SCHARP
Statistical Center for HIV/AIDS Research and Prevention

STATISTICAL ANALYSIS PLAN SYNOPSIS

OLE Pregnancy

HPTN 084

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LIST OF ABBREVIATIONS AND ACRONYMS

Term/Abbreviation	Definition
OLE	Open Label Extension
PK	Pharmacokinetics
CAB	Cabotegravir
CAB-LA	Long-acting injectable Cabotegravir
TDF/FTC	Tenofovir Disoproxil Fumarate/Emtricitabine
PrEP	Pre-Exposure Prophylaxis
AE	Adverse Event
SAE	Serious Adverse Event
HIV	Human Immunodeficiency Virus
EAC	Endpoint Adjudication Committee
LC	HPTN Laboratory Center
BMI	Body Mass Index
CI	Confidence Interval
GA	Gestational Age
SGA	Size for Gestational Age
US	Ultrasound
STI	Sexually Transmitted Infection

1. INTRODUCTION

1.1 General Design Considerations

This statistical analysis plan describes the testing and analysis strategy to support the primary assessments related to safety and pharmacokinetics (PK) of long-acting injectable cabotegravir used as PrEP in pregnant participants and their infants in the OLE of HPTN 084. This includes women who did and did not join the pregnancy and infant sub-study during the OLE.

Overview of study periods and protocols

This overview highlights some changes in the protocol over time, which affect the pregnancy-related protocols and analyses. Broadly, HPTN 084 can be divided into three periods: blinded, unblinded, and open-label extension (OLE).

Blinded period

In the blinded period, participants were randomized 1:1 to receive CAB or TDF/FTC and received placebo treatments to protect blinding. Women were tested for pregnancy at scheduled visits, usually every 8

weeks. Pregnancy testing was done before administering each injection of placebo or active CAB-LA. If a participant had a reactive pregnancy test, injections were temporarily discontinued, and women were offered TDF/FTC until after the pregnancy had ended and they were no longer breastfeeding. Potential pregnancies identified by a reactive pregnancy test were defined as 'confirmed pregnancies' if there was a second reactive pregnancy test at least four weeks later. Participants with confirmed pregnancies were then unblinded.

Starting in May 2018, women were asked to use long-acting, reversible contraceptives for the duration of the blinded and unblinded study periods.

Unblinded period

For the most part, study procedures in the unblinded period were similar to those in the blinded period. Participants continued to receive the treatment they were randomly assigned to (except in cases of study product discontinuation, so participants who were randomized to CAB may have received TDF/FTC). However, participants were made aware of their treatment assignment and stopped receiving placebo pills or placebo injections.

OLE

In the OLE, some study procedures (e.g., pregnancy testing) were similar to procedures in the blinded and unblinded periods. Here we focus on the issues and procedures unique to the OLE.

In the OLE period, participants chose whether they wanted to receive CAB or TDF/FTC instead of remaining in their randomized treatment arms. This was done so that participants who had been randomized to TDF/FTC could access CAB (which was found to be more effective than TDF/FTC during the blinded period). As a result, exposure groups in the OLE are non-randomized and often have imbalanced sample sizes.

Participants from 084-01 (which studied the effectiveness of CAB in adolescent girls) were permitted to join the 084 OLE cohort. Because 084-01 participants who joined the OLE were eligible for the pregnancy and infant sub-study, we will include pregnancies from 084-01 participants in this analysis. These participants followed the same OLE procedures, but their data is stored separately from the main 084 database. Throughout, 'participants' during the OLE period includes 084-01 participants who joined the OLE.

During the OLE, there was no requirement for participants to use contraceptives.

In the OLE, pregnancy could be confirmed by a second independent sample on the same day as the initial reactive test.

The pregnancy and infant sub-study in the OLE was offered to women with prior or current exposure to CAB. Participants who consented to the sub-study could choose whether they wanted to receive CAB or TDF/FTC during pregnancy. In order for a pregnancy to be eligible for the sub-study, either: (1) the participant had a history of CAB exposure or (2) the pregnancy overlapped with any of the first 24 weeks of the OLE, and the participant started CAB. Both pregnancies that were ongoing at the beginning of the OLE and pregnancies that began during the OLE were enrolled in the sub-study. Participants who

joined the sub-study had the choice to consent to ongoing CAB-LA injections during pregnancy or opt for TDF/FTC. The pregnancy and infant sub-study involved additional sample and data collection during and after pregnancy. Participants who were not eligible for the sub-study or declined the sub-study were offered TDF/FTC during pregnancy, but participants who had been taking CAB-LA prior to pregnancy could re-start CAB-LA after pregnancy, even if they were still breastfeeding.

Participants who consented to the pregnancy and infant sub-study chose whether to provide parental consent for infant sample collection. Regardless of sub-study participation, all participants with pregnancies that resulted in a live infant were asked to provide information about their infant, including information about the delivery, SAEs, and an infant exam 48 weeks after birth. Collecting data on participants and infants who did not have exposure to CAB (and did not join the sub-study) allows them to be included as a comparison group in some planned analyses. However, more detailed follow-up and sample collection was done for infants included in the sub-study.

Contribution of the OLE period

Given the long-acting nature of CAB, even with discontinuation of injections at the first positive pregnancy test during the blinded and unblinded periods, pregnancies were still exposed to declining levels of CAB-LA and have provided some insights into the safety and pharmacology of CAB-LA in pregnancy. By contrast, the OLE provides an opportunity to investigate the safety and pharmacology of active CAB injections during pregnancy. Analysis of the OLE data will expand on the safety assessments from the blinded and unblinded periods.

One major limitation of the analysis of OLE period data is that participants chose their own treatment instead of being randomized. We will describe any differences between the exposure groups, and statistical analyses of primary outcomes will include adjustments for any differences.

1.2 Study Objectives

Safety Objectives

• To evaluate safety and pregnancy outcomes among pregnant participants and compare between exposure groups (Active CAB, Prior CAB, or No CAB)

• To evaluate safety in infants exposed to CAB-LA during pregnancy and compare infant outcomes between exposure groups (CAB during pregnancy, CAB after pregnancy, CAB before pregnancy, or No CAB)

• To characterize HIV infections that occur in the pregnant or post-partum periods

Pharmacokinetics (PK) Objectives

• To evaluate CAB-LA PK in a subset of participants in the Active CAB exposure group

• To compare CAB-LA drug concentrations in the pre-pregnant period with CAB concentrations observed in the 1st, 2nd, and 3rd trimesters of pregnancy among a subset of the Active CAB group

• To evaluate CAB-LA drug concentrations in the postpartum period, among a subset of the Active CAB group

• To evaluate CAB-LA drug exposures in infants born of mothers from a subset of the Active CAB exposure group via CAB-LA measurement in cord blood plasma, maternal breastmilk, and infant plasma

• To evaluate CAB-LA drug concentrations after pregnancy in women who breastfeed and describe any trends relative to non-pregnant concentrations

Other Objectives

• To estimate pregnancy incidence during the OLE and compare pregnancy incidence between exposure groups (chose CAB vs. chose TDF/FTC or no PrEP at the beginning of the OLE)

2. GENERAL DATA ANALYSIS CONSIDERATIONS

2.1 Analysis Sets

Pregnancy incidence cohort

All OLE participants with at least one OLE follow-up visit where a pregnancy test was scheduled will be included in the pregnancy incidence analysis.

Pregnancy and pregnant participant safety cohort

The assessment of safety outcomes for pregnancies and pregnant participants will include both incident OLE pregnancies (which began after participants joined the OLE), and prevalent pregnancies (which were ongoing when participants joined the OLE). This will include only pregnancies that were confirmed by pregnancy test, ultrasound, or outcome (see definition below).

Safety assessments will include all pregnancies with relevant follow-up, including pregnancies that were not enrolled in the pregnancy and infant sub-study.

Participants who are included in this analysis population and have relevant weight measurements will be included in the weight gain analysis.

Infant safety cohort

All live births from prevalent and incident pregnancies will be included in the analysis of infant safety outcomes. Infants who were not included in the pregnancy and infant sub-study will be included as much as possible for comparison, although some measurements are specific to the sub-study.

Pregnancy PK cohort

The pregnancy PK cohort will include up to 75 pregnancies from the sub-study. Pregnancies included in this cohort will have CAB exposure before and during pregnancy. Pregnancies that lasted less than 36 weeks and did not result in a live birth are excluded, as are participants who are HIV-positive.

Samples from all available visits after initiation of CAB will be tested, including from the pre-pregnant, pregnant, and post-partum periods.

Lactation PK cohort

The lactation PK cohort will include up to 75 mother-infant pairs from the sub-study who provided infant samples. Participants included in this cohort will have CAB exposure during and after pregnancy (while breastfeeding). Participants who are HIV-positive will be excluded.

For mother-infant pairs included in this cohort, maternal samples from the pre-pregnant and pregnant period will be tested. Additionally, all relevant samples (maternal plasma, cord blood, breast milk, infant plasma) in the 24 weeks after delivery will be tested.

This population may overlap with mothers from the pregnancy PK cohort.

2.2 Exposure groups

For incidence analysis:

Pregnancy incidence will be stratified by product choice during the beginning of the OLE: CAB vs. TDF/FTC or no PrEP.

For pregnancy and pregnant participant safety analyses:

Pregnancies will be sorted into exposure groups as defined below:

Active CAB: Pregnancies during which participants received ≥ 1 CAB-LA injections.

Prior CAB: Pregnancies from participants who received at least one CAB-LA injection prior to pregnancy, but no CAB-LA injections during pregnancy. Participants in this group may or may not have enrolled in the pregnancy sub-study.

No CAB: Pregnancies with no CAB-LA injections or oral CAB pills during pregnancy, and no CAB-LA injections prior to pregnancy. Participants in this group are unlikely to be eligible for the pregnancy sub-study, but are included as a comparison group.

Note that if a participant had multiple pregnancies during the OLE, the pregnancies might belong to different exposure cohorts.

For infant safety analyses:

Infants will be sorted into exposure groups as defined below for any outcomes that could be affected by post-birth exposure. For outcomes that could only plausibly be affected by in utero exposure, the pregnancy exposure groups (Active CAB, Prior CAB, No CAB) will be used.

CAB during pregnancy: during the respective pregnancy, the participant received ≥ 1 CAB-LA injections. This group will include infants of participants who may or may not have had CAB exposure prior to and/or following pregnancy.

CAB after pregnancy: between delivery and 24 weeks of age (while breastfeeding), the infant's mother received ≥ 1 CAB-LA injections, but no injections during pregnancy. This group will include infants of participants who may or may not have had CAB exposure prior to pregnancy.

CAB before pregnancy: the infant's mother received ≥ 1 CAB-LA injections prior to the pregnancy in question, but no injections during pregnancy or in the 24 weeks after pregnancy.

No CAB: the infant's mother received no CAB-LA injections or oral CAB pills during pregnancy, and no CAB-LA injections prior to pregnancy or in the 24 weeks after pregnancy. Participants with infants in this group may have received oral CAB prior to pregnancy but must have stopped taking pills prior to the beginning of pregnancy. Participants with infants in this group are unlikely to be eligible for the pregnancy sub-study, but are included as a comparison group.

For HIV infection characterization:

When available, EAC adjudication will be used to identify which participants are living with HIV and when HIV acquisition occurred. For participants with reactive HIV tests that have not been adjudicated by the EAC, available test results will be used to categorize participants' HIV status and identify whether HIV acquisition may have occurred during the time periods of interest.

2.3 Key variable definitions

Participant: in this document, 'participant' refers to the adult participants from HPTN 084 and young adult or adolescent participants from HPTN 084-01. Infants born during the OLE are referred to throughout as 'infants', even if they may have been consented to participate in study procedures as well.

First positive pregnancy test date: the date of the first positive pregnancy test for each pregnancy.

Pregnancy: unless otherwise specified, the duration of pregnancy is defined as the first positive test date through the date of the pregnancy outcome.

Incident pregnancies: pregnancies with a first positive test date after the participant's OLE decision date.

Prevalent pregnancies: pregnancies with a first positive test date on or before the OLE decision date, and an outcome after the OLE decision date. This includes pregnancies which began in the randomized period, but the participant's OLE choice could have impacted their pregnancy outcomes.

Confirmed pregnancies: incident pregnancies are considered confirmed if there is a second independent pregnancy test with positive results on the same day that the pregnancy was identified. If an incident pregnancy did not have a second same-day pregnancy test, confirmation status will be determined by other factors, including later pregnancy testing, pregnancy outcome, and ultrasound results. If an incident pregnancy had a second same-day pregnancy test that was non-reactive, but the pregnancy ended with a definitive outcome (e.g., live birth), it will be counted as confirmed. Prevalent pregnancies may be confirmed by a second independent test after the initial reactive test, or via ultrasound, or based on the pregnancy outcome.

Non-confirmed pregnancies: Incident pregnancies with a same-day non-reactive confirmatory test are considered unconfirmed, with the exception of pregnancies that ended with a definitive outcome (e.g. live birth). Many of these may reflect false positive pregnancy tests. Prevalent pregnancies may be unconfirmed because they ended prior to confirmation, or did not have a confirmatory test and ended before a definitive outcome.

3. ANALYSIS METHODS AND ISSUES

All statistical tests will have alpha level 0.05 and be two-sided unless otherwise specified. All confidence intervals will be 95% confidence intervals. When appropriate, we will use exact methods for confidence intervals. No formal corrections will be made for multiple comparisons, since we would prefer to be liberal in identifying potential signals related to safety issues.

Although we expect it to be uncommon, there may be some correlated observations. At the pregnancy level, one participant may have had multiple pregnancies over the course of the OLE. At the infant level, one pregnancy may have resulted in multiple infants (e.g. twins). Some analyses collapse closely related observations; others treat observations as independent. For all data summaries, we will note which approach is being used and provide information about the prevalence of potentially correlated observations.

Note that all comparisons involve non-randomized groups. Evaluations of exposure group comparability will be important. When reasonable, we will try to adjust analyses for important pre-pregnancy risk factors, such as age and pregnancy history.

If there is substantial missing data, we will try to address it if possible using methods such as inverse probability-of-censoring weights.

Participants and infants enrolled in the sub-study will have more frequent clinic visits, and sub-study participation is strongly related to the exposure groups. Any comparison of AE rates between exposure groups will need to acknowledge the potential for ascertainment bias. To help understand the magnitude of this issue, we will summarize information about follow-up and frequency of visits by exposure group.

4. TRIAL PARTICIPANT DISPOSITION

We will describe the disposition of participants and infants in the OLE, including data completeness and timing of data collection (e.g. when pregnancies were reported). We will describe exposure to study products separately for each exposure cohort, including number and timing of CAB injections prior to, during, and after pregnancy.

5. PRE-PREGNANCY DATA

We will describe demographics and other characteristics of participants who became pregnant, overall and by exposure cohort. We will present analogous data for infants (e.g., age of mother), by infant

exposure cohort. We will also present this information for specific analysis cohorts, to describe the pregnancies that are included or excluded in key analyses. The characteristics described will include potential confounders between CAB exposure and key outcomes, such as age at the beginning of pregnancy and BMI immediately prior to pregnancy.

6. PREGNANCY INCIDENCE ANALYSES

Analysis of pregnancy incidence

Population: Pregnancy incidence cohort

Outcomes: Incidence of confirmed pregnancies

Analysis overview: We will calculate OLE pregnancy incidence rates overall and by exposure group based on initial OLE treatment choice (CAB or TDF/FTC), and compare incidence rates between the two exposure groups.

7. SAFETY ANALYSES

7.1 Analysis of Maternal, Birth, and Infant Safety Outcomes

To assess the safety of CAB exposure in pregnancy, three domains of outcomes will be analyzed: maternal outcomes measured on participants (e.g., during pregnancy), birth outcomes at the time of delivery, and infant outcomes following delivery.

Part 1: Analysis of maternal safety outcomes

Population: Pregnancy and pregnant participant safety cohort

Outcomes:

- Pregnancy-related mortality, also divided by timing relative to pregnancy and direct vs. indirect obstetric deaths
- Grade 2+ AEs
  - Overall
  - Non-pregnancy-related AEs
  - AEs in the system organ class pregnancy, puerperium and perinatal conditions
- All AEs (of any grade) in the system organ class pregnancy, puerperium and perinatal conditions (e.g., eclampsia, gestational diabetes)
- Mean weight gain per month during pregnancy

Analysis overview: AE incidence rates and average monthly weight change during pregnancy will be calculated and compared by exposure group (active CAB, prior CAB, or no CAB). We will not try to compare incidence rates for individual AEs that are not related to pregnancy and occur very rarely.

Part 2: Analysis of birth safety outcomes

Population: Pregnancy and pregnant participant safety cohort for outcomes measured at the pregnancy level, and infant safety cohort for outcomes measured at the infant level

Outcomes:

- Birth outcomes for all pregnancies
  - Pregnancy outcome: spontaneous abortion (<20 weeks), therapeutic/elective abortion, ectopic pregnancy, stillbirth/intrauterine fetal demise ≥20 weeks, pre-term birth (<37 weeks), full-term birth (37+ weeks), or other
  - Place of delivery and delivery method
  - Complications associated with delivery
  - Congenital anomalies observed at birth that are major structural abnormalities of prenatal origin that affect health, survival, physical or cognitive functioning of the individual
  - Composite pregnancy outcome defined as: spontaneous abortion (<20 weeks of gestation), stillbirth (≥20 weeks of gestation), preterm delivery (<37 weeks of gestation in live-born babies), or small for gestational age at birth.
- Birth outcomes for pregnancies that ended in a live birth (infant-level outcomes)
  - Apgar score at 1 minute and 10 minutes
  - Size for gestational age at birth based on US (large, appropriate, small, very small for gestational age) using Intergrowth-21 charts

Analysis overview: All pregnancy and birth outcomes will be summarized by the appropriate exposure group. For AEs, SAEs, and congenital anomalies, we will compare incidence rates (or risk) between exposure groups. For the composite pregnancy outcome, we will compare the risk of a negative outcome between exposure groups, both unadjusted and adjusted for potential confounders.

Part 3: Analysis of infant safety outcomes

Population: Infant safety cohort

Outcomes:

- Infant deaths from birth to week 48, also divided by timing
- Hospitalizations through ~1 year of life
- Congenital anomalies observed through 48 weeks of life
- Growth parameters (length, weight, head circumference z-scores)
  - At birth (or week 8 if missing at birth)
  - At 48 weeks
- Grade 2+ AEs in sub-study infants from delivery through 24 weeks

Analysis overview: For AEs, deaths, hospitalizations, and congenital anomalies, incidence rates (or risk) will be calculated and compared between exposure groups (CAB during pregnancy, CAB after pregnancy, CAB before pregnancy, and no CAB for outcomes plausibly affected by post-birth exposure; Active CAB, Prior CAB, and No CAB otherwise).

For growth parameters at birth and separately at 48 weeks, mean values will be calculated and compared by exposure group. We will report both unadjusted differences, and differences adjusted for potential confounders.

7.2 Analysis of Other Risk Factors

Population: Pregnancy and pregnant participant safety cohort for outcomes measured at the pregnancy level, and infant safety cohort for outcomes measured at the infant level

Outcomes:

- Birth outcomes for all pregnancies:
  - Pregnancy outcome (stillbirth, pre-term birth, etc.)
  - Composite pregnancy outcome, as defined above: spontaneous abortion (<20 weeks of gestation), stillbirth (≥20 weeks of gestation), preterm delivery (<37 weeks of gestation in live-born babies), or small for gestational age at birth.
  - Maternal mortality
- Birth outcomes for pregnancies that ended in a live birth:
  - Small for gestational age
  - Infant mortality (within ~1 year of life)
  - Neonatal mortality (within first 28 days of life)

Analysis overview: We will examine the association between adverse pregnancy outcomes and the following factors overall and stratified by CAB exposure (exposure group and/or gestational age of exposure) when sample size allows:

- Maternal age
- Location of delivery (in/out of facility)
- Infant sex
- AE during pregnancy (including STI co-infection)
- Obstetric history
- Multiple birth
- Baseline BMI
- Country and/or study site

We will present summary statistics for all outcomes, and compare risk factor levels for the composite pregnancy outcome.

7.3 Analysis of HIV Seroconversions

Population: Confirmed and unconfirmed pregnancies (prevalent and incident), and all live infants

Outcomes: HIV infections in women during pregnancy, and HIV infections in infants

Analysis overview: We will report the number of infections by exposure cohort if there are infections during pregnancy.

8. PHARMACOKINETIC ANALYSES

8.1 Analysis of Plasma CAB Concentrations During Pregnancy

Population: Pregnancy PK cohort

Outcomes: Plasma CAB concentrations

Analysis overview: We will summarize and compare CAB drug concentrations and PK parameters between different time periods, including during pregnancy (overall and by trimester), during the post-natal period, and while participants are not pregnant.

8.2 Analysis of Plasma CAB Concentrations After Pregnancy and Infant Exposure

Population: Lactation PK cohort

Outcomes: CAB concentrations in maternal plasma, breastmilk, cord blood, and infant plasma.

Analysis overview: We will summarize CAB drug concentrations in maternal plasma, breastmilk, cord blood, and infant plasma, and quantify the association between PK metrics during different time periods.

For maternal CAB concentrations over time, we will describe any differences between time periods (e.g., during pregnancy, while breastfeeding, and after the post-natal period). If there are meaningful differences between pregnant and non-pregnant CAB concentrations, we will describe trends in the post-partum concentrations and how quickly they return to pre-pregnancy levels. We will test for differences in CAB concentrations and/or PK metrics between different time periods.