

Section 9. Clinical Considerations

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9.1 Overview of Section 9

This section provides information on the clinical considerations for participants in HPTN 084 protocol, version 3.0, 4.0 and 5.0 of the Open Label Extension (OLE) and versions OLE. The Schedule of Evaluations (SOE) in Appendix VIII of the protocol indicates when specific clinical, counseling, and questionnaire procedures are required along with relevant laboratory testing.

Safety assessments will be obtained at every visit throughout the study. However, the IoR or designee should perform any additional symptom-directed examinations at his/her discretion at any time during any visit if s/he determines it to be clinically necessary, particularly if there are any on-going conditions which may require follow-up.

Information pertaining to participant safety monitoring and Adverse Event (AE) reporting procedures are provided in Section 10 of this SSP manual. Information on performing laboratory procedures is described in Section 11 of this manual. Further instructions for the electronic data capture systems are provided in Sections 13 and 14 of this manual.

Steps for the HPTN 084 Versions 3.0, 4.0 and 5.0 study are listed below:

- 1) Step 4a- Procedures for Participants Initially Randomized to TDF/FTC Who Elect to Move to OL CAB LA with Optional Oral Lead-in first
- 2) Step 4b- Procedures for Participants Initiating or Re-starting CAB LA without the Optional Oral Lead-in; the Initial Dose Visit
- 3) Step 4c- Procedures for Participants on Maintenance Doses of CAB LA or TDF/FTC
- 4) Step 4d- Procedures for Pregnant/Breastfeeding Participants and their Infants
- 5) Step 5- Procedures for Participants Taking OL TDF/FTC for 48 Weeks after Premature CAB LA discontinuation (this Step may also be used for participants who were pregnant on 4c, as is appropriate)
- 6) Step 6- Procedures for Participants on Maintenance Doses of CAB LA, weeks 49-96, and through to week 112 if additional visits are needed because local access has not yet been secured.

Figure 1: HPTN 084, v3.0 (OLE1) non-pregnant Protocol High Level Study Flowchart

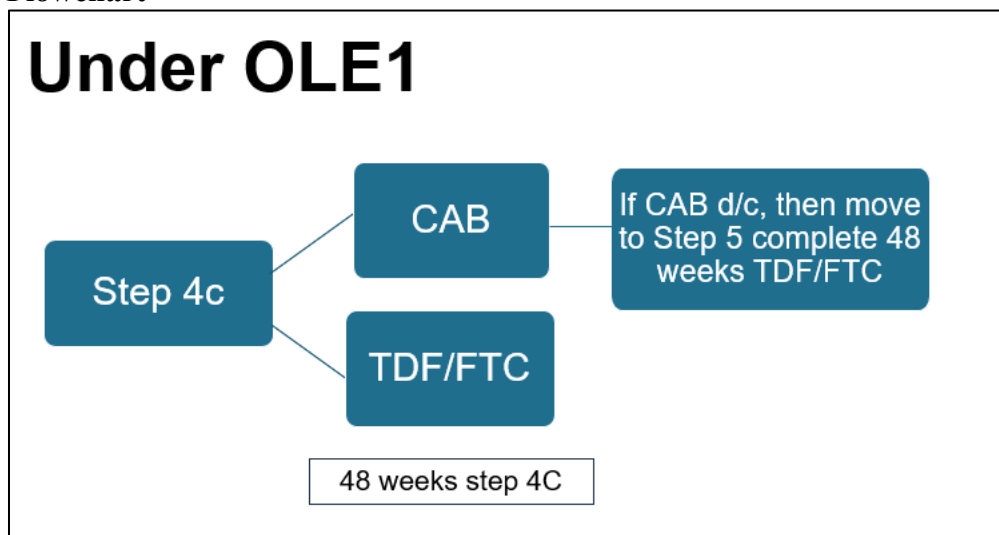
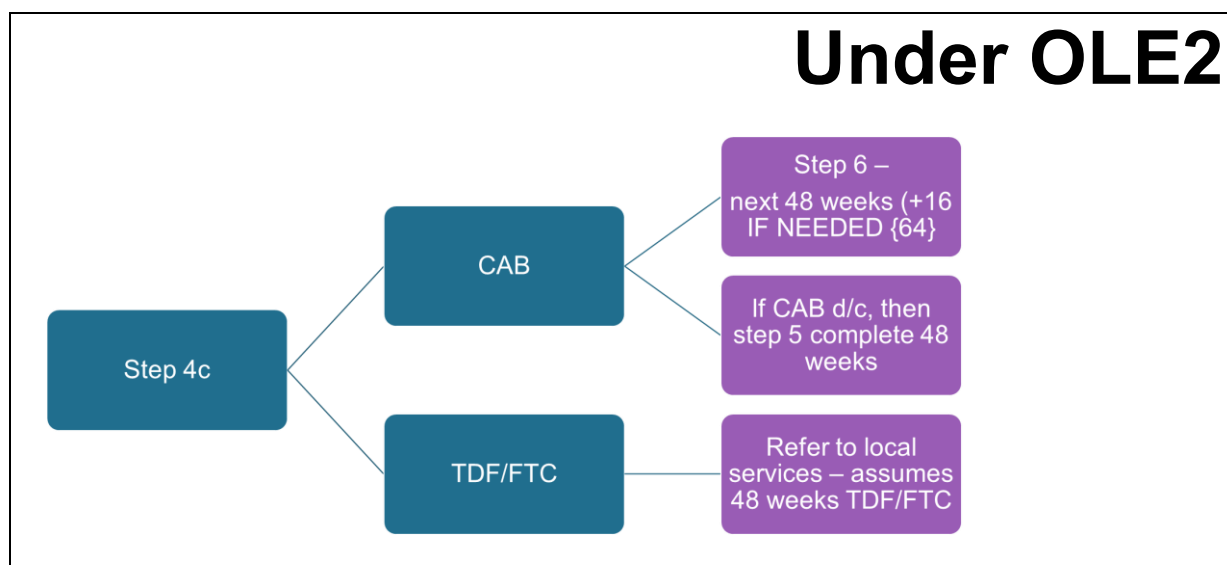


Figure 2: HPTN 084, v4.0 and 5.0, (OLE2) non-pregnant Protocol High Level Study Flowchart



Any questions regarding the safety assessments and clinical management of participants in HPTN 084 must be directed to the HPTN 084 Clinical Management Committee (CMC) (084CMC@hptn.org). Protocol-related queries should be directed to the 084 management alias (084mgmt@hptn.org). Queries about visit coding should be directed to SDMC (sc.084cdm@scharp.org).

9.2 Clinical Management Committee

As outlined in the HPTN Manual of Operations (MOP), a CMC is constituted for each HPTN study with a biomedical intervention. The HPTN 084 CMC continues to provide consultation and decision-making regarding management of toxicities and study product administration, interpretation of clinical or laboratory eligibility criteria, and other questions related to general clinical management of participants. The CMC is comprised of a designated CMC Safety medical officer and also includes the Protocol Chair and Co-Chair, pharmaceutical sponsor medical officers, DAIDS Medical Officer, DAIDS Protocol Pharmacist, and representatives from the HPTN LOC, HPTN LC, and the HPTN SDMC. The CMC has a primary responder who is “on call” and is responsible for soliciting input and responding to site queries within a 24-hour time period. The scope of the CMC is described in the CMC charter (CMC Operating Guidelines).

Sites that plan to conduct visits during off hours (nights or weekends) should notify the CMC and their local laboratories in advance so that a responder will be available, and samples will be able to be received and processed within protocol requirements.

Sites should be mindful that throughout the HPTN 084 protocol and associated protocol appendices, as well as the SSP manual, are examples of situations and AEs that require consultation with the CMC.

Queries from sites are submitted to the following email alias list: 084CMC@hptn.org.

Queries must be formatted to include the information outlined below.

- Include “084 CMC: [Insert PTID] – [One-line summary of query – for example – “Elevated ALT Grade 3” in the subject line of the email message.
- Include all of the following in the body of the email message:
 1. **Site name and number**
 2. **Name of person submitting query**
 3. **Participant Identification number (PTID) and Week on Study (Use “Screen” if pre-enrollment)**
 4. **Query submission type (*choose one of the following*)**
 - **Initial submission**
 - **Follow-up submission (this pertains to the PTID, i.e., a follow-up query to the initial submission)**
 5. **Reason for query and case narrative**

An example of the suggested e-mail is provided here:

Subject line of email: 084 CMC: Participant 103-000011 – Elevated ALT Grade 3

Body of email:

Site name and number: Site 103 –Prevention Clinic

Person submitting query: Felicity Bones, Study Coordinator

PTID and Week on Study: 103-000011, Week 2

Query Type: Initial submission

Reason for query: 32-year-old participant week 2 on blinded oral study medication found to have Grade 4 CK elevation after cross-fit competition with Grade 3 ALT elevation. Per protocol, participant will be unable to progress to injection phase. Please advise on further work-up and follow-up schedule (unless CMC can envision a way to continue participant on-study products).

Con meds: Tylenol, Ibuprofen, Naprosyn, Isoniazid, Rifampin, PZA, Ethambutol

Denies Alcohol, other recreational drug use

Pertinent laboratory values with chronology, values, and DAIDS toxicity table grade:

	Reference Ranges*	4/6/17 W2	3/23/17 EntryW0	3/19/17 screen
AST	10-40 U/L	812 (G4 25xULN)	15	16
ALT	9-46 U/L	225 (G3 7xULN)	15	15
CK	21-215 U/L	7100 (G4 20x ULN)	43	49
creatinine	0.60-1.35 mg/dL	0.97	0.97	1.04

**NOTE: Reference Ranges included on this table are for example purposes only; it does not represent ranges to be used in the study.*

Sites that submit queries will print and file the full CMC correspondence regarding the query and place in the relevant participant regulatory binder/participant study file. Keeping this documentation will help explain to monitors why the site followed a particular course of action.

Note: Any Grade 5 (Death) EAE/SAE must be reported to the CMC within 72 hours of site discovery.

Note: Due to the relaxed contraceptive requirements under the OLE (Protocol V3.0 and Protocol V4.0), sites will no longer need to report to the CMC cases when a participant's LARC (Long-acting reversible contraceptives) is delayed.

9.3 Participant-Reported Medical History during Follow up

Medical History should include, but is not limited to, symptoms, conditions, and diagnoses that affect eligibility or participation in the study, bleeding history, concomitant medications, contraceptive methods, and a history of hospitalizations, surgeries and allergies. The medical history collects a participant's medical information by major body systems, including a participant's drug, tobacco and alcohol use history. The history explores any medical conditions or any medications that are deemed exclusionary for this study, including a previous history of psychiatric illness or severe cardiovascular disease. The purpose for obtaining this information is to:

- Assess and document continued participant eligibility to participate in the study.
- Assess and document the participant's medical conditions and symptoms for comparison with signs, symptoms and conditions that may be identified or reported during follow-up.
- Monitor any potential AEs associated with the use of the study product during the course of the study.

When collecting past medical history from the participant, the clinician should ask probing questions in order to collect the most complete and accurate information possible, especially with regard to severity and frequency. Sites must have a consistent method for documenting this information. In all cases, information obtained at visits must be documented in the participant's chart and on appropriate e-case report forms.

Assessment of Acute HIV Infection

During follow-up, prior to study product administration, assess for signs and symptoms of acute HIV infection. Acute HIV infection is defined as the period of rapid viral replication that immediately follows the initial establishment of infection with HIV. Symptoms of acute HIV infection may be indistinguishable from a typical viral syndrome. Symptoms of acute HIV infections are listed below.

Clinicians should assess the possible causes of these symptoms, length of time the participant has been experiencing these symptoms, and severity grade. Symptoms should be managed clinically per standard of care. If a participant has signs or symptoms consistent with acute HIV infection, or expresses a concern about recent HIV acquisition, testing will be performed per protocol.

- Signs and symptoms of acute HIV infection should be assessed:
 - Fever
 - Fatigue
 - Headache
 - Myalgia
 - Weight loss
 - Pharyngitis or sore throat
 - Lymphadenopathy,
 - Rash
 - Diarrhea
 - Oral or genital ulcers

Site staff must assess the possible causes of these symptoms, length of time the participant has been experiencing these symptoms, and severity grade.

Under the OLE, HIV RNA is required at every visit (in addition to other HIV testing). Refer to the HIV testing algorithm for follow up visits in SSP, Section 11 for details. For split visits excluding HIV confirmatory visits, the HIV viral load does not need to be repeated if the split visit occurs less than 7 days from the initial visit. See SSP, Section 11 for further procedures.

9.3.1 AE Review of Medical History at Follow-Up Visits

Note: baseline refers to the timepoint at which the participant enrolled in the original blinded trial. At scheduled follow-up visits, collection of interval medical history should be obtained to:

- Determine whether previously reported and/or documented conditions are ongoing or have changed with regard to severity or frequency
- Determine whether newly-identified symptoms, illnesses, or condition have occurred since the last medical history was performed

Note: For purposes of this study, “newly-identified” is defined as a condition that:

- Was not present at baseline (Enrollment)
- Was present at baseline (ongoing at Enrollment) BUT has now increased in severity grade or frequency or has resolved after Enrollment and prior to the current report;
- Has already been reported as an AE but it has increased in severity grade/frequency

At the participant’s follow-up visits, retrieve the complete medical history source document and look up the Medical History Case Report Form (CRF) for reference.

At each follow-up visit, begin the follow-up medical history by reviewing with the participant and eliciting updates (resolution, outcome date, severity grade, etc.) on those symptoms/conditions that were documented as ongoing since the participant’s last visit. Site clinicians should then probe and evaluate for any new onset conditions/symptoms since the participant’s last visit. Clinicians should use their clinical experience and judgment to elicit complete and accurate medical history information from participants.

- New onset conditions/symptoms that began since the last visit may require completion of an AE Log e-CRF. This MAY include reoccurrences of conditions/symptoms that were reported at baseline and had resolved at a prior visit (only if the condition has increased in severity grade or frequency since baseline).
- Ongoing conditions that have increased in severity grade or frequency should be recorded as new events.
- Ongoing conditions that have not changed in severity or frequency, or have improved but not yet resolved, do not warrant any changes to the AE Log e-CRF.
- Ongoing conditions that have completely resolved since the last visit should have their AE LOG updated with an “Outcome Date”.

If during follow-up, a condition is identified as being present at baseline and the participant inadvertently did not report it as part of the baseline medical history, the clinician should add the information to the Medical History documentation. A chart note should also be documented to explain why the information is recorded retrospectively.

For all abnormal conditions or symptoms identified during follow-up, the severity grade of the condition or symptom must be documented, as must onset and resolution dates, when applicable.

9.4 Targeted Physical Exam at Follow-Up Visits

A targeted physical examination is required at most visits (Refer to Appendix VIII of the Protocol). A physical exam may be conducted at the discretion of the IoR or designee during an interim visit in response to clinically indicated and/or reported symptoms.

Targeted physical exams are performed at each follow-up visit. These exams are driven by the signs and symptoms that the participant reports. At a minimum, the participant must be weighed (see instructions in Section 9.4.1 below) and vital signs recorded at each visit (including temperature, weight, body mass index [BMI], blood pressure, pulse).

As safety is one of the objectives of this study, the goal at each visit is for the clinician to be assured that through the targeted physical exam and any ensuing conversation (history) that the participant is healthy enough to continue in the study and on the study drugs. Minimally, collecting vital signs at the follow-up visits gives the clinician a rudimentary idea of the participant's health state that may be overlooked by conversation (history) alone.

9.4.1 Instructions for Weight Collection

Collecting participants' weight is required as part of all physical exams (complete and targeted physical exams). To ensure consistency and accuracy in weight measurements, any time weight is collected, sites should follow the steps below:

- Measurements should be made at the same time of day each time, *if possible*.
- Participant should remove shoes, sweaters, coats, scarves, etc. prior to weighing.
- Participants should be asked to void (urinate/empty bladder) before weight is measured.
- Whenever possible, weight should not be measured during bouts of severe diarrhea or other obvious disturbances of hydration status.
- Participants should not engage in strenuous exercise for 8 hours preceding the measurements because of its potential effect on hydration status. If the participant reports that he/she did engage in strenuous exercise for 8 or more hours preceding the measurement, weight measurement should be performed anyway and documented on participant's record.
- The same scale should be used for all measurements performed for this protocol to the extent possible. The scale should be calibrated at minimum annually.
- Before the participant is weighed, make certain that the scale is in balance if it is a beam-balance scale or reads zero if it is an electronic scale.
- Instruct the participant to stand with both feet centered on the scale with arms at the sides. The participant should not move or hold onto anything during the measurement.
- Allow the scale to stabilize and record the weight in the units shown on the scale (lbs or kg).

Weight data will be recorded when applicable.

9.5 Additional Considerations for Medical History and Physical Exams

The following additional assessments will be made throughout the study as part of the medical history and physical exams:

9.5.1 Adverse events

All abnormal findings for adult participants (i.e., Grade 1 and higher) are to be graded and recorded in the participant's source documentation. AE Grade 1 or higher and any AE that leads to a study product hold (temporary or permanent) will be captured on the electronic Adverse Experience (AE) Log. For each AE, an assessment must be made by a study clinician of whether the event is related to the study product. Clinicians should review the relevant study product Investigator Brochures (IBs) and Package Inserts (PIs) to help make a determination. AEs will be assessed as specified in Version 2.0, January 2010 of the DAIDS EAE Reporting Manual.

Please note, if a laboratory result cannot be graded per the DAIDS toxicity table, it will not be reported as an AE. For example, the DAIDS toxicity table does not provide grading for non-fasting lipid profile; thus, these results will not be graded or reported as an AE.

See Section 10 of the SSP for more details regarding the reporting of AEs, as well as the HPTN 084 protocol Section 6.

See section 10.7.3 for how to handle AEs detected under the V2.0 protocol where tests were performed but are not required under V3.0. Similarly, see Section 10.7.3 for managing any AEs noted while performing testing under v3.0 that is not required by the versions 4.0 or 5.0 protocol.

For infant AEs, refer to SSP Section 10

9.5.2 Neurologic Symptoms

It is not required to actively assess neurologic symptoms: seizure, trouble sleeping, vivid/strange dreams, dizziness, problems concentrating, lightheaded, tremor, vision changes, weakness, numbness/tingling, fainting. However, these symptoms will be assessed as part of the targeted physical exam as needed.

9.5.3 Injection site reaction (ISR) assessment

ISRs are captured on the Injection Site Reaction e-Log post-injection (refer to Protocol Appendix VIII Step 4). Note: Step 4d has specific ISR reporting requirements. ISR assessments are required at these visits and sites should document that ISR assessments were performed at these visits.

Please note that for data to be consistent across all sites, sites should not telephone participants the day after an injection. Instead, they should only assess any reactions at the visits specified in the SOEs UNLESS a participant contacts the site with any questions or concerns about an ISR. If a participant contacts the site, then the site may

choose to schedule an interim visit. Any ISR symptoms noted during the interim visit will be documented on the Injection Site Reaction Log.

ISR examinations will include an assessment of pain, tenderness, pruritus, warmth, purulence, rash, erythema, swelling, induration, and nodules (granulomas or cysts). Participants should be instructed that ISR discomfort can be managed symptomatically (e.g., cold/warm compress, acetaminophen, ibuprofen) as necessary. See the last bullet in Section 9.6 of the SSP (below) for instructions to the participant upon leaving the clinic following an injection.

Participants should be instructed to contact the site regarding any ISRs of concern (and they may take a picture if they wish and email it to the site or return for an interim/unscheduled visit). **Per the HPTN 084 Protocol, Modified Toxicity Management Appendix VIII, the CMC must be notified of refractory cases in extreme circumstances.** Any questions regarding assessment of ISRs should be directed to the CMC.

It is important to distinguish between signs and symptoms from the injection process itself versus an ISR. Although these definitions are somewhat arbitrary, for protocol consistency, sites should follow the following definitions: An ISR typically begins 24-48 hours after an injection. However, if for example a participant experiences pain or discomfort from the actual procedure of giving an injection, e.g., the insertion of the needle beginning at time of, during or immediately after the procedure, this is, for purposes of reporting, considered associated with the injection procedure and is not considered an ISR. If a participant reports that on the day after the injection or later, she experienced symptoms (e.g., pain, redness, swelling, etc.) at the injection site, this would be an ISR. If an ISR is reported, use the Injection Site Reaction eCRF, using the “Site Reactions to Injections and Infusions” category for grading as found in the DAIDS Table for Grading the Severity of Adult and Pediatric Events, Corrected Version 2.1. If a participant experiences immediate pain or discomfort or other immediate signs and symptoms due to the procedure of giving an injection, it may be reported as an AE on the AE log eCRF using the category “Estimating Severity Grade for Parameters Not Identified in the Grading Table” for grading.

Sites should document all interventions that have been attempted to mitigate injection site reactions, which should include at a minimum:

- Pre-treatment (prior to injection administration) warm compresses
- Topical or oral pre-treatment with NSAID preparations, unless contraindicated
- Immediate post-injection massage to injection location
- Post-treatment warm or cold compresses
- Post-treatment NSAID or other analgesic preparations, topically or orally

Such interventions and their outcome should be documented in the source documents and the CMC consulted.

9.5.4 Concomitant medications

Sites must document on the Concomitant Medications Log all medications/preparations (prescription and non-prescription) including alternative/complementary medications/preparations (e.g., herbs, vitamins) taken by study participants within 30 days prior to Enrollment and anytime thereafter during study participation.

Contraception should be recorded on the Concomitant Medications Log as well.

Participants who seroconvert and start ART need to have their ART documented in the CM log.

For infants, do not record concomitant medications on the CM log; however, they should be documented in the source documentation.

It is helpful to ascertain the baseline medication information in the context of the baseline medical history. Participants should be asked open-ended questions to elicit participant report of current medications, and use the information obtained in the medical history to probe for additional medications that the participant may otherwise forget to report. For example, if the participant reports headaches as part of their medical history but does not spontaneously list any medications taken for headaches, ask what medications they take for headaches. Similarly, if a participant reports taking a medication for a condition that she inadvertently did not report when providing medical history information, add the condition to the baseline medical history source document.

At each follow-up clinic visit, retrieve the participant's previously completed Concomitant Medications Log, record any new medications provided to the participant by study staff, and actively ask the participant whether she is still taking all previously-recorded medications, at the same dose and frequency. Also, actively ask whether the participant has taken any new medications since the last medical history was taken. To further probe for updates, if the participant reports any intercurrent illnesses, symptoms, etc. since her last medical history, ask whether she took any medications for those. Add all new information to the Concomitant Medications Log. If a participant reports taking a new medication for a condition that they inadvertently did not report when providing follow-up medical history information, add the condition to their follow-up medical history source document. To help ensure accurate reporting of concomitant medications information, participants should be encouraged to bring all medications to all study visits.

- Consult the CMC for instructions when a participant or provider decides it is in the participant's best interest to initiate PEP.
- Consult the CMC for guidance in the case of a participant who has used TDF/FTC as PrEP during an extended absence from the study, such as extended lost to follow-up. If the participant returns to the site, she may be allowed to continue with study participation once use of clinically (outside of the study) obtained TDF/FTC for PrEP is stopped and study visits resume.

9.5.4.1 Precautionary and Prohibited Medications

In order to avoid AEs caused by drug interactions, whenever a concomitant medication is taken, site staff must review the concomitant medication's and study product's most recent PI for Truvada® and IB for cabotegravir to obtain the most current information on drug interactions and contraindications. Concomitant medications (prescription and non-prescription) should be administered only as medically necessary during the study.

For any precautionary or prohibited drug listed in the Truvada PI or cabotegravir IB, **it is required that the HPTN 084 CMC be notified for recommendations for continuing or stopping (or holding) study product.**

Experimental agents not otherwise specified in the SSP Manual may not be administered. Precautionary and prohibited medications may be found in the most recent versions of the protocol, Investigator's Brochures, and template Informed Consent Forms.

9.5.4.2 Drugs to be used with caution in people using TDF/FTC

- Co-administration of the following drugs should be clinically monitored by site clinician, as per considerations below:
 - drugs that are eliminated by active tubular secretion (e.g. drug, cidofovir, ganciclovir, valacyclovir, valganciclovir, aminoglycosides (e.g., gentamicin), and high-dose (please refer to the table below) or multiple NSAIDS), as these may increase concentrations of emtricitabine, tenofovir, and/or the co-administered drug.
 - Drugs that decrease renal function (e.g., cause nephrotoxicity) as these may increase concentrations of emtricitabine and/or tenofovir.
- *NOTE: Please report to the CMC if a participant takes a total daily dose of NSAIDS that meets or exceeds high dose, as designated in the table below, for MORE than 72 consecutive hours.*
- *NOTE: Acyclovir and valacyclovir may be used when indicated. If needed for treatment – sites do NOT need CMC permission for the use of these products, but sites should counsel the participant to increase hydration to avoid additive nephrotoxicity; no additional laboratory monitoring is required per protocol.*

Table: Comparable NSAID Dose Levels*

Nonselective NSAIDs	Low Dose	Medium Dose	High or Max Dose
Diclofenac potassium	50mg bid	50mg tid	50mg qid (in OA/RA only)
Diclofenac sodium	50mg bid	75mg bid	50mg qid or 100mg SR bid (in RA only)
Fenoprofen	200-300mg qid	600mg tid-qid	800mg qid
Flurbiprofen	50mg bid	50mg tid-qid	100mg tid
Ibuprofen	400mg tid	600mg tid-qid	800mg qid
Ketoprofen	25–50mg tid	75mg tid	IR =300mg/day (divide), SR =200mg/day
Naproxen	250mg tid	500mg bid	1250mg/day (divided)
Naproxen sodium	275mg tid	550mg bid	1375mg/day (divided)
Oxaprozin	600mg qd	1,200mg qd	1,200mg qd
Sulindac	150mg bid	200mg bid	200g bid
Piroxicam	10mg qd	20mg qd	40mg per day (not indicated for OA or RA)
Partially-selective NSAIDs	Low Dose	Medium Dose	High or Max Dose
Etodolac	200mg tid	400mg bid	1,200mg max (IR or SR divided doses)
Meloxicam/Mobic	7.5mg qd	7.5mg qd	15mg qd
Nabumetone	1,000mg qd	1,000mg bid	2,000mg/day (qd or divided bid)
Cox-2 inhibitors	Low Dose	Medium Dose	High or Max Dose
Celecoxib/Celebrex	200mg qd	200mg bid	200mg bid

COX = cyclo-oxygenase; IR = immediate release; NSAID = nonsteroidal antiinflammatory drug; OA = osteoarthritis; RA = rheumatoid arthritis; SR = sustained release

*This table does not represent exact or equivalent dosing conversions. It is based on U.S. Food and Drug Administration approved dosing ranges and comparative doses from clinical trials.

Source: www.ashp.org/emlibrary/NSAIDsConversiontools.pdf

9.6 Injection Administration

As outlined in the SSP Section 8 – Study Product Considerations, injections must be administered within **two hours of study product preparation by the site pharmacy**. Therefore, coordination with the site pharmacy is important when scheduling and setting up the flow of these visits.

Instructional videos for administering IM injections in the gluteal muscle can be found on <https://hptn.org/research/studies/hptn084> (password is “HPTN”). These videos are provided as examples only. Sites should use their clinical judgement and be guided by participant preference regarding which approach (ventrogluteal or dorsogluteal locations) to use for injections.

Specific instructions for the injections are as follows:

- Participants should be instructed not to take their oral study product on the day of their injection visit if they opted for an oral lead-in. However, if a participant takes study product on the day of the visit, DO NOT defer injection and document in the participant’s file.
- Ensure appropriate supplies are on hand: alcohol wipes, gloves, and a filled syringe with the appropriate gauge and inch needle.

- An appropriate needle size (per BMI, as outlined above) should be used for each intramuscular (IM) injection. The needle should be long enough to reach the muscle mass and ensure an IM injection, but not so long as to involve underlying nerves, blood vessels, or bones. Longer needle lengths may be necessary for participants with higher body mass indexes (BMI > 30), to ensure that injections are administered intramuscularly as opposed to subcutaneously. The clinical staff should consult with the pharmacy staff regarding each participant and the appropriate needle length that should be used.
- Wash hands.
- Use alcohol to clean the area of the body to be injected.
- Use discretion as to where in the gluteus muscle each injection is given according to individual participant circumstance. If possible, injections should be spaced approximately 2 cm from one another, from the site of any previous injection or any injection site reaction.
- Hold the muscle of the injection site firmly between your thumb and fingers of one hand.
- With the other hand, hold the needle and syringe like a pencil. Using a quick dart-like motion, insert the needle at a 90-degree angle through the skin and into the muscle.
- Release your hold on the skin and muscle.
- Pull back slightly on the plunger to see if blood is present. If there is blood, remove the needle and syringe and start over with a new needle and syringe. If a new needle and syringe is needed, please discard the contaminated needle and syringe and request new participant's study product from pharmacy. If there is no blood, inject the medicine.

NOTE: In the rare case the needle malfunctions, such that the full amount of the study product is not administered, remove the needle from the end of the syringe, place a new needle, and continue the injection with the same study product.

- Push the plunger slowly down to inject the study product into the muscle.
- Take the needle out.
- Apply pressure at the injection site and gently rub the site.
- Apply a bandage if needed.
- Discard the used needle and syringe properly.
- Check for any immediate injection site or other adverse reactions. There is no need to keep a participant in the clinic under observation after an injection.

- Instruct participants regarding how to manage any ISR at home, including:
 - If possible and if disclosure about participating in this study is not an issue, have someone look at the injection site if they cannot see/access it.
 - Note color, tenderness, any drainage. A picture should be taken if possible.
 - For pain, paracetamol, Ibuprofen/other NSAIDS, hot packs should be administered.
 - For swelling, Ibuprofen/other NSAIDS should be administered.
 - If any drainage, fever, chills, fatigue, weakness, the site should be contacted immediately.
 - Do not attempt to squeeze or drain any fluid from injection site.
 - Cover with a sterile bandage and contact clinic immediately if drainage occurs.

Questions regarding the injection instructions should be directed to the CMC.

9.6.1 Schedule of Injections

The injection schedule is included in Appendix VIII of the protocol.

Note that participants who elect to either begin or re-start CAB LA during the OLE must do so within the first 24 weeks of the OLE period. Participants initiating CAB LA will be permitted to choose between an oral run-in (4a) or a moving directly to injections (4b). Participants then move to Step 4c for 48 weeks of CAB LA injections.

9.6.2 Injection Visit Window Considerations

Timeliness of injections and adherence to visit windows must be carefully explained to participants. If participants present to the clinic outside of the visit windows (see Section 13 of this SSP for visit windows and refer to 9.7.3 below), contact the CMC for guidance. Injections may never be given with less than three weeks between them.

If participants who have delayed injections at study visits during Steps 4a, 4b and 4c, the sites must consult the CMC. Sites should also refer to all Data Communiques for visit coding.

9.6.3 Missed or Late Injections

First, CONTACT THE CMC.

Visit windows are contiguous. The following principles will be considered when advising sites on how to address missed injection visits.

- The interval between injections:
 - i. Injections must not be given closer together than three weeks.
 - ii. Delays between injections may require participants to be re-loaded.
- The visit schedule: The team should attempt to get the participant back onto her visit schedule; this may require the use of interim visits.

- The availability of safety assessments: Prior to injection, a recent set of safety bloods should be available to confirm that it is safe to administer injections. At a minimum HIV testing and pregnancy testing should be performed prior to injection administration.

The site **must consult the CMC** regarding possible re-loading of the participant with delayed or missed visits. The CMC will use the guidance below to advise the sites:

CAB LA Dose Delay For Any Injection (time from planned dose injection date)	Recommendation for All Participants
0-7.5*+ weeks delayed	Give delayed dose and 600mg Q8W thereafter
≥7.5* weeks delayed	Give delayed dose, 600mg 4 weeks later, and 600mg Q8W thereafter (reloading required)

* An exception to the 7.5 week delayed interval re-load rule applies only to PPTs who were on a maintenance CAB LA dose prior to the OLE.

If the interval between the last **target injection** visit date and current visit is 7.5 weeks or less (52 days or less), then there is no requirement to re-load. The participant should be provided with her missed injection no matter the study week but not before confirming that all safety assessments are within normal limits. She should then return to her regular visit schedule, making sure that the subsequent injection is not less than 3 weeks after the last injection, and that safety parameters are within normal limits.

If the interval between the target visit date and the current visit is 7.5 or more weeks (53 days or more) then re-loading is required. The goal of this process is to ensure that participants are returned to steady state and target drug concentrations, which may have waned as a result of a long period without receiving injection. During re-loading participants will be required to receive the missed injection, and another 4 weeks later similar to the process observed with injections at the original study weeks 5 and 9. Thereafter there should be an attempt to ensure that participant visits return to the appropriate SOE. During the re-loading process, necessary safety assessments should be completed prior to injection.

The participant must be confirmed HIV and pregnancy negative prior to any injections being given. Once the first of the two loading dose injections is administered, the timing of subsequent injections will be adjusted to ensure that the participant is able to return to her visit schedule as soon as possible.

9.7 Specimen Collection

Blood and urine will be collected throughout the study. The protocol outlines the clinical procedures and corresponding testing to be performed according to Modified Section 5.0 of the HPTN 084 protocol. Sections 6 and 11 (checklists and lab) of the SSP also should

be consulted for further specifications. The following additional considerations should be noted:

- Since plasma samples for drug levels will be collected throughout the study, blood sample must be collected at injection visits PRIOR to the injections.
- Calculated creatinine clearance must be performed at every visit where chemistry testing is being performed. The formula is in Section 11.3.5 "Creatinine Clearance" of the SSP (Laboratory and Specimen Management Procedures Section). Note: Participants who initiated the trial on HPTN 084-01 using the Modified Bedside Schwartz equation will have creatinine clearance assessed per the Modified Schwartz equation at follow up visits.

9.8 Toxicity and Clinical Management

Sites should regularly consult the HPTN 084 Modified Protocol Appendix VIII – Toxicity Management as well as the Toxicity Management Diagrams at the end of this section, for guidance related to toxicities. It should be noted that Appendix VIII of the Protocol refers to several instances where the CMC must be contacted in the case of AE management and grading. For AEs that require CMC consultation, the CMC should be notified as soon as possible after site awareness, ideally within 72 hours.

All toxicity management must be fully documented in participant study records. When the CMC is consulted in relation to toxicity management, all communication should be filed in participant study records.

9.8.1 Suspected hepatotoxicity

In addition to the diagrams at the end of this SSP Section 9, sites should consider and investigate any potential causes leading to liver damage as proposed in the protocol.

In the event of permanent discontinuation for liver criteria, the site should consider the following tests to determine possible causes of hepatotoxicity in consultation with the CMC:

- Hep A IgM
- Hep B sAg; Hep B cAb
- Hep C RNA
- Hep E IgM
- CMV IgM
- EBV IgM
- RPR and syphilis screening
- Tox screen
- ANA; a-smooth muscle Ab; type - anti-liver kidney microsomal Ab, total IgG
- APAP (acetaminophen) level of reported use
- Review of any herbal meds and supplement use

9.9 HIV Considerations During Study Conduct

At all follow-up visits, HIV test results from previous visits and at least one HIV test result from the current visit must be available and reviewed by designated staff. All available HIV test results (results from previous visit and a current visit rapid test) must be confirmed to be negative/non-reactive prior to study product administration.

Positive/Reactive HIV Test

If a participant has a reactive or positive HIV test, product will be held. Sites should email the 084HIV@hptn.org and 084CMC@hptn.org alias lists in cases of reactive or “indeterminate” results regardless of the site interpretation (false positive, discordant, discrepant) or with questions about the HIV test algorithm. When emailing these groups, make sure to attach the template for documenting of all HIV results for the participant.

Further testing for confirmation of HIV infection will be done per Section 3.2 in Appendix VIII of the Protocol. Note: It may take several visits to confirm HIV infection. The SOE for seroconverters refers to the final steps once a participant has HIV infection confirmed and is linked to ART.

Participants who are determined not to be infected (i.e. false positive) may resume study products ONLY after CMC consultation.

HIV testing log template for positive or indeterminate results

The subject line of the email: 084 HIV: Participant 333-333-33333 – Reactive ELISA

Body of email:

Site name and number: 31033 Nowhere CRS

The person submitting a query: Zeb McGillicuty

PTID and Week on Study: 333-333-33333 Week 41

Query Type: Initial

Reason for query: rapid HIV positive

Site name and number:	Nowhere CRS	31033
The person submitting the query:	Zeb McGillicuty	
PTID and Week on Study:		41
Query Type:	Initial Query	
Treatment assignment during blinded trial:	TDF/FTC	
Treatment assignment during OLE	CAB LA	
Reason for query:	Positive Rapid HIV	
<p>A 32-year-old participant's rapid HIV test for week 40 was reactive. She had flu-like symptoms 3 weeks ago and has missed taking her pills on two occasions. She denies having unprotected sex in the past 6 months. We have called the participant to stop taking the study medication, and to come next week for confirmatory lab work.</p> <p>Please advise if our plan is in order.</p>		

Summary table of relevant HIV test results

Date/ Visit Week	Date of last product	Rapid test 1	Rapid test 2	Laboratory based Instrumente d Ag/Ab immunoass ay	HIV RNA	Geenius if HIV Ag/Ab available and Instrumen ted test reactive	Other relevant test results

Management of participants with discrepant HIV results.

Study staff should follow the guidance of the HIV alias regarding additional testing to confirm HIV status. Guidance on management of participants is provided in the Appendix I: Guidance for the Management of “Discordant/discrepant” HIV Testing Results – HPTN 083 and 084.

For some participants even with repeat testing their final HIV status may be uncertain. Investigators under guidance of CMC and HIV alias should engage participants on their options (see section 12 for counseling considerations).

For participants where treatment is recommended but in the context of atypical test results, investigators may want to explore with participants the option to start treatment to avoid the potential for emergence of INSTI resistance, with the potential for a subsequent treatment interruption 12-18 months later.

Some sites may be able to refer participants with atypical test results for enrolment and follow up in ACTG A5321. Sites should contact their CTU coordinator to determine whether this protocol is active at their CTU.

Some participants may be reluctant to start ART and may wish to wait for further test results. In this situation, participants should ideally be counselled about the potential risks for HIV infection if they are on PrEP hold and uninfected in addition to the risks for resistant infection if they are in fact HIV infected. All participant discussions should be adequately documented, and participants should be supported to make an informed choice that is appropriate to her personal circumstances.

9.10 Sexually Transmitted Infections (STIs)

As noted in the HPTN 084 protocol, treatment for STIs will be provided per local guidelines (and may include referral for treatment).

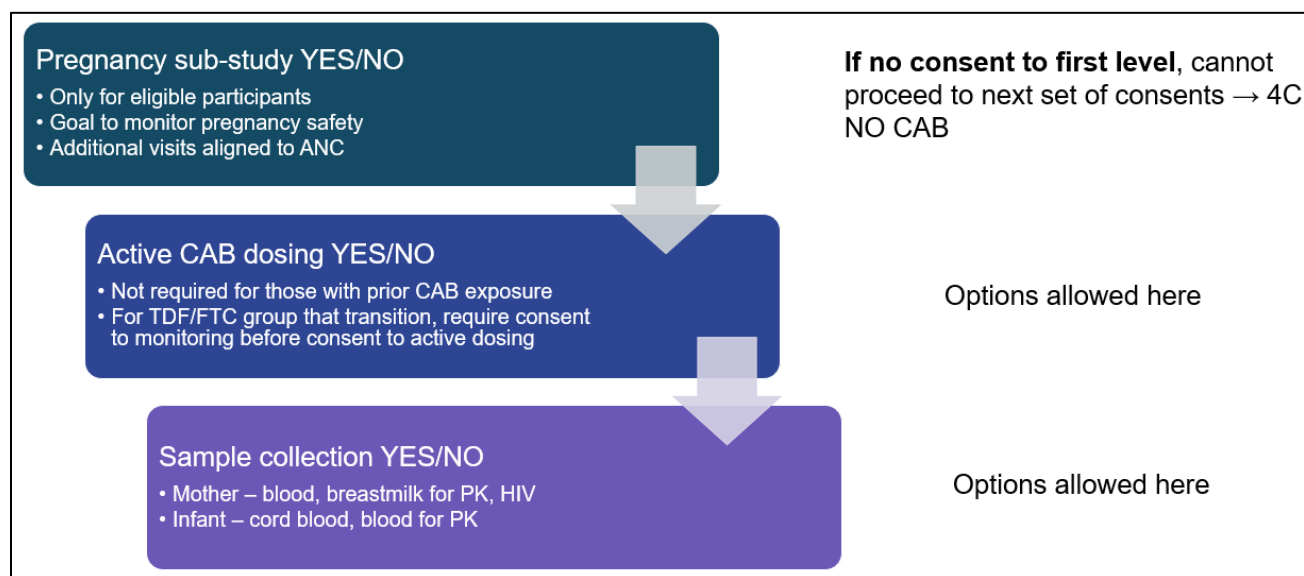
Symptomatic screening, or oropharyngeal screening for STIs beyond what is required by the protocol may be done at a site’s discretion and cost. Costs associated may come out of each site’s respective per participant study reimbursements.

9.11 Tuberculosis

As noted above in section on Concomitant Medications, rifampicin, rifapentine and rifabutin are contraindicated to concurrent use with cabotegravir. If TB treatment is required contact the CMC for guidance. For participants with suspected or confirmed tuberculosis, **contact the CMC at 084cmc@hptn.org for further guidance.**

9.12 Pregnancy

Prior to implementing version 3.0 or subsequent versions of the protocol, all sites should have a pregnancy management SOP in place that details how they will manage participants in terms of antenatal care, delivery and post-natal follow-up. The plan should include details about access to and recording of ultrasound information. See an example SOP attached in Appendix 9c. This SOP was loaned to 084 from a site; sites may modify/adapt it to best suit their needs as long as all 084 protocol requirements are met. Sites are not required to use the example SOP format.



- Pregnancy must be confirmed on two separate samples. Per protocol version 3.0 onwards, pregnancy can be confirmed on two separate samples on the same day.
- All participants interested in participating in Step 4d will be provided informed consent for this Step prior to any study activities. Participants cannot receive CAB LA during pregnancy without consenting to Step 4d.
- Participants with a positive pregnancy test may be ambivalent about their pregnancy. Participants can be given time within the visit window to decide about their pregnancy options and whether or not they wish to participate in the sub-study.
- Participants who are pregnant during Step 4 and Step 6 and who received at least one CAB LA injection during HPTN 084 (either blinded study, unblinded phase or during the OLE) are eligible to participate in Step 4d. In addition, participants in Step 5 who received a CAB LA injection within 8 weeks of pregnancy confirmation may join the Pregnancy and Infant Sub-Study.
- Participants who were in the TDF/FTC arm and are pregnant at the time of transition to the OLE and choose to take CAB during pregnancy are also eligible for Step 4d.

- Participants who received CAB LA and are pregnant at the transition are eligible for Step 4d.
- Sites should seek guidance from the CMC regarding study product administration procedures for participants who are pregnant at the time of the transition to the OLE.

IN CONSULTATION WITH THE CMC, Women who are PREGNANT AT THE TIME OF TRANSITION TO THE OLE will be managed as follows:

- Sites should consult with the CMC regarding pregnant participants transitioning to the OLE before implementing the guidance below.
- When transitioning to the 4d schedule, they will be allocated to the 4d visit week closest to gestational age. This guidance applies to participants who are pregnant at the time of transition ONLY.
- If an injection reload is required because they were on open-label Truvada, they will begin with a visit 4b prior to transitioning to the 4d schedule.
- If Estimated Gestational Age >12 weeks they should be referred for ultrasound at the time pregnancy is detected (or first pregnancy SOE visit).
- Syphilis testing should be conducted at the time pregnancy is detected (or first pregnancy SOE visit) if it has not been done as part of the step 2 pregnancy SOE. The rationale for this is that there is a 6 month gap in syphilis testing between week 0 and week 24 of the pregnancy SOE.
- GC/CT testing should be done at the time pregnancy is detected (or first pregnancy SOE visit) if there has been a > 3 month gap since last GC/CT testing and/or there is a long gap until the next scheduled GC/CT testing at the week 24 pregnancy visit. For women who present late in pregnancy (after week 24) and have not had GC/CT testing in the last three months, GC/CT testing should be done.

With respect to participants who become pregnant **AFTER** their transition to the open-label extension, the following considerations apply:

- Consult the CMC for guidance regarding product administration.
- Per above, if they require more time to consider their participation complete the visit 4c procedures for that visit up until product administration.
- Ask participant to return for a split visit within the window once she has had an opportunity to consider her pregnancy and study participation options.
- See section 12 on counseling support options.
- Participant will follow the schedule of evaluations for step 4d from week 0; participants should NOT be allocated to a visit on the SOE based on estimated gestational age.

For participants in Step 4d who experience pregnancy loss prior to 40 weeks gestational age

- Consult the CMC.
- Participants can return to either Step 4c or Step 6, whichever is appropriate, after entering 4d in these cases.
- Participants should return to the visit in the schedule of evaluations that reflects their last visit plus the period that they were on step 4d.
 - E.g. participant tested positive for pregnancy at Step 4 week 16 and had a miscarriage at step 4d week 16 would return to step 4c week 32.
- Report the pregnancy outcome on the appropriate CRF.

Ultrasound during pregnancy in all participants

All pregnant participants should have an ultrasound ideally before gestational age 12 weeks. Gestational age should ideally be calculated based on ultrasound. Ultrasound is preferred for the identification of fetal anomalies. With respect to fetal anomaly reporting, these should only be reported as an SAE/EAE at the time of delivery of the infant when surface examination can confirm the anomalies. Where there is pregnancy loss prior to delivery, the pregnancy outcome report should include comments on the fetal anomalies observed on ultrasound as part of the pregnancy outcome report. The CMC should be contacted regarding any pregnancy loss associated with fetal anomalies detected on ultrasound. ultrasound not available contact SDMC.

Management of Participants who are pregnant but decline participation OR are not otherwise eligible for Step 4d

As noted in Protocol Section 5.14, regardless of the step a pregnant participant is followed on, first semester ultrasound findings and pregnancy outcome data (infant growth assessment at delivery and approximately 48 weeks post partum) will be collected.

Note: ALL INFANT SAEs THAT OCCUR UP TO 48 WEEKS POST PARTUM WILL BE COLLECTED AND REPORTED.

Infant assessment

- Sites should aim to ensure that mother and infant visits are coordinated.
- Infant outcomes should be reported on the appropriate CRF.
- An Infant PTID should be created in Rave for all live births. In the event of a stillbirth if it is feasible to collect cord blood samples an Infant PTID number is also required.
- When preparing for an infant exam ensure that you
 - Plan assessments in advance
 - Supplies are laid out and within reach
 - Room is warm and well lit
 - Mother is informed and comfortable
 - Provider has washed hands
- Assess for any infant danger signs
 - stopped feeding well,
 - history of convulsions,
 - fast breathing,
 - severe chest in-drawing,

- no spontaneous movement,
- temperature >37.5°C,
- temperature <35.5°C
- any jaundice in first 24 hours of life, or yellow palms and soles at any age
- Complete infant examination in a systematic, step-wise manner and assess
 - Physical appearance
 - Length
 - Weight
 - Skin
 - Head (including fontanelles and circumference)
 - Face (including mouth)
 - Neck
 - Chest
 - Abdomen and anus
 - Hips and genitalia
 - Arms, legs, fingers, and toes
 - Spine
 - Auscultation of chest
 - Neurologic assessment
- The following tools may assist with infant assessments
 - Video Guide to a Stepwise Surface Examination of Newborns
who.int/tdr/publications/videos/stepwise-surface-examination-newborns/en/
 - Global Birth Defects App for the assessment and classification of birth defects
<https://globalbirthdefects.tghn.org/download-birth-defects-surveillance-app/>
 - Complete Examination of the Newborn. Effective Perinatal Care Geneva: World Health Organization
https://www.euro.who.int/data/assets/pdf_file/0006/146814/EP_C_FAC_guide_pt2_mod_1N_7N.pdf
 - World Health Organization. Training Course on Child Growth Assessment. Geneva, WHO, 2008.
https://apps.who.int/iris/bitstream/handle/10665/43601/9789241595070_B_eng.pdf?sequence=2&isAllowed=y
 - WHO recommendations on newborn health: guidelines approved by the WHO Guidelines Review Committee. Geneva: World Health Organization; 2017 (WHO/MCA/17.07). Licence: CC BY-NC-SA 3.0 IGO.
<https://www.who.int/publications/i/item/WHO-MCA-17.07>
- To note only major structural congenital anomalies that per the WHO definition have significant medical, social or cosmetic consequences for the affected individual, and typically require medical intervention should be reported. E.g. cleft lip and spina bifida. Major structural anomalies are the conditions that account for most of the deaths, morbidity and disability related to congenital anomalies. In contrast, minor congenital anomalies, although more prevalent among the population, are structural changes that pose no significant health problem in the neonatal period and tend to have limited social or cosmetic consequences for the affected individual. E.g. single palmar crease and

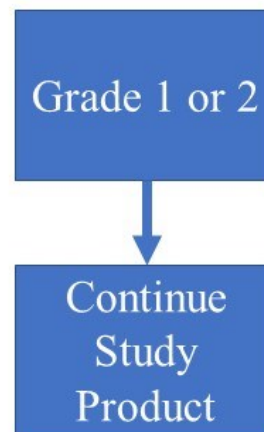
clinodactyly. See WHO Birth defects surveillance A manual for program managers 2nd edition [/https://iris.who.int/bitstream/handle/10665/337425/9789240015395-eng.pdf?sequence=1] for more information

- In version 3.0, 4.0 and 5.0 all pregnant participants required follow-up of their infants until one year of age (for convenience this was linked to a week 48 visit), including those not in step 4d. In version 5, we have clarified what information we are seeking over the first 12 months of infant life. Specifically, we would like updates on provide updates on any SAEs, growth parameters, and congenital anomalies. This information will be captured on the Ultrasound-OLE, Pregnancy Outcome-OLE, Infant Assessment form, for all live births in addition to the, Adverse Events- Infants form, where applicable.
- For participants in step 4d only, infant sample collection is required at visits specified in the protocol.
 - Ideally, a staff member with pediatric experience should collect infant samples to minimize discomfort and ensure adequate sample collection.
 - The following guidance may assist with guiding infant sample collection:
https://www.euro.who.int/data/assets/pdf_file/0005/268790/WHO-guidelines-on-drawing-blood-best-practices-in-phlebotomy-Eng.pdf
- For infants in step 4d, Infant adverse events should be discussed with CMC if these are considered related to potential product exposure. The CMC will provide guidance on product administration in these situations.

For missed injections during step 4d, consult the CMC.

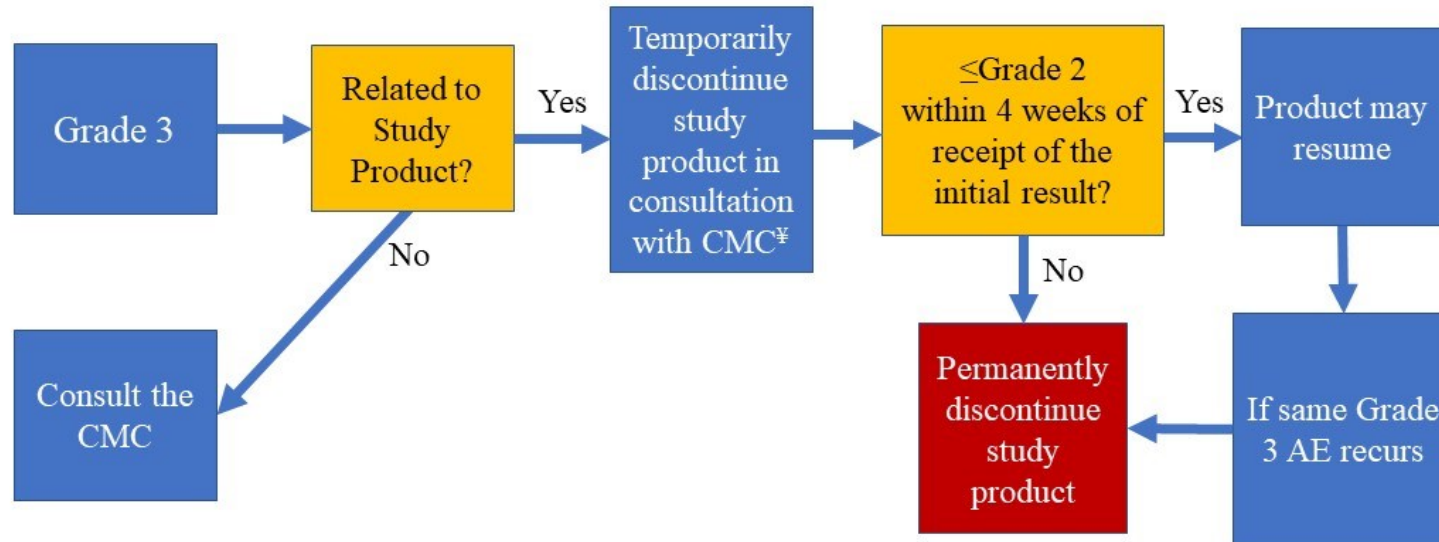
Toxicity Management Diagrams (Only applies to direct recipients of study product)

General Guidance*



*General Guidance applies only to toxicities not addressed under *Guidance on Toxicity Management for Specified Toxicities*

General Guidance*



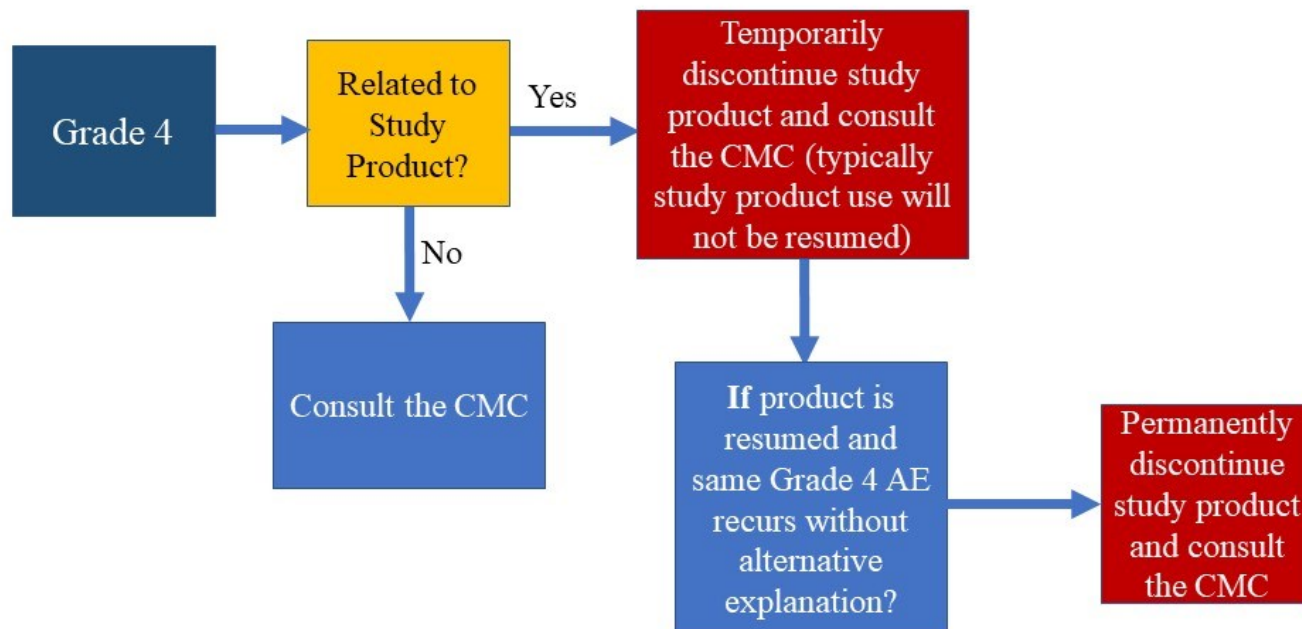
* General Guidance applies only to toxicities not addressed under *Guidance on Toxicity Management for Specified Toxicities*

± Any grade 3 or higher clinical or laboratory AE observed prior to their first injection of active CAB (i.e. in STEP 4b) will prompt consultation with the CMC prior to any injectable dosing

‡ Investigator should re-evaluate the participant until resolution of the toxicity.

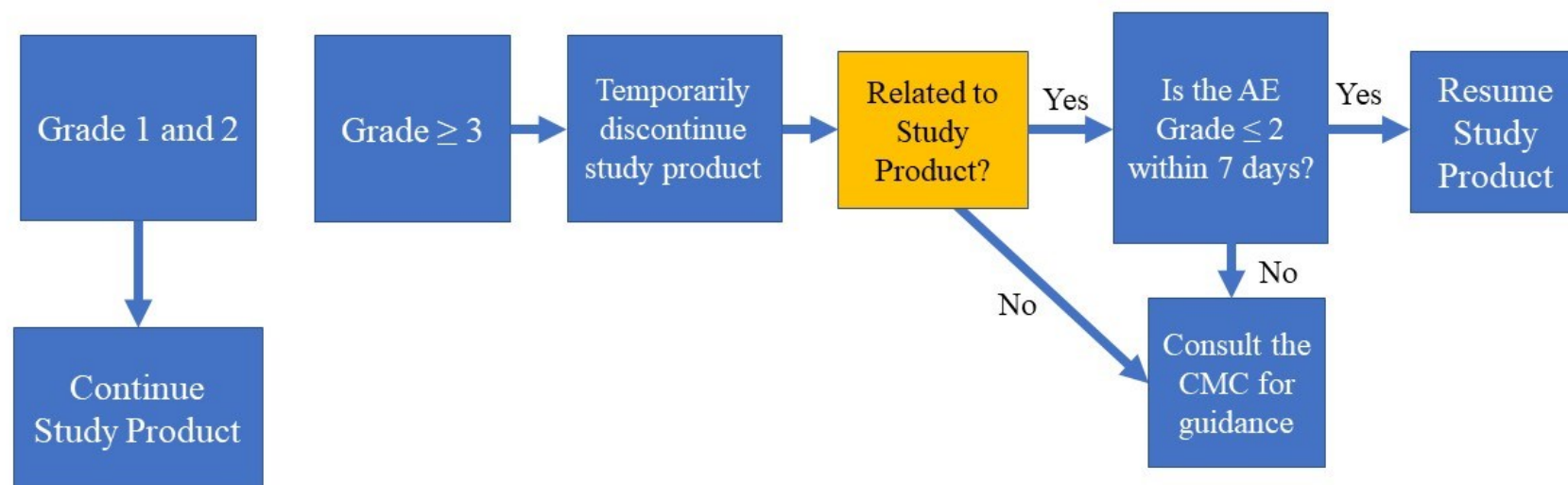
If study product is temporarily or permanently discontinued have participants return any pills as soon as possible.

General Guidance*



*General Guidance applies only to toxicities not addressed under *Guidance on Toxicity Management for Specified Toxicities*
±Any grade 4 or higher clinical or laboratory AE observed **prior to their first injection** of active CAB (i.e. in STEP 4b) will prompt permanent study product discontinuation.

Guidance on Toxicity Management for Specified Toxicities Nausea, Vomiting, and Diarrhea*

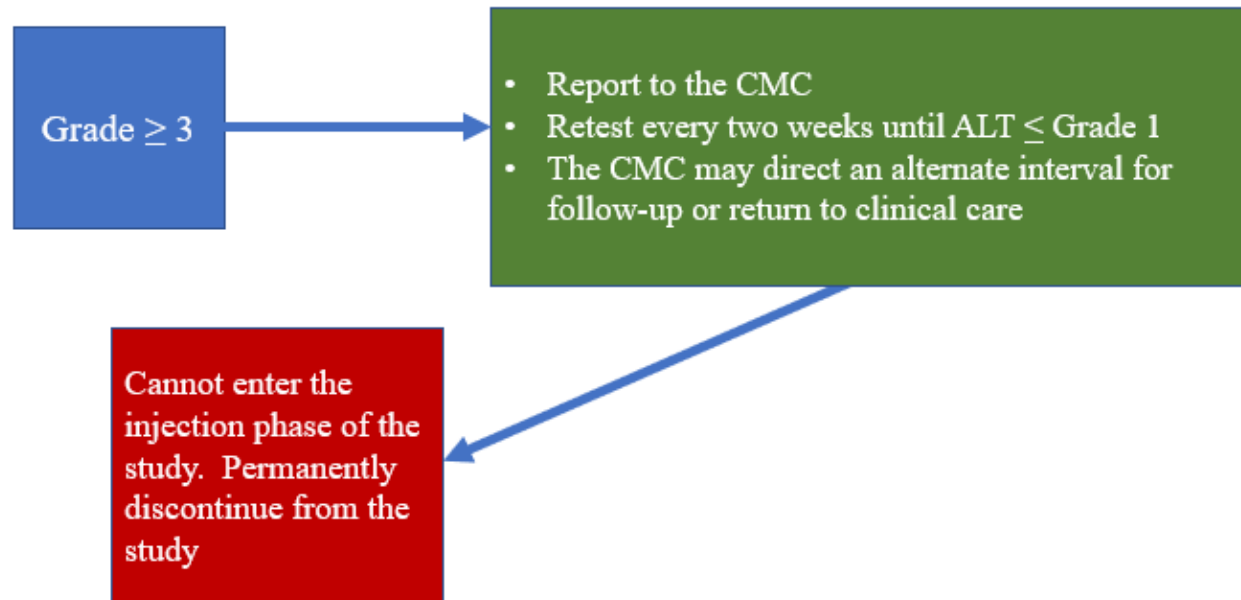


*For all grade levels, treat symptomatically

Guidance on Toxicity Management for Specified Toxicities

ALT Elevations

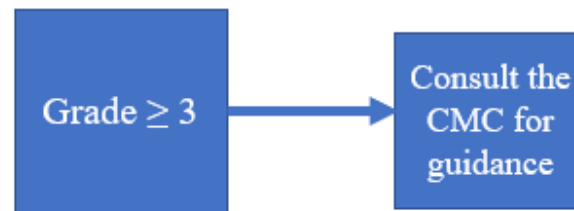
Oral CAB



Guidance on Toxicity Management for Specified Toxicities

ALT Elevations

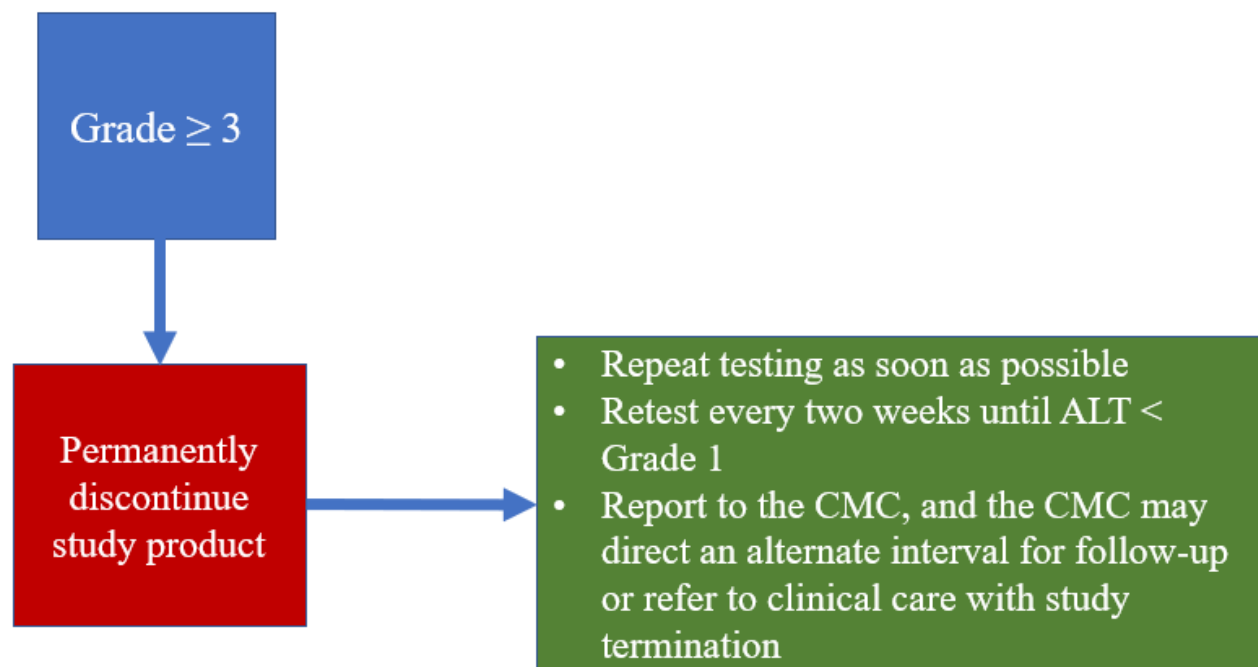
Oral open label TDF/FTC



Guidance on Toxicity Management for Specified Toxicities

ALT Elevations

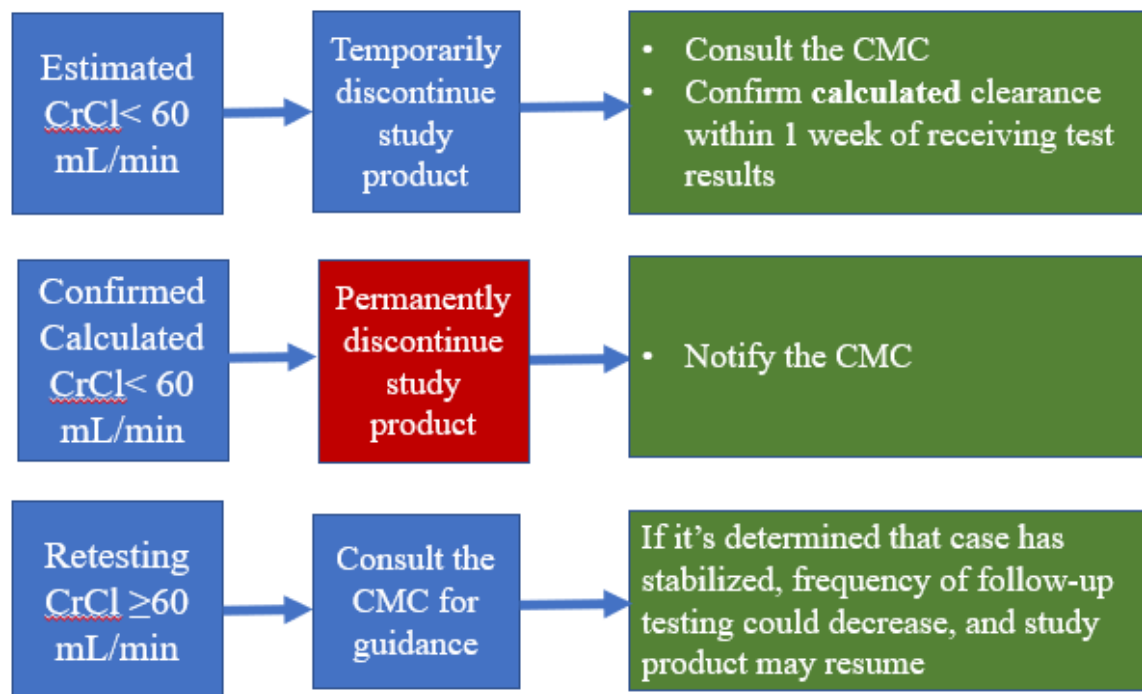
Injectable CAB



Guidance on Toxicity Management for Specified Toxicities

Creatinine Clearance

Only applicable to Oral label TDF/FTC



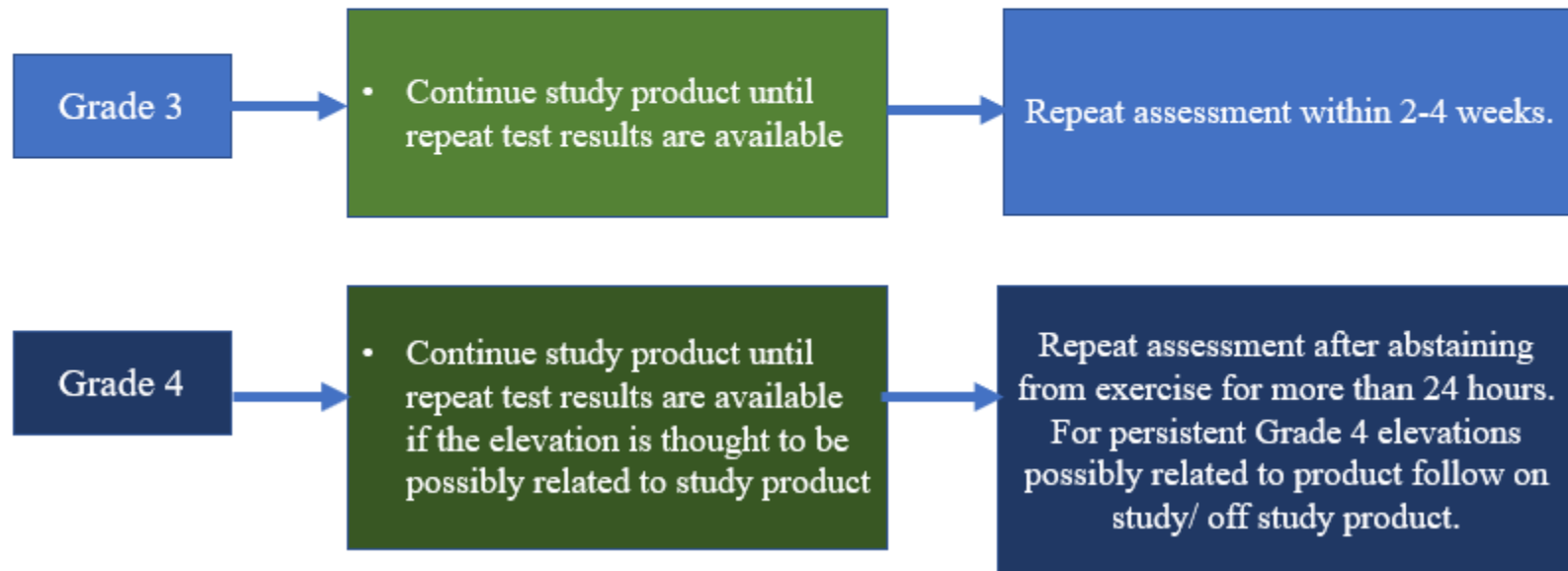
Adverse events related to creatinine clearance should be based on examination of BOTH the absolute creatinine clearance AND the change in creatinine clearance from baseline (Enrollment/ Visit 2.0).

Guidance on Toxicity Management for Specified Toxicities

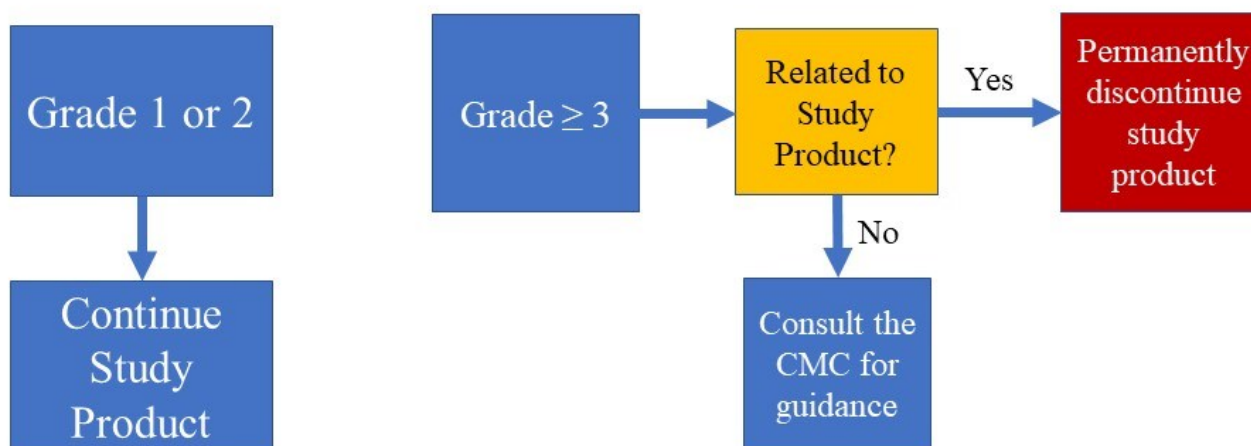
Injection Site Reactions (ISRs)

- Manage ISR discomfort symptomatically (e.g. cold/warm compress, acetaminophen, ibuprofen) Recommended interventions include:
 - Pre-treatment (prior to injection administration) warm compresses
 - Topical or oral pre-treatment with NSAID preparations, unless contraindicated
 - Immediate post-injection massage to injection location
 - Post-treatment warm or cold compresses
 - Post-treatment NSAID or other analgesic preparations, topically or orally

Guidance on Toxicity Management for Specified Toxicities: CPK



Guidance on Toxicity Management for Specified Toxicities Allergic Reactions



Appendix 9a: HPTN 084 Cheat Sheet for Transitioning PPTs from V2.0 to V3.0

Note: Contact the CMC if there is any doubt whatsoever.

*Participants can choose CAB up until and including week 24, thereafter no changes to CAB allowed per protocol.

Participant Status under v2.0 Protocol	Participant Options under v3.0	Where to Transition the Participant Under v3.0
PPT on TDF/FTC with no contraindications chooses between:	joining v3.0, staying on TDF/FTC	Start with Step 4c
	joining v3.0, transitioning to CAB LA	Offer oral lead in (Step 4a) and straight to injection (Step 4b); Participant chooses; After completing Step 4b move to Step 4c
	joining v3.0, does not want to take either product	Start with Step 4c, but without study product administration
	not joining v3.0	Complete termination procedures
PPT on CAB LA with no contraindications chooses between:	joining v3.0, staying on CAB LA	Start with Step 4c
	joining v3.0, transitioning to TDF/FTC	Start with Step 4c
	joining v3.0 but does not want to take either product	Start with Step 4c, but without study product administration
	not joining v3.0	Complete termination procedures
PPT who is confirmed HIV+ on v2.0 chooses between:	joining v3.0	Consent to v3.0. Contact the HIV alias AND the CMC . Follow their guidance for PPT management.
	not joining v3.0	Complete termination procedures
PPT on the Contraceptive Sub-study chooses between:	joining v3.0 and continuing on contraceptive sub-study	Have PPT sign the ICF signature block for continuing the sub-study, Contact the CMC for PPT management NOTE: participants are permitted to change contraceptive method.

Participant Status under v2.0 Protocol	Participant Options under v3.0	Where to Transition the Participant Under v3.0
	joining v3.0 and stopping the contraceptive sub-study	Have PPT sign the ICF signature block for declining the sub-study Manage PPT as regular study PPT
	not joining v3.0	Complete termination procedures
PPT on Annual Testing Schedule, with no safety contraindications, chooses between:	joining v3.0, taking TDF/FTC	Start with Step 4c
	joining v3.0, wanting to take CAB LA	Offer oral lead in (Step 4a) and straight to injection (Step 4b); Participant chooses; After completing Step 4b move to Step 4c
	not joining v3.0	Complete termination procedures
PPT on Annual Testing Schedule, WITH SAFETY contra-indications:	Participant may not join v3.0	Complete termination procedures
Participant who discontinued study product during v2.0 for safety reasons and was transitioned to open-label TDF/FTC for 48 weeks	joining v3.0	Consent to v3.0. Contact the CMC alias. Follow their guidance for PPT management. <i>Note: we will follow PPTs who on v2.0 are on OL TDF/FTC due to safety discontinuations according to the v3.0 protocol, Step 5. Each PPT will complete a total of 48 weeks of TDF/FTC. So, if the PPT was at Week 36 under v2.0 she still will be at Week 36 of Step 5 under v3.0.</i>
	not joining v3.0	Complete termination procedures
PPT who was on TDF/FTC (and never took CAB LA) and who is pregnant on v2.0 at the time of site transition to	joining v3.0, staying on TDF/FTC	Start with Step 4c
	(note: This PPT is not eligible for the Pregnancy and Infant Sub-Study. She was never exposed to	

Participant Status under v2.0 Protocol	Participant Options under v3.0	Where to Transition the Participant Under v3.0
version 3.0, chooses between:	CAB LA and elects TDF/FTC for the pregnancy on v3.0.)	
	joining 3.0, transitioning to CAB LA, agrees to Pregnancy and Infant Sub-Study (note: This PPT is eligible for the Pregnancy and Infant Sub-Study since she is electing to take CAB LA on v3.0. In fact, she must agree to join the Pregnancy and Infant Sub-Study for safety monitoring if she wants to take CAB LA.)	Site staff to consult CMC for initiating CAB LA relative to due date Offer oral lead in (Step 4a) and straight to injection (Step 4b); After completing Step 4b move to Step 4d
	joining v3.0, declines study product	Follow up on 4c without study product administration; collect outcomes at delivery and 48 weeks if possible
	not joining v3.0	Complete termination procedures

Participant Status under v2.0 Protocol	Participant Options under v3.0	Where to Transition the Participant Under v3.0
PPT who was on CAB LA (and had at least one CAB LA injection) and who is pregnant on v2.0 at the time of site transition to version 3.0, chooses between:	joining v3.0, staying on TDF/FTC for the pregnancy, declines Pregnancy and Infant Sub-Study (note: This PPT is eligible for Pregnancy and Infant Sub-Study because she had at least one CAB LA injection on the v2.0 protocol. However, she may choose not to join the Sub-Study if she takes TDF/FTC during pregnancy.)	Start with Step 4c

Participant Status under v2.0 Protocol	Participant Options under v3.0	Where to Transition the Participant Under v3.0
	<p>joining v3.0, staying on TDF/FTC for the pregnancy, and agrees to join the Pregnancy and Infant Sub-Study</p> <p>(note: This PPT is eligible for Pregnancy and Infant Sub-Study because she had at least one CAB LA injection on the v2.0 protocol.)</p>	Start with Step 4d
	<p>joining v3.0, transitioning to CAB LA and joining the Pregnancy and Infant Sub-Study</p> <p>(note: Any PPT who is eligible and elects to take CAB LA during pregnancy must join the Pregnancy and Infant Sub-Study for safety monitoring.)</p>	<p>Site staff to consult CMC for initiating CAB LA relative to due date</p> <p>Offer oral lead in (Step 4a) and straight to injection (Step 4b); After completing Step 4b move to Step 4d</p>
	not joining v3.0	Complete termination procedures; if possible, try to at least get pregnancy outcome information
Participant who had a laboratory AE on either CAB or TDF/FTC and not discontinued but tests not required in new SOE	Transition to product choice	Follow up AE until grade 1; testing is acceptable under clinical care. Contact the CMC for guidance.

Appendix 9b: HPTN 084 Cheat Sheet for PPT transitions from V3.0 to V4.0

Not all participants who were followed under the first OLE (v3.0 of the protocol) are eligible for the v4.0 protocol (OLE2).

Below are the most common scenarios sites will encounter when transitioning PPTs from the v3.0 amendment to the v4.0 amendment. Please note that sites may have participants who do not fall neatly into the below categories; when that occurs the site must contact the CMC for transition guidance.

Participant Status under v3.0 Protocol at the Consent Visit for v4.0			How to Manage PPT Under v4.0
Not Pregnant, PPT on Step 4c TDF/FTC	Has the PPT completed 48 weeks of TDF/FTC during the first OLE?	yes	Do not consent to v4.0 Release PPT from the study and transition to local HIV PrEP program
		no	Consent to v4.0 Continue following PPT until step 4c completed full 48 weeks of TDF/FTC
Not Pregnant, in Step 4c PPT on CAB LA	Does the PPT wish to continue CAB LA?	yes	Consent to v4.0 Continue following PPT on the appropriate Week of Step 4c (so that the PPT receives the full 48 weeks of CAB LA) Once the Step 4c SOE is completed move the PPT to Step 6 for the full 48 weeks of CAB LA.
		no	Consent to v4.0 Continue following PPT on the appropriate Week of Step 4c (so that the PPT receives the full 48 weeks of CAB LA) Once 48 weeks of step 4c completed, transition to TDF/FTC on Step 5 to cover the PK tail
Not Pregnant, on step 5	Completed step 5	yes	Release participant from study
		no	Consent to v4 Once all visits in step 5 completed, release from protocol

Participant Status under v3.0 Protocol at the Consent Visit for v4.0			How to Manage PPT Under v4.0
Not Pregnant, PPT seroconverted	Has participant had infection confirmed, been linked to care and evidence of viral suppression on ART confirmed	yes	Release PPT from study per protocol
		no	Consent to v4.0 Continue to follow up with PPT until infection status confirmed, and/or participant referred to ART and viral suppression is confirmed, then release PPT from the study.
Pregnant, on Step 4c and taking TDF/FTC	Step 4c visits completed?	yes	Consent to v4.0 Once the Step 4c SOE is completed move the PPT to Step 5 for the full 48 weeks of TDF/FTC. Collect pregnancy outcome information
		no	Continue following PPT on the appropriate week of Step 4c. Once the Step 4c SOE is completed move the PPT to Step 5 for the full 48 weeks of TDF/FTC. Collect pregnancy outcome information
Pregnant, on Step 4d taking CAB LA or TDF/FTC and being followed	Visits in step 4d completed?	yes	Consent to v4.0 Consult CMC regarding continuation on step 6
		no	Consent to v4.0 Continue following PPT on the appropriate week of Step 4d until 48 weeks post delivery, then consult CMC about step 6

Appendix 9c: Example SOP for the management of pregnancy

Effective Date:	Version:	Supersedes Version:
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Prepared/Revised By	Signature	Date

Approved By	Signature	Date

Annual Review By	Signature	Date

DOCUMENT HISTORY

Version	Effective Date	Changes

I. Purpose

To describe the procedures regarding management of participants who become pregnant.

II. Scope

This SOP applies to all [site] staff that manage the study participants who are pregnant such as study PI's, Coordinator, Counselors, Nurses and Clinicians. This procedure applies to all studies. Specifics for the HPTN 084 study are included below in the Addendum.

III. Responsibilities

1. Clinicians

- a. To correctly identify clinical situations requiring obstetric care
- b. To deliver appropriate obstetric care to the participant and refer accordingly.
- c. To inform referral facility staff of the participant's arrival.

2. Nurses

- a. To perform nursing duties to facilitate the appropriate obstetric care and monitoring to the participant

3. Community Educators

- a. Tracing participants and tracking medical records

4. HTS Counsellors

- a. Providing HIV testing and counselling

5. Clinic Aides

- a. Sample transportation and escorting participants to [XXXXX].

IV. Allowable Exceptions

This SOP is meant to be followed without deviation. However, it is an allowable exception to follow procedures specified in a protocol or Study Specific Procedure Manual (SSP) that may supersede this SOP.

1. BACKGROUND:

[Site Name] CRS has extensive experience in research involving pregnant women and therefore already has existing collaborations and structures that will ensure the study participants have access to antenatal care including delivery and postnatal care. [XXX] has [XX] Obstetricians (Drs. XXXXX and XXXX) who are available to do obstetric scans for gestational age assessment as well as fetal anomaly scan [within the study site **or** referred to XXXX].

The study site has a memorandum of understanding and strong working relationship with staff at the referral facilities in XXXX and therefore the study team will be able to access hospital records whenever required. The site team through its community educators will closely trace all participants referred for further care to obtain copies of medical records.

V. PROCEDURES

1. Referral of pregnant participants for antenatal care (ANC)

1. To ensure access to antenatal care during pregnancy, a participant with a confirmed pregnancy on 2 different samples collected will be counselled about the need to

attend antenatal care services as required per XXXX Ministry of Health Guidelines. The pregnant participant will be referred for antenatal care to their health facility of choice. The study clinic will refer the participant for all applicable pregnancy-related services and will provide participant a referral letter to the antenatal care services detailing participation in the trial; certified copy of referral letter must be kept on participant file. However, the site will not be responsible for paying for pregnancy-related care.

2. We shall encourage participants to attend antenatal care at [XXX]. These facilities are affiliated with the site and we hope this will enable the site to collect the hospital records and the required samples at delivery as per the HPTN 084 study requirements.

3. Pregnant participants will be escorted by study community educator to register for antenatal care if necessary. The community educator will confirm that participant is enrolled in antenatal care as feasibly possible.

4. Pregnant participants will be asked to share their antenatal care records and certified copies of these will be made and kept in the participant chart. In the event that the participant is unable to bring the antenatal care records, the community educator will confirm from the health facility and obtain as much information as possible. This will only be done following verbal permission from the participant.

5. The study clinician will offer early monitoring to a participant who becomes pregnant and will refer participant for an ultrasound scan and evaluation, within 12 weeks of gestation.

6. Dating ultrasound scans for participants will be conducted by [XXXX]. All enrolled participants will be booked for a review by the obstetrician and will be scanned accordingly using a standard case report form. In cases where the site Obstetrician is not available, the participant may be referred for dating ultrasound scan at [XXXX]. Study clinicians (non-specialists) who are trained and certified to provide obstetric ultrasound scans may be allowed to offer the services as long as this is allowable by the study protocol and they are listed accordingly on the delegation of duty log. The Ultrasound scan reports will be given to the study participant and a copy of these will be kept on the participant chart.

- The Ultrasound will include the following reporting capabilities and parameters:

1. Number of fetuses
2. Ultrasound-estimated gestational age on the date of scan*
3. Estimated date of delivery based on the scan
4. Viability of fetus (heartbeat)
5. Fetal abnormality
6. Additional comments, if applicable

*Estimated gestational age should be measured via

- First Trimester Crown-Rump length

OR

- Later Trimesters
 - Femur length
 - Abdominal circumference
 - Biparietal diameter OR Head circumference

- Trans cerebellar diameter (optional if the other biometry is present)

In the event that the participant comes to the study clinic with an ultrasound scan performed outside these providers; an ultrasound scan with all the above required parameters will be acceptable and a certified copy will be made and kept on the participant chart .A ultrasound scan will be repeated in case some parameters above are missing.

7. The study staff will discuss with the pregnant participant their delivery plan as they come for their scheduled visits. The participants will be encouraged to inform the study staff in case of any changes in their delivery plans. These delivery plans will enable the study staff to plan accordingly for the participant to ensure that the required samples at delivery are collected and the participant receives adequate care during their delivery as per the national guidelines.

8. For planning purposes, the study site will create schedules for expectant mothers with their expectant delivery dates (EDDs) and these will be shared with the community educators. The community educators will keep in contact with these participants and send reminders for required study visits and also regarding their delivery plans. Mothers will be asked to contact the study site at onset of labor or when admitted in hospital for delivery or any other complications.

9. Referral for obstetric complications will be made to [XXXX]. The site has already existing working relationship with [XXXX] team and two site Obstetricians who also provide clinical care at [XXX]. The site Obstetricians that are affiliated with [XXXX] will be contacted in case of any complications. Consultations will be done for non-study related complications of pregnancy and delivery, abnormalities on fetal ultrasound, birth outcomes and phenotyping of abnormalities etc.

10. Management of all obstetric emergencies will be done per site **S.O.P XXXXX on Medical and Obstetric Emergencies**. Pregnant participants with obstetric complications will be escorted by the clinic aide to [XXXX] to ensure they are worked on adequately. This will also enable easy follow up of participant in the hospital and access to their medical records as per permission from the hospital and the study participant.

11. The study site will consult Dr. [XXXXX] for birth outcomes and phenotyping of abnormalities noted during study follow up.

12. All efforts will be made to ensure that participants are followed up to ascertain outcome of pregnancy and appropriate study CRFs will be completed. Participants who are pregnant at the termination visit will continue to be followed until the pregnancy outcome is ascertained in consultation with the study clinical management teams.

2. Referral of pregnant participants and seroconverters for Prevention Mother To Child Transmission (PMTCT) of HIV programs

1. Refer to **SOP XXXX HIV Seroconversion** for guidance on participants who seroconverts during study follow up. A participant may be identified as being pregnant and a seroconverter (or possible seroconverter) in one of three ways.
 - A participant known to be pregnant (already off study drug) has a positive rapid HIV test.
 - A known seroconverter (already off study drug) has a positive pregnancy test.
 - A participant has a positive rapid HIV test and a positive pregnancy test at the same visit.
2. All pregnant HIV-1 positive participants will be referred by a study clinician to ANC health facilities with PMTCT services. Appropriate counseling concerning pregnancy and the importance of PMTCT will be provided at the study clinic by the study clinician and HTC counsellors.
3. The pregnancy and HIV test result information will be availed on the referral form to the health workers at the PMTCT Antenatal clinic. This will be documented on the participant's chart and a certified copy of the referral form kept on the participants file.
4. Infant feeding counseling will be provided for HIV infected women by study clinician. As per WHO/[XXXX] Ministry of Health current guidelines, mothers known to be HIV-infected (and whose infants are HIV uninfected or of unknown HIV status) should exclusively breastfeed their infants for the first 6 months of life, introducing appropriate complementary foods thereafter, and continue breastfeeding for the first 12 months of life. Breastfeeding should then only stop once a nutritionally adequate and safe diet without breast milk can be provided. The mother may still choose not to breastfeed and this is acceptable. The study counselors may also provide this counseling.

3.0 ADDENDUM FOR HPTN 084 STUDY

3.1 Background

HPTN084/LIFE is 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.

During HPTN 084, women were required to be on a long-acting, reversible contraceptive (LARC). This was because we did not know how well CAB LA worked in women and a report from Botswana was released raising the possibility that a drug called dolutegravir (DTG) may have caused a very serious birth defect of the spinal cord and the brain in women who were taking DTG at the time they became pregnant for treatment of HIV. DTG is similar to CAB LA so we wanted to be careful during HPTN 084. Ever since the first Botswana report, doctors have continued to monitor babies born to mothers who have taken DTG during pregnancy. It now seems much less likely that DTG was the cause of the birth defects in babies. We now know that the difference in the rate of birth defects in mothers who took DTG and those that used other antiretrovirals for HIV treatment is essentially the same. Other studies that study large groups of pregnant women that use medications, including DTG during have not found this problem. CAB LA is not the same as DTG. CAB LA has not been shown to cause birth defects in animal studies. In blinded portion of HPTN 084 there were 50 confirmed pregnancies; none of the babies born to women in HPTN 084 had any birth defects.

Now that we know that CAB LA is safe and works to prevent HIV in women, we no longer will require study participants to use a LARC during this study.

Study staff will talk with participants about ways to avoid pregnancy if they wish to do so.

Addressing the use of CAB LA for HIV PrEP in pregnancy is important and timely. Women in high HIV prevalence settings may be at increased risk for HIV when planning to conceive, and need HIV prevention options, like PrEP that go beyond condoms. Pregnancy may also be a vulnerable period for HIV acquisition. Pregnancy and breastfeeding are periods marked by significant biological and behavioral changes that may have varying effects on the risk of HIV.

Preventing HIV in high-risk populations who are also at risk for pregnancy remains a priority for reducing both maternal and infant morbidity and mortality. As access to PrEP expands, data on the safety, acceptability and dosing requirements of PrEP agents during pregnancy are a priority.

Data on the safety and PK of CAB LA in pregnant women compared to non-pregnant women are critical. In particular, data on PK are important for informing the need for dose adjustments in pregnancy. Data on CAB LA concentrations in breastmilk are extremely limited. In pre-clinical pre- and post-natal development studies in female rats, no effect of CAB on lactation was seen at any dose. There was also no effect on rat pup growth and development, or AEs with exposure to CAB in maternal milk.

The HPTN 084 amendment provides an opportunity to offer participants the chance to reconsent to active CAB LA dosing during pregnancy and breastfeeding, while ensuring adequate monitoring of safety in both mother and infant. These data will provide important information on acceptability, tolerability, safety and PK of CAB LA during pregnancy and breastfeeding prior to wide scale implementation in demonstration projects and national programs where extensive monitoring may be limited.

3.2 Precautions taken to prevent pregnancy in HPTN084

3.2.1 Contraceptive requirements in the Open label extension (OLE) of the study;

Pregnancy prevention in the OLE is optional. Following counselling, a participant can decide to remain on family planning or stop family planning. Participants that opt to stop family planning will continue receiving study product depending on the choice of study product they will choose during the OLE. Participants that opt for a family planning method will receive it at the study clinic where possible and in case they receive it outside the clinic, we shall request for a copy of the family planning card or documents so that we can update the concomitant med Log and contraceptive Log in Medidata appropriately

3. Procedures for HPTN 084 Pregnant Participants

- 1. All pregnancies that occur during the course of the study must be reported to the CMC within seven (7) days of site awareness** (either upon confirmation by urine or blood pregnancy testing during a study visit or as reported by the participant between study visits). The CMC will now be contacted following the first positive pregnancy test.
- 2. At the first pregnancy test positive visit, participants will have their pregnancy confirmed on a second independent sample that could be taken off on the same day.**
- 3. Participants should be counselled about the risks and benefits of continuing CAB through pregnancy and breastfeeding, and offered an opportunity to re-consent to receive CAB LA injections during pregnancy. Participants who need more time to consider their**

decision can have their CAB LA injection temporarily deferred, within the remaining visit window.

4. Participants who decline to continue CAB LA during pregnancy and breastfeeding will be offered Open Label (OL) TDF/FTC.

5. All pregnant participants who have had at least one CAB LA injection will be followed up in accordance with the pregnancy schedule of evaluations in Step 4d. CAB LA injections will be administered every eight weeks in those that consent. Additional safety assessments and PK samples will be collected at study visits four weeks after every injection.

6. At delivery, a maternal blood sample and cord blood sample will be collected from the mother, and where feasible an infant blood sample will be collected (week 0).

7. During the post-partum period, blood and breastmilk samples will be collected from the mother, and blood samples from the infant per the Step 4d SOE. Infant outcomes will be assessed at delivery up to approximately 12 months later (Week 48 of Step 4d).

8. Participants who do not have a live birth outcome will be followed up in accordance with Step 4c visits. Pregnancy outcome data will still be collected in these participants at the time of the pregnancy outcome.

9. Participants who have never received a CAB LA injection will be followed up through Step 4c and through to pregnancy outcome. They will remain on the Step 4c SOE.

10. All participants who complete Steps 4c or d will have the option to link to a CAB LA access program or local HIV prevention program if preferred.

4.0 Tracking and documentation of pregnancy outcomes

4.1 All efforts will be made to ensure that participants are followed up to ascertain outcome of pregnancy. Participants who are pregnant at the termination visit will continue to be followed until the pregnancy outcome is ascertained or, in consultation with CMC, it is determined that the pregnancy outcome cannot be ascertained. In the event that a pregnant participant is lost to follow up, this will be documented on the CRF and source documents.

2. Data will be collected on outcomes of all participant pregnancies and recorded on appropriate study CRFs. Whenever possible, medical records documenting pregnancy outcomes will be obtained, photocopied and certified and filed in participant's study records.

3. For all pregnancies which do not continue to term or end in stillbirth, data on the timing and nature of the loss will be recorded, including whether termination was spontaneous or elective.

4. Pregnancy outcomes meeting criteria for AE and/or EAE reporting per protocol will be reported accordingly (see HPTN084 Safety monitoring and reporting SOP).

5.0 Procedures for delivery, collection and processing of required samples at delivery

5.1 Study staff will encourage pregnant participants to deliver at XXX which is in the same facility as XXXX. XXX already has an existing MOU with XXXX allowing the conduct of several studies within the hospital. The study site will obtain clearance from the hospital to work with the HPTN084 study team on the pregnancy infant study. Each pregnant participant who consents to participate in the pregnancy infant sub study will also be asked to provide verbal permission to access her medical records at the point of consent to participate in the pregnancy infant sub study. This will be documented in the participant chart notes.

5.2 Since the management of pregnant participants will follow the standard of care, the site will on case by case support participants in need beyond the standard of care.

5.3 Part time midwives at XXX will be contracted by XXX to support pregnant participants as contact persons when participants report in for ANC or labor and deliver to inform study staff when needed. These midwives will be trained on the study prior to their addition to the Delegation of duties Log. After adequate training and delegation, they will collect the study samples as required at delivery.

5.6 Processing of samples collected at delivery; the protocol requires that the samples collected at delivery for participants in the pregnancy infant sub study are processed within 6 hours of sample collection. The samples that will be collected at XXX will be primarily processed by the XXX Lab. The samples will be transported in cooler boxes as soon as possible within the allowable protocol time by the XXX staff . These staff who transport the samples will be trained and delegated to do so on the study delegation of duties Log.

5.7 We however anticipate that some of the deliveries will be occur outside the XXX lab operational times. In such instances;

- The study staff will keep in contact with the contracted midwives at XXXX and inform the XXXX Lab about any pregnant participants in labor that will not have delivered by 5.30pm on a daily basis so that the XXXX study team can prepare accordingly and have staff available to ensure samples collected at delivery are transported to the Lab and processed within the allowable 6 hour period.
- For any participant who reports to the hospital in labor outside the XXX Lab operational time, the contracted midwives at XXX will be requested to inform the study staff as soon as possible with details on labor progress so that arrangements are made accordingly.
- Special support will be provided to the XXXX staff that will be required to deliver the samples to XXXX Lab processing staff who will ensure the samples collected are adequately processed within the required time as per SOE.

5.8 In case the site is unable to collect or process required samples at delivery for a participant as required, CMC will be informed and protocol deviation will be reported accordingly. This also applies to participants that will deliver in health facilities where we are unable to get the required samples at delivery.

5.9 Sample collection in the postpartum period; Postpartum samples will be collected at XXXXXX clinic. Transport will be provided using the UNCPM vehicles. Mother and baby in the postpartum period will be picked up and taken back home for their scheduled visits to ease their movements.

6.0 Procedures for Infant assessments in HPTN 084

6.1 Pregnancy outcome assessment including abbreviated infant examination will be conducted at week 8 and week 48 postpartum. Whenever feasible, site will use delivery notes plus complete assessment in clinic.

6.2 Infant feeding history will also be collected at weeks 8, 16 and 24 postpartum. These will be documented in the chart notes.

6.3 Infant HIV testing will be performed if the mother is confirmed to have HIV infection. If HIV testing indicates that an infant has HIV infection, a second confirmatory visit should be conducted to confirm HIV infection in the infant. If infant infection is confirmed, resistance testing should be performed locally using a separate (additional) infant sample collected for this purpose.

6.4 Cord blood and infant plasma collection and storage will be conducted at delivery and weeks 2,4,8,16,24 and 48. Assessments on stored samples will be performed retrospectively; results will not be returned to study sites or participants, except as noted in the SSP. These samples will be used for PK analysis and may be used for other assessments, including virology testing.

6.5 In the event that an infant is sick, the site will manage the infant accordingly, document in the required CRFs .Those that need referral will be referred for care as per national guidelines.

Training Date and Method

Unless otherwise specified:

1. All new or revised SOPs are presented at the next study team meeting. The IoR has ultimate responsibility for study conduct, including appropriate training of study staff. The CRS Coordinator or designee is responsible for assisting the IoR in training staff that are absent from study team meetings.
2. All staff are responsible for reviewing all SOPs yearly.
3. New employees are responsible for job specific SOPs within 30 days of hire and all SOPs within 90 days of hire.