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 version 3.0/OLE and higher. The Schedule of Evaluations 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 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.

The HPTN 084 Version 3.0/OLE study is summarized 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

Any questions regarding the safety assessments and clinical management of participants in HPTN 084 should be directed to the HPTN 084 Clinical Management Committee (084CMC@hptn.org).

9.2 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.

- 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, Figure 11.3 for details.

9.2.1 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 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 a participant reports issues swallowing the Truvada/ placebo tablets due to its size, they may split the tablet in half and then swallow immediately. Although a pill cutter is preferred, it's not required for pill-splitting. The Truvada/placebo should not be chewed, ground, or otherwise dissolved.

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.

9.2.2 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 9.2.3 below) and vital signs recorded at each visit (including temperature, weight, 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.

9.2.3 Instructions for Weight Collection

Collecting participants' weight is required as part of <u>all</u> physical exam (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 document 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.

9.2.4 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:

9.2.5 Adverse events

All abnormal findings (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 and Package Inserts 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.

It is important to counsel participants prior to visits requiring lipid profile testing (Weeks 57 and 105) to come to the visit fasting at least 8 hours prior to the visit. If the participant has not fasted for at least 8 hours, you may proceed with ALL study

procedures except for the lipid profile testing. Reschedule the fasting profile within the next few days or as soon as possible within the visit window. Prior to initiation of these visits, confirm with participants when was the last time they had anything to eat or drink. To ensure participant's comfort, prioritize participants who are fasting so testing is done as quickly as possible and if possible provide a snack to the participant after blood is collected (or ask participants to bring something to eat to the visit).

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

For infant AEs, refer to section 10.3.1 "Considerations for Infants in Step 4d"

9.2.6 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.

9.2.7 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 Schedule of Evaluations UNLESS a participant contacts the site with any questions or concerns about an ISR. If a participant contacts the site, then the site may then 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, pruritis, 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 9.3 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.

9.2.8 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.

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 package insert (PI - for Truvada®) and investigator's brochure (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 (as of the time this section of the SSP was written) pare listed below.

<u>Cabotegravir:</u>

- Not to be administered concurrently:
  - Cytotoxic chemotherapy or radiation therapy
    - Note: Systemically administered immunomodulators are removed as a prohibited medication; that is, they can be administered to a participant on CAB.
  - Immunomodulators
  - barbiturates
  - carbamazepine
  - oxcarbazepine
  - phenytoin
  - pheonobarbital
  - rifabutin

- rifampin
- rifapentine
- St. John's wort

- Prohibited within 7 days before and 7 days after an injection
  - high dose aspirin (>325 mg per day)
  - anagrelide
  - apixaban
  - argatroban
  - bivalirudin
  - clopidogrel
  - dabigatran
  - dalteparin
  - enoxaparin
  - fondaparinux
  - heparin
  - lepirudin
  - prasugrel
  - rivaroxaban
  - ticagrelor
  - ticlopidine
  - warfarin
- Oral formulation precautions
  - Antacid products containing divalent cations (e.g., aluminum, calcium, and magnesium) must be taken at least 2 hours before or at least 4-6 hours after the oral CAB administration

Truvada:

- Medications containing the following ingredients should not be administered concurrently:
  - emtricitabine or tenofovir disoproxil fumarate (e.g. ATRIPLA®, COMPLERA®, EMTRIVA, GENVOYA®, ODEFSEY®, STRIBILD®, or VIREAD, Descovy).
  - lamivudine (e.g. Combivir, Dutrebis, Epivir, Epivir-HBV, Epivir A/F, Epzicom, Triumeq, or Trizivir)
  - adefovir (e.g. HEPSERA®)
  - tenofovir alafenamide (e.g. Vemlidy)
  - didanosine (e.g. Videx EC)
  - atazanavir (e.g. Reyataz, Evotaz (atazanari/cobicistat))
  - ledipasvir/sofosbuvir (e.g. HARVONI®)
  - darunavir (e.g. Prezista)
  - lopinavir/ritonavir (e.g. Kaletra)
  - orlistat (e.g. Alli, Xenical)

Please note the following general notes related to precautionary and prohibited medications:

- Medications containing these ingredients and brand names may vary per county. Always verify ingredients of concomitant medications to avoid use of prohibited medications.
- It is acknowledged that the listing of prohibited and precautionary medications for Truvada can be confusing since there is no distinction between prohibited and precautionary medications; however, this listing is consistent with the Truvada package insert and should not be altered.

Additional information regarding recommended, prohibited, and precautionary concomitant medications can be found in the cabotegravir IB and the Truvada® PI.

Considerations for Co-Administration of Precautionary and Prohibited Medications

- 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/emplibrary/NSAIDsConversiontools.pdf

- 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, he/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.

9.3 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 onhttps://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.

9.3.1 Schedule of Injections

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

9.3.2 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.

9.3.3 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: Injections should ideally not be closer than 3 weeks apart. Longer 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

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+ weeks	Give delayed dose and 600mg Q8W thereafter
≥8 weeks	Give delayed dose, 600mg 4 weeks later, and 600mg Q8W thereafter (reloading required)

i.e. if the interval between the last planned injection visit and current visit is 7 weeks 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 not less than 3 weeks after the last injection, and that safety parameters are within normal limits.

Participants that have missed their last planned injection visit by 8 or more weeks will require re-loading. 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 step 2 visit schedule. 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.

9.4 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 "Creatine Clearance" of the SSP (Laboratory and Specimen Management Procedures Section). Note: Participants who initiated the trial on HPTN 084-01 using the Schwartz equation will have creatinine clearance assessed per Schwartz equation at follow up visits.

9.5 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 physicians from a subset of the sites, and also includes the Protocol Chair and Co-Chair, pharmaceutical sponsor investigators, 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.

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, sites will no longer need to report to the CMC cases when a participant's LARC is delayed.

9.6 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. 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.

9.6.1 Liver toxicities/ damage

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.

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

9.7 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 HIV test results must be confirmed to be negative/non-reactive prior to study product administration.

<u>Positive/Reactive HIV Test</u>

If a participant has a reactive or positive HIV test, product will be held. Further testing for confirmation of HIV infection will be done per Modified 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. **During the open-label part of this study, both the CMC (084cmc@hptn.org) and HIV alias (084HIV@hptn.org) lists should be contacted about any HIV reactive or positive results or seroconversion events. The 084 HIV**

team is an independent group that is available for sites to seek guidance regarding the requirements of HIV confirmatory testing. Both the HIV alias and CMC may comment on clinical management of participants who acquire HIV infection.

Sites should email the 084HIV@hptn.org alias 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 this group, make sure to attach the template for documenting of all HIV results for the participant.

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

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 above.

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.

9.8 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.

9.9 Tuberculosis

As noted above in Section 9.2.8, 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**.

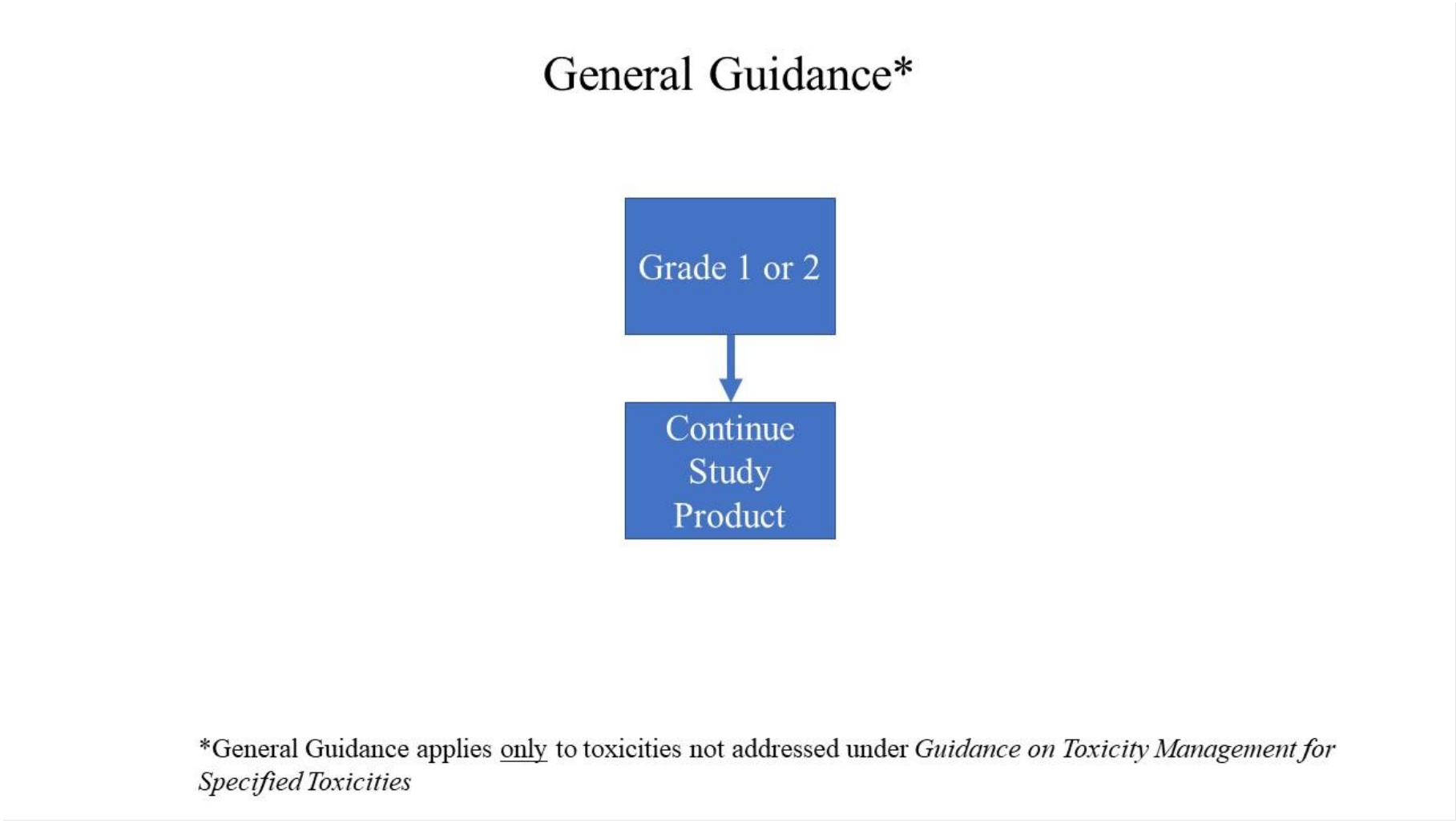
9.10 Pregnancy

Pregnancy must be confirmed on two separate samples.

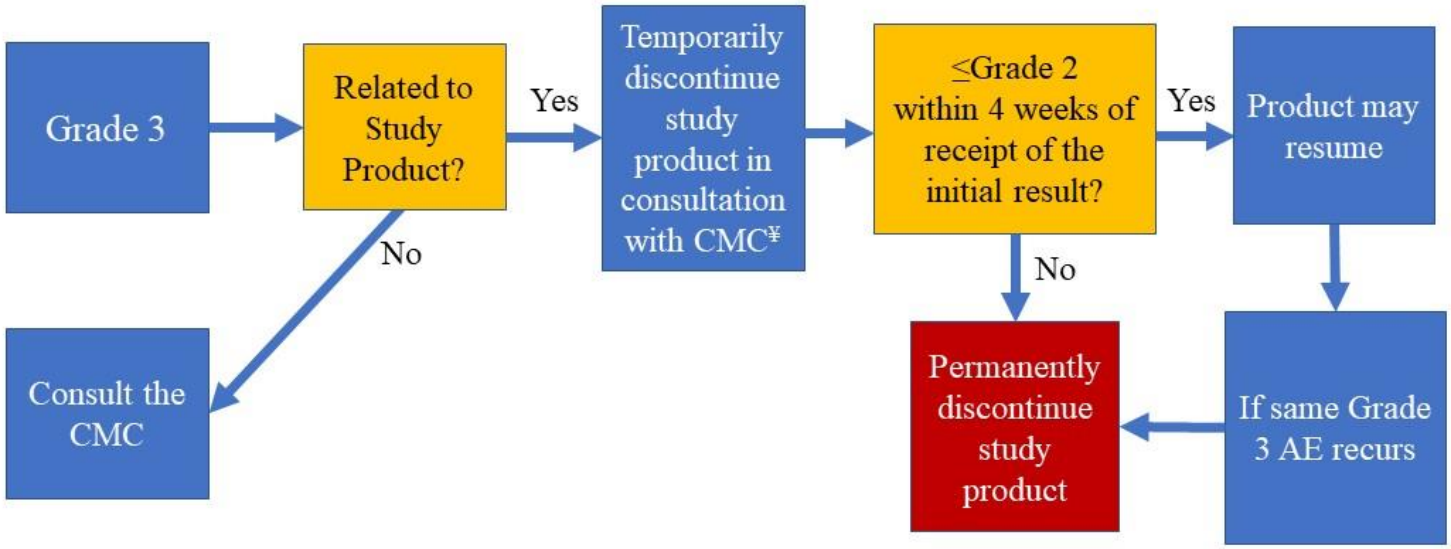
Participants who are pregnant during Step 4 and who received at least one CAB LA injection during HPTN 084 (either blinded study, unblinded phase or during the OLE) are eligible to participate in Step 4d. In addition, participants in Step 5 who received a CAB LA injection within 8 weeks of pregnancy 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. Participants cannot receive CAB during pregnancy without consenting to Step 4d. All participants interested in participating in Step 4d will be provided informed consent for this Step prior to any study activities.

Each site must have a pregnancy SOP in place.

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



General Guidance*



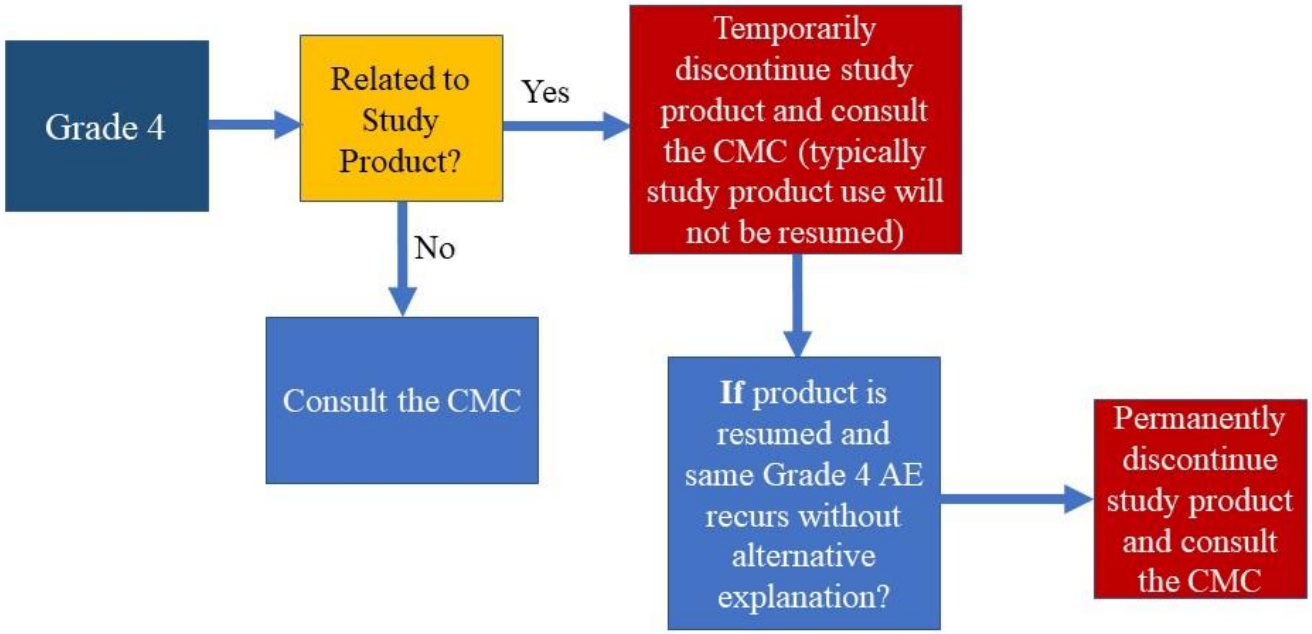
* General Guidance applies only to toxicities not addressed under *Guidance on Toxicity Management for Specified Toxicities*

± 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.

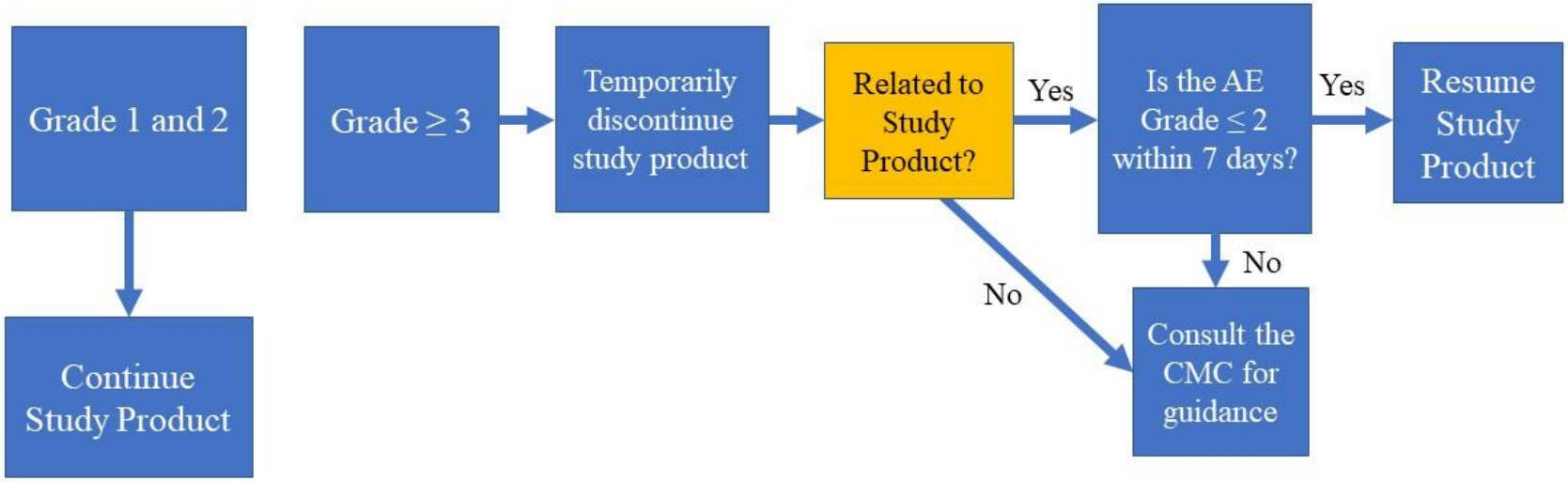
If study product is temporarily or permanently discontinued have participants return any pills as soon as possible.

General Guidance*



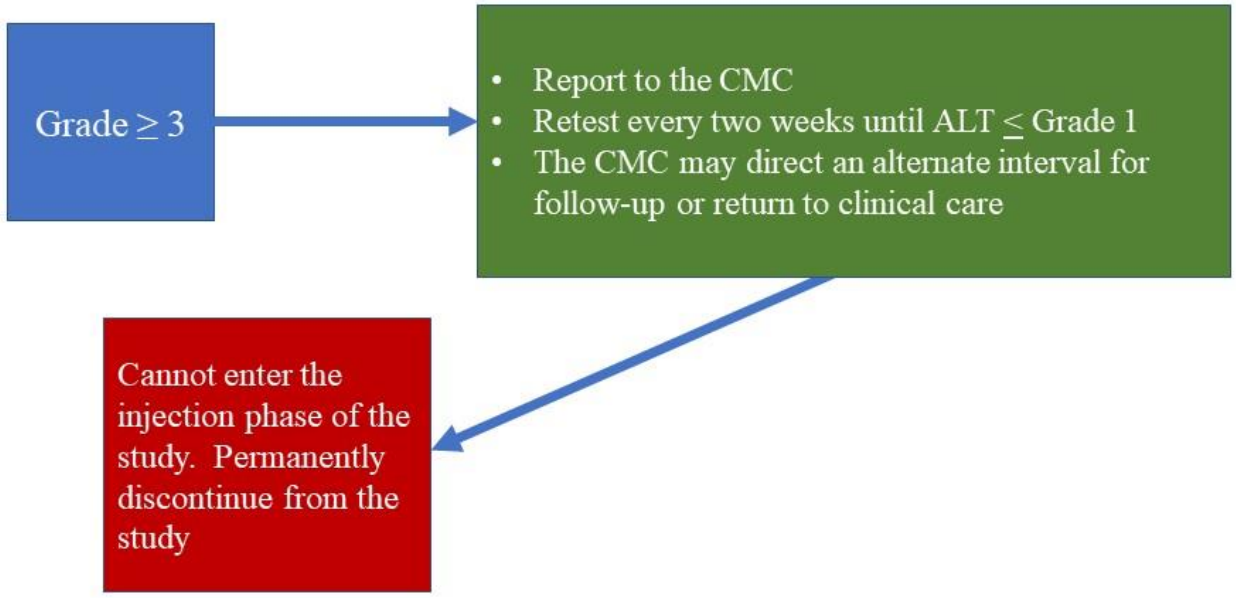
*General Guidance applies only to toxicities not addressed under *Guidance on Toxicity Management for Specified Toxicities*
±Any grade 4 or higher clinical or laboratory AE observed **prior to their first injection** of active CAB (i.e. in STEP 4b) will prompt permanent study product discontinuation.

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

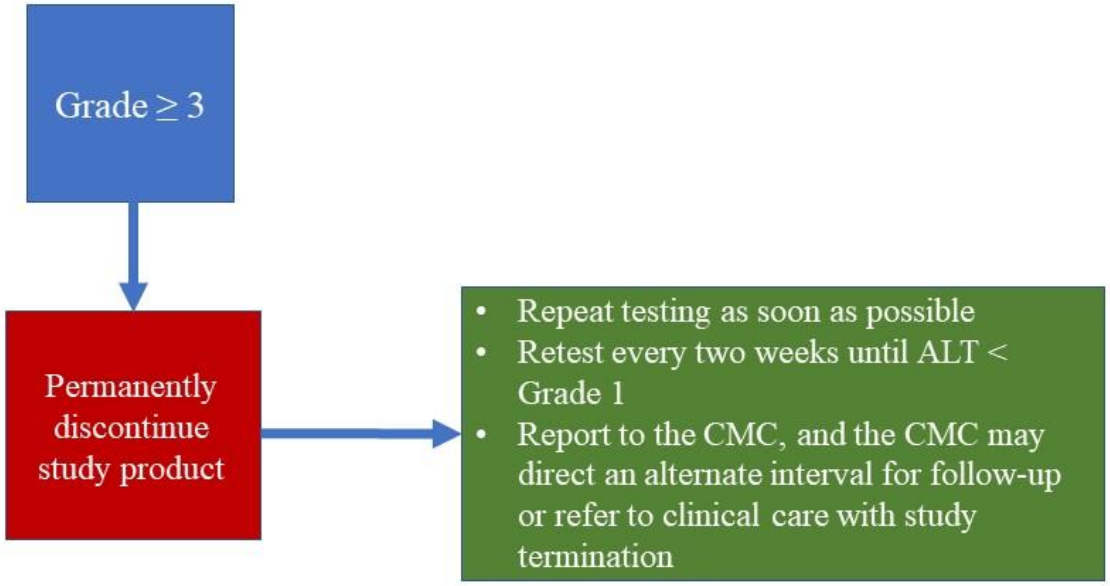


*For all grade levels, treat symptomatically

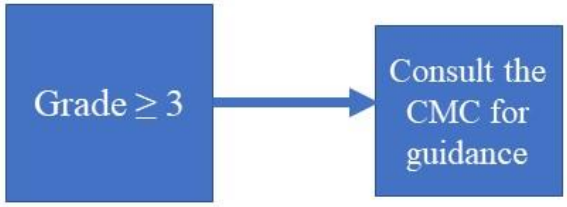
Guidance on Toxicity Management for Specified Toxicities
ALT Elevations
Oral CAB (Step 4a)

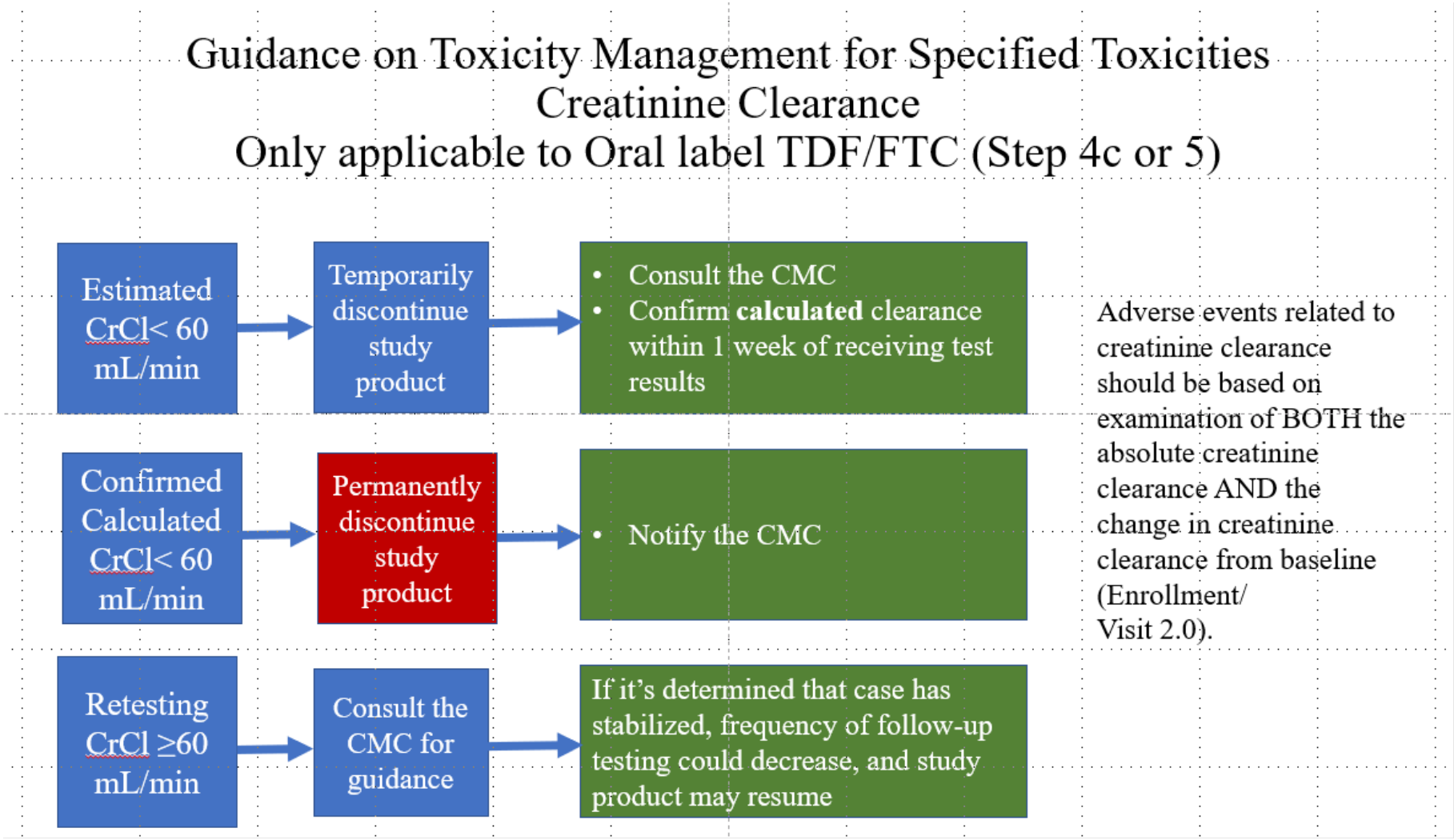


Guidance on Toxicity Management for Specified Toxicities
ALT Elevations
Injectable CAB (Step 4c)



Guidance on Toxicity Management for Specified Toxicities
ALT Elevations
Oral open label TDF/FTC (Step 5)

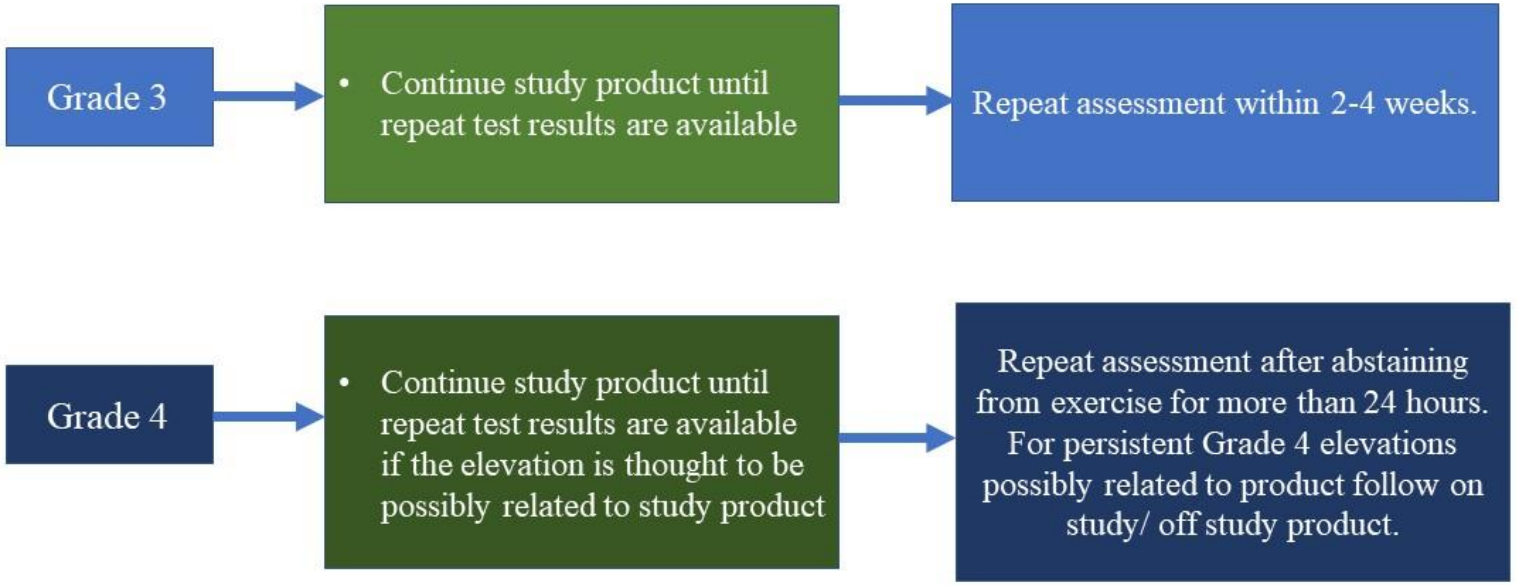



Guidance on Toxicity Management for Specified Toxicities
Creatinine Clearance
Only applicable to Oral label TDF/FTC (Step 4c or 5)
Estimated CrCl< 60 mL/min
Temporarily discontinue study product
Consult the CMC
Confirm calculated clearance within 1 week of receiving test results
Confirmed Calculated CrCl< 60 mL/min
Permanently discontinue study product
Notify the CMC
Retesting CrCl ≥60 mL/min
Consult the CMC for guidance
If it's determined that case has stabilized, frequency of follow-up testing could decrease, and study product may resume
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).

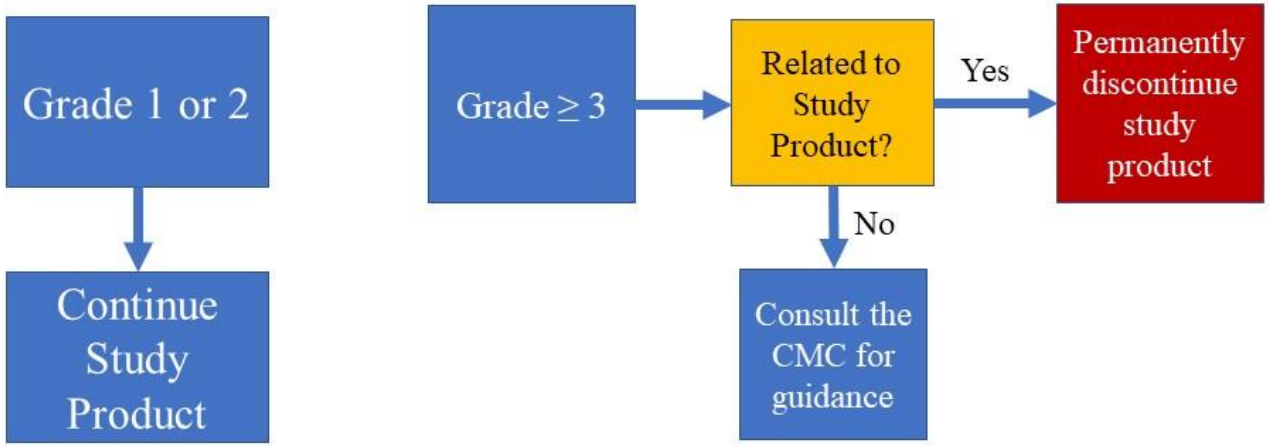
Guidance on Toxicity Management for Specified Toxicities Injection Site Reactions (ISRs)

- 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
- CMC should be notified of premature transition from Step 4c to Step 5 in extreme circumstances.

Guidance on Toxicity Management for Specified Toxicities: CPK



Guidance on Toxicity Management for Specified Toxicities
Allergic Reactions



Appendix 9A: 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	
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. Please advise if our plan is in order.		

Summary table of relevant HIV test results

Date/ Visit Week	Submitting by	Rapid test 1	Rapid test 2	4th Gen	Geenius if available	HIV RNA	HIV DNA	CD4	DBS	Resistance

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

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

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 3.0	Consent to v3.0. Contact the HIV alias **AND the CMC**. Follow their guidance for PPT management.
	not joining v3.0	Complete termination procedures

Participant Status under v2.0 Protocol	Participant Options under v3.0	Where to Transition the Participant Under v3.0
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.
	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, taking 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
	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.

	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 TDF/FTC (and **never took CAB LA**) 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 (**note:** This PPT is not eligible for the Pregnancy and Infant Sub-Study. She was never exposed to CAB LA and elects TDF/FTC for the pregnancy on v3.0.)	Start with Step 4c
	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
	joining v3.0, staying on TDF/FTC for the pregnancy, and agrees to join the 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.)	Start with Step 4d
	joining v3.0, transitioning to CAB LA and joining the Pregnancy and Infant Sub-Study (**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.)	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
	not joining v3.0	Complete termination procedures; if possible, try to at least get pregnancy outcome information