    - Check your blood cells, liver, and kidneys.
    - Check how much HIV is in your blood (HIV viral load).
    - Check how much CAB LA and RPV LA is in your blood.
- Give you the CAB LA and RPV LA injections.

14. You may have an extra visit if your HIV is not controlled.

While receiving the study products, the amount of HIV in your blood (HIV viral load) should stay low. If tests show that your viral load is higher than expected, you will have an extra visit. At this visit we will:

- Look at your medical records.
- Ask about your health, HIV medicines, and other medicines.
- Talk to you about the importance of getting your HIV medicine on time.
- Do a physical examination.
- Do extra tests, if necessary for your health.

- Collect about 14 mL (about three teaspoons) of blood for tests. The tests will re-check your viral load and the amount of CAB LA and RPV LA in your blood.
- If your viral load is still high, we will test for resistance.

We will give you the results of these tests and explain them to you. If the results show that your HIV medicine may need to be changed, we will discuss that with you.

15. Your baby may have an extra visit if your baby tests positive for HIV.

While getting the study products, the amount of HIV in your blood (HIV viral load) should stay low. This makes it harder for your baby to get HIV. If we receive a positive HIV test result for your baby, you will have to bring in your baby for an extra visit. At this visit we will:

- Collect about 6 mL (about one and a half teaspoons) of blood from your baby for tests. The tests will re-check your baby for HIV and test for HIV resistance.
- Talk to you about starting HIV medicine for your baby and the care available locally

We will give you the results of these tests and explain them to you. If the extra tests confirm that your baby has HIV, we will talk to you about care options for your baby.

16. You may choose to leave the study at any time or we may need to take you off the study early.

You are free to leave the study, or take your baby off the study, at any time for any reason. Leaving the study will not affect the care you and your baby receive, but it is important that you tell us before you or your baby leave the study.

Some people may have to stop the study products or stop the study early. This could happen if:

- You are not able to come to the study visits or meet other study requirements.
- You need to take medication that is not allowed in this study.
- The study is stopped for any reason.
- The study doctor decides that being in the study would be unsafe or otherwise not in the best interest for you or your baby.

If you leave the study early, we will ask you to come back for one last clinic visit.

For you, the parent, we will:

- Look at your medical records.
- Ask about your health, HIV medicines, and other medicines.
- Do a physical exam.
- Do extra tests, if necessary for your health.
- Collect chest/breastmilk, if you are chest/breastfeeding.
- Collect urine for a pregnancy test, if needed
- Give you information about ways to prevent pregnancy.
- Collect about 19 mL (almost four teaspoons) of blood for tests to:
    - Check your blood cells, liver, and kidneys.
    - Check how much HIV is in your blood (HIV viral load).
    - Check how much CAB LA and RPV LA is in your blood.
- Ask some questions about what you think about the study products.

- Ask you questions about your mental health.
- Give you the CAB LA and RPV LA injections, if required based on your injection schedule
- Talk about your HIV medicine options.

For your baby, we will:
- Look at your baby's medical records.
- Ask about your baby's health, medicines, and feeding.
- Do a physical exam.
- Do extra tests, if necessary for your baby's health.
- Draw about 5 mL (one teaspoon) of blood for tests to:
    - Check if your baby has HIV. Some blood may be saved for later to test if it is resistant to HIV medicines. This test shows whether different HIV medicines may work against the HIV in your baby's blood (if your baby has HIV).
    - Check your baby's liver and kidneys
    - Check how much CAB LA and RPV LA is in your baby's blood, if you are chest/breastfeeding.

If you leave the study early for any reason, we will tell you where you can go for any care or treatment you or your baby may need. It is very important for you to keep taking HIV medicine after leaving the study. We will talk with you about your options and help make sure you can get HIV medicine from outside the study. We will answer any questions you may have and tell you how to contact us in the future, if you wish.

Risks of the study

17. There are several possible risks of the study.

Being in this study may involve some risks and discomfort. Most procedures done in this study are routine medical procedures, with little risk to you or your baby. Collecting chest/breastmilk could be uncomfortable. There is no risk from ultrasound. Study risks include risks from collecting blood, risks from getting injections, risks from the study products, and risks to your privacy. You may feel nervous or embarrassed when answering questions for the study.

Your baby will be tested for HIV while in this study. You may become worried or anxious about your baby's test results. We will explain all tests to you and give you counseling to help with feelings you may have about the tests and your baby's results.

18. There are risks from collecting blood and getting injections.

Giving blood. Collecting blood can cause pain, swelling, bruising, or bleeding where the needle is inserted. Rarely, collecting blood can cause fainting or infection.

Feeling faint after injection. Getting injections can cause some people to feel light-headed or feel like they might faint. This reaction, also called a 'vasovagal reaction', can happen with many medical procedures. This reaction usually improves quickly and is generally not a bad sign regarding your health.

Injection site reactions. CAB and RPV injections can cause the following reactions where the needle is inserted:

- pain and discomfort, or a hardened lump (very common)
- swelling, redness, itching, bruising, warmth or discoloration, which may include a collection of blood under the skin (common)
- cellulitis (heat, swelling or redness), abscess (collection of pus), numbness, minor bleeding, or discoloration (uncommon)

Some reactions may happen quickly, but others may happen a day or two later. Most reactions go away in a week or less, but sometimes they can last longer. Most people who have reactions can continue the study injections.

Post-injection reaction. Some people experience reactions soon after receiving their RPV injection. Most reactions resolved within a few minutes after the injection. Reactions may include: difficulty breathing, stomach cramps, rash, sweating, numbness of the mouth, blood pressure changes, and pain (back and chest), feeling anxious, feeling warm, or feeling lightheaded or faint. These cases may be due to an accidental injection of part of the medication into a blood vessel instead of the muscle. Not all people who may have received an injection in a blood vessel by mistake had these reactions. Most of the reactions resolved in a few minutes. Your study doctor may need to give you treatment to help with these reactions. You will be observed briefly (approximately 15 minutes) after each injection.

Other possible side effects from the injection procedure. Another risk is that the injection could be given too deeply, not deeply enough, or part of the injection may be injected into a blood vessel, a nerve, or into the skin only instead of a muscle by mistake. The risks of getting an injection the wrong way are not well understood, but it could make the amount of CAB or RPV in your body too high or too low. If too low, the medicines may not work against your HIV. If the RPV levels are too high, there could be a change in your heart beat due to a change in the electrical activity in your body. Very rarely, in severe cases this can be life-threatening and could lead to sudden death; however, no such severe changes in electrical activity or sudden deaths have been seen in clinical studies with RPV. If your study doctor thinks that the injection was not given in the right way, we may need you to stay in the clinic for extra time for observation or for additional treatment and tests to make sure you are safe.

19. There are risks from the study HIV medicines

All HIV medicines can cause side effects. This includes the HIV medicines you are taking right now and any other HIV medicines you would receive outside the study. A side effect is a bad effect that may be caused by the drugs you are taking. Some side effects are minor, others can be severe. Some side effects are common, others are rare. Some people have some of the side effects. Other people have no side effects. If you join the study, you will stop taking your current HIV medicines on the day when your study doctor starts your CAB and RPV injections. Any time a person switches HIV medicine, there is a chance that they could experience new side effects.

The known side effects for CAB and RPV are listed in the tables below but there may be other side effects that we do not know about at the moment. This may be especially true for pregnant people, because this is the first study of the CAB and RPV combination for HIV treatment in pregnant people. It is possible that new and previously unknown side effects for the pregnant person as well as the unborn baby could be serious or even life-threatening. It is also possible that the CAB and RPV injections might not work as well to treat your HIV as the medications you are currently using. The amount of CAB and RPV in your blood may be lower right after you switch from your current oral medications to injections, which could make the amount of HIV in your blood (HIV viral load) increase. This is why we will closely monitor your HIV viral load several times during the study and schedule extra visits if your HIV is not well controlled (see #13 above). If the CAB LA and RPV LA do not control the HIV in your body very well, there may be a higher chance that you can give HIV to your baby or to any sexual partners.

If you join the study, we will tell you more about the study products you will be taking. At each study visit, we will check on whether the study products are causing any side effects. We will also tell you what to do if you have side effects. If you have questions or concerns at any time, please tell us.

20. Side effects from the CAB injection.

Many adults and a small number of adolescents have received CAB injections in other studies. The table below lists side effects from other studies of CAB in people who have HIV. Note that these side effects have been seen in people taking CAB together with RPV.

Side Effects of CAB (when taken together with RPV)*

Very Common (may affect at least 1 in 10 people)	**Common** (may affect up to 1 in 10 people)	**Uncommon** (may affect up to 1 in 100 people)
• Injection site reaction • Headache • Pyrexia (fever)	• Rash • Diarrhea or loose stools • Nausea (feeling sick to the stomach) • Flatulence (passing gas or wind) • Vomiting (being sick) • Abdominal pain (stomach pain and discomfort) • Insomnia (problems sleeping) • Abnormal dreams/nightmares • Feeling light-headed (dizziness) • Anxiety (feeling anxious) • Depression (feelings of deep sadness and unworthiness) • Myalgia (muscle pain) • Fatigue (lack of energy) • Asthenia (feeling weak) • Malaise (feeling generally unwell) • Weight increase • Hemorrhoids	• Hypersensitivity (allergic reaction) (including angioedema (swelling), urticaria/hives (raised and itchy rash)). • Somnolence (Sleepiness or drowsiness) • Vasovagal reactions (lightheadedness or fainting, during or following an injection) • Hepatotoxicity (liver problems) • Transaminase increase (blood test may show increase in the level of liver enzymes) • Suicidal thoughts and actions (suicidal ideation and suicide attempt)* *Mainly in people who had depression or mental health conditions before.

*In addition to risks from receiving injections, as described in Section 17.

More details on the side effects of CAB are described below:

Hypersensitivity. Some people have hypersensitivity reactions (also known as allergic reactions) when using CAB. These reactions have mostly included signs and symptoms of swelling and/or a raised and itchy rash (hives).

Hypersensitivity reactions for other medicines similar to CAB also included a general feeling of being sick, a high temperature, lack of energy, blisters, mouth ulcers, conjunctivitis (also known as pink eye), muscle or joint aches and swelling (sometimes of the face or mouth which caused difficulty breathing). While more serious allergic reactions have not yet been seen for CAB, it is possible that you may have one of these reactions. If you have any of these symptoms during the study, you must call your study doctor immediately. The study doctor may decide to do tests on your liver, kidneys or blood, and may tell you to stop taking CAB LA + RPV LA.

Abnormal liver tests. A small number of people in CAB research studies had abnormal liver tests and had to stop CAB treatments. For some people, the abnormal liver tests were explained by other causes (such as an illness). A smaller number of people (less than 1% of all people in the studies) did not have other causes that could explain the abnormal test, so it is possible that a mild form of liver damage happened from taking CAB. The liver tests got better after stopping CAB, suggesting that the damage was temporary.

Blood tests to check the health of your liver will be done during the study. Your study doctor will tell you if you need to stop taking the study products or if other actions are needed. If you stop taking the study product, you may be able to re-start the study product or may need to change to a non-study HIV medicine.

If you have a history of seizures, please let your study doctor know.

21. Side effects from the RPV pills and RPV injection

Oral RPV is a drug that many people throughout the world take to treat HIV, so we know a lot about it. In addition, many adults and a small number of adolescents get RPV injections in other studies. The following side effects have been seen in people with HIV taking RPV.

Side Effects of RPV*

Very Common (may affect at least 1 in 10 people)	**Common** (may affect up to 1 in 10 people)	**Uncommon** (may affect up to 1 in 100 people)
• Headache • Fever (pyrexia), feeling hot, body temperature increase	• Feeling less hungry (decreased appetite) • Sleep disorders, insomnia (sleeplessness) • Abnormal dreams • Dizziness • Fatigue (lack of energy) • Asthenia • Malaise • Myalgia (muscle pain)	• Immune reconstitution syndrome (this can be an overreaction of the body's recovering defense system to a previously present infection, or problems in the immune system) • Depressed mood • Sleepiness (somnolence) • Abdominal (belly) discomfort • Dry mouth

Very Common (may affect at least 1 in 10 people)	**Common** (may affect up to 1 in 10 people)	**Uncommon** (may affect up to 1 in 100 people)
	• Rash • Depression • Diarrhea • Nausea, vomiting abdominal pain or discomfort (belly ache) • Upper abdominal (belly) pain	• Transaminases increased (increased levels in the blood of certain liver function tests)

*In addition to risks from receiving injections, as described in Section 17.

More information on the side effects of RPV are listed below:

Liver problems. Changes in blood tests have been seen. People with Hepatitis B or C, or who have possible liver damage before starting RPV, may have worse liver tests while taking RPV. A few cases of liver problems were found in people taking RPV who did not already have any liver problems.

Sometimes allergic reactions can affect body organs. For example, an allergic reaction can cause liver problems which can lead to liver failure. Contact your study doctor right away if you have any of the following signs or symptoms of liver problems:

- Yellowing of the skin or whites of the eyes
- Dark or tea colored urine
- Pale colored stools/bowel movements
- Nausea/vomiting
- Loss of appetite
- Pain, aching or tenderness on the right side below the ribs
- Itchy skin
- Unexplained weight loss

Skin rash. Most rashes were mild or moderate, and happened within the first four weeks of taking RPV. Most rashes got better after one week, and the people did not need to stop taking RPV. However, the study HIV medicines will need to be stopped for some types of moderate rash and all types of severe rash, which can be life-threatening. If this happens to you, you will need to come for extra study visits to monitor their health. Some people with rash may also have other signs and symptoms of allergic reaction.

If you have any type of rash or other skin problems during the study you must tell your study doctor right away, and the doctor may tell you to stop taking the study products.

22. There may be other possible risks.

Risk of your HIV becoming resistant. With any drug used to treat HIV, there is a risk that the virus in your body will become resistant, meaning that the drug will not work as well or not work at all against your HIV.

The risk of your HIV becoming resistant is not known. It will depend on how well the study products work against your virus and how well you are able to follow the injection schedule. To prevent resistance, it is important that you get your study injections as instructed, and do not miss any injections.

Talk to your study doctor any time you miss or if you think you will be late or early for getting injections—this includes vacations or work-related travel that may affect your scheduled visits.

Do not change or skip of any of your study injections unless your study doctor tells you to do so.

Possible effects on pregnancy, unborn babies, and chest/breastfeeding babies. Taking HIV medicine is the best known way for you to maintain your health and to avoid passing HIV to your baby during pregnancy and chest/breastfeeding. HIV and HIV medicine may lead to some pregnancy complications, like early delivery or a low birth weight for the baby. We do not yet know if CAB is safe or works well to treat HIV in pregnancy or prevent pregnant parents from giving HIV to their babies. There is little information from people on the effects of CAB in pregnancy, but CAB LA and RPV LA have been found in the body for up to 12 months or longer after an injection and the effects of the drugs on an unborn baby are currently unknown. Most of the information we have is from studies on animals. RPV does not seem to have bad effects on pregnancy and the baby from what we know now, but more information is still being collected.

Babies who chest/breastfeed may get the HIV medicine taken by their parents through chest/breastmilk. We do not know how much of the HIV medicine goes into chest/breastmilk, how long after an injection the HIV medicine may be in the chest/breastmilk, or what effects getting CAB LA and RPV LA through chest/breastfeeding may have on babies. Your study doctor and health care provider(s) outside the study can tell you about the possible benefits and risks of different infant feeding options you may be considering.

We are doing this study to learn more about safety of CAB LA and RPV LA for pregnant people and their babies. We will also learn how much of this HIV medicine is passed to babies and what effects this may have.

Mental illness or depression. Some people with chronic health conditions, including HIV, sometimes have feelings of depression or may feel sad or hopeless, feel anxious or restless, or may have thoughts of hurting or killing themselves (suicide). A small number of people being treated with CAB and RPV have had thoughts or killing themselves and have tried to do so, particularly people with a history of depression or mental health illness.

Tell the study doctor if you have a history of mental health illness. If you are worrying more often, feeling low or sad, having sleep problems, have thoughts of hurting or killing yourself, or have any other unusual or uncomfortable thoughts during this study, you should tell the study doctor or go to the nearest hospital right away.

Immune reconstitution syndrome. In some people with advanced HIV, signs and symptoms from other infections or certain diseases (for example a liver condition called autoimmune hepatitis) may start soon after starting HIV medicine or later into treatment. Some of these symptoms may be life threatening. This would be very rare, but if you start having new symptoms, or if you notice that any existing symptoms are getting worse after starting the study products, tell your doctor immediately.

Abnormal distribution of body fat and wasting. The use of strong HIV medicine may cause some types of body changes, especially related to where fat is in your body. Body changes could include more fat

around the waist and stomach area or on the back of the neck. Other body changes include bigger chest/breast and/or less fat in the face, legs, and arms.

General side effects of CAB LA and RPV LA injections:

The study injections stay in your body for a long time. The injections you get in this study are long-acting, meaning they stay in the body for a long time. In most people, the drugs will no longer be in the body one year after an injection, but in some people, low levels of CAB and RPV may still be in the body after one year.

If you develop a side effect to the study product after the injection, there will be no way to remove the drug from your body. If you develop a symptom from these drugs while the drugs are still in your body, every effort will be made to treat the side effects. The amount of drug in your body will decrease overtime and will eventually disappear.

If you stop getting the study injections, the study products will stop working to treat HIV, as the amount of drug in the body decreases slowly over time. When stopping these drugs, it will be very important for you to start taking other HIV medications, as directed by your doctor.

Risks of disclosure of your information. In addition to the risks of study procedures and the study products, there is a risk of that someone may learn about your and your baby's information. We will make every effort to keep your and your baby's information private and confidential. Study records and blood and chest/breastmilk samples will be kept in secure locations. All samples and most records will be labeled only with a code number. However, your and your baby's name will be written on some records.

<<To be included at US sites>> U.S. Federal laws protect the privacy of your and your baby's protected health information ("personal/private information"). However, there are exceptions to these laws. The Researchers will ask you to sign a form ("HIPAA Authorization") to give your permission for certain uses and sharing of your and your baby's personal (private) information for the study. That form provides more details about the types of information that may be used and shared, and how it will be protected.

<<To be included at South African sites>> In addition, the Protection of Personal Information Act (POPIA) ensures that all South African institutions conduct themselves in a responsible manner when collecting, processing, storing and sharing your and your baby's personal information by holding them accountable should they abuse or compromise your personal information in any way.

<<All sites to include any other relevant country-specific data-sharing requirements, as applicable>>

<<To be included at US sites>> You and your baby's privacy may also be protected by a Certificate of Confidentiality that helps us avoid being forced to release information that may identify you or your baby, such as by the courts or police. The certificate cannot be used in all situations, but it can be used to resist demands for information that would identify you or your baby. The certificate does not protect against requests for information from the United States federal government or from the United States Food and Drug Administration. Regardless of the certificate, you can release information about your or your baby's participation in the study to others, if you wish.

Samples collected from you and your baby will be used for study testing only, as described in this form. None of the testing involves whole genome sequencing. The samples will not be used for other research now or in the future. The samples will not be sold or used for commercial profit. For example, the samples will not be used to make a new product that could be sold.

The information we collect about you and your baby for this study will be combined with information collected about all other participants in the study. This will be done at an organization called a statistical and data management center. The IMPAACT Network statistical and data management center is in the United States. We will send your and your baby's information to this center, but your and your baby's name and other information that could personally identify you will not be sent. The information will be sent securely, following applicable laws and policies.

Information collected for this study may be used for other research in the future. For example, researchers may use information from this study to try to answer different questions about pregnant people with HIV. Any future research done with the information from this study must be approved by the IMPAACT Network. If any future research is done, information about you or your baby may be used without additional informed consent. Your and your baby's information will be labeled with a code number, and the only link between the code number and your and your baby's name will be kept here at this clinic.

We will try our best to keep your and your baby's information private. However, it is still possible for someone who should not have your or your baby's information to get it. If this happens, you or your baby could be treated badly or unfairly.

Benefits of the study

23. There may or may not be benefits to you from joining the study.

By joining the study, you will be part of the search for new treatments for pregnant people with HIV. There may be a direct benefit to you by joining the study, but we cannot guarantee that being in the study will benefit you or your baby in any way. There may also be benefit if the information from this study lead to a safe and effective dose of the study products for pregnant people. One possible benefit is that you might prefer getting CAB and RPV as a monthly (or every two months) injection instead of taking pills every day. If you have pregnancy nausea and/or vomiting, you may find injections easier than taking pills. If you like the injections, and they are working well, you may be able to continue getting them after the study is over. Information learned from this study may help other pregnant people who have HIV.

You and your baby will have regular visits and frequent checks on your health, including checking how much HIV is in your blood (HIV viral load). It is possible the study HIV medicine will slow the progress of HIV for you.

Other information about the study

24. There are no costs to you for joining the study.

There are no costs to you or your baby for study visits or procedures, or the study products.

<<Sites insert information about compensation/reimbursement here.>> You will be reimbursed for the cost of travel to study visits and your time spent here. For each visit, you will be given *<<specify amount>>*.

25. Your and your baby's records may be looked at by study staff and groups that oversee the study.

Groups that oversee the study include:

- *<<U.S. sites insert sIRB>>*
- *<<Sites insert local IRBs/ECs as applicable>>*
- *<<Sites insert applicable drug regulatory authorities and other regulatory entities>>*
- The United States National Institutes of Health and its study monitors
- The United States Food and Drug Administration
- The United States Office for Human Research Protections
- Other United States, local, and international regulatory entities
- The IMPAACT Network that is coordinating the study
- The companies that make the study products, ViiV Healthcare and Janssen Research and Development

Like the study staff, these groups are required to make efforts to keep study records private and confidential.

The results of the study may be presented publicly or published. However, no presentation or publication will use your baby's name or identify your baby personally.

A description of this clinical trial will be available on https://www.clinicaltrials.gov/, as required by U.S. 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.
Your or your baby's study information may be given to other authorities if required by law. *<<Sites may add more specific detail here describing local laws that may be applicable.>>*

26. If you or your baby gets sick or injured, contact us immediately.

Your and your baby's health is important to us. We will make every effort to protect your and your baby's well-being and lower risks. It is possible, however, that you or your baby could have an illness or injury that is study-related. This means that the illness or injury occurred as a direct result of being in the study.

<<Sites may modify this paragraph to reflect local institutional policies; information regarding coverage available through clinical trial insurance obtained by the site should be included if applicable; the statement regarding no program for compensation through the NIH may not be removed.>> If a study-related illness or injury occurs, we will treat you or your baby or tell you where you can get the treatment you need. The cost for this treatment may be charged to you or your health insurance. There is no program to pay money or give other forms of compensation for study-related illness or injury through *<<site name>>* or the United States National Institutes of Health.

Who to contact

27. If you have questions, concerns, or problems at any time, use these contacts.

If you have questions, concerns, or problems at any time, use these contacts.

- If you have questions about the study or your or your baby's health, or if you want to leave the study:
  <<Name, phone number, and other relevant contact details of investigator or other study staff>>

- If you have questions about your or your baby's rights as a study participant, or problems or concerns about how you or your baby is being treated in the study:
  <<Name, phone number, and other relevant contact details of IRB contact person or other appropriate person or organization; US sites to include sIRB contact information>>

Permission for Off-Site Visits

On rare occasions, members of the research team may be able to schedule visit activities off-site at your home or at another location. Before any visits take place off-site, the study staff will discuss the location and time so that the visit is at a convenient time and place where you feel comfortable and confidentiality can be maintained. To have visits outside of the clinic, you will need to give us your written permission to do so.

Please read the following statements carefully and write your initials or make your mark next to the option you prefer.

_____ I do agree to have study visits at a location other than the study clinic, when necessary.

_____ I do not agree to have study visits at a location other than the study clinic, when necessary.

Signatures

If you decide to have you and your baby join this study, please sign or make your mark below.

Before deciding whether to have you and your baby join this study, make sure you have read this form or had it read to you. Make sure all your questions have been answered. You should feel that you understand the study, its risks and benefits, and what is expected of you and your baby.

We will tell you any new information from this study or other studies that may affect your willingness to keep you and your baby in the study. You are welcome to ask questions or request more information at any time.

You do not give up any rights by signing this form.

<<Sites insert signature blocks as required by IRB and institutional policies.>>

Name of Participant (print)	Participant Signature	Date
Name of Witness (if applicable, print)	Witness Signature	Date
Study Staff Conducting Permission Process Name (print)	Study Staff Signature	Date

Appendix VI: Study Product Preparation Requirements for CAB and RPV Long-Acting Injectables

This appendix provides requirements for the long-acting (LA) injectable study product preparation for both CAB and RPV. The study product regimen, administration, formulation, storage requirements, supply and other relevant information are described in protocol Section 5.

The investigational pharmacist(s) must be proficient in the preparation of injectable study products using aseptic technique under a pharmacy biological safety cabinet (BSC) Class II or better isolator. Local regulations and site institutional policies and procedures for use of personal protective equipment, such as gloves, gowns, masks, and safety glasses, must be followed.

Suggested Sterile Compounding Supplies for CAB LA and RPV LA:
(All supplies below or equivalent supplies must be sterile)

- BD 5-mL syringe, Luer-Lok Tip, Reference No.: 309646, or equivalent
- BD 3-mL syringe, Luer-Lok Tip, Reorder No.: 309585, 309657, or equivalent
- Needle for aspiration: BD Precision Glide Needle, 21G 1 inch, Reference No.: 305165, or equivalent
- Needle for IM injection:
    - 23G x 1.5" SurGuard Safety Hypodermic Needle CE MARKED Mfg Catalog Number: SG3-2338 (Central Supply as applicable per country)
    - BD Precision Glide Needle, 23G 1.5 inches, Reference No.: 305194, or equivalent
    - Variable needle lengths (e.g., 1.5 inch, 2 inch) and/or variable needle gauge sizes (CAB LA: 21 to 25 gauge; RPV LA: 21 to 23 gauge) are permitted if needed to accommodate individual body types. **Note: The use of 25 gauge needles is not permitted for administration of RPV LA.**

Appendix VI-A: CAB LA Injectable Preparation Requirements

I. Preparation of CAB LA 600mg/3mL (using one 600 mg/3mL vial or two 400 mg/2 mL vials)

One syringe containing 3 mL (600 mg) of CAB LA study product must be prepared using aseptic technique under a pharmacy BSC/isolator.

1. Remove one 3 mL CAB LA vial or two 2 mL CAB LA vials (as available) from storage. If CAB LA 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. Record the time when vial(s) were removed from the refrigerator. Once removed, the vial(s) cannot be placed back into the refrigerator.

2. Remove vial(s) from the carton and vigorously shake the vial for a full 10 seconds by shaking the vial with long arm movements.

3. Invert the vial(s) and inspect to ensure complete re-suspension. If sediments are observed, repeat Steps 2-3 until all material is uniformly suspended. After re-suspending, it is recommended to use the suspension immediately.

4. Using aseptic technique under a pharmacy biological safety cabinet, flip off the plastic cap from the vial(s). Wipe the top of the vial(s) with disinfecting tissue of isopropyl alcohol 70% or similar and allow the alcohol to dry.

5. Remove one 5 mL syringe and aspiration needle from the blister pouch (see suggested supplies). Take one aspiration needle and attach the needle to the Luer-Lok connection of the syringe.

6. If using one 3 mL CAB LA vial:
   - With the sheath on the needle, pull back on the syringe plunger to allow approximately 1 mL of air into the syringe. Pull the needle sheath off the needle with a straight pull.
   - Push the needle through the stopper of the vial and inject 1mL of air into the vial by putting the vial in the inverted position while the needle and syringe are in the upright position.
   - Withdraw the entire contents (3 mL) of the vial into the syringe. Because the suspension can contain some air after having shaken the vial, take out enough suspension in order to be able to de-aerate the syringe properly (Step 9).
   - Record the time withdrawn into the syringe.

7. If using **two** 2 mL CAB LA vials:
   - With the sheath on the needle, pull back on the syringe plunger to allow approximately 1 mL of air into the syringe. Pull the needle sheath off the needle with a straight pull.
   - Push the needle through the stopper of the first vial and inject 1 mL of air into the vial by putting the vial in the inverted position while the needle and syringe are in the upright position.
   - Withdraw 1.5 mL of suspension from the first vial and put vial aside.
   - Remove the needle from the syringe and attach a new aspiration needle. Repeat the steps above to withdraw 1.5 mL of suspension from the second vial, for a total of 3 mL from two vials. Because the suspension can contain some air after having shaken the vial, take out enough suspension in order to be able to de-aerate the syringe properly (Step 9).
   - Record the time when the contents of the first vial was withdrawn into the syringe.

8. Keep the syringe with the needle in the upright position and remove the vial from the needle. Pull down on the plunger to ensure there is no study product remaining in the needle and remove the

needle that was used to withdraw the suspension and discard it appropriately. Attach a new needle for intramuscular (IM) administration to the Luer-Lok connection of the syringe or attach a syringe cap (per site's SOP). Consult with clinic staff regarding the recommended needle for IM administration (see suggested supplies).

9. 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 upright position until a drop of suspension appears. Remove the excess suspension in order to administer the correct volume (3 mL).

10. Label the syringe appropriately. Include a beyond-use-date (BUD) on the label per guidance below.

    After withdrawal of the suspension from the vial(s) into a syringe, it is recommended to administer the suspension immediately. **Do not exceed two hours between the time the suspension was withdrawn and time of administration to the study participant.**

    The prepared CAB LA suspension in a syringe must be stored at controlled room temperature between 20°C to 25°C from the time it is withdrawn into a syringe until the time it is administered.

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

II. Preparation of CAB LA 400mg/2mL (using one 400 mg/2 mL vial [or one 600 mg/3 mL vial if 400 mg/2 mL vial is not available))

One syringe containing 2 mL (400 mg) of CAB LA study product must be prepared using aseptic technique under a pharmacy BSC/isolator.

1. Remove one 2 mL CAB LA vial (or one 3 mL CAB LA vial if 2 mL CAB LA vial is not available) from storage. If CAB LA vials are stored in the refrigerator (2°C to 8°C), remove vial from the refrigerator and wait at least 15 minutes to equilibrate to room temperature. Record the time when vial was removed from the refrigerator. Once removed, the vial cannot be placed back into the refrigerator.

2. Remove the vial from the carton and vigorously shake the vial for 10 seconds by shaking the vial with long arm movements.

3. Invert the vial and inspect the vial to ensure complete re-suspension. If sediments are observed, repeat Steps 2-3 until all material is uniformly suspended. After re-suspending, it is recommended to use the suspension immediately.

4. Using aseptic technique under a pharmacy biological safety cabinet, flip off the plastic cap from the vial. Wipe the top of the vial with a 70% isopropyl alcohol pad or similar and allow the alcohol to dry.

5. Remove one 3 mL syringe and one aspiration needle from the blister pouch (see suggested supplies). Attach the needle to the Luer-Lok connection of the syringe.

6. With the sheath on the needle, pull back on the syringe plunger rod to allow approximately 1 mL of air into the syringe. Pull the needle sheath off the needle with a straight pull.

7. Push the needle through the stopper of the vial and inject 1 mL of air into the vial by putting the vial in the inverted position while the needle and syringe are in the upright position.

8. Withdraw 2 mL from the vial. Since the suspension can contain some air after shaking, take out all suspension in order to be able to de-aerate the syringe properly (Step 11).

9. Record the time that the suspension is withdrawn into the syringe.

10. Keep the syringe with the needle in the upright position and remove the vial from the needle. Pull down on the plunger to ensure there is no study product remaining in the needle and remove the needle that was used to withdraw the suspension and discard it appropriately. Attach a new needle for IM administration to the Luer-Lok connection of the syringe or attach a syringe cap (per site's SOP). Consult with clinic staff regarding the recommended needle for IM administration (see suggested supplies).

11. 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 upright position until a drop of suspension appears. Remove the excess suspension in order to administer the correct volume (2 mL).

12. Label the syringe appropriately. Include a BUD on the label per guidance below.

    After withdrawal of the suspension from the vial into a syringe, it is recommended to administer the suspension immediately. **Do not exceed two hours between the time the suspension was withdrawn into a syringe and time of administration to the study participant.**

    The prepared CAB LA suspension in a syringe must be stored at controlled room temperature between 20°C to 25°C 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.

Appendix VI-B: RPV LA Injectable Preparation Requirements

I. Preparation of RPV LA 900mg/3mL (using one 900mg/3 mL vial or two 600 mg/2 mL vials)

One syringe containing 3 mL (900 mg) of RPV LA study product must be prepared using aseptic technique under a pharmacy BSC/isolator.

1. Remove one 3 mL RPV LA vial or two 2 mL RPV LA vials (as available) from the refrigerator and allow the vial(s) to sit for 15 minutes to come to room temperature (keep vial in the carton while coming to room temperature). RPV LA may sit at room temperature for a maximum of six hours at 25°C. During this period, excursions are allowed up to 30°C for a maximum of 2 hours. Record the time when vial(s) were removed from the refrigerator. Once removed, the vial(s) cannot be placed back into the refrigerator.

2. Remove the vial(s) from the carton and vigorously shake the vial(s) a full 10 seconds by shaking the vial with long arm movements.

3. Invert the vial(s) and inspect to ensure complete re-suspension. If sediments are observed, repeat Steps 2-3 until all material is uniformly suspended. After re-suspending, it is recommended to use the suspension immediately.

4. Using aseptic technique under a pharmacy biological safety cabinet, flip off the plastic cap from the vial(s). Wipe the top of the vial(s) with a 70% isopropyl alcohol pad or similar and allow the alcohol to dry.

5. Remove one 5 mL syringe and one aspiration needle from the blister pouch (see suggested supplies). Remove 2 needles if using two 2 mL vials. Attach one needle to the Luer connection of the syringe.

6. If using one 3 mL RPV LA vial:
   - With the sheath on the needle, pull back on the syringe plunger to allow approximately 1 mL of air into the syringe. Pull the needle sheath off the needle with a straight pull.
   - Push the needle through the stopper of the vial and inject 1 mL of air into the vial by putting the vial in the inverted position while the needle and syringe are in the upright position.
   - Withdraw the entire contents (3 mL) of the vial into the syringe. Because the suspension can contain some air after having shaken the vial, take out enough suspension in order to be able to de-aerate the syringe properly (Step 9).
   - Record the time the vial was withdrawn into the syringe.

7. If using **two** 2 mL RPV LA vials:
   - With the sheath on the needle, pull the syringe plunger rod slowly to allow approximately 1 mL of air into the syringe. Pull the needle sheath off of the needle with a straight pull.
   - Push the needle through the stopper of the first vial and inject 1 mL of air into the vial by putting the vial in the inverted position while the needle and syringe are in the upright position.

- Withdraw approximately 1.5 mL of suspension from the vial into the syringe.
- Remove the needle from the syringe and attach a new aspiration needle. Repeat the steps above to withdraw 1.5 mL of suspension from the second vial, for a total of 3 mL from two vials. Because the suspension can contain some air after having shaken the vial, take out enough suspension in order to be able to de-aerate the syringe properly (Step 9).
- Record the time the contents of the first vial was withdrawn into the syringe.

8. Keep the syringe with the needle in the upright position and remove vial from the needle. Pull down on the plunger to ensure there is no study product remaining in the needle and remove the needle that was used to withdraw the suspension and discard it appropriately. Attach a new needle for intramuscular (IM) administration to the Luer-Lok connection of the syringe or attach a syringe cap (per site's SOP). Consult with clinic staff regarding the recommended needle for IM administration (see suggested supplies).

9. 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 upright position until first drop appear. Remove the excess suspension in order to administer the correct volume (3 mL).

10. Label the syringe appropriately. Include a BUD on the label per guidance below.

After withdrawal of the suspension from the vial into a syringe, it is recommended to administer the suspension immediately. If required, the prepared syringe containing RPV LA may remain at room temperature for **a maximum period of two hours between the time the suspension was withdrawn into a syringe and time of administration** to the study participant. The prepared RPV LA syringe must be protected from light (e.g., syringe covered or enclosed within an amber bag) until ready to administer.

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

II. Preparation of RPV LA 600mg/2mL (using one 600mg/2 mL vial [or one 900 mg/3 mL vial if 600 mg/2 mL vial is not available])

One syringe containing 2 mL (600 mg) of RPV LA study product must be prepared using aseptic technique under a pharmacy BSC/isolator.

1. Remove one 2 mL RPV LA vial (or one 3 mL RPV LA vial if 2 mL RPV LA vial is not available) from the refrigerator. Document the time at which the vial was removed from the refrigerator. Allow the vial to sit for 15 minutes to come to room temperature (keep vial in the carton while coming to room temperature). RPV LA may sit at room temperature for a maximum of six hours at 25°C. During this period, excursions are allowed up to 30°C for a maximum of two hours. Once removed, the vial cannot be placed back into the refrigerator.

2. Remove the vial from the carton and vigorously shake the vial for a full 10 seconds by shaking the vial with long arm movements.

3. Invert the vial and inspect the vial to ensure complete re-suspension. If sediments are observed, repeat Steps 2-3 until all material is uniformly suspended. After re-suspending, it is recommended to use the suspension immediately.

4. Using aseptic technique under a pharmacy biological safety cabinet, flip off the plastic cap from the vial. Wipe the top of the vial with a 70% isopropyl alcohol pad or similar and allow the alcohol to dry.

5. Remove one 3 mL syringe and one aspiration needle from the blister pouch (see suggested supplies). Attach the aspiration needle to the Luer connection of the syringe.

6. With the sheath on the needle, pull the syringe plunger rod to allow approximately 1 mL of air into the syringe. Pull the needle sheath off the needle with a straight pull.

7. Push the needle through the stopper of the vial and inject 1 mL of air into the vial by putting the vial in the inverted position while the needle and syringe are in the upright position.

8. Withdraw (2 mL) from the vial. Since the suspension can contain some air after shaking, take out all suspension in order to be able to de-aerate the syringe properly (Step 12).

9. Keep the syringe with the needle in the upright position and remove vial from the needle.

10. Record the time withdrawn from the vial.

11. Keep the needle with the syringe in the upright position and remove the vial from the needle. Pull down on the plunger to ensure there is no study product remaining in the needle and remove the needle that was used to withdraw the suspension and discard it appropriately. Attach a new needle for IM administration to the Luer-Lok connection of the syringe or attach a syringe cap (per site's SOP). Consult with clinic staff regarding the recommended needle for IM administration (see suggested supplies).

12. 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 upright position until the first drop appears. Remove the excess suspension in order to administer the correct volume (2 mL).

13. Label the syringe appropriately. Include a BUD on the label per guidance below.

After withdrawal of the suspension from the vial into a syringe, it is recommended to administer the suspension immediately. If required, the prepared syringe containing RPV LA may remain at room temperature for **a maximum period of two hours between the time the suspension was withdrawn into a syringe and time of administration** to the study participant. The prepared RPV LA syringe must be protected from light (e.g., syringe covered or enclosed within an amber bag) until ready to administer.

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

Appendix VII: Pharmacokinetic Modelling to Support Opening the Q8W Continuation Group to Enrollment upon Study Initiation

Pharmacokinetic modelling was conducted to support opening the Q8W Continuation Group to enrollment upon initiation of the study, rather than waiting for results of the interim analysis. In this modeling, a pharmacokinetic worst-case scenario was simulated based on the protocol design and treatment requirements for the Q8W Continuation Group at Entry. Based on Inclusion Criterion 4.1.13, the latest possible point at which a Q8W Continuation Group adult-participant can receive their first dose of CAB LA + RPV LA to be included in the study is the day of conception. This is an unlikely scenario but represents the maximum effect of change in pregnancy interposed with the minimal number of doses. The figures below show the 5th, 50th and 95th percentiles for 1000 virtual individuals simulated under these conditions. For CAB LA, an increase of apparent clearance of 20% in the second trimester and 50% in the third trimester was assumed. For RPV LA, a 43% increase in apparent clearance was assumed for the second and third trimester. These changes were implemented to occur maximally and instantaneously at the beginning of the 2nd and 3rd trimester for CAB and beginning of the 2nd trimester for RPV. At parturition, elimination returns instantaneously to pre-second trimester values.

Less than 10% of the first and second post-study entry predicted troughs for cabotegravir were below the four times the $PAIC_{90}$ (approximately equivalent to the 5th percentile of exposures). Less than 5% of the 3rd troughs were below four times the $PAIC_{90}$ (5th percentile exposures). For RPV, less than 10% of the first and second troughs and approximately 1% of the third troughs in this scenario were below the threshold concentration of 17.3ng/mL. The troughs potentially observed during the study given that range of study entry are shown at 20 weeks, 28 weeks, 36 weeks and at parturition (39 weeks in both figures).

Figure 1: Pharmacokinetic simulation of Q8W Continuation Group for CAB LA assuming first dose on day of conception.

The bottom dashed line represents the $PAIC_{90}$, the next highest dashed line the four times the $PAIC_{90}$ (approximately the 5th percentile exposure)

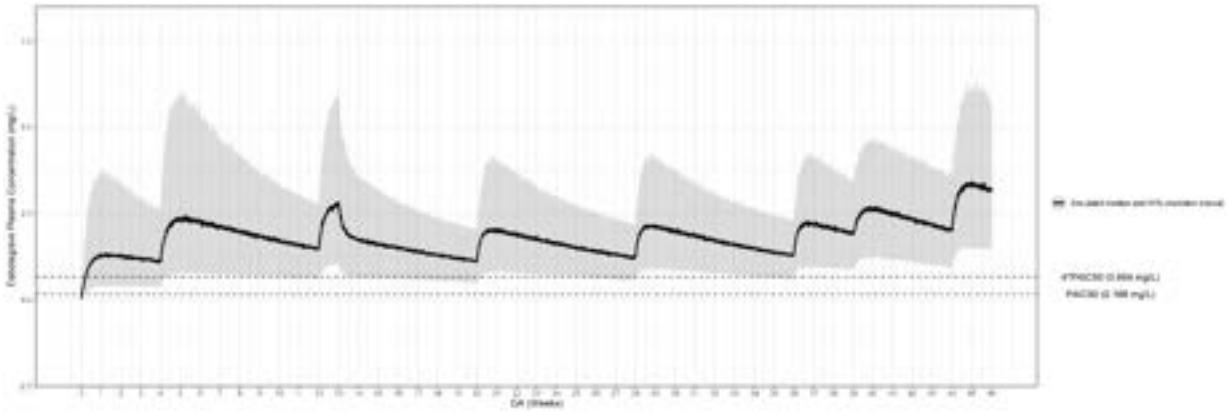


Figure 2: Pharmacokinetic simulation of Q8W Continuation Group for RPV LA assuming first dose on day of conception.

The bottom dashed line illustrates the concentration threshold of 12.1ng/mL and the top dashed line the concentration threshold of 17.3ng/mL.