# STATISTICAL ANALYSIS PLAN

## A Phase 3 Double Blind Safety and Efficacy Study of Long-Acting Injectable Cabotegravir Compared to Daily Oral TDF/FTC for Pre-Exposure Prophylaxis in HIV-Uninfected Women

## HPTN 084

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LIST OF ABBREVIATIONS

| Term/Abbreviation | Definition |
|---|---|
| AE | Adverse Event |
| AIDS | Acquired immunodeficiency syndrome |
| ART | Antiretroviral therapy |
| BMI | Body Mass Index |
| CASI | Computer Assisted Self Interview |
| CRF | Case Report Form |
| CSR | Clinical Study Report |
| DAIDS | Division of AIDS |
| DMPA | Medroxyprogesterone |
| DSMB | Data and Safety Monitoring Board |
| EOS | End of Study |
| HPTN | HIV Prevention Trials Network |
| ITT | Intent to Treat |
| LA | Long Acting |
| NET-EN | Etonogestrel |
| NIAID | National Institute of Allergy and Infectious Diseases |
| OBSP | On Blinded Study Product |
| PYR | Person-Years |
| SDMC | Statistics and Data Management Center |
| SAE | Serious Adverse Event |
| SMC | Study Monitoring Committee |
| SOC | System Organ Class |
| TDF | tenofovir disoproxil fumarate |
| TDF/FTC | tenofovir/emtricitabine (trade name: Truvada®) |
| TFV | tenofovir |
| TFV-DP | tenofovir diphosphate |

# 1. INTRODUCTION

This statistical analysis plan (SAP) details the statistical procedures that address the primary study objectives specified in Version 2.0 of Protocol HPTN 084 (dated: 6 November 2019): ***A Phase 3 Double Blind Safety and Efficacy Study of Long-Acting Injectable Cabotegravir Compared to Daily Oral TDF/FTC for Pre-Exposure Prophylaxis in HIV-Uninfected Women***. Any meaningful changes or additions to this SAP (e.g., in response to protocol amendments or violations of assumptions underlying pre-planned analyses), and the timing of such changes in relation to unblinding of statisticians performing the analyses, will be documented in a designated section of the SAP. New versions of the SAP will be issued to document updates and changes in the plan. Analysis plans for sub-studies not addressed in the protocol, and for secondary analyses not anticipated prior to study completion, and for exploratory analyses will be developed as separate documents.

Plans for formal interim analysis of trial data are outlined in Section 7.2. A more detailed plan is documented separately in HPTN 084 Interim Monitoring Guidelines. Any substantive modifications to analysis methods or type I error control made in response to DSMB reviews or changes in the protocol will be documented in subsequent versions of the SAP. In DSMB reviews, the HPTN Statistical and Data Management Center (SDMC) will routinely report on operational metrics (e.g., rates of recruitment, retention, study drug discontinuation). These reports are also routinely shared with the study sites to monitor operational performance based on these metrics.

# 2. GENERAL DESIGN CONSIDERATIONS

## 2.1 Purpose:

To evaluate the safety and efficacy of the injectable agent, cabotegravir (CAB LA) compared to daily oral tenofovir disoproxil fumarate/emtricitabine (TDF/FTC), for pre-exposure prophylaxis (PrEP) in HIV-uninfected women.

## 2.2 Design:

Multi-site, double blind, two-arm, randomized (1:1), controlled superiority trial of the safety and efficacy of CAB LA compared to daily oral TDF/FTC for HIV prevention.

## 2.3 Population:

HIV-uninfected women at risk for acquiring HIV, 18 to 45 years old.

## 2.4 Study Size:

The original sample size calculation was to enroll 3200 women. In response to a recommendation from the HPTN Study Monitoring Committee in October 2020, this target was increased to 3350 in LOA 3.

## 2.5 Study Duration:

Approximately 4.6 years total, with individual participants being followed on randomized study product between 1.6 years (for the last enrolling participants) to approximately 3.6 years (for the earliest enrolling participants), and on oral TDF/ FTC for an additional 48 weeks. Accrual will require approximately 2 years.

### 2.6 Study Sites:

Study sites will be in sub-Saharan Africa (SSA).

### 2.7 Study Regimen and Follow-up:

Once randomized to one of two arms, participants will move through the following steps (active study products are shown in bold text):

#### *2.7.1. Step 1, Oral Run-in Phase:*

Arm A – **Daily oral cabotegravir (CAB)** and oral TDF/FTC placebo for five weeks plus an HIV prevention package including behavioral risk reduction and adherence counseling, provision of condoms.

Arm B – **Daily oral TDF/FTC** and oral CAB placebo for five weeks plus an HIV prevention package including behavioral risk reduction and adherence counseling, provision of condoms.

Individuals who discontinue study participation after receiving oral product in Step 1, but do not receive any study product in Step 2 will be offered the option to be followed annually with HIV testing until study end.

A participant that becomes HIV-infected during Step 1 of the study will permanently discontinue study product, be terminated from the study, and referred for HIV-related care.

#### 2.7.2 Step 2, Injection Phase:

Arm A – **CAB LA** as a single intramuscular [IM] injection at two time-points four weeks apart and every eight weeks thereafter and daily oral TDF/FTC placebo plus an HIV prevention package including behavioral risk reduction and adherence counseling, provision of condoms.

Arm B – **Daily oral TDF/FTC** and IM placebo (matching vehicle, identical volume as active injectable product in Arm A) at two time-points four weeks apart and every eight weeks thereafter plus an HIV prevention package including behavioral risk reduction and adherence counseling, provision of condoms.

Step 2 will continue until the required number of endpoints (114) is reached, estimated to be 81 weeks after enrolling the last participant.

Participants who prematurely discontinue blinded study products during Step 2 (having received at least one injection) for any reason other than HIV infection will be offered to transition to 48 weeks of open-label TDF/FTC followed by annual testing through the duration of step 3.

A participant who becomes HIV-infected during Step 2 of the study will permanently discontinue study product, be placed on immediate suppressive ART, and will be facilitated into locally provided ART, and followed at quarterly intervals for 48 weeks after

their last injection prior to diagnosis of HIV in order to test for safety parameters, as well as CD4 cell count and HIV viral load. After 52 weeks, they will be terminated from the study and transitioned to continued HIV-related care.

#### 2.7.3 *Step 3, Follow-up Phase:*

Arms A and B – Open-label daily TDF/FTC (in order to cover the pharmacokinetic [PK] tail for Arm A participants) will be provided no later than eight weeks after the last injection visit, for up to 48 weeks plus an HIV prevention package including behavioral risk reduction and adherence counseling, and provision of condoms. Participants will then transition to locally available HIV prevention services, including services for PrEP, if available.

Participants with confirmed HIV infection during Step 3 will have their TDF/FTC stopped and be followed quarterly at least for the duration of Step 3, with possible additional assessments and follow-up to be determined by guidance from members of the HIV alias. Study product will be discontinued and participants will be referred for care.

#### *2.7.4. Pregnancy*

A participant with a first positive pregnancy test will temporarily discontinue blinded injections and receive a 4-week supply of open label TDF/FTC and may resume blinded treatment if a second test after 4 weeks indicates that she is not pregnant. All pregnant participants with a confirmed positive pregnancy test (four weeks after the initial pregnancy test) will be unblinded and followed by the study every 12 weeks. Regardless of the randomization assignment or point in the study, all pregnant participants will be placed on open-label TDF/FTC for the duration of the pregnancy. Once pregnancy outcome is reached, and after the participant is not breastfeeding, she may resume study product, according to original randomized arm but open-label, and resume visits per the study schedule.

If participants decline to use an approved contraceptive method, they will be given open-label TDF/FTC for 48 weeks starting no later than eight weeks after her last CAB LA/placebo injection. If study follow-up is ongoing she will be required to be followed up at least annually for HIV testing thereafter. If a participant transitioned to open-label TDF/FTC during Step 2, either because she wanted to become pregnant or declined to continue using long-acting contraception, and subsequently changes her mind she may continue in the study on blinded study product (per original randomization) once she has documentation of a negative pregnancy test and of resuming long-acting contraception.

## 3. STUDY OBJECTIVES

### 3.1. Primary Objective:

- Efficacy: To evaluate the relative efficacy of oral CAB/CAB LA (oral run-in and injections, Steps 1 and 2) vs. daily oral TDF/FTC for HIV prevention (Steps 1 and 2).

- Safety: To evaluate the relative safety of oral CAB/CAB LA (oral run-in and injections, Steps 1 and 2) vs. daily oral TDF/FTC for HIV prevention (Steps 1 and 2).

### 3.2. Secondary Objectives:

- To compare HIV incidence among participants receiving oral CAB/CAB LA vs. daily oral TDF/FTC (Steps 1, 2 and 3).
- To evaluate relative efficacy of oral CAB/CAB LA vs. oral TDF/FTC in subgroups defined by the baseline factors of age, herpes simplex virus-2 (HSV-2) serostatus, contraceptive method, and body mass index (BMI).
- To describe and model the relationship between HIV incidence and drug concentration, within each arm.
- To describe the distribution and correlates of drug concentration, within each arm.
- To compare the acceptability of and preferences for CAB LA vs. oral TDF/FTC.

### 3.3. Tertiary Objectives:

- To estimate sexual risk behaviors, as measured by self-report and rates of incident sexually transmitted infections (STIs).
- To compare Grade >2 adverse event (AE) rates in women with baseline BMI </≥ 30 kg/$m^2$, within each study arm.
- To compare differences in weight gain and BMI, by arm.
- To compare pregnancy incidence and outcomes between arms.
- To evaluate rates of HIV drug resistance among participants who acquire HIV infection during the study among participants receiving oral CAB/CAB LA vs. oral TDF/FTC.
- To determine plasma concentrations of medroxyprogesterone (DMPA) or norethisterone (NET-EN) or etonogestrel when co-administered with CAB LA.

## 4. STATISTICAL CONSIDERATIONS

### 4.1 Sample Size and Power

The primary analysis will be based on HIV incidence during Steps 1 and 2. As described previously, we assume that participants will be followed between 81 (latest enrollees) and 185 (earliest enrollees) weeks in Steps 1 and 2 (1.6 – 3.6 years), with a uniform distribution of enrollments over a two-year period. Thus, average time in Steps 1 and 2 will be 133 weeks (2.6 years). Sample size calculations are based on the following assumptions:

- Background HIV incidence, in the absence of any PrEP, is 3.5% per year
- Both CAB LA and TDF/FTC are 85% effective when used with 100% adherence
- 2.5% one-sided type I error rate and 90% power at the indicated alternative
- Average follow-up duration of 2.6 years (range: 1.6 – 3.6 years)
- Maximum 5% lost-to-follow-up per year

Table 4.1 presents five scenarios and associated total sample sizes. All are superiority designs. The first scenario assumes that adherence to TDF/FTC and CAB/CAB LA will be 50% and 85%, respectively, averaged over the entire Step 1 and 2 follow-up period. The second and third scenarios assume a higher adherence to TDF/FTC (second line) and lower adherence to CAB LA (80%) (third line) (these scenarios are considered unlikely). The last two scenarios retain the conservative assumption of 80% adherence to CAB LA and assume lower adherence to TDF/FTC of 45% and 48%. The largest blinded trials of TDF/FTC among women in a similar setting have shown even lower adherence than assumed in Table 4.1.

Given this history we believe that a sample size of at least 3,128 (111 events for a fixed sample size trial; we will target 114 events to allow for interim monitoring) provides an adequate degree of robustness against uncertainties in adherence rates to the two drug regimens. The trial will continue until we reach 114 events, or a stopping boundary is crossed (see below).

**Table 4.1. Five Case Scenarios**

| Adherence | | HIV Incidence (%/year)[1] | | | | |
|---|---|---|---|---|---|---|
| TDF/FTC | CAB LA | TDF/FTC | CAB LA | RR | Number Events | Sample Size |
| .50 | .85 | 2.01 | 0.97 | .48 | 78 | 2352 |
| .55 | .85 | 1.86 | 0.97 | .52 | 98 | 3112 |
| .50 | .80 | 2.01 | 1.12 | .56 | 125 | 3590 |
| .48 | .80 | 2.07 | 1.12 | .54 | 111 | 3128 |
| .45 | .80 | 2.16 | 1.12 | .52 | 98 | 2686 |

*[1]Background incidence is reduced by a weighted average of fully adherent and non-adherent individuals e.g. 2.01 = 3.5*((1-.85)*.5 + 1*(1-.5))*

This study will be monitored by a NIAID DSMB, which will meet at least annually to review safety and efficacy data, as well as data quality. The DSMB will use an **O'Brien-Fleming boundary** to consider stopping the trial early for efficacy.

### *4.1.1 Sample Size Calculation and Monitoring for Efficacy and Harm*

Table 1 reviews the key sample size assumptions. We propose five analyses of the 084 data (four interim and one final). Figure 1 shows the times of the interim analyses and the expected accumulation of participants and information (HIV events) over the course of the trial (assuming a constant incidence). The times of the interim analyses are chosen to correspond to the times of the DSMB reviews (every six months). No interim analyses are proposed prior to 1.5 years because of the small amount of information (HIV events) expected early in the trial. The software nTerim 3.0 was used for calculations.

**Table 1. Key sample size calculation parameters and results. EOS = end of steps 1 and 2.**

| Parameter | Value | Comment |
|---|---|---|
| Test Significance level, $\alpha$ (2 sided) | 0.05 | |
| Average duration of follow-up | 133 wks | (81 + 185)/2 |
| Proportion uninfected at EOS, Cab | .9718 | Exp(-.0112*133/52) (1.12%/yr incidence) |
| Proportion uninfected at EOS, TDF/FTC | .9484 | Exp(-.0207*133/52) (2.07%/yr incidence) |
| Hazard ratio | .54 | Assuming constant hazard in each arm |
| Power | 90% | |

| | | |
|---|---|---|
| Number of events | 114 | Slightly inflated from fixed sample size 111 due to interim monitoring |
| Total sample size | 3257 | 2834/.87 where overall retention = .87 |
| Interim monitoring times (expressed as % information) | .22, .39, .59, .78, 1 | Corresponds to 6-month intervals, starting at 1.5 years |

**Figure 1. Planned accumulation of sample size and statistical information, along with proposed times of interim analyses, based on HPTN 084 study design.**

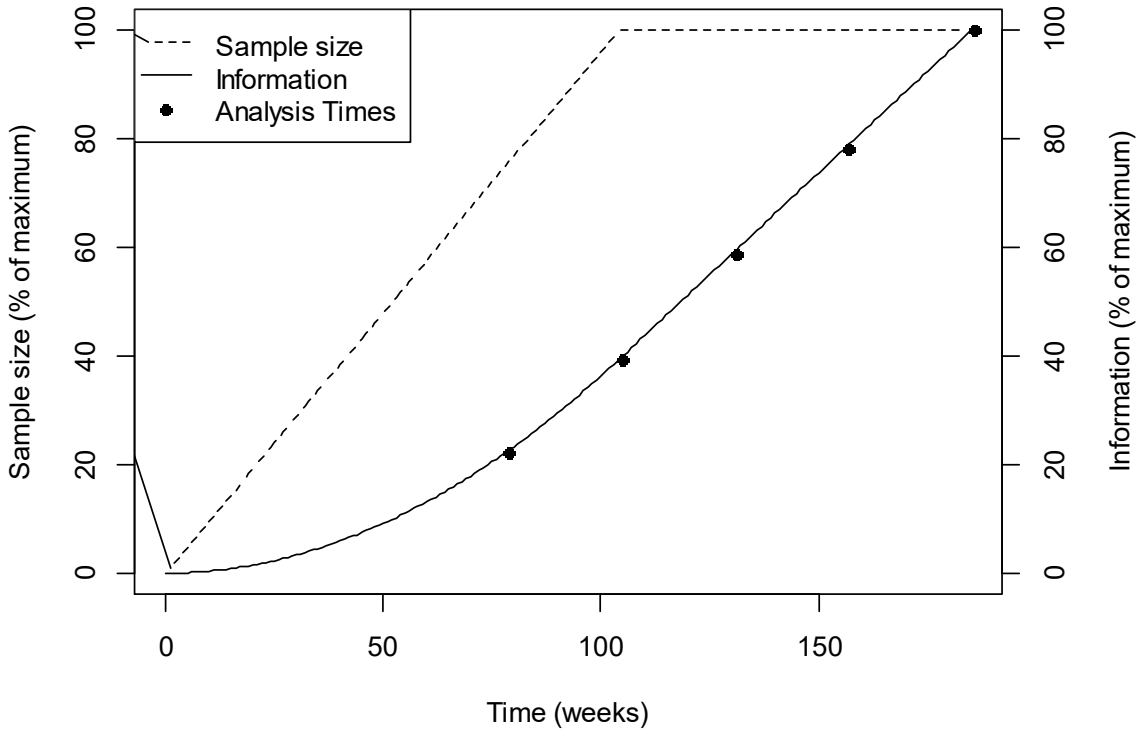


Table 2 provides detailed information on monitoring the trial for early stopping at the interim analyses. The O'Brien-Fleming spending function is used to determine stopping boundaries. By the time of the first or second analysis we should have a better understanding of enrollment rates and HIV incidence; the timing of the final 3-4 analyses may be modified at that time. Any modifications, if needed, will use the O'Brien-Fleming spending function applied to the cumulative information available at the time of the analysis.

**Table 2. Interim analysis plan for monitoring HPTN 084 based on expected accrual and HIV incidence rates. Ho: RR = 1; Ha RR = .54. Type I error rates (a) in the table are for 2-sided tests.**

| Time (years) | % Information | Expected no. events | Efficacy boundary (Z) | Harm boundary (Z) | Efficacy boundary (RR) # | Nominal α | Cumulative α | Cumulative Stop Prob. under Ha |
|---|---|---|---|---|---|---|---|---|
| 1.5* | 22 | 25.3 | -4.64 | 4.64 | .04 | .000001 | .000001 | 0.1 |
| 2.0 | 39 | 44.8 | -3.40 | 3.40 | .30 | .00066 | .00066 | 8.7 |
| 2.5 | 59 | 67.0 | -2.70 | 2.70 | .50 | .00682 | .00704 | 42.7 |
| 3.0 | 78 | 89.2 | -2.32 | 2.32 | .60 | .02010 | .0223 | 72.2 |
| 3.56 | 100 | 114 | -2.02 | 2.02 | .68 | .0429 | .05 | 90.0 |

** Removing the first interim analysis has virtually no effect on the boundaries at subsequent times*
*# RR boundary = (#events Cab/# events TDF), conditional on expected number of events; these RR correspond to approximately 1, 10, 22, 33, 46 events in the CAB arm, respectively*

### 4.2 Randomization

Participants will be randomized to one of two study arms in a 1:1 ratio. Randomization will be stratified by study site, and a permuted blocks design will be used to ensure balanced treatment assignments within study site. The randomization scheme will be generated, operationalized and maintained by the HPTN Statistics and Data Management Center.

### 4.3 Blinding

Study site staff, except for the site Pharmacist of Record or their designee, and participants will be blinded to the random assignments. Blinding will be maintained until the trial is completed or stopped, i.e., the trial is stopped early, or the required number of endpoints (114) has been met. At a specified time directed by the HPTN Statistics and Data Management Center, participants will be notified of their treatment assignment.

In addition, as described in sections 5.14 and 5.18 of the HPTN Protocol 084, v2.0, participants with a confirmed pregnancy will be unblinded. Participants who are unblinded due to pregnancy may restart open-label study product in their original randomization arm (open label CAB LA or TDF/FTC) following delivery and cessation of breastfeeding.

### 4.4 Accrual and Retention

Approximately 3,350 participants will be enrolled in approximately 24 months and followed through Steps 1 and 2 for 1.6 to 3.6 years and on oral TDF/ FTC for an additional 48 weeks. An average annual retention rate of at least 95% percent will be targeted (87 - 88% for the entire Step 1 and 2 follow-up period).

## 5. PROTOCOL DEVIATIONS

All protocol deviations will be reported and reviewed on a regular basis, and each case will be managed clinically and with regards to ongoing product administration by the CMC and DAIDS MOs during the course of the trial. Certain serious protocol deviations, identified during the blinded review, may warrant the exclusion of participants from the ITT or Per-Protocol analysis (guidance for adjudication for these deviations is provided in the HPTN 084 Deviation Adjudication Terms of Reference document). Generally, exclusions from the mITT analysis are expected to be limited to participants deemed inappropriately enrolled and resulting in termination from the study. Any exclusion must be carefully adjudicated and scientifically justified prior to breaking the blind for individuals involved in the adjudication process.

## 6. ANALYSIS POPULATIONS

### 6.1 Randomized Population

All participants who were randomized

### 6.2 Intent to Treat (ITT) Population

All participants who were randomized, excluding those who were subsequently found to be inappropriately enrolled due to violations of the inclusion/exclusion criteria that were deemed to warrant exclusion by the adjudication committee.

### 6.3 Modified ITT (mITT) Population
All women who are included in the ITT Population and who were not HIV infected at enrollment are included in the mITT population.

### 6.4 Per-Protocol (PP) Population
The mITT population excluding all participants with protocol violations that were determined by the protocol deviation adjudication committee to be exclusionary from the per-protocol population.

### 6.5 Injection (Step 2) Efficacy Population
The mITT population who receive at least one injection and are uninfected at the time of the first injection, and had at least one follow-up visit with HIV status determined after the first injection.

### 6.6 Safety Population (Primary Safety)
All ITT participants who received any oral or injectable product.

### 6.7 Injection (Step 2) Safety Population
All Safety Population participants who receive at least one injection

### 6.8 Longitudinal Pharmacokinetic CAB Concentration Population
A longitudinal evaluation of CAB PK in the CAB arm will be conducted in 150 participants, excluding any participant who has had any positive HIV testing at any visit (exclude HIV final status= “positive” or "additional testing needed"). Participant selection should be limited to participants who have reached week 57 before 3.1.2020 and have no late injections beyond 2 weeks of target date prior to week 57. The window for late injections is defined as 2 weeks after target date. Selected participants should have no missed injections (including regular injection visits, as well as no missing injection). These 150 participants present the following distribution across sites:

- 40% cisgender women <25 years of age at enrollment
- 40% cisgender women between 25 and 30 years of age at enrollment
- 20% cisgender women ≥ 30 years of age at enrollment

This population will be used for the CAB concentration listing and to enhance the population represented in the global modelling of CAB-LA PK.

### 6.9 TDF-FTC Adherence Population
The TDF-FTC adherence population consists of approximately 400 participants in the TDF/FTC arm who were randomly selected for assessment of adherence to oral pill taking. To achieve balance across geographic regions and balance over time, selection of the Adherence Population was stratified by study sites or regions and was selected throughout the enrollment period by randomly choosing approximately 25% of all new enrollees in the TDF/FTC arm each quarter. Plasma and DBS samples for selected follow-up visits are tested for TFV and FTC throughout the follow-up period.

### 6.10 Contraceptive Substudy Population
All participants who are invited and agree to participate in the Contraception sub study.

### 6.11 Pregnancy Population
All participants who have a positive pregnancy test result while on treatment.

### 6.12 Confirmed Pregnancy Population

All participants who have a positive pregnancy test result while on treatment that is followed by a positive confirmatory test result or confirmation by another method. (Ultrasound, full- or pre-term live birth.).

### 6.13 Declined contraception population

All participants who decline to use long-acting contraception at any point during step 1 or 2 after LOA 3 to protocol v1.0 was implemented.

### 6.14 Seroconverter Population

All ITT participants who, during the course of the trial, are either identified to have been HIV infected prior to randomization, or who acquired HIV infection during trial the primary analysis follow-up period.

### 6.15 Primary Seroconverter Population

All ITT participants who are HIV-uninfected at randomization and acquire HIV infection during the primary analysis follow-up period.

### 6.16 Infected at Enrollment Population

All ITT participants who were subsequently determined to be HIV-infected at randomization.

### 6.17 Subgroups

Important participant subgroups are

- Age:<25 vs ≥25 years old
- HSV-2 status at baseline*
- Method of contraception during follow-up**
- BMI </≥ 30 kg/m2

* Note: HSV-2 status at baseline will not be available for the Clinical Study Report
**Note: Contraceptive method will be modeled as a time-dependent covariate. This analysis will not be presented in the Clinical Study Report.

## 7. STATISTICAL ANALYSES

### 7.1 General Analysis Considerations

Any deviations from the original statistical plan will be described in the final report.

#### *7.1.1. Summary Statistics*

Summary statistics for categorical variables will include frequency and percentage. For continuous variables, number of subjects with non-missing value (n), mean, median, standard deviation (SD), minimum (min), and maximum (max) will be reported. For change from baseline calculations, baseline is defined as Day 0/Randomization visit. If a baseline value is not available from the randomization visit, for certain parameters the baseline value may be obtained from the enrollment visit.

#### *7.1.2. Visit Windows*

All data will be tabulated per the evaluation visit as recorded on the CRF even if the assessment is outside of the visit window. Visit windows are displayed in Appendix A. In

data listings, the relative day, of all dates will be presented e.g. from date of randomization, or date of last injection.

## 7.2. Interim Analyses

An independent Data Safety and Monitoring Board (DSMB) will meet approximately every six months throughout the study. The DSMB will do the following:

I. Periodically review and evaluate the accumulated study data for participant safety, study conduct and progress and treatment efficacy.
II. Make recommendations to the study investigators and DAIDS concerning the continuation, modification, or termination of the trial.

The DSMB will consider study-specific data as well as relevant background knowledge about the disease, test agents and patient population under study.

Analyses presented to the DSMB will include information on accrual and retention, comparability of the CAB LA and TDF/FTC arms at enrollment, and adherence, adverse events and HIV incidence by arm. The DSMB may also ask for additional analyses they deem relevant.

Below we provide guidelines for monitoring HPTN 084 for:

| | |
|---|---|
| Study progress and validity | Futility monitoring |
| Efficacy monitoring | Safety monitoring |

### *7.2.1. Study progress and validity*

At each meeting the DSMB will review data on enrollment (as necessary), retention of participants, delivery of the intervention and all protocol violations. The DSMB will also compare the (pooled) observed HIV incidence rate to the (pooled) expected HIV incidence rate to determine if the HIV incidence rate among study participants is similar to the incidence rate assumed in the study design. The DSMB will recommend any changes to the study design they believe are needed to ensure study validity.

Expected event rate: 2.07/100 person-years in the TDF/FTC arm and 1.12/100 person-years in the treatment arm; 1.6/100 person-years overall. Note: In general, person-years are calculated as the sum of the total follow-up time for all participants included in the analysis, using the censoring rules as described for each individual analysis. Start and end dates and censoring rules for the primary analysis are defined in Appendix B.

### *7.2.2. Efficacy monitoring*

This analysis determines the Sample Size of the study, therefore kindly refer to section 4.1.1 of the SAP.

### *7.2.3. Futility monitoring*

The DSMB may determine that the trial is operationally futile if enrollment rates are substantially lower than expected (such that accrual cannot be completed in a timely manner) or retention is so poor that results of the trial would lack validity.

However, other aspects of the trial which are typically evaluated for futility (low HIV event rate, lack of difference between the arms) must be evaluated in the context of participant adherence to the study drugs. While high adherence is expected in the CAB LA arm, high rates of adherence in the TDF/FTC arm would likely lead to a lower than expected HIV event rates and little difference in HIV incidence between the arms. Such a result should

not lead to a futility finding. While HPTN 084 is designed as a superiority trial, a contingency plan for a supplementary non-inferiority analysis in the case of high TDF/FTC adherence has been developed. This analysis is described in detail in the **protocol HPTN 084 v2.0, in the section 7.8.4 entitled** "***Considerations for a Supportive Analysis if Adherence to TDF/FTC is Higher than Expected***". To aid in this evaluation, detailed information on adherence to the study drugs, by arm, will be provided to the DSMB.

#### *7.2.4. Safety monitoring*

At each 6 months visit the DSMB will be provided with a list of all adverse events, by grade and broken down by study arm. The relationship of the event to the treatment (definitely related, probably related, possibly related, not related) will also be described. In the closed report at each visit the study team will provide the DSMB with a (nominal) p-value comparing the rate of grade 3 or higher adverse events in the two study arms. However, no formal stopping rule for safety monitoring is proposed so as to give the DSMB maximum flexibility in balancing the risks and benefits of the treatments.

## 7.3. Endpoint Analyses

#### *7.3.1. Primary Efficacy Analysis*

**Objective**: To evaluate the relative efficacy of oral CAB/CAB LA (oral run-in and injections, Steps 1 and 2) vs. daily oral TDF/FTC for HIV prevention
**Population**: mITT population
**Outcome**: Time of HIV-1 Infection (censored at end of step 2)

Time from randomization to HIV-1 infection (see definition in appendix B) will be the primary endpoint for this analysis. HIV-1 status will be assumed to be negative for any missing visits prior to the first positive HIV-1 test (unless defined differently by the endpoints committee prior to analysis). Person-time and HIV events will be included in this analysis based on each individual's scheduled participation in steps 1 and 2, as determined at randomization. Specifically, individuals who refuse/discontinue injections, pills or both, or who receive open-label study product (e.g. due to pregnancy) will be included in this analysis in their original randomization arm for the duration of their originally scheduled participation in Steps 1 and 2. Individuals who drop out of the study and refuse further testing prior to completion of follow-up and individuals who die prior to completion of follow-up will be treated as uninformatively censored as of their last valid HIV test.

**Descriptive analysis:** The number of participants, number of infections and cumulative person-years will be presented by arm and overall. The HIV incidence rate will be calculated as the total number of participants with confirmed incident HIV infection during steps 1 and 2 of study follow-up, divided by the person-years accumulated in each arm. Corresponding 95% CIs will be calculated based on Poisson assumptions. Cumulative incidence over follow-up for each arm will be computed using product limit estimates and plotted with 95% CIs.

**Statistical Analysis**: The primary "intent-to-treat" analysis will be based on a Cox model using time to HIV detection (as defined above) as the outcome. The model will include an indicator for intervention arm (TDF/FTC = 0; CAB LA = 1) and be stratified by site. Consistent with an intent-to-treat analysis, women will be included in the analysis in their original randomization group whenever endpoint information is available within the prespecified timeframe of follow-up. Participants who remain HIV-1 uninfected will be censored at their last negative HIV test. A formal statistical comparison between study arms will be performed using a Wald test of the hypothesis

Ho: HR = 1

Ha: HR < 1

A two-sided test with α= .05 will be used. The estimated hazard ratio (HR), a 95% confidence interval, and a p-value for the hypothesis shown above will be given. If the number of events is small (<40) then the p-value will be confirmed using a permutation test based on 100,000 random permutations of the treatment assignments; if there is a meaningful difference between the permutation and asymptotic procedures, the permutation p-value will be used. Treatment efficacy will be estimated as TE = 1 - HR.

If the trial is stopped early (prior to the final analysis), then the primary results will be reported as a bias-adjusted mean HR and design-adjusted 95% CI (Emerson S and Fleming TR. Symmetric Group Sequential Test Designs. Biometrics 45:904-923, 1989).

#### 7.3.1.1. Sensitivity of the Primary mITT results:

The following sensitivity analyses are proposed to aid in interpretation of the primary ITT results :

- A per-protocol analysis, excluding participants with exclusionary protocol violations, will be conducted if the number of participants affected exceeds 2% of the enrolled population.
  Population: Per Protocol
  This analysis will be identical to the mITT analysis, except that for partial exclusions, the follow-up will be censored on the last non-missing HIV test result date on or prior to the date of the deviation that resulted in exclusion from the per-protocol population.

- A supportive analysis will be presented using the OBSP censoring in the Injection (Step 2) Efficacy population (see OBSP censoring definitions in appendix B), where study follow-up is censored when a participant does not receive blinded injection study product on time.

- In this active control trial, the superiority of CAB LA is predicated in part on incomplete adherence to daily oral TDF/FTC. Specifically, we assume that overall adherence to TDF/FTC will be less than 50%. If adherence to TDF/FTC is high (greater than 50%) then, as described in section 7.8.4 of the protocol, a supportive non-inferiority (NI) analysis of CAB LA versus TDF/FTC may provide valuable information for interpreting the trial results.

  Adherence in the TDF/FTC arm will be measured during the trial in an adherence assessment cohort (see below). If adherence in the TDF/FTC arm is greater than 50% then an NI margin will be computed as described in section 7.8.4.3 of the protocol. The primary analysis described above will then be repeated using the recomputed NI margin instead of 1.0 in the null hypothesis. This supportive NI analysis will not replace the pre-specified primary analysis or change the conclusion of the primary analysis but may provide valuable insight with respect to determining the prevention effectiveness of CAB LA in women.

#### 7.3.1.2. Adherence Assessment Cohort:

A sample of 400 participants in the active TDF/FTC arm will be selected at random during the enrollment period and available plasma samples from selected visits (Step 1: week 4; Step 2: weeks 9, 17, 33, 57, 81, 105, 129, 153, 177) will be assessed for the presence of TDF/FTC and associated metabolites. The TDF/FTC adherence-assessment cohort will be stratified by site or

region and will be selected to ensure uniform representation over the course of the enrollment period. Average, study-wide adherence will be computed as the overall proportion of all tested samples where study drug (TDF/FTC) is detected (i.e. concentrations greater than approximately 0.31 ng/ml).

### *7.3.2. Primary Safety Analysis*

**Objective**: To evaluate the relative safety of oral CAB/CAB LA (oral run-in and injections, Steps 1 and 2) vs. daily oral TDF/FTC for HIV prevention (Steps 1 and 2).
**Population**: Safety population

The primary pre-specified safety comparison between arms will be based on all AEs with maximum grade ≥2. In general, formal statistical comparison of Individual types of safety events across arms is not planned since interpretation of differences must rely heavily upon clinical judgment. Where formal statistical testing is considered necessary to guide judgement of observed differences for any single event or collection of events, differences in events grade 2 and higher will be assessed. The event rate and 95% robust confidence interval for each treatment arm will be calculated using a log-linear model for counts using log(person-time) as an offset, treatment as a covariate, assuming a Poisson distribution and using a robust variance (i.e. generalized estimating equations). Event rates will be compared between treatment arms using this same model. Event rates will be compared between treatment arms using this same model and a type I error rate of $\alpha$=0.05 is prespecified. Very rare events will be compared using an exact Poisson test. Additional supporting descriptive safety analyses will be presented.

For Safety OBSP analysis, adverse event follow-up will be censored after the last injection before a termination or a permanent product discontinuation regardless of any delays in injections. If termination or a permanent product discontinuation occurs prior to their first injection, the participant's follow-up time will be censored at the termination or permanent product discontinuation date +1. If termination or a permanent product discontinuation occurs after the first injection, the participants follow-up time will be censored up through 6 weeks after the Week 5 injection, if that is the last injection, or 10 weeks after the last injection for subsequent injections.

### *7.3.3. Adverse events in Step 1*

Objective: To compare the safety of oral CAB vs. oral TDF/FTC in Step 1
Population: Primary Safety
Censoring: AEs are censored at 120 days after randomization for participants who never received an injection; at 1 day after the date of termination or investigational product discontinuation; at date of first injection, whichever occurs first. Reported AEs will be excluded if they occur after the censoring time.
Descriptive and Statistical Analysis as above

### *7.3.4. Adverse events Step 2 only OBSP*

Objective: To compare the safety of CAB LA vs. oral TDF/FTC proximal to blinded study drug administration
Population: Step 2 safety
Censoring: AEs are censored using ON BLINDED STUDY PRODUCT (OBSP) censoring. Details of the OBSP censoring definitions are given in Appendix B. Reported AEs will be excluded if they occur before the first injection or after the OBSP censoring time.

Descriptive and Statistical Analysis will be performed as above

### *7.3.5. Laboratory evaluations*

Population: Primary Safety

Descriptive: Laboratory findings for CBC, chemistries (urea, creatinine, CPK, glucose, calcium, phosphorous, amylase, lipase), liver function (AST, ALT, total bilirubin, alkaline phosphatase) and fasting lipid profile (total cholesterol, triglycerides, HDL, LDL) will be reported by grade, as defined in the "Division of AIDS (DAIDS) Table for Grading the Severity of Adult and Pediatric Adverse Events". The proportion of laboratory findings qualifying as Grade 2 or above will be presented. Laboratory values will be reported by arm as median, 1st and 3rd quartiles, min and max, and (at follow-up visits) as median, 1st and 3rd quartile change from baseline (see below). Summaries involving values and changes from baseline at scheduled visit time points will consider values from scheduled visits only, and in the case of missing values, results will not be carried forward from interim (unscheduled) visits. For summaries and analyses involving changes in laboratory values over time or maximum change from baseline (e.g. shift tables), values from interim (unscheduled) visits will also be considered.

Formal comparisons of laboratory values will be conducted as follows:

- Absolute values: A mixed-effects model with participant as the random effect and site and arm as fixed effects will be used to assess overall differences in each laboratory outcome by arm. Outcomes with highly skewed distributions will be log-transformed. A continuous time (elapsed study time) term and an interaction of time with study arm will be added to model time trends in laboratory values that may emerge with continuous exposure to study drug. Only post baseline visits will be included.

- Change from baseline. A fixed effect model with site and arm as covariates will be used to assess overall change from baseline for each laboratory outcome by arm. A continuous time (elapsed study time) term and an interaction of time with study arm will be added to model differences in laboratory values that may emerge with continuous exposure to study drug.

Note: Formal comparisons of laboratory values as described above will not be included in the Clinical Study Report.

### *7.3.6. Secondary Analyses*

a. **Objective**: To compare HIV incidence among participants receiving oral CAB/CAB LA vs. daily oral TDF/FTC (Steps 1, 2 and 3).
**Population**: mITT population
**Outcome**: Time of HIV-1 Infection

This analysis will be similar to the primary analysis of HIV incidence but will include the entire follow-up period (steps 1, 2 and 3) for each participant. The analysis will be based on a Cox model using time to HIV detection (as defined in the primary analysis) as the outcome. The model will include an indicator for intervention arm (TDF/FTC = 0; CAB LA = 1) and be stratified by site. Participants who remain HIV-1 uninfected will be censored at their last negative HIV test. A formal statistical comparison between study arms will be performed using a Wald test of the hypothesis

Ho: HR = 1

Ha: HR < 1

A one-sided test with α= .025 will be used. The estimated hazard ratio (HR), a 95% confidence interval, and a p-value for the hypothesis shown above will be given.

b. **Objective**: To evaluate relative efficacy of oral CAB/CAB LA vs. oral TDF/FTC in subgroups defined by the baseline factors of age, herpes simplex virus-2 (HSV-2) serostatus, and body mass index (BMI).
**Population**: mITT population
**Outcome**: Time of HIV-1 Infection

These analyses will be similar to the primary analysis of HIV incidence and will include data from follow-up steps 1 and 2 for each participant. The number of events, person-years and incidence will be calculated for each arm within each subgroup.

Subgroups will be defined as follows:

Age (<25 vs ≥25)
HSV-2(positive or negative)
BMI (<30.0 vs ≥30.0 )
Contraceptive method during treatment (DMPA, Net_EN, Implants, Other)

Age, HSV-2 and BMI will be based on baseline status while contraception will be treated as a time-varying covariate.

The analyses of efficacy will be based on a Cox model using time to HIV detection (as defined in the primary analysis) as the outcome. Separate models will be fit for each of the three baseline covariates of interest. Each model will be stratified by site and will include an indicator for intervention arm (TDF/FTC = 0; CAB LA = 1), the covariate of interest and their interaction.

A formal statistical comparison of efficacy between the subgroups will be performed using a Wald test of the hypothesis

Ho: interaction term = 0

Ha: interaction term ≠ 0

A two-sided test with α= .05 will be used.

The efficacy (relative hazard) of CAB LA versus TDF/FTC and
95% CI will be calculated for each subgroup using standard methods for linear combinations of the Cox model coefficients.

c. **Objective**: To describe and model the relationship between HIV incidence and drug concentration, within each arm.

**Population**: PK analysis population
**Outcome**: Time of HIV-1 Infection

These analyses will include data from follow-up steps 1 and 2 for each participant in the PK analysis population. Separate analyses will be conducted for each arm. The analyses will be based on a logistic regression of all available intervals with drug concentration/PK parameter data. The outcome will be HIV infection (yes/no) as measured at the end of the interval. For each arm, the drug concentration/ PK parameter of interest in each interval will be determined in conjunction with colleagues from the central lab and ViiV (see separate document with more details on the PK study design). A plot of the model predicted relative hazard of HIV infection (y-axis) versus drug concentration (x-axis) with a 95% confidence interval will be generated from the final model.

d. **Objective**: To describe the distribution and correlates of drug concentration, within each arm.
**Population**: PK analysis population
**Endpoint**: Drug concentration

These analyses will include data from follow-up steps 1 and 2 for each participant. Separate analyses will be conducted for each arm.

**Descriptive analyses**: A histogram of all measured drug concentrations/PK parameter estimates will be generated. Boxplots of these outcomes will be generated both overall, over time and for key subgroups (age, HSV-2 serostatus, BMI, reported/documented adherence).

**Statistical Analyses**: Multiple linear regression analyses with correction for correlated data and robust variances (i.e. generalized estimating equations) will be used to relate log of the drug concentration to age, HSV-2 serostatus, BMI and any other covariates of interest. Reported (oral pills) or documented (injection) level of adherence will be included in the models. The coefficient of each covariate and a 95% confidence interval will be provided.

e. **Objective**: To compare the acceptability of and preferences for CAB LA vs. oral TDF/FTC.
**Population**: mITT population
**Outcomes**: Two primary outcome variables will be used:

- Response to CASI question (step 3, day 0, visit 33.0) “If you wanted to protect yourself from getting HIV, which of the following product(s) would you prefer to use?”
- Response to (Likert-scale) CASI questions (step 3, day 0, visit 33.0) i) “How often do you find it inconvenient or difficult to take your oral study medication (i.e. the tablets) as recommended?” ii) “How often do you find it inconvenient or difficult to receive your injection as recommended?”

**Descriptive analysis**: Responses to these questions will be summarized by arm for the CSR.

**Statistical Analysis**: The CSR will only display descriptive summaries as described above. Subsequent analyses will be conducted on data collected at the end of step 2 (visit 33.0). Chi-square tests and Fisher-exact tests will be used as appropriate, with Likert scales converted to Binary by distributions within the response levels (e.g. at the median response). Inference for differences by arm will be analyzed using logistic regression models. Each model will contain two terms:

- Country
- Randomized study arm.

### *7.3.7. Tertiary Analyses*

a. **Objective**: To estimate sexual risk behaviors, as measured by self-report and rates of incident sexually transmitted infections (STIs).
**Population**: mITT population
**Outcomes**:

i. Sexual risk
- Any condomless sex with an HIV-infected or HIV-unknown status partner
- >1 sexual partners in past 1 months

ii. Incident STIs (measured at weeks 33, 57, 81, 105, 129, 153 and 177 during Step 2, and weeks 24 and 48 during Step 3)
- Time to incident STI (any of Gonorrhea, Chlamydia, Syphilis)

**Analysis**: Data from steps 1, 2 and 3 will be used unless indicated otherwise.

The proportion of participants reporting any high-risk behavior will be assessed at each visit. Mixed effects logistic regression will be used to estimate prevalence and 95% confidence intervals for each behavior. Time trends during follow-up will be estimated using mixed effects logistic regression. Linear and non-linear models (with respect to time) will be explored.

Rates of incident STI's will be computed as number of new STI's divided by total person-years. Poisson regression with a robust variance will be used to model the number of incidents STI for each woman. Person-time will be used as an offset. Incidence and a 95% CI will be reported overall and by arm.

b. **Objective**: To compare Grade >2 adverse event (AE) rates in women with baseline BMI </≥ 25 kg/m2, within each study arm.
**Population**: Primary Safety Population
**Outcome**: Counts of grade 2 or higher AE

For each arm, tables will summarize the number of grade 2 or higher AEs by MedDRA System Organ Class and BMI. Participant with multiple AEs within a category will be counted once under the maximum severity. The overall grade 2 or higher event rate and a 95% confidence interval will be calculated for those with BMI < and > 30 kg/m2 at baseline based on a log-linear model for counts using log(person-time) as an offset, assuming a Poisson distribution, and using a robust variance (i.e. generalized estimating equations). Event rates will be compared between those with BMI < and ≥30 kg/m2 at baseline using a similar model.

c. **Objective**: To compare differences in weight gain, by arm.
**Population**: Primary Safety Population
**Outcome**: Weight (kg)

Weight gain will be computed as change from baseline (enrollment) at each follow-up visit. We will plot mean weight gain over follow-up by treatment arm. A linear mixed model with random person and time effects will be fit with (i) continuous time and (ii) categorical intervals for time in study, treatment and time by treatment interaction to evaluate the effect of CAB LA on weight gain. The interaction between time and treatment will quantify the difference in weight gain by arm. A second analysis that removes women when they become pregnant will be conducted.

d. **Objective**: To compare pregnancy incidence and outcomes between arms.
**Population**: mITT Population and PREGNANCY Subgroup Population
**Outcome**: New pregnancies and pregnancy outcomes

Data from steps 1 and 2 (PRIMARY mITT dataset) will be used. Tables will summarize the number of pregnancies and pregnancy rate by arm. The pregnancy rate and 95% robust confidence interval for each treatment arm will be calculated using a log-linear model for counts using log(person-time) (excluding time spent pregnant) as an offset, assuming a Poisson distribution, and using a robust variance (i.e. generalized estimating equations).

Outcomes of all detected pregnancies (PREGNANCY dataset) and all confirmed pregnancies (CONFIRMED PREGNANCY dataset), including information of drug exposure during the conception period and pregnancy period, will be tabulated by arm.

e. **Objective**: To evaluate rates of HIV drug resistance among participants who acquire HIV infection during the study among participants receiving oral CAB/CAB LA vs. oral TDF/FTC.
**Population**: Primary SEROCONVERTER Population

Data from steps 1, 2 and 3 will be included. The number of cases of drug resistance will be summarized by arm and step. All cases of drug resistance among incident HIV infections during the study will be described.

f. **Objective**: To determine plasma concentrations of medroxyprogesterone (DMPA) or norethisterone (NET-EN) or etonorgestrel (from implants) when co-administered with CAB LA.
**Population**: CONTRACEPTION Subgroup Population
**Outcome**: Plasma concentration of medroxyprogesterone or norethisterone.

Boxplots of plasma concentrations of DMPA/NET_EN/etonorgestrel will be generated by arm. For women in the CAB-LA arm, a plot of plasma concentrations versus time since last injection will be plotted and a smooth line will be fit through the data. Proportion of women with plasma concentrations below 0.1 ng/mL (DMPA) or TBD (NET_EN) or 90pg/mL (etonorgestrel) will be reported and compared (separately, for women using each drug) between arms using a Fisher's exact test or a permutation test if multiple observations are available on each woman.

In addition, we will compare mean contraceptive drug levels (and/or other PK parameters) between the CAB LA and TDF/FTC arms for each contraceptive subgroup using a t-test (or a t-test with robust variance if multiple observations on each woman are available).

# 8. MISSING DATA AND IMPUTATIONS

Data may be missing due to participant dropout, participant nonresponse, or due to failures in data collection. In general, the last category (failures in data collection) is quite rare in HPTN trials. Further, it is common to assume that such data are missing completely at random (MCAR) (Rubin DB. Biometrika 1976; 63:581–592) and so will not bias results. However, participant dropout and/or nonresponse are unlikely to be MCAR and so attention must be paid to the potential for bias if there are high levels of missing data for these reasons. Here we discuss the approaches we will take for analyses in the presence of missing data.

For the primary endpoints, HIV infections and safety events, and other biological endpoints the primary cause of missing data is participant dropout. Historically, HPTN trials have had good retention of participants and we expect that to be the case for this trial. Therefore, analyses will be conducted assuming uninformative censoring. If loss-to-follow-up is low and similar between the arms we will not conduct any additional sensitivity analyses. However, if loss-to-follow-up is greater than 20% or meaningfully different between arms (>5%-points), then we will investigate the sensitivity of the results to assumptions about the missing data. Specifically, we will use inverse probability-of-censoring weights to adjust for loss-to-follow-up (Cain LE. Stat Med 2009; 28:1725-1738) and compare the adjusted treatment effect to the unadjusted treatment effect.

Behavioral and self-reported endpoints (e.g. acceptability) may be subject to participant nonresponse. The analyses described below are based on a complete-case approach. However, if non-response is high (>15%) or differential between arms (> 5%-points) then we will perform sensitivity analyses using multiple imputation. Baseline data will be used to develop the imputation model and standard errors will be adjusted using Rubin's method (Rubin DB. Multiple Imputation for Nonresponse in Surveys, Wiley, New York, 1987). Both complete case and multiple imputation results will be reported.

## 8.1. Missing Start and Stop Dates for Prior and Concomitant Medication, and Medical History

The Assumption is to consider the most conservative judgment when imputing.

Start date:
When imputing a start date ensure that the new imputed date is sensible i.e. is prior to the end date and the general rules are:

i. If start date is completely missing, start date will not be imputed
ii. If year and month are present and day is missing, set day to the 1st day of month.
iii. If year and day are present and month is missing, then set month to January.
iv. If year is present and month and day are missing, set month and day to January 1st.

Stop date:

i. If end date is completely missing, end date will not be imputed
ii. If year and month are present and day is missing, set day to the last day of month.
iii. If year and day are present and month is missing, set month to December

iv. If year is present and month and day are missing, set month and day to December 31st.

### 8.2. Missing Start and Stop Dates for Adverse Events

The Assumption is to consider the most conservative judgment when imputing.

Start date:

1. If start date is completely missing, start date is set to date of first dose.
2. If (year is present, and month and day are missing) or (year and day are present, and month is missing):
    a. If year = year of first dose, then set month and day to month and day of first dose.
    b. If year < year of first dose, then set month and day to December 31st.
    c. If year > year of first dose, then set month and day to January 1st.
3. If month and year are present and day is missing:
    a. If year = year of first dose and
        1. If month = month of first dose, then set day to day of first dose date.
        2. If month < month of first dose, then set day to last day of month.
        3. If month > month of first dose, then set day to 1st day of month.
    b. If year < year of first dose, then set day to last day of month.
    c. If year > year of first dose, then set day to 1st day of month.

Stop date:
If the outcome of the AE was ongoing or unknown, then the rules outlined below will not be applied.

1. If stop date is completely missing, stop date is set to date of study discontinuation.
2. If (year is present, and month and day are missing) or (year and day are present, and month is missing):
    a. If year = year of study discontinuation, then set month and day to month and day of study discontinuation.
    b. If year < year of study discontinuation, then set month and day to December 31st.
    c. If year > year of study discontinuation, then set month and day to December 31st.
3. If month and year are present and day is missing:
    a. If year = year of study discontinuation and
        i. If month = month of study discontinuation, then set day to day of study discontinuation date
        ii. If month < month of study discontinuation, then set day to last day of month.
        iii. If month > month of study discontinuation, then set day to last day of month.
    b. If year < year of study discontinuation, then set day to last day of month.
    c. If year > year of study discontinuation, then set day to last day of month.

## 9. MONITORING REPORTS

### 9.1. Performance Metric, SMC & DSMB Reports

This section describes the main tables and reports. A subset of these will be presented to the DSMB at each meeting. When results are presented by study arm, the arms will be labeled Arm A and Arm B. A separate document attached to the DSMB report will unblind the arms (i.e., TDF/FTC or CAB). The study accrual table will report on all enrolled women; subsequent tables will report on women who are HIV-uninfected at enrollment only.

Real-time reports will be available to the protocol team. The content of these reports will be developed by the protocol team and will generally include the following information:

- **Study Accrual**
  The number of individuals enrolled and randomized per study month will be presented in a table overall and (1) by site and (2) by study arm. No formal statistical testing will be performed.

- **Baseline Demographic and Clinical Characteristics of Young women**
  A table that includes baseline demographic and clinical characteristics (e.g. age, employment, marital status, education, race, BMI, HSV-2 status, etc.) will be presented. Summary statistics appropriate for the measurement scale will be used to describe the distribution of these variables. These summary statistics will be presented in tables overall, by site and by study arm. No formal statistical testing will be performed.

- **Baseline Behavioral Characteristics**
  A set of tables will describe baseline behavioral characteristics for participants. Measures included in these tables will include age of sexual debut, and the number of partners in lifetime and the last 3 months, contraceptive method, and STI. Summary statistics appropriate for the measurement scale will be used to describe the distribution of these variables. These summary statistics will be presented in tables overall, by site and by study arm. No formal statistical testing will be performed.

- **Retention**
  A set of tables will describe retention in follow-up for participants at each scheduled study visit. Number of women enrolled, number of women expected at each visit, number of women attending the visit early, late and on time, and percent retained will be presented. A separate retention report will be generated for women who have moved to alternative visit schedules (e.g. pregnancy, open-label TDF/FTC, annual testing); these women's visits will not be included in the standard retention table after they move to an alternative visit schedule. Retention will be presented overall and by site in the open report and by study arm in the closed report. No formal statistical testing will be performed.

- **Fidelity of Intervention**
  A set of tables will describe the proportion of injections provided and the proportion of pill bottles distributed at each visit, among those retained at the visit. These tables will be presented overall and by site in the open report and by study arm in the closed report. No formal statistical testing will be performed.

- **Safety Reports (Closed Reports)**
  The number and percentage of participants experiencing local reactions to the injections will be tabulated by severity and treatment arm. For a given local reaction type, each participant's

reaction will be counted once under the maximum severity for all injection visits. In addition to the individual reaction types, the maximum severity of local pain or tenderness, induration or erythema, and of systemic symptoms will be calculated. AEs will be summarized using MedDRA System Organ Class and preferred terms. Tables will show by treatment arm the number and percentage of participants experiencing an AE within a System Organ Class or within preferred term category by severity. For the calculations in these tables, a participant with multiple AEs within a category will be counted once under the maximum severity.

A listing of SAEs reported to the DAIDS Regulatory Support Center (RSC) Safety Office will provide details of the events including severity, time between onset and last dosing, and cumulative number of doses received.

Box plots of local laboratory values will be generated for baseline values and for values measured during the study by treatment arm and visit. Each box plot will show the first quartile, the median, and the third quartile. Outliers will also be plotted. If appropriate, horizontal lines representing boundaries for abnormal values will be plotted. The number (percentage) of participants with local laboratory values recorded as meeting Grade 3 AE criteria or above as specified in the DAIDS AE Grading Table will be tabulated by treatment arm. Reportable clinical laboratory abnormalities without an associated clinical diagnosis will also be included in the tabulation of AEs described above.

- **Efficacy Reports**
  The efficacy reports will be shared with the DSMB committee when required as per the analysis methodology mentioned in section 7.2.2 and 7.3.1 of the SAP ()above.

## 9.2. Clinical Study Report

The tables described below will be included in the CSR. Additional tables and analyses may be included, at the discretion of the protocol team or sponsor, e.g., depending on the availability of additional laboratory evaluations. All reports and analyses will be presented by study arm.

Subjects will be pooled across all sites. Data will be presented by treatment group and overall. Categorical variables will be summarized by frequency distributions (number and percentages of subjects) and continuous variables will be summarized by descriptive statistics (mean, standard deviation, etc.).

Adverse events will be summarized by treatment group using the Medical Dictionary for Regulatory Activities (MedDRA) system organ class and preferred term. Tabulations will be produced for all treatment-emergent AEs (TEAEs) defined as AEs with an onset date on or after the start of treatment, treatment-related AEs (those considered by the Investigator as at least possibly drug related), SAEs, discontinuations due to AEs, and AEs by severity grade. By-subject listings will be provided for any deaths, SAEs, and AEs leading to discontinuation.

Descriptive statistics for each treatment group will be provided for clinical laboratory values (e.g., hematology, serum chemistry, and urinalysis) and vital signs data, presented as both actual values and changes from baseline relative to each on-study evaluation. Abnormal clinical laboratory values will be listed. All data will be provided in by-subject listings.

Displays of the cumulative incidence of events such as HIV infection, or treatment discontinuation, will include at-risk tables as follows: Numbers of subjects having had the event of interest, and at risk to have had the event will be shown at selected weekly timepoints under the horizontal axis. The number at risk will be computed as the number of subjects with event times greater than or equal to the given timepoint

- **Subjects Disposition**
  The subject disposition summary will include the number screened, the number of screen failures, the number enrolled, the number in each patient population for analysis, the number who completed the study, the number who discontinued the study and reason for discontinuation from the study.

  Disposition data will be summarized by treatment and overall. A by-subject data listing of study completion information including the reason for study discontinuation will be presented. A by-subject listing of inclusion/exclusion criteria not met will also be presented.

- **Protocol Deviations**
  A summary of all protocol deviations on ITT population by type will be generated. Protocol deviation data will be summarized by treatment and overall. A by-subject data listing of protocol deviations will also be presented. All protocol deviations will be presented in a data listing.

- **Demographic and Baseline Characteristics**
  Demographic and baseline characteristic data summarization will be performed to descriptively assess the comparability of treatment groups. Data to be tabulated will include age, race, ethnicity, height, weight, and BMI, as well as other baseline characteristics.

- **Exposure and Adherence**
  Drug Exposure and adherence will be calculated and will be presented in a tabulation form and by listing.

- **Medical History**
  A by subject listing of verbatim medical history will be presented.

- **Concomitant Medication**
  Concomitant medications will be coded using the World Health Organization (WHO) dictionary. Results will be tabulated by anatomic therapeutic class (ATC) and preferred term. This data will be summarized by treatment group. Previous and concomitant medications will be presented in a data listing.

- **Vital Signs and Physical Examination**
  Vital sign measurements will be presented for each subject in a data listing. Systolic blood pressure, diastolic blood pressure, heart rate, and weight will be summarized as actual value and change from baseline by visit. All physical examination findings will be presented in a data listing.

- **Laboratory Data**
  Clinical laboratory values will generally be expressed in SI units .

The actual value and change from screening will be summarized for each clinical chemistry, hematology, lipid panel, HbA1C and urinalysis parameters and by each visit. In the event of repeat values, the last non-missing value per visit will be used.

All laboratory data will be also provided in data listings. Values outside of the lab parameter's normal range will be flagged as high, low, or abnormal based on the range of the test. Laboratory results will be summarized by scheduled study visit. Summary calculations such as maximum post-baseline level will include data from interim (unscheduled visits). Formal comparisons of laboratory findings between arms will not be included in the CSR.

- **Adverse Events**
  The reporting of safety data is descriptive and will include all subjects who receive at least one dose of investigational product. AEs will be summarized based on the frequency of AEs and their severity for all treated subjects. All AEs will be coded using Medical Dictionary for Regulatory Activities (MedDRA) and summarized by treatment group. Data will be summarized using preferred term and primary system organ class.

  If a subject experiences multiple events that map to a single preferred term, the greatest severity will be assigned to the preferred term for the appropriate summaries.

  Summaries of AEs will include any AEs reported beginning with the first dose of investigational product on Day 1. The occurrence of adverse events will be summarized by treatment group using preferred terms, system organ classifications, and severity. Separate summaries of serious adverse events, adverse events related to investigational product, and events leading to the discontinuation of investigational product will be generated. All adverse events reported will be listed for individual subjects showing both verbatim and preferred terms.

- **Efficacy and Efficacy Subgroups**
  In the Clinical Study Report, primary efficacy analysis will be presented as described in Section 7.3.1. For subgroup analyses, the age and BMI subgroup analyses will be presented in the Clinical Study Report, but analyses considering contraceptive use and HSV-2 status at baseline will not be presented in the Clinical Study Report.

## 10. Summary of changes

**10.1 Version 3.0** was prepared during the planning process for the Clinical Study Report. The blinded statistician continued to not have access to individual level data.

***10.1.1. Analysis Populations***

- Populations were adjusted, renamed, or clarified: mITT; Per Protocol; Seroconverter; Contraceptive Substudy; Pregnancy.
- Populations were added: Randomized; ITT; Primary Safety; Step 2 Safety; Step 2 Efficacy; Longitudinal Pharmacokinetic Cabotegravir; TDF/FTC Adherence Population; Confirmed Pregnancy; Seroconverter Population; Primary Seroconverters; Declined Contraception; Infected at Enrollment
- The Version 2.0 "Per-Protocol" analysis dataset was redefined and renamed as On Blinded Study Product (OBSP) censoring. The new "Per-Protocol" population was

defined as being based upon deviation adjudication. The adjudication process was described.

- The age and BMI subgroups were modified with adjusted cut-points.

#### *10.1.2. Analysis Details and Clarifications*

- Clarifications and additional details were added throughout the Statistical Analysis section.
- A section was added to describe missing data handling and imputations.
- Appendices were added to provide detail for visit windowing, efficacy and safety analysis censoring details and OBSP specifications, a listing of study sites, a listing of adverse events of special interest (AESI). Key variable definitions, which were based on data fields found in the CRF data, were removed.

#### *10.1.3. Reports*

- A new section was added to describe the contents of the following reports: Performance metrics, SMC, DSMB, and CSR.

**10.2 Version 4.0 (current version)** contains corrections and additional details requested for Clinical Study Report programming. The blinded statistician continued to not have access to individual level data during these revisions.

#### *10.2.1. Adverse Events of Special Interest*

- The appendix describing AESI was inadvertently truncated in Version 3.0. This has been corrected.

#### *10.2.2. Censoring details for Time to Treatment Discontinuation due to Safety*

- Definitions for events, competing events, and censored observations were added as Appendix

#### *10.2.3. Description of the per-protocol efficacy analysis*

- Censoring definition for per-protocol partial exclusions was added to Section 7.3.1

#### *10.2.4. Revision to the date imputation algorithm for Concomitant and Prior Medications*

- A modification was made to section 8.1 to account for the fact that prior medications would have a start date prior to the randomization date.

#### *10.2.5. Description of the per-protocol efficacy analysis*

- Censoring definition for per-protocol partial exclusions was added to Section 7.3.1

#### *10.2.6. Clarification of the Injection (Step 2) Efficacy Population*

- A modification was made to section 6.5 to state that a participant had to have at least one follow-up visit with HIV status evaluated to be included in this population.

#### *10.2.7. Clarification of Confirmed Pregnancy Population*

- Clarification added to Section 6.12 to define additional ways that a pregnancy can be confirmed.

#### *10.2.8. Subgroup definitions*

- Section 6.17 was revised. Formerly, the age subgroups were defined as:

  "Age: <= 24 vs > 24 years old." This was rewritten as:

"Age:<25 vs > =25years old." )This would not affect the classification of subjects into age categories.)

- The contraception subgroups were clarified to indicate reference to method during follow-up. Details of efficacy analyses involving this time-dependent covariate were added to Section 7. 3.6.
- A note was added to indicate that HSV-2 status at baseline will not be available for the Clinical Study Report. This note is repeated in Section 9.2.

## APPENDIX A - Study Visit Windows

HPTN 084 Visit Codes, Target Days, and Visit Windows

### HPTN 084 Visit Codes, Target Days, and Visit Windows

| Week | Visit Code | Day allowable window opens | Day target window opens | Target Day | Day target window closes | Day allowable window closes |
|---|---|---|---|---|---|---|
| Screening | 1.0 | -- | -- | -- | -- | -- |
| **Step 1** | | | | | | |
| Day 0/Enrollment | 2.0 | 0 | 0 | **0** | 3 | 6 |
| Week 2 | 3.0 | 7 | 11 | **14** | 17 | 20 |
| Week 4* | 4.0 | 21 | 25 | **28** | 31 | 31 |
| **Step 2*** | | | | | | |
| Day 0/Week 5* | 5.0 | 0 | 0 | **0** | 3 | 3 |
| Week 6 | 6.0 | 4 | 4 | **7** | 10 | 17 |
| Week 9 | 7.0 | 18 | 25 | **28** | 31 | 41 |
| Week 13 | 8.0 | 42 | 53 | **56** | 59 | 69 |
| Week 17 | 9.0 | 70 | 81 | **84** | 87 | 97 |
| Week 21 | 10.0 | 98 | 109 | **112** | 115 | 125 |
| Week 25 | 11.0 | 126 | 137 | **140** | 143 | 168 |
| Week 33 | 12.0 | 169 | 189 | **196** | 203 | 224 |
| Week 41 | 13.0 | 225 | 245 | **252** | 255 | 255 |
| Week 42 | 14.0 | 256 | 256 | **259** | 266 | 283 |
| Week 49 | 15.0 | 284 | 301 | **308** | 315 | 336 |
| Week 57 | 16.0 | 337 | 357 | **364** | 371 | 392 |
| Week 65 | 17.0 | 393 | 413 | **420** | 427 | 448 |
| Week 73 | 18.0 | 449 | 469 | **476** | 483 | 504 |
| Week 81 | 19.0 | 505 | 525 | **532** | 539 | 560 |
| Week 89 | 20.0 | 561 | 581 | **588** | 595 | 616 |
| Week 97 | 21.0 | 617 | 637 | **644** | 651 | 672 |
| Week 105 | 22.0 | 673 | 693 | **700** | 707 | 728 |
| Week 113 | 23.0 | 729 | 749 | **756** | 763 | 784 |
| Week 121 | 24.0 | 785 | 805 | **812** | 819 | 840 |
| Week 129 | 25.0 | 841 | 861 | **868** | 875 | 896 |
| Week 137 | 26.0 | 897 | 917 | **924** | 931 | 952 |
| Week 145 | 27.0 | 953 | 973 | **980** | 987 | 1008 |
| Week 153 | 28.0 | 1009 | 1029 | **1036** | 1043 | 1064 |
| Week 161 | 29.0 | 1065 | 1085 | **1092** | 1099 | 1120 |
| Week 169 | 30.0 | 1121 | 1141 | **1148** | 1155 | 1176 |
| Week 177 | 31.0 | 1177 | 1197 | **1204** | 1211 | 1232 |
| Week 185 | 32.0 | 1233 | 1253 | **1260** | 1267 | 1288 |

| Week | Visit Code | Day allowable window opens | Day target window opens | Target Day | Day target window closes | Day allowable window closes |
|---|---|---|---|---|---|---|
| **Step 3**** | | | | | | |
| Day 0 (Step 3 only) | 33.0 | 0 | 0 | **<8 weeks from last injection** | 14 | 42 |
| Week 12 | 34.0 | 43 | 70 | **84** | 98 | 126 |
| Week 24 | 35.0 | 127 | 154 | **168** | 182 | 210 |
| Week 36 | 36.0 | 211 | 238 | **252** | 266 | 294 |
| Week 48 | 37.0 | 295 | 322 | **336** | 350 | 378 |

*Please note that the Week 4 and Week 5 Visits must be completed in order for a participant to move to Step 2. If a Week 4 or Week 5 Visit is delayed or missed, contact the CMC for further guidance.

**The target dates for all Step 2 visits are based off of the actual date of the Week 5 Visit. The target dates for all Step 3 visits are based off of the first Step 3 Visit, called "Step 3/Day 0".

| Open Label Truvada Schedule | | | | | | |
|---|---|---|---|---|---|---|
| **Week** | **Visit Code** | **Day allowable window opens** | **Day target window opens** | **Target Day** | **Day target window closes** | **Day allowable window closes** |
| Day 0 (date injections permanently discontinue) | V201/or other* | 0 | 0 | **0** | 14 | 42 |
| Week 12 | 202.0 | 43 | 70 | **84** | 98 | 126 |
| Week 24 | 203.0 | 127 | 154 | **168** | 182 | 210 |
| Week 36 | 204.0 | 211 | 238 | **252** | 266 | 294 |
| Week 48 | 205.0 | 295 | 322 | **336** | 350 | 378 |

- Day 0 for Open Label Truvada Schedule may be a Step 2 visit code or 201. See Section 13.5 Alternate Visits.

| Pregnancy Schedule* | | | | | | |
|---|---|---|---|---|---|---|
| | | | | | | |
| **Week** | **Visit Code** | **Day allowable window opens** | **Day target window opens** | **Target Day** | **Day target window closes** | **Day allowable window closes** |
| Day 0 (First positive Pregnancy Test) | XX.X | 0 | 0 | **0** | 0 | 0 |
| 4 weeks after first positive pregnancy test | Interim visit XX.X | 21 | -- | **28** | -- | 35 |

| | | | | | | |
|---|---|---|---|---|---|---|
| Quarterly Visit 1 (12 weeks since first positive pregnancy test) | 101 | 43 | 70 | **84** | 98 | 126 |
| Quarterly Visit 2 (24 weeks since first positive pregnancy test) | 102 | 127 | 154 | **168** | 182 | 210 |
| Quarterly Visit 3 (36 weeks since first positive pregnancy test) | 103 | 211 | 238 | **252** | 266 | 294 |

*Pregnancy schedule is to be followed throughout pregnancy and while participant is breastfeeding.

| **Yearly/Annual Visits** | | | | | | |
|---|---|---|---|---|---|---|
| **Week** | **Visit Code** | **Day allowable window opens** | **Day target window opens** | **Target Day** | **Day target window closes** | **Day allowable window closes** |
| Day 0 (Last visit participant at clinic HIV Test conducted) | XX.X | 0 | 0 | **0** | 0 | 0 |
| Yearly Visit 1 | 50.0 | 182 | 358 | 365 | 372 | 548 |
| Yearly Visit 2 | 51.0 | 547 | 723 | 730 | 737 | 913 |
| Yearly Visit 3 | 52.0 | 912 | 1088 | 1095 | 1102 | 1278 |
| Yearly Visit 4 | 53.0 | 1277 | 1453 | 1460 | 1467 | 1643 |
| Yearly Visit 5 | 54.0 | 1642 | 1818 | 1825 | 1832 | 2008 |

| **Seroconverter Schedule** | | | | | | |
|---|---|---|---|---|---|---|
| **Week** | **Visit Code*** | **Day allowable window opens** | **Day target window opens** | **Target Day** | **Day target window closes** | **Day allowable window closes** |
| HIV Confirmatory Visit | XX.X | 0 | 0 | **0** | 14 | 42 |
| Week 12 | XX.X | 43 | 70 | **84** | 98 | 126 |
| Week 24 | XX.X | 127 | 154 | **168** | 182 | 210 |
| Week 36 | XX.X | 211 | 238 | **252** | 266 | 294 |
| Week 48 | XX.X | 295 | 322 | **336** | 350 | 378 |

*Due to unblinding considerations, there are no unique visit codes for seroconverters. The visit codes should reflect the next study visits for the participants.

## APPENDIX B - Details of Efficacy Analysis Definitions

**Population Definition:**

**Modified ITT**

- Participant is randomized
- Participant is HIV uninfected at randomization (determined by EAC)
- Participant does not have a major enrollment violation – determined by independent adjudication

Note: Only participants with at least one follow-up visit (of any type, including safety and interim visits) with HIV status determined after enrollment will contribute study time to the efficacy analysis.

**Censoring for primary efficacy analysis:**

- If a study-wide transition to Step 3 occurred, all data from the enrollment visit through the date of transition (plus one month?) will be included
- If no study-wide transition to Step 3 occurred or if the study is stopped early, all ongoing follow-up at the time of decision to stop the blinded portion of the study will be censored on the date of study closure.

**Censoring for on blinded study product (OBSP) analysis**

Participants will be censored when an injection is delayed, defined as follows:

- **Last non-delayed injection:** The earliest of an injection whose subsequent injection is delayed for the first time (i.e. given >6 weeks after the Week 5 injection or >10 weeks after any other injection) or the last injection before a termination or a permanent product discontinuation
- Follow-up time will be censored at the last visit with HIV status determined up through 6 weeks after the Week 5 injection, if that is the last non-delayed injection, or 10 weeks after the last non-delayed injection for subsequent injections.

**Calculation of study time for primary efficacy analysis:**

- If HIV infected, study time will be calculated as the number of days between enrollment and the mid-point between first visit where HIV infection was detected and the most recent prior visit where HIV infection was not detectable, as determined by the EAC.
- If HIV uninfected, study time will be calculated as the number of days between enrollment and the last visit with HIV status at or before the censoring time.

**Calculation of study time for OBSP analysis:**

- If HIV infected prior to OBSP censoring, study time will be calculated as the number of days between enrollment and the mid-point between first visit where HIV infection was detected and the most recent prior visit where HIV infection was not detectable, as determined by the EAC.
- If HIV uninfected At OBSP censoring time, study time will be calculated as the number of days between enrollment and the last visit with HIV status at or before the OBSP censoring time.

**Primary endpoint:**

- Only infections that are confirmed by the EAC and detected within the analysis timeframe at the time of the final primary analysis adjudication (date of first positive visit as determined by the EAC within the analysis timeframe) will be considered. Infections that are not confirmed by the EAC or that occur out of the analysis timeframe will not be included as primary endpoints.

**Interim Analysis (mITT and OBSP) specification**

Interim analysis procedures will follow the primary analysis definitions above with the exception that the analysis timeframe will be truncated at the interim-analysis data cut date, as follows.

**mITT analysis**

- All data from enrollment through the interim analysis cut date will be considered

**OBSP analysis**

- If there is an injection delay prior to the data cut, all data up to the last visit with HIV status determined that occurred prior to the data cut date and within 6/10 weeks for the first/subsequent injection of the last non-delayed injection will be considered.
- If there is no injection delay prior to the data cut point, data included as for the ITT analysis

## APPENDIX C - Definition of Censoring used in analysis of discontinuations due to safety

- Discontinuations due to death, investigator decision and HIV−infection are censored on the discontinuation date
- Participants who exit the study at a scheduled exit visit or at the end of the study are also censored, on the termination date.
- Participants who do not reach the scheduled exit visit and do not discontinue study medications are censored at their last attended visit.
- Permanent discontinuation and/or termination due to participant refusal are treated as competing events, on the discontinuation or termination date, and include: participant unwilling or unable to comply study procedures, injection intolerance, other participant request, or refuse further participation.

The Safety events of interest are:

- Permanent discontinuation due to safety concerns including: clinical/laboratory AE, ISR, CMC recommendation and other clinical reason.

The earliest occurrence of any of the above is selected to determine events versus censored observations versus competing events.

**Detailed event/censoring/competing event classifications for reasons for treatment discontinuation or termination:**

Events of interest, based on reason for treatment discontinuation:
- CLINICAL AE (PROTOCOL MANDATED)
- LABORATORY AE (PROTOCOL MANDATED)
- CMC RECOMMENDATION BASED ON A CLINICAL EVENT
- CMC RECOMMENDATION BASED ON A LABORATORY VALUE
- CMC RECOMMENDATION FOLLOWING DRUG DISPENSING ERROR
- RASH WHICH THE PARTICIPANT STARTED AFTER THE INITIATION OF INJECTION
- OTHER CLINICAL REASON

Competing events, based on reason for termination:
- PARTICIPANT REFUSED FURTHER PARTICIPATION
- PARTICIPANT RELOCATED, NO FOLLOW-UP PLANNED
- OTHER

Competing events, based on reason for treatment discontinuation:
- PARTICIPANT REQUEST - PARTICIPANT IS UNWILLING OR UNABLE TO COMPLY WITH REQUIRED STUDY PROCEDURES
- PARTICIPANT REQUEST FOR INJECTION INTOLERANCE (AE OR ISR NOT PROTOCOL MANDATED)
- PARTICIPANT REQUEST – OTHER REASON
- PARTICIPANT IS CURRENTLY USING OR PLANNING TO USE PREP OR PEP (OTHER THAN STUDY PRODUCT)
- LOW ORAL ADHERENCE - STEP 1
- PARTICIPANT REFUSED LONG ACTING CONTRACEPTION
- PERCEIVED SIDE EFFECTS OF STUDY DRUG
- POSITIVE PREGNANCY TEST RESULT

Censored observations, based on reason for termination:
- DEATH
- INVESTIGATOR DECISION, SPECIFY
- SCHEDULED EXIT VISIT/END OF STUDY

- HIV INFECTION - STEP 1

Censored observations, based on reason for treatment discontinuation:

- ONE OR MORE REACTIVE HIV TEST RESULTS OR ACUTE HIV INFECTION SUSPECTED
- AS PER CMC: ENROLLMENT ERROR DUE TO DISCORDANT RESULTS (censored on date of randomization)
- HEPATITIS B INFECTION (censored on date of positive test result)

Censored observation, based on loss to follow-up (censored on date of last visit):
(Reason for termination is NULL and Reason for discontinuation is NULL) or Reason for treatment discontinuation = ”PARTICIPANT RECEIVED WRONG STUDY PRODUCT AT VISIT 12.0”

Multiple conditions:

Note that a participant may have more than one condition flag indicated for these analyses. The analysis date, ADT, is chosen as the earliest date when multiple conditions are indicated by flag. The event/competing risk/censor variable, CNSR, is chosen as the CNSR value associated with the earliest date when multiple conditions are indicated by flag. If multiple conditions have the same date, the CNSR value is indicated by the earlier value in the following list.

1) Safety event,
2) Competing events conditions 1, 2, and 3,
3) Censoring conditions 1,2, 3, or 4.
4) LFU.

Numbers of subjects having had the event of interest, and at risk to have had the event will be shown at selected weekly timepoints under the horizontal axis. The number at risk will be computed as the number of subjects with event times greater than or equal to the given timepoint. The **cumulative** number of events will be computed as the number of subjects with event times **less** than or equal to the event time.

## APPENDIX D – Study Sites

| Country | City | Site Name | CRS ID |
|---|---|---|---|
| Botswana | Gaborone | Botswana: Gaborone: Gaborone CRS | 12701 |
| Kenya | Kisumu | Kenya: Kisumu: Kisumu CRS | 31460 |
| Malawi | Blantyre | Malawi: Blantyre: Blantyre CRS | 30301 |
| Malawi | Lilongwe | Malawi: Lilongwe: Malawi CRS | 12001 |
| South Africa | Botha's Hill | South Africa: Botha's Hill: Botha's Hill CRS | 31445 |
| South Africa | Cape Town | South Africa: Cape Town: Emavundleni CRS | 30346 |
| South Africa | Cape Town | South Africa: Cape Town: Stellenbosch University (DTTC-SU) CRS | 31790 |
| South Africa | Johannesburg | South Africa: Johannesburg: Ward 21 | 31966 |
| South Africa | Kwa Zulu Natal | South Africa: Kwa Zulu Natal: Isipingo CRS | 31635 |
| South Africa | Kwa Zulu Natal | South Africa: Kwa Zulu Natal: Verulam CRS | 31663 |
| South Africa | Soweto | South Africa: Soweto: Soweto HPTN CRS | 31610 |
| Swaziland | Siteki | Swaziland: Siteki: Swaziland Prevention Center | 31994 |
| Uganda | Entebbe | Uganda:<br>Entebbe:<br>UVRI-IAVI | 30924 |
| Uganda | Kampala | Uganda: Kampala: Baylor-Uganda CRS | 31798 |
| Uganda | Kampala | Uganda: Kampala:<br>MU-JHU Research Collaboration CRS | 30293 |
| Zimbabwe | Chitungwiza | Zimbabwe: Chitungwiza: Seke South CRS | 30294 |
| Zimbabwe | Chitungwiza | Zimbabwe: Chitungwiza: St.Mary's CRS | 30303 |
| Zimbabwe | Chitungwiza | Zimbabwe: Chitungwiza: Zengeza CRS | 30320 |
| Zimbabwe | Harare | Zimbabwe: Harare: Parirenyatwa CRS | 30313 |
| Zimbabwe | Harare | Zimbabwe: Harare: Spilhaus CRS | 30314 |

## APPENDIX E – Adverse Events of Special Interest

Adverse events of special interest (AESI) have been determined for CAB based on pre-clinical and clinical experience, along with information for the integrase inhibitor class of HIV medications safety profile. These are adverse events for which more detailed summaries of event characteristics are of interest. Details of the analyses of AESI are contained in Section **Error! Reference source not found.** based on the current MedDRA version used for the study, v23.1.

The identification and classification of AESI will have occurred as a clinical review of preferred terms for adverse events, lab data, ECG and vital signs prior to the unblinding of the studies. (see Appendix E Section 1).

Table 1 shows the adverse events of special interest identified and reasons for including.

### Table 1 Adverse Events of Special Interest

| AESI | Product Implicated | Reason for Including as AESI |
|---|---|---|
| Hepatic Safety Profile: Assessment of risk of hepatoxicity | CAB | Clinical, Class, Regulatory Interest, |
| Hypersensitivity Reactions (HSR) | CAB | Class, Regulatory Interest, |
| Rash | CAB | Class, Regulatory Interest |
| Neuropsychiatric Events<br>• Suicidal Ideation/Behaviour<br>• Depression<br>• Bipolar Disorder<br>• Psychosis<br>• Mood Disorders<br>• Anxiety<br>• Sleep Disorders | CAB | Clinical, Class, Regulatory Interest, |
| Injection Site Reactions (ISR) | CAB | Clinical, Regulatory Interest |
| Seizures and Seizure-like events | CAB | Clinical, Regulatory Interest |
| Weight Gain | CAB | Clinical, Class, Regulatory Interest |
| Rhabdomyolysis | CAB | Clinical, Class, Regulatory Interest |
| Pancreatitis | CAB | Clinical, Therapeutic Area, Regulatory Interest |

| | | |
|---|---|---|
| Impact on Creatinine | CAB | Regulatory Interest, Therapeutic Area |
| Safety in Pregnancy (Does not apply to HPTN083) | CAB | Regulatory Interest, Class |
| Hyperglycaemia/new onset diabetes mellitus | CAB | Observation from 083, Class |

Common ISR adverse events are defined by MedDRA preferred terms including injection site pain, injection site induration, injection site nodules and preferred terms of any other ISR with ≥5% participants in either treatment arm. ISRs are summarized and listed regardless of IP relationship.

Although not pre-specified as an AESI, further analysis of pyrexia and related terms (Pyrexia Plus), sciatica and specific musculoskeletal related terms, and pancreatitis and related terms (Pancreatitis Plus) will be conducted, based on regulatory interest in the treatment indication, in order to characterise these phenomena in the PrEP population.

The following preferred terms have been identified for these areas of interest:

Pyrexia Plus includes PT: (Chills – 10008531, Feeling of Body Temperature Change - 10061458, Feeling Hot - 10016334, Body Temperature Increased - 10005911, Pyrexia - 10037660, Influenza Like Illness - 10022004, Fever – 10016558).

Sciatica PT: (Sciatica - 10039674) and specific Musculoskeletal includes PT: (Back pain – 10003988, Myalgia – 10028411, Pain in extremity – 10033425, Musculoskeletal pain - 10028391).

Pancreatitis Plus includes PT: (Pancreatitis - 10033645, Pancreatic enzymes increased - 10061900, Abdominal pain - 10000081, Abdominal pain upper - 10000087, Abdominal discomfort - 10000059, Nausea - 10028813). When looking at Pancreatitis Plus events after elevated lipase, the elevated lipase is defined as lipase above the upper limit of normal (ULN).

## Section 1: AE Preferred Term for AESI identification (based on MedDRA v23.1)

**Hepatotoxicity (Hepatic failure, fibrosis and cirrhosis and other liver damage-related conditions)**

| PT | PT Code |
|---|---|
| Acquired hepatocerebral degeneration | 10080860 |
| Acute hepatic failure | 10000804 |
| Acute on chronic liver failure | 10077305 |
| Acute yellow liver atrophy | 10070815 |
| Ascites | 10003445 |
| Asterixis | 10003547 |
| Bacterascites | 10068547 |
| Biliary cirrhosis | 10004659 |
| Biliary fibrosis | 10004664 |
| Cardiohepatic syndrome | 10082480 |

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|---|---|
| Cholestatic liver injury | 10067969 |
| Chronic hepatic failure | 10057573 |
| Coma hepatic | 10010075 |
| Cryptogenic cirrhosis | 10063075 |
| Diabetic hepatopathy | 10071265 |
| Drug-induced liver injury | 10072268 |
| Duodenal varices | 10051010 |
| Flood syndrome | 10084797 |
| Gallbladder varices | 10072319 |
| Gastric variceal injection | 10076237 |
| Gastric variceal ligation | 10076238 |
| Gastric varices | 10051012 |
| Gastric varices haemorrhage | 10057572 |
| Gastrooesophageal variceal haemorrhage prophylaxis | 10066597 |
| Hepatectomy | 10061997 |
| Hepatic atrophy | 10019637 |
| Hepatic calcification | 10065274 |
| Hepatic cirrhosis | 10019641 |
| Hepatic encephalopathy | 10019660 |
| Hepatic encephalopathy prophylaxis | 10066599 |
| Hepatic failure | 10019663 |
| Hepatic fibrosis | 10019668 |
| Hepatic hydrothorax | 10067365 |
| Hepatic infiltration eosinophilic | 10064668 |
| Hepatic lesion | 10061998 |
| Hepatic necrosis | 10019692 |
| Hepatic steato-fibrosis | 10077215 |
| Hepatic steatosis | 10019708 |
| Hepatitis fulminant | 10019772 |
| Hepatobiliary disease | 10062000 |

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|---|---|
| Hepatocellular foamy cell syndrome | 10053244 |
| Hepatocellular injury | 10019837 |
| Hepatopulmonary syndrome | 10052274 |
| Hepatorenal failure | 10019845 |
| Hepatorenal syndrome | 10019846 |
| Hepatotoxicity | 10019851 |
| Immune-mediated cholangitis | 10083406 |
| Immune-mediated hepatic disorder | 10083521 |
| Intestinal varices | 10071502 |
| Intestinal varices haemorrhage | 10078058 |
| Liver dialysis | 10076640 |
| Liver disorder | 10024670 |
| Liver injury | 10067125 |
| Liver operation | 10062040 |
| Liver transplant | 10024714 |
| Lupoid hepatic cirrhosis | 10025129 |
| Minimal hepatic encephalopathy | 10076204 |
| Mixed liver injury | 10066758 |
| Nodular regenerative hyperplasia | 10051081 |
| Nonalcoholic fatty liver disease | 10082249 |
| Non-alcoholic steatohepatitis | 10053219 |
| Non-cirrhotic portal hypertension | 10077259 |
| Oedema due to hepatic disease | 10049631 |
| Oesophageal varices haemorrhage | 10030210 |
| Peripancreatic varices | 10073215 |
| Portal fibrosis | 10074726 |
| Portal hypertension | 10036200 |
| Portal hypertensive colopathy | 10079446 |
| Portal hypertensive enteropathy | 10068923 |
| Portal hypertensive gastropathy | 10050897 |

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|---|---|
| Portal vein cavernous transformation | 10073979 |
| Portal vein dilatation | 10073209 |
| Portopulmonary hypertension | 10067281 |
| Primary biliary cholangitis | 10080429 |
| Regenerative siderotic hepatic nodule | 10080679 |
| Renal and liver transplant | 10052279 |
| Retrograde portal vein flow | 10067338 |
| Reye's syndrome | 10039012 |
| Reynold's syndrome | 10070953 |
| Splenic varices | 10067823 |
| Splenic varices haemorrhage | 10068662 |
| Steatohepatitis | 10076331 |
| Subacute hepatic failure | 10056956 |
| Sugiura procedure | 10083010 |
| Varices oesophageal | 10056091 |
| Varicose veins of abdominal wall | 10072284 |
| White nipple sign | 10078438 |

**Hepatotoxicity Continued (Hepatitis, non-infectious)**

| PT | PT Code |
|---|---|
| Acute graft versus host disease in liver | 10066263 |
| Allergic hepatitis | 10071198 |
| Alloimmune hepatitis | 10080576 |
| Autoimmune hepatitis | 10003827 |
| Chronic graft versus host disease in liver | 10072160 |
| Chronic hepatitis | 10008909 |
| Graft versus host disease in liver | 10064676 |
| Hepatitis | 10019717 |
| Hepatitis acute | 10019727 |

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|---|---|
| Hepatitis cholestatic | 10019754 |
| Hepatitis chronic active | 10019755 |
| Hepatitis chronic persistent | 10019759 |
| Hepatitis fulminant | 10019772 |
| Hepatitis toxic | 10019795 |
| Immune-mediated hepatitis | 10078962 |
| Ischaemic hepatitis | 10023025 |
| Lupus hepatitis | 10067737 |
| Non-alcoholic steatohepatitis | 10053219 |
| Radiation hepatitis | 10051015 |
| Steatohepatitis | 10076331 |

**Hyperglycaemia/new onset diabetes mellitus**

| PT | PT Code |
|---|---|
| Acquired lipoatrophic diabetes | 10073667 |
| Blood 1,5-anhydroglucitol decreased | 10065367 |
| Blood glucose increased | 10005557 |
| Diabetes complicating pregnancy | 10012596 |
| Diabetes mellitus | 10012601 |
| Diabetes mellitus inadequate control | 10012607 |
| Diabetes with hyperosmolarity | 10012631 |
| Diabetic arteritis | 10077357 |
| Diabetic coma | 10012650 |
| Diabetic coronary microangiopathy | 10080788 |
| Diabetic hepatopathy | 10071265 |
| Diabetic hyperglycaemic coma | 10012668 |
| Diabetic hyperosmolar coma | 10012669 |
| Diabetic ketoacidosis | 10012671 |
| Diabetic ketoacidotic hyperglycaemic coma | 10012672 |
| Diabetic ketosis | 10012673 |

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|---|---|
| Diabetic metabolic decompensation | 10074309 |
| Diabetic wound | 10081558 |
| Euglycaemic diabetic ketoacidosis | 10080061 |
| Fructosamine increased | 10017395 |
| Fulminant type 1 diabetes mellitus | 10072628 |
| Gestational diabetes | 10018209 |
| Glucose tolerance impaired | 10018429 |
| Glucose tolerance impaired in pregnancy | 10018430 |
| Glucose urine present | 10018478 |
| Glycated albumin increased | 10082836 |
| Glycosuria | 10018473 |
| Glycosuria during pregnancy | 10018475 |
| Glycosylated haemoglobin abnormal | 10018481 |
| Glycosylated haemoglobin increased | 10018484 |
| Hyperglycaemia | 10020635 |
| Hyperglycaemic hyperosmolar nonketotic syndrome | 10063554 |
| Hyperglycaemic seizure | 10071394 |
| Hyperglycaemic unconsciousness | 10071286 |
| Impaired fasting glucose | 10056997 |
| Insulin resistance | 10022489 |
| Insulin resistant diabetes | 10022491 |
| Insulin-requiring type 2 diabetes mellitus | 10053247 |
| Ketoacidosis | 10023379 |
| Ketonuria | 10023388 |
| Ketosis | 10023391 |
| Ketosis-prone diabetes mellitus | 10023392 |
| Latent autoimmune diabetes in adults | 10066389 |
| Monogenic diabetes | 10075980 |
| Neonatal diabetes mellitus | 10028933 |
| New onset diabetes after transplantation | 10082630 |

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|---|---|
| Pancreatogenous diabetes | 10033660 |
| Steroid diabetes | 10081755 |
| Type 1 diabetes mellitus | 10067584 |
| Type 2 diabetes mellitus | 10067585 |
| Type 3 diabetes mellitus | 10072659 |
| Urine ketone body present | 10057597 |

**Hypersensitivity Reactions Drug reaction with eosinophilia and systemic symptoms syndrome**

| PT | PT Code |
|---|---|
| Drug reaction with eosinophilia and systemic symptoms | 10073508 |
| Pseudolymphoma | 10037127 |
| Granulomatous T-cell pseudolymphoma | 10084214 |
| Drug hypersensitivity | 10013700 |
| Hypersensitivity | 10020751 |
| Type IV Hypersensitivity reaction | 10053613 |
| Eosinophillia | 10014950 |
| Eye swelling | 10015967 |
| Eyelid oedema | 10015993 |
| Lip swelling | 10024570 |
| Angioedema | 10002424 |
| Circumoral oedema | 10052250 |
| Face oedema | 10016029 |
| Idiopathic angioedema | 10073257 |
| Lip oedema | 10024558 |
| Mouth swelling | 10075203 |
| Oedema mouth | 10030110 |
| Periorbital oedema | 10034545 |
| Swelling face | 10042682 |
| Periorbital swelling | 10056647 |
| Swelling of eyelid | 10042690 |

**Rash (Severe cutaneous adverse reactions )**

| PT | PT Code |
|---|---|
| Acute generalised exanthematous pustulosis | 10048799 |
| Bullous haemorrhagic dermatosis | 10083809 |
| Cutaneous vasculitis | 10011686 |
| Dermatitis bullous | 10012441 |
| Dermatitis exfoliative | 10012455 |
| Dermatitis exfoliative generalised | 10012456 |
| Drug reaction with eosinophilia and systemic symptoms | 10073508 |
| Epidermal necrosis | 10059284 |
| Erythema multiforme | 10015218 |
| Erythrodermic atopic dermatitis | 10082985 |
| Exfoliative rash | 10064579 |
| Oculomucocutaneous syndrome | 10030081 |
| SJS-TEN overlap | 10083164 |
| Skin necrosis | 10040893 |
| Stevens-Johnson syndrome | 10042033 |
| Target skin lesion | 10081998 |
| Toxic epidermal necrolysis | 10044223 |
| Toxic skin eruption | 10057970 |
| Eyelid rash | 10074620 |
| Genital rash | 10018175 |
| Mucocutaneous rash | 10056671 |
| Nodular rash | 10075807 |
| Perineal rash | 10075364 |
| Rash | 10037844 |
| Rash erythematous | 10037855 |
| Rash generalised | 10037858 |
| Rash macular | 10037867 |

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|---|---|
| Rash maculo-papular | 10037868 |
| Rash maculovesicular | 10050004 |
| Rash morbilliform | 10037870 |
| Rash papular | 10037876 |
| Rash rubelliform | 10057984 |
| Rash scarlatiniform | 10037890 |
| Rash vesicular | 10037898 |
| Rash pruritic | 10037884 |
| Rash follicular | 10037857 |
| Rash pustular | 10037888 |
| Drug eruption | 10013687 |

**Neuropsychiatric Events** - consisting of Suicide/self-injury, Depression, Bipolar Disorder, Psychosis and Psychotic Disorders, Mood Disorders, Anxiety, and Sleep Disorders terms will be summarized separately.

**Suicide/self-injury**

| PT | PT Code |
|---|---|
| Assisted suicide | 10079105 |
| Columbia suicide severity rating scale abnormal | 10075616 |
| Completed suicide | 10010144 |
| Depression suicidal | 10012397 |
| Intentional overdose | 10022523 |
| Intentional self-injury | 10022524 |
| Poisoning deliberate | 10036000 |
| Self-injurious ideation | 10051154 |
| Suicidal behaviour | 10065604 |
| Suicidal ideation | 10042458 |
| Suicide attempt | 10042464 |
| Suicide threat | 10077417 |
| Suspected suicide | 10082458 |
| Suspected suicide attempt | 10081704 |

**Depression (excl suicide and self injury)**

| PT | PT Code |
|---|---|
| Activation syndrome | 10066817 |
| Adjustment disorder with depressed mood | 10001297 |
| Adjustment disorder with mixed anxiety and depressed mood | 10001299 |
| Agitated depression | 10001496 |
| Anhedonia | 10002511 |
| Antidepressant therapy | 10054976 |
| Childhood depression | 10068631 |
| Decreased interest | 10011971 |
| Depressed mood | 10012374 |
| Depression | 10012378 |
| Depression postoperative | 10012390 |
| Depression rating scale score increased | 10084390 |
| Depressive symptom | 10054089 |
| Discouragement | 10084257 |
| Dysphoria | 10013954 |
| Electroconvulsive therapy | 10014404 |
| Feeling guilty | 10049708 |
| Feeling of despair | 10016344 |
| Feelings of worthlessness | 10016374 |
| Helplessness | 10077169 |
| Major depression | 10057840 |
| Menopausal depression | 10067371 |
| Mixed anxiety and depressive disorder | 10080836 |
| Perinatal depression | 10078366 |
| Persistent depressive disorder | 10077804 |
| Post stroke depression | 10070606 |
| Postictal depression | 10071324 |

**Bipolar Disorder**

| PT | PT Code |
|---|---|
| Bipolar I disorder | 10004939 |
| Bipolar II disorder | 10004940 |
| Bipolar disorder | 10057667 |
| Cyclothymic disorder | 10011724 |
| Hypomania | 10021030 |
| Mania | 10026749 |
| Manic symptom | 10084119 |

**Psychosis and psychotic disorders**

| PT | PT Code |
|---|---|
| Acute psychosis | 10001022 |
| Alcoholic psychosis | 10001632 |
| Alice in wonderland syndrome | 10001666 |
| Brief psychotic disorder with marked stressors | 10048549 |
| Brief psychotic disorder without marked stressors | 10056395 |
| Brief psychotic disorder, with postpartum onset | 10006362 |
| Charles Bonnet syndrome | 10063354 |
| Childhood psychosis | 10061040 |
| Clang associations | 10009232 |
| Cotard's syndrome | 10059591 |
| Delusion | 10012239 |
| Delusion of grandeur | 10012241 |
| Delusion of parasitosis | 10012242 |
| Delusion of reference | 10012244 |
| Delusion of replacement | 10012245 |
| Delusion of theft | 10084030 |

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|---|---|
| Delusional disorder, erotomanic type | 10012249 |
| Delusional disorder, grandiose type | 10012250 |
| Delusional disorder, jealous type | 10012251 |
| Delusional disorder, mixed type | 10012252 |
| Delusional disorder, persecutory type | 10053195 |
| Delusional disorder, somatic type | 10012254 |
| Delusional disorder, unspecified type | 10012255 |
| Delusional perception | 10012258 |
| Dementia of the Alzheimer's type, with delusions | 10012295 |
| Depressive delusion | 10063033 |
| Derailment | 10012411 |
| Epileptic psychosis | 10059232 |
| Erotomanic delusion | 10015134 |
| Flight of ideas | 10016777 |
| Hallucination | 10019063 |
| Hallucination, auditory | 10019070 |
| Hallucination, gustatory | 10019071 |
| Hallucination, olfactory | 10019072 |
| Hallucination, synaesthetic | 10062824 |
| Hallucination, tactile | 10019074 |
| Hallucination, visual | 10019075 |
| Hallucinations, mixed | 10019079 |
| Hypnagogic hallucination | 10020927 |

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|---|---|
| Hypnopompic hallucination | 10020928 |
| Hysterical psychosis | 10062645 |
| Ideas of reference | 10021212 |
| Illusion | 10021403 |
| Jealous delusion | 10023164 |
| Loose associations | 10024825 |
| Mixed delusion | 10076429 |
| Neologism | 10028916 |
| Neuroleptic-induced deficit syndrome | 10075295 |
| Paranoia | 10033864 |
| Paranoid personality disorder | 10033869 |
| Parkinson's disease psychosis | 10074835 |
| Paroxysmal perceptual alteration | 10063117 |
| Persecutory delusion | 10034702 |
| Postictal psychosis | 10070669 |
| Post-injection delirium sedation syndrome | 10072851 |
| Posturing | 10036437 |
| Psychosis postoperative | 10065617 |
| Psychotic behaviour | 10037249 |
| Psychotic disorder | 10061920 |
| Psychotic disorder due to a general medical condition | 10061921 |
| Reactive psychosis | 10053632 |
| Rebound psychosis | 10074833 |

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|---|---|
| Schizoaffective disorder | 10039621 |
| Schizoaffective disorder bipolar type | 10068889 |
| Schizoaffective disorder depressive type | 10068890 |
| Schizophrenia | 10039626 |
| Schizophreniform disorder | 10039647 |
| Schizotypal personality disorder | 10039651 |
| Senile psychosis | 10039987 |
| Shared psychotic disorder | 10040535 |
| Somatic delusion | 10041317 |
| Somatic hallucination | 10062684 |
| Substance-induced psychotic disorder | 10072388 |
| Tangentiality | 10043114 |
| Thought blocking | 10043495 |
| Thought broadcasting | 10052214 |
| Thought insertion | 10043496 |
| Thought withdrawal | 10043497 |
| Transient psychosis | 10056326 |
| Waxy flexibility | 10047853 |

**Mood Disorders**

| PT | PT Code |
|---|---|
| Affect lability | 10054196 |
| Affective ambivalence | 10077173 |
| Affective disorder | 10001443 |
| Alexithymia | 10077719 |

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|---|---|
| Anger | 10002368 |
| Apathy | 10002942 |
| Blunted affect | 10005885 |
| Boredom | 10048909 |
| Constricted affect | 10010778 |
| Crying | 10011469 |
| Diencephalic syndrome of infancy | 10012774 |
| Discouragement | 10084257 |
| Dysphoria | 10013954 |
| Emotional disorder | 10014551 |
| Emotional distress | 10049119 |
| Emotional poverty | 10014557 |
| Euphoric mood | 10015535 |
| Flat affect | 10016759 |
| Frustration tolerance decreased | 10077753 |
| Inappropriate affect | 10021588 |
| Irritability | 10022998 |
| Laziness | 10051602 |
| Lethargy | 10024264 |
| Listless | 10024642 |
| Moaning | 10027783 |
| Mood altered | 10027940 |
| Mood disorder due to a general medical condition | 10027944 |
| Mood swings | 10027951 |
| Morose | 10027977 |
| Neuroleptic-induced deficit syndrome | 10075295 |
| Premenstrual dysphoric disorder | 10051537 |
| Premenstrual syndrome | 10036618 |
| Screaming | 10039740 |
| Seasonal affective disorder | 10039775 |
| Steroid withdrawal syndrome | 10042028 |
| Substance-induced mood disorder | 10072387 |

**Anxiety**

| PT | PT Code |
|---|---|
| Acrophobia | 10000605 |
| Activation syndrome | 10066817 |
| Acute stress disorder | 10001084 |
| Aerophobia | 10080300 |
| Agitation | 10001497 |
| Agitation postoperative | 10049989 |
| Agoraphobia | 10001502 |
| Akathisia | 10001540 |
| Algophobia | 10078056 |
| Animal phobia | 10002518 |
| Anniversary reaction | 10074066 |
| Anticipatory anxiety | 10002758 |
| Anxiety | 10002855 |
| Anxiety disorder | 10057666 |
| Anxiety disorder due to a general medical condition | 10002859 |
| Arachnophobia | 10051408 |
| Astraphobia | 10078372 |
| Autophobia | 10071070 |
| Body dysmorphic disorder | 10052793 |
| Burnout syndrome | 10065369 |
| Catastrophic reaction | 10082329 |
| Cibophobia | 10082413 |
| Claustrophobia | 10009244 |
| Compulsions | 10010219 |
| Compulsive cheek biting | 10076510 |
| Compulsive handwashing | 10071263 |
| Compulsive hoarding | 10068007 |
| Compulsive lip biting | 10066241 |
| Compulsive shopping | 10067948 |
| Cryophobia | 10082662 |
| Dermatillomania | 10065701 |
| Dysmorphophobia | 10049096 |

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|---|---|
| Emetophobia | 10070637 |
| Fear | 10016275 |
| Fear of animals | 10016276 |
| Fear of closed spaces | 10016277 |
| Fear of crowded places | 10050365 |
| Fear of death | 10066392 |
| Fear of disease | 10016278 |
| Fear of eating | 10050366 |
| Fear of falling | 10048744 |
| Fear of injection | 10073753 |
| Fear of open spaces | 10016279 |
| Fear of pregnancy | 10067035 |
| Fear of surgery | 10084519 |
| Fear of weight gain | 10016280 |
| Fear-related avoidance of activities | 10080136 |
| Generalised anxiety disorder | 10018075 |
| Glossophobia | 10080077 |
| Haemophobia | 10073458 |
| Haphephobia | 10067580 |
| Herpetophobia | 10081809 |
| Hydrophobia | 10053317 |
| Hyperarousal | 10080831 |
| Immunisation anxiety related reaction | 10075205 |
| Kinesiophobia | 10078430 |
| Limited symptom panic attack | 10024511 |
| Mysophobia | 10078769 |
| Nail picking | 10066779 |
| Nervousness | 10029216 |
| Neurosis | 10029333 |
| Noctiphobia | 10057946 |
| Nocturnal fear | 10057948 |
| Nosocomephobia | 10083993 |
| Nosophobia | 10063546 |
| Obsessive need for symmetry | 10077179 |

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|---|---|
| Obsessive rumination | 10056264 |
| Obsessive thoughts | 10029897 |
| Obsessive-compulsive disorder | 10029898 |
| Obsessive-compulsive symptom | 10077894 |
| Ochlophobia | 10050095 |
| Osmophobia | 10060765 |
| Paediatric autoimmune neuropsychiatric disorders associated with streptococcal infection | 10072147 |
| Panic attack | 10033664 |
| Panic disorder | 10033666 |
| Panic reaction | 10033670 |
| Paruresis | 10069024 |
| Performance fear | 10034432 |
| Phagophobia | 10050096 |
| Pharmacophobia | 10069423 |
| Phobia | 10034912 |
| Phobia of driving | 10056676 |
| Phobia of exams | 10034913 |
| Phobic avoidance | 10034918 |
| Phonophobia | 10054956 |
| Photaugiaphobia | 10064420 |
| Postpartum anxiety | 10082233 |
| Postpartum neurosis | 10036419 |
| Postpartum stress disorder | 10056394 |
| Post-traumatic stress disorder | 10036316 |
| Procedural anxiety | 10075204 |
| Pseudoangina | 10056610 |
| Selective mutism | 10039917 |
| Separation anxiety disorder | 10040045 |
| Sitophobia | 10080170 |
| Social anxiety disorder | 10041242 |
| Social fear | 10041247 |
| Stress | 10042209 |
| Tension | 10043268 |

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|---|---|
| Terminal agitation | 10077416 |
| Thanatophobia | 10064723 |
| Thermophobia | 10075147 |
| Trichotemnomania | 10072752 |
| Trichotillomania | 10044629 |

**Sleep Disorders**

| PT | PT Code |
|---|---|
| Abnormal dreams | 10000125 |
| Abnormal sleep-related event | 10061613 |
| Advanced sleep phase | 10001423 |
| Behavioural induced insufficient sleep syndrome | 10081938 |
| Behavioural insomnia of childhood | 10072072 |
| Breathing-related sleep disorder | 10006344 |
| Cataplexy | 10007737 |
| Circadian rhythm sleep disorder | 10009191 |
| Confusional arousal | 10067494 |
| Delayed sleep phase | 10012209 |
| Dyssomnia | 10061827 |
| Exploding head syndrome | 10080684 |
| Hypersomnia | 10020765 |
| Hypersomnia related to another mental condition | 10020767 |
| Hypersomnia-bulimia syndrome | 10053712 |
| Hypnagogic hallucination | 10020927 |
| Hypnopompic hallucination | 10020928 |
| Hyposomnia | 10067530 |
| Initial insomnia | 10022035 |
| Insomnia | 10022437 |
| Insomnia related to another mental condition | 10022443 |
| Irregular sleep phase | 10022995 |
| Irregular sleep wake rhythm disorder | 10080301 |
| Loss of dreaming | 10065085 |
| Middle insomnia | 10027590 |
| Narcolepsy | 10028713 |

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|---|---|
| Nightmare | 10029412 |
| Non-24-hour sleep-wake disorder | 10078086 |
| Parasomnia | 10061910 |
| Paradoxical insomnia | 10083337 |
| Periodic limb movement disorder | 10064600 |
| Pickwickian syndrome | 10035004 |
| Poor quality sleep | 10062519 |
| Rapid eye movement sleep behaviour disorder | 10077299 |
| Rapid eye movements sleep abnormal | 10037841 |
| Shift work disorder | 10078088 |
| Sleep apnoea syndrome | 10040979 |
| Sleep attacks | 10040981 |
| Sleep disorder | 10040984 |
| Sleep disorder due to a general medical condition | 10063910 |
| Sleep disorder due to general medical condition, hypersomnia type | 10040985 |
| Sleep disorder due to general medical condition, insomnia type | 10040986 |
| Sleep disorder due to general medical condition, mixed type | 10040987 |
| Sleep disorder due to general medical condition, parasomnia type | 10040988 |
| Sleep inertia | 10067493 |
| Sleep paralysis | 10041002 |
| Sleep sex | 10067492 |
| Sleep talking | 10041009 |
| Sleep terror | 10041010 |
| Sleep-related eating disorder | 10067315 |
| Somnambulism | 10041347 |
| Somnolence | 10041349 |
| Somnolence neonatal | 10041350 |
| Sopor | 10058709 |
| Stupor | 10042264 |
| Terminal insomnia | 10068932 |
| Upper airway resistance syndrome | 10063968 |

**Injection site Reactions**

Use CRF terms for ISR.

**Safety in Pregnancy (084 only)**

Use AE terms co-reported in pregnancy exposures to CAB.

**Seizures/Convulsions**

| PT | PT Code |
|---|---|
| 1p36 deletion syndrome | 10082398 |
| 2-Hydroxyglutaric aciduria | 10078971 |
| Acquired epileptic aphasia | 10052075 |
| Acute encephalitis with refractory, repetitive partial seizures | 10076948 |
| Alcoholic seizure | 10056347 |
| Alpers disease | 10083857 |
| Aspartate-glutamate-transporter deficiency | 10079140 |
| Atonic seizures | 10003628 |
| Atypical benign partial epilepsy | 10056699 |
| Automatism epileptic | 10003831 |
| Autonomic seizure | 10049612 |
| Baltic myoclonic epilepsy | 10054895 |
| Benign familial neonatal convulsions | 10067866 |
| Benign rolandic epilepsy | 10070530 |
| Biotinidase deficiency | 10071434 |
| CEC syndrome | 10083749 |
| CDKL5 deficiency disorder | 10083005 |
| Change in seizure presentation | 10075606 |
| Clonic convulsion | 10053398 |
| Congenital bilateral perisylvian syndrome | 10082716 |

| | |
|---|---|
| Convulsion in childhood | 10052391 |
| Convulsions local | 10010920 |
| Convulsive threshold lowered | 10010927 |
| CSWS syndrome | 10078827 |
| Deja vu | 10012177 |
| Double cortex syndrome | 10073490 |
| Dreamy state | 10013634 |
| Drug withdrawal convulsions | 10013752 |
| Early infantile epileptic encephalopathy with burst-suppression | 10071545 |
| Eclampsia | 10014129 |
| Epilepsy | 10015037 |
| Epilepsy surgery | 10079824 |
| Epilepsy with myoclonic-atonic seizures | 10081179 |
| Epileptic aura | 10015049 |
| Epileptic psychosis | 10059232 |
| Faciobrachial dystonic seizure | 10084187 |
| Febrile convulsion | 10016284 |
| Febrile infection-related epilepsy syndrome | 10079438 |
| Focal dyscognitive seizures | 10079424 |
| Frontal lobe epilepsy | 10049424 |
| Gelastic seizure | 10082918 |
| Generalised onset non-motor seizure | 10083376 |
| Generalised tonic-clonic seizure | 10018100 |

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|---|---|
| Glucose transporter type 1 deficiency syndrome | 10078727 |
| GM2 gangliosidosis | 10083933 |
| Grey matter heterotopia | 10082084 |
| Hemimegalencephaly | 10078100 |
| Hyperglycaemic seizure | 10071394 |
| Hypocalcaemic seizure | 10072456 |
| Hypoglycaemic seizure | 10048803 |
| Hyponatraemic seizure | 10073183 |
| Idiopathic generalised epilepsy | 10071081 |
| Infantile spasms | 10021750 |
| Jeavons syndrome | 10084303 |
| Juvenile myoclonic epilepsy | 10071082 |
| Lafora's myoclonic epilepsy | 10054030 |
| Lennox-Gastaut syndrome | 10048816 |
| Migraine-triggered seizure | 10076676 |
| Molybdenum cofactor deficiency | 10069687 |
| Multiple subpial transection | 10079825 |
| Myoclonic epilepsy | 10054859 |
| Myoclonic epilepsy and ragged-red fibres | 10069825 |
| Neonatal epileptic seizure | 10082068 |
| Neonatal seizure | 10082067 |
| Partial seizures | 10061334 |
| Partial seizures with secondary generalisation | 10056209 |

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|---|---|
| Petit mal epilepsy | 10034759 |
| Polymicrogyria | 10073489 |
| Post stroke epilepsy | 10076982 |
| Post stroke seizure | 10076981 |
| Postictal headache | 10052470 |
| Postictal paralysis | 10052469 |
| Postictal psychosis | 10070669 |
| Postictal state | 10048727 |
| Post-traumatic epilepsy | 10036312 |
| Schizencephaly | 10073487 |
| Seizure | 10039906 |
| Seizure anoxic | 10039907 |
| Seizure cluster | 10071350 |
| Seizure like phenomena | 10071048 |
| Severe myoclonic epilepsy of infancy | 10073677 |
| Simple partial seizures | 10040703 |
| Status epilepticus | 10041962 |
| Sudden unexplained death in epilepsy | 10063894 |
| Temporal lobe epilepsy | 10043209 |
| Tonic clonic movements | 10051171 |
| Tonic convulsion | 10043994 |
| Tonic posturing | 10075125 |
| Topectomy | 10073488 |

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|---|---|
| Transient epileptic amnesia | 10081728 |
| Tuberous sclerosis complex | 10080584 |
| Uncinate fits | 10045476 |
| Confusional state | 10010305 |
| Loss of consciousness | 10024855 |
| Syncope | 10042772 |
| Sopor | 10058709 |
| Stupor | 10042264 |
| Altered state of consciousness | 10050093 |
| Depressed level of consciousness | 10012373 |
| Consciousness fluctuating | 10050093 |

**Weight Gain**

| PT | PT Code |
|---|---|
| Abdominal fat apron | 10077983 |
| Overweight | 10033307 |
| Abnormal weight gain | 10000188 |
| Central obesity | 10065941 |
| Obesity | 10029883 |
| Weight abnormal | 10056814 |
| Weight increased | 10047899 |
| Waist circumference increased | 10064863 |
| Body mass index abnormal | 10074506 |
| Body mass index increased | 10005897 |
| Fat tissue increased | 10016251 |
| Sarcopenic obesity | 10083992 |

**Rhabdomyolysis**

| PT | PT Code |
|---|---|
| Muscle necrosis | 10028320 |
| Myoglobin blood increased | 10028625 |
| Myoglobin blood present | 10059888 |
| Myoglobin urine present | 10028631 |
| Myoglobinaemia | 10058735 |
| Myoglobinuria | 10028629 |
| Myopathy | 10028641 |
| Myopathy toxic | 10028648 |
| Necrotising myositis | 10074769 |
| Rhabdomyolysis | 10039020 |
| Thyrotoxic myopathy | 10081524 |
| Myalgia | 10028411 |
| Myositis | 10028653 |

**Pancreatitis**

| PT | PT Code |
|---|---|
| Cullen's sign | 10059029 |
| Grey Turner's sign | 10075426 |
| Haemorrhagic necrotic pancreatitis | 10076058 |
| Hereditary pancreatitis | 10056976 |
| Immune-mediated pancreatitis | 10083072 |
| Ischaemic pancreatitis | 10066127 |
| Oedematous pancreatitis | 10052400 |
| Pancreatic abscess | 10048984 |
| Pancreatic cyst drainage | 10082531 |

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|---|---|
| Pancreatic haemorrhage | 10033625 |
| Pancreatic necrosis | 10058096 |
| Pancreatic phlegmon | 10056975 |
| Pancreatic pseudoaneurysm | 10081762 |
| Pancreatic pseudocyst | 10033635 |
| Pancreatic pseudocyst drainage | 10033636 |
| Pancreatic pseudocyst haemorrhage | 10083813 |
| Pancreatic pseudocyst rupture | 10083811 |
| Pancreatitis | 10033645 |
| Pancreatitis acute | 10033647 |
| Pancreatitis haemorrhagic | 10033650 |
| Pancreatitis necrotising | 10033654 |
| Pancreatitis relapsing | 10033657 |
| Pancreatorenal syndrome | 10056277 |
| Subacute pancreatitis | 10084554 |

**Impact on Creatinine**

| PT | PT Code |
|---|---|
| Acute kidney injury | 10069339 |
| Acute phosphate nephropathy | 10069688 |
| Anuria | 10002847 |
| Azotaemia | 10003885 |
| Continuous haemodiafiltration | 10066338 |
| Dialysis | 10061105 |
| Foetal renal impairment | 10078987 |
| Haemodialysis | 10018875 |
| Haemofiltration | 10053090 |

| | |
|---|---|
| Neonatal anuria | 10049778 |
| Nephropathy toxic | 10029155 |
| Oliguria | 10030302 |
| Peritoneal dialysis | 10034660 |
| Prerenal failure | 10072370 |
| Renal failure | 10038435 |
| Renal failure neonatal | 10038447 |
| Renal impairment | 10062237 |
| Renal impairment neonatal | 10049776 |
| Subacute kidney injury | 10081980 |
| Atypical haemolytic uraemic syndrome | 10079840 |
| Cardiorenal syndrome | 10068230 |
| Chronic kidney disease | 10064848 |
| Crush syndrome | 10050702 |
| Diabetic end stage renal disease | 10012660 |
| End stage renal disease | 10077512 |
| Foetal renal impairment | 10078987 |
| Haemolytic uraemic syndrome | 10018932 |
| Hepatorenal failure | 10019845 |
| Hepatorenal syndrome | 10019846 |
| Nail-patella syndrome | 10063431 |
| Neonatal anuria | 10049778 |
| Oliguria | 10030302 |
| Pancreatorenal syndrome | 10056277 |
| Postoperative renal failure | 10056675 |
| Postrenal failure | 10059345 |
| Prerenal failure | 10072370 |
| Propofol infusion syndrome | 10063181 |
| Renal failure | 10038435 |
| Renal failure neonatal | 10038447 |
| Renal impairment | 10062237 |
| Renal impairment neonatal | 10049776 |
| Renal injury | 10061481 |
| Scleroderma renal crisis | 10062553 |

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|---|---|
| Traumatic anuria | 10044501 |

## Section 2: Events of Interest in Relation to Injections

**Pyrexia Plus**

| PT | PT Code |
|---|---|
| Body temperature increased | 10005911 |
| Chills | 10008531 |
| Feeling of body temperature change | 10061458 |
| Feeling hot | 10016334 |
| Pyrexia | 10037660 |
| Influenza like illness | 10022004 |
| Fever | 10016558 |

**Sciatica**

| PT | PT Code |
|---|---|
| Sciatica | 10039674 |

**Musculoskeletal Events**

| PT | PT Code |
|---|---|
| Back pain | 10003988 |
| Myalgia | 10028411 |
| Pain in extremity | 10033425 |
| Musculoskeletal pain | 10028391 |

## Section 3: Additional Analysis of Pancreatitis

**Pancreatitis Plus**

| PT | PT Code |
|---|---|
| Pancreatitis | 10033645 |
| Pancreatic enzymes increased | 10061900 |
| Abdominal pain | 10000081 |
| Abdominal pain upper | 10000087 |
| Abdominal discomfort | 10000059 |

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|---|---|
| Nausea | 10028813 |