Section 6: Clinical Considerations

6.1. Overview of Section 6

This section provides information on the clinical considerations for participants in HPTN 091. The Schedule of Procedures and Evaluations in Appendices Ia-Ib and Toxicity Management in Appendix II 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 Investigator of Record or designee should perform any additional symptom-directed examinations at their discretion at any time during any visit if they determine it to be clinically necessary, particularly if there are any on-going medical or mental health conditions which may require follow-up.

Information pertaining to participant safety monitoring and adverse event reporting procedures are provided in Section 7 of this manual. Information on performing laboratory procedures is described in Section 8 of this manual, and information on management of GAHT is described in Appendix II of this manual. Further instructions for the electronic data capture system are provided in Section 10 of this manual.

The HPTN 091 study will begin with the Screening visit, followed by:

- Enrollment Visit: within 40 days of signing the ICF
- GAHT Initiation Visit:
    - For participants randomized to Immediate Intervention Arm who accept GAHT to occur within approximately 10 days but no more than 14 days following the Enrollment Visit
    - For participants randomized to the Deferred Intervention Arm who accept GAHT to occur within approximately 10 days but no more than 14 days following the Week 26 (Month 6) study visit
- Quarterly Follow-up visits: Week 13 (Month 3), Week 26 (Month 6), Week 39 (Month 9), Week 52 (Month 12), Week 65 (Month 15), Week 78 (Month 18) after participant enrollment

Any questions regarding the safety assessments and clinical management of participants in HPTN 091 should be directed to the HPTN 091 Clinical Management Committee (091CMC@hptn.org). See Section 6.6 of this SSP for further information about the CMC.

6.2. Participant-Reported Medical History at Baseline (Pre-Existing Conditions) and during Follow up

In order to obtain a complete, accurate, and relevant medical history at screening and enrollment and to assess medical eligibility, it will be necessary to ask the participant about their past medical conditions as well as any conditions the participant is currently experiencing at the time of the Screening and Enrollment visits (i.e., pre-existing conditions).

Information pertaining to the participants' medical history (particularly symptoms, conditions, and diagnoses that affect eligibility or participation in the study) should be obtained. This includes, but is not limited to, a history of hospitalizations, surgeries, allergies, any condition that required prescription or chronic medication (that is, more than 2 weeks in duration), and acute conditions occurring prior to Enrollment (see section 4.5 of the SSP manual for definition of enrollment).

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. The purpose of obtaining this information during screening/enrollment is to:

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

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

6.2.1. Pre-existing conditions

Pre-existing Conditions are a subset of a participant's medical history and consist of all ongoing and/or relevant medical and mental conditions, problems, signs, symptoms and abnormal findings that are observed and/or reported prior to enrollment (randomization) into the study. Participants have not yet been exposed to study product at this time, thus, these conditions are not considered AEs. However, new conditions identified during follow-up that were not present at enrollment and pre-existing conditions that increase in severity (grade) or frequency during follow-up, are considered AEs.

NOTE: Any abnormal laboratory value from samples collected at the enrollment visit, but prior to randomization (i.e., baseline sample) are considered pre-existing conditions and should be recorded as such.

All ongoing conditions recorded as pre-existing are to be documented in the source documents and transcribed onto the Pre-existing Conditions e-CRF. This form is to be completed at the Enrollment Visit based on all screening and enrollment source documents. The purpose of recording pre-existing conditions is for comparison with signs, symptoms and conditions that may be identified or reported during follow-up (after initiation of study products). Therefore, as much information as possible should be recorded about the severity and frequency of any pre-existing condition in source documents as well as in the comments field of the Pre-existing Conditions form to best describe the condition at study entry. This allows for greater objectiveness in noting any grade increase of the pre-existing condition.

All pre-existing conditions noted at screening and on-going at enrollment (prior to the initiation of the oral study product) must be graded even though they are not considered to be adverse events. The purpose of grading a pre-existing condition is because the Pre-existing Conditions e-CRF serves as the "starting point" from which study clinicians must determine whether abnormal conditions, signs, symptoms, and findings identified during follow-up are adverse events (AEs).

6.2.2. Complete Medical History for Ascertainment of Eligibility

A participant's medical history must be obtained at screening for ascertainment of eligibility by performing a complete medical history, based primarily on the inclusion and exclusion criteria listed in the protocol (Sections 4.1 and 4.2 of the protocol). Guidelines for collecting the complete baseline medical history include:

- Probe for history of conditions by body system.
- Document symptoms, illnesses, allergies, hospitalizations, and surgeries.

- Document both acute and chronic conditions, and both ongoing and resolved conditions.
- As part of the medical history, collect information on participant's mental health history, including any conditions, medication, hospitalization, or any other relevant mental health information.
    - Note: Mental health information is collected using the Patient Health Questionnaire (PHQ) at all visits where a physical exam is expected. Sites may also administer this form as needed at other study visits. Sites may opt to develop their own local forms to collect mental health information that is not included in the PHQ form.
- Otherwise, eligible participants with an exclusionary laboratory test result (other than reactive HIV tests and Hepatitis surface antigen positive (HBsAG)) can be re-tested once during the screening process. If a participant is re-tested and a non-exclusionary result is documented within 40 days of ICF collection, the participant may continue with enrollment. If after re-testing the laboratory test results continue to be exclusionary, participant screen fails. At the discretion of the IoR or designee, an additional screening attempt may be done (see Section 4.4 of this manual and Section 4.1 of the Protocol for further information).
- Participants who practice vaginal sex cannot be provided Descovy as it is not approved for this indication. These participants should be counselled prior to randomization so they are aware Descovy is not an option for them.
- Sample to test lipid profile could be collected at either the Screening or the Enrollment visit, per clinician's discretion. Participants must have fasted for at least 8 hours, preferably 12 hours, prior to lipid profile sample collection. Sites should verify that a participant has fasted prior to sample collection. If the participant has not fasted, the specimen should not be collected, and the participant should be scheduled to return to the site for sample collection within 72 hours from the Enrollment Visit.

6.2.3. Interim Medical History at Enrollment

An interim medical history must be obtained at Enrollment by reviewing and updating (as appropriate) the history collected at the Screening Visit. If new signs/conditions are identified at Enrollment (prior to randomization), these newly identified conditions should be documented on the Pre-existing Conditions e-form as needed.

- Signs and symptoms of acute HIV infection should be assessed. These symptoms may include:
    - Fever
    - Fatigue
    - Headache
    - Myalgia
    - Weight loss
    - Pharyngitis or sore throat
    - Lymphadenopathy
    - Rash
    - Diarrhea

- Oral or genital ulcers

Site staff should assess the possible causes of these symptoms, length of time the participant has been experiencing these symptoms, and severity grade. If a constellation of symptoms suggestive of acute HIV infection (per the judgment of the IoR or designee) is present at the Enrollment visit, or if the participant reports a possible recent exposure to HIV, participant should not be enrolled. Participants with symptoms concerning for acute HIV infection may be re-screened in consultation with the CMC once appropriate testing has ruled out acute HIV infection. Consult with the CMC if further guidance is needed.

- Document whether each condition is currently ongoing; conditions ongoing at the time of enrollment/randomization are entered on the Pre-existing Conditions e-case report form. For ongoing recurrent conditions that are expected to be experienced during follow-up (e.g., headaches), the condition need not be present on the day of enrollment to be considered ongoing at the time of enrollment, and should be entered on to the Pre-Existing Conditions e-case report form, including the date of resolution of the most recent episode if it resolves prior to enrollment.
- For all ongoing conditions, assess and record the current severity of the condition per the DAIDS Toxicity Table. See Section 7 of this SSP for further clarifications and guidelines regarding severity grading.

6.2.4. Targeted Medical History at Follow-Up Visits

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 and mental history was performed

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

- was not present at baseline
- was present at baseline (ongoing at enrollment) and 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 adverse event but it has increased in severity grade/frequency

At the participant's first follow-up visit, retrieve their complete medical history source document and look up the Pre-existing Conditions form for reference. At each subsequent visit, retrieve the participant's most recent follow-up medical history source document 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 in a respectful and gender-affirming manner 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 includes any reoccurrences of conditions/symptoms that were previously reported and had resolved at a prior visit, documentation should include the current severity grade.
- 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 resolved since the last visit should have their entries updated with an "Outcome Date".
- In the case of study staff assessment of psychological distress (defined clinically, or outside of the scope of what study staff is comfortable handling), within or outside of the context of the study-related assessments, sites should refer such participants to locally available support or acute care services. A compendium of such services should include but not be limited to: Acute and chronic (longitudinal) mental health support, substance abuse treatment, intimate partner violence services, and primary care. The compendium should be available to all study staff who have study participant contact, particularly Peer Health Navigators (PHN).
- If a participant reports issues swallowing the Truvada 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 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 Pre-existing Conditions 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.

6.2.5. Physical Exams

A symptom-directed physical examination is required at Screening, Enrollment, and all follow-up visits, as per Appendices Ia-Ib. A physical exam may be conducted at the discretion of the Investigator of Record or designee during an interim visit in response to clinically indicated and/or reported symptoms.

A Targeted physical exam is performed at screening for ascertainment of eligibility, based primarily on the inclusion and exclusion criteria listed in the protocol (see Sections 4.1 and 4.2 of the HPTN 091 protocol).

Any abnormal findings at Screening (if still present at enrollment) and at the Enrollment visits should be documented on the Pre-existing Conditions e-CRF. It is important to grade these pre-existing conditions in the source document so that adverse events (AEs) can be reported if the severity of the conditions increases.

The physical exam should include:

- Height (this is a one-time measurement at Screening)
- Weight (see instructions in Section 6.3.1 below)
- Vital signs (temperature, blood pressure, pulse)
- Mental health assessment

And examination of the following body systems/components as needed:

- HEENT (head, eyes, ears, nose and throat)
- Neck
- Lymph nodes
- Cardiovascular
- Pulmonary
- Abdomen
- External genital exam (if clinically relevant)
- Skin
- Neurological
- Extremities

These exams are driven by the signs and symptoms that the participant reports since the previous visit (or initially reported at Screening and Enrollment).

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.

6.2.5.1. Instructions for Weight Collection

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

- Participant should remove shoes, sweaters, coats, scarves, etc. prior to weighing.
- Participants should be asked to void (urinate/empty bladder) before weight is measured, if possible.

- 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).

6.2.5.2. Post GAHT Initiation Safety Visit for GAHT-Naïve Participants

Participants who are initiating GAHT for the first time AND their medications include either spironolactone or cyproterone should have an ad-hoc safety visit approximately one month following GAHT initiation. This additional safety visit is done only if deemed necessary by IoR or designee.

At this visit, sites should do a clinical evaluation, including vital signs and review of medical history. In addition, the following safety laboratory samples should be collected:

- ALT, AST, CBC (if taking cyproterone)
- Potassium (if taking spironolactone)

6.2.6. Please refer to Section 10 of the SSP manual for information about visit documentation. Additional Considerations for Complete and Targeted Medical History and Physical Exams

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

6.2.6.1. Adverse events

All abnormal findings (i.e., Grade 1 and higher) are to be graded and recorded in the participant's source documentation. Grade 3 or higher, any AE (clinical or laboratory) that leads to a study product hold (temporary or permanent), and all SAE/EAE will be captured on the electronic Adverse Experience (AE) Log. 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. Therefore, it is important to counsel participants prior to visits requiring lipid profile testing – baseline (either at Screening or Enrollment visit), Week 26, and Week 78 study visits – to come to the visit fasting. 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). If a participant is not fasting when she/he presents to the clinic, do not collect blood for lipid profile, rather, reschedule the participant to return to the clinic as soon as possible to collect the sample.

See Section 7 of the SSP for more details regarding the reporting of AEs, as well as the Section 7 of the HPTN 091 protocol.

6.2.6.2. Concomitant medications

Sites should document in the participant chart all medications/preparations (prescription and non-prescription) including alternative/complementary medications/preparations (e.g., herbs, vitamins) taken by study participants within 40 days prior to enrollment and anytime thereafter during study participation.

Any gender affirming hormone therapy the participant is taking during the time of enrollment should be documented on the GAHT tracking log eCRF. If the participant transitions to study provided GAHT a new entry should be recorded on the log form. Document specific types of GAHT under the 'Route' option. For example, estradiol valerate 2mg tablets would be recorded as Therapy name – Estradiol tablets, Route – Other, Other specify – oral estradiol valerate.

Any PrEP products the participant is taking during the time of enrollment should be documented on the PrEP tracking log eCRF. If the participant transitions to study provided PrEP a new entry should be recorded on the log form.

Per Section 5.8 of the HPTN 091 protocol, alcohol and recreational and street drug use reported by a participant during the study will by recorded in the participant's study chart only (and not captured on the concomitant medication e-log). Tobacco use and medical marijuana use also should be included in the participant's study chart only. Chart notes for these items should include the specific substances used and dates and frequency of use.

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 they 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 form, record any new medications provided to the participant by study staff, and actively ask the participant whether they are 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 their last medical history, ask whether they took any medications for those. Add all new information to the Concomitant Medications e-CRF. 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.

Note: It is preferable to list the generic name of a concomitant medication on the Concomitant Medications e-CRF; however, listing the trade/brand name is acceptable.

6.2.6.3. Drug Interactions

In order to avoid adverse events caused by drug interactions, whenever a concomitant medication is taken, site staff should review the concomitant medication's and study product's most recent package insert (PI) for the specific study product participant is taking (Truvada®, Descovy®, GAHT) 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 all participants, sites will document all GAHT and PrEP agents obtained outside the study site on the respective GAHT and PrEP tracking log eCRFs.

The CMC should be contacted for any questions regarding coadministration of any of the drugs listed below.

Since GAHT use will be determined by clinicians based on discussion with participant and clinical assessment, staff should consult the specific hormonal treatment's PI for information on drug interactions.

Please note that the PIs for Truvada® or Descovy® do not list any prohibited medications. The drug interaction information listed below comes directly from the Package Insert for each product.

Truvada® Drug Interaction:

Drugs Affecting Renal Function

Coadministration of Truvada® with drugs that are eliminated by active tubular secretion may increase concentrations of FTC, tenofovir, and/or the co-administered drug. Some examples include, but are not limited to, acyclovir, adefovir dipivoxil, cidofovir, ganciclovir, valacyclovir, valganciclovir, aminoglycosides (e.g., gentamicin), and high-dose or multiple NSAIDs. Drugs that decrease renal function may increase concentrations of FTC and/or tenofovir.

Established and Other Potentially Significant Interactions

Established and Significant[a] Drug Interactions: Alteration in Dose or Regimen May Be Recommended Based on Drug Interaction Trials (Table 7 under section 7.2 of the Truvada® Package Insert)

Concomitant Drug Class: Drug Name	Effect on Concentration	Clinical Comment
NRTI: didanosine[c]	↑ didanosine	Patients receiving TRUVADA and didanosine should be monitored closely for didanosine-associated adverse reactions. Discontinue didanosine in patients who develop didanosine-associated adverse reactions. Higher didanosine concentrations could potentiate didanosine-associated adverse reactions, including pancreatitis, and neuropathy. Suppression of CD4+ cell counts has been observed in patients receiving TDF with didanosine 400 mg daily. In patients weighing greater than 60 kg, reduce the didanosine dose to 250 mg when it is coadministered with TRUVADA. Data are not available to recommend a dose adjustment of didanosine for adult or pediatric patients weighing less than 60 kg. When coadministered, TRUVADA and Videx EC may be taken under fasted conditions or with a light meal (less than 400 kcal, 20% fat).
HIV-1 Protease Inhibitors: atazanavir[c]	↓ atazanavir	When coadministered with TRUVADA, atazanavir 300 mg should be given with ritonavir 100 mg.
lopinavir/ritonavir[c] atazanavir/ritonavir[c] darunavir/ritonavir[c]	↑ tenofovir	Monitor patients receiving TRUVADA concomitantly with lopinavir/ritonavir, ritonavir-boosted atazanavir, or ritonavir-boosted darunavir for TDF-associated adverse reactions. Discontinue TRUVADA in patients who develop TDF-associated adverse reactions.
Hepatitis C Antiviral Agents: sofosbuvir/velpatasvir[c] sofosbuvir/velpatasvir/voxilaprevir[c]	↑ tenofovir	Monitor patients receiving TRUVADA concomitantly with EPCLUSA® (sofosbuvir/velpatasvir) or VOSEVI® (sofosbuvir/velpatasvir/voxilaprevir) for adverse reactions associated with TDF.
ledipasvir/sofosbuvir[c]		Monitor patients receiving TRUVADA concomitantly with HARVONI® (ledipasvir/sofosbuvir) without an HIV-1 protease inhibitor/ritonavir or an HIV-1 protease inhibitor/cobicistat combination for adverse reactions associated with TDF. In patients receiving TRUVADA concomitantly with HARVONI and an HIV-1 protease inhibitor/ritonavir or an HIV-1 protease inhibitor/cobicistat combination, consider an alternative HCV or antiretroviral therapy, as the safety of increased tenofovir concentrations in this setting has not been established. If coadministration is necessary, monitor for adverse reactions associated with TDF.

a. This table is not all inclusive.
b. ↑=Increase, ↓=Decrease
c. Indicates that a drug-drug interaction trial was conducted.

Descovy® Drug Interaction:

Drugs Affecting Renal Function

Coadministration of Descovy® with drugs that reduce renal function or compete for active tubular secretion may increase concentrations of FTC, tenofovir, and other renally eliminated drugs and this may increase the risk of adverse reactions. Some examples of drugs that are eliminated by active tubular secretion include, but are not limited to, acyclovir, cidofovir, ganciclovir, valacyclovir, valganciclovir, aminoglycosides (e.g., gentamicin), and high-dose or multiple NSAIDs.

Established and Other Potentially Significant[a] Drug Interactions (Table 5 under section 7.3 of the Descovy® Package Insert)

Concomitant Drug Class: Drug Name	Effect on Concentration[b]	Clinical Comment
Antiretroviral Agents: Protease Inhibitors (PI)		
tipranavir/ritonavir	↓ TAF	Coadministration with DESCOVY is not recommended.
Other Agents		
Anticonvulsants: carbamazepine oxcarbazepine phenobarbital phenytoin	↓ TAF	Consider alternative anticonvulsant.
Antimycobacterials: rifabutin rifampin rifapentine	↓ TAF	Coadministration of DESCOVY with rifabutin, rifampin, or rifapentine is not recommended.
Herbal Products: St. John's wort *(Hypericum perforatum)*	↓ TAF	Coadministration of DESCOVY with St. John's wort is not recommended.

a. This table is not all inclusive.
b. ↓=Decrease

6.3. Specimen Collection

Blood, urine, and rectal and pharyngeal swabs will be collected throughout the study. The protocol outlines the clinical procedures and corresponding testing to be performed on the specimens in Appendix Ia and Ib of the HPTN 091 protocol. Sections 8 (Laboratory and Specimen Management Procedures) of the SSP and the HPTN 091 visit checklists also should be consulted for further specifications. The following additional considerations should be noted:

- At Enrollment and quarterly follow-up visits, GC/CT testing will be performed using urine, and rectal and pharyngeal swabs. Results from the enrollment visit are not required prior to enrollment. (See Section 11 of this manual for further information.)

- At baseline*, and Weeks 26 and 78, a fasting lipid profile is obtained. Participants should be fasting for at least 8 (preferably 12) hours before sample collection. Prior to initiation of these visits, confirm with participants when was the last time they had anything to eat or drink. If a participant is not fasting when they present to the clinic, do not collect blood for lipid profile, rather, reschedule the participant to return to the clinic as soon as possible to collect the sample. Study drug should not be held if a fasting sample was not obtained. If the fasting lipid profile cannot be collected at baseline – meaning at either the Screening or the Enrollment Visit – schedule the participant to return to the clinic for sample collection within 72 hours of the Enrollment visit (that is, within 72 hours of study product initiation). If a sample cannot be obtained within this timeframe, contact the CMC for guidance on an acceptable timeframe to collect the sample.

  *Note: At baseline, lipid profile could be collected at either the Screening or the Enrollment visit, based on clinician discretion. If collected at the Enrollment visit, it should be done prior to randomization/product dispensation.

- Calculated creatinine clearance must be performed at every visit where chemistry testing is being performed, using the Cockcroft-Gault formula. The formula for males is:

  eCcr (male) in mL/min = [(140 - age in years) x (actual body weight in kg)] / (72 x serum creatinine in mg/dL).

  Notes related to the creatinine clearance:

  - *Creatinine clearance calculation for TGW is based on sex assigned at birth.*
  - *"Age in years" refers to participant's current age. It should not be rounded up, even if next birthday is in the near future. For example, a 26 year-old participant presents to the clinic on 11 February, but she is turning 27 the following day, 12 February. The age to be used for calculation is 26 and not 27. Age should not include decimal places (i.e., 26.5 or 26.75)*

6.4. 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 091 CMC will 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, an expert on transgender health, and representatives from the HPTN LOC, HPTN LC, and the HPTN SDMC. The CMC primary responder will be responsible for soliciting input and responding to site queries within a 24-hour time period.

Sites should be mindful that throughout the HPTN 091 protocol and associated protocol appendices, as well as the SSP manual, are examples of situations and adverse events that require consultation with the CMC.

Queries from sites are submitted to the following email alias list: 091CMC@hptn.org.

Queries must be formatted to include the information outlined below.

- Include "091 CMC: [Insert PTID] – [One-line summary of query – for example – "Elevated ALT" 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: 091 CMC: Participant 103-000011 – Elevated ALT

Body of email:

Site name and number: Site 103 – HIV Prevention Clinic

Person submitting query: Hedda Lettuce, Study Coordinator

PTID and Week on Study: 103-000011, Week 26

Query Type: Initial submission

Reason for query: 32-year-old participant attending Week 39 study visit and using Descovy found to have Grade 3 ALT elevation. This participant previously had a Grade 3 ALT elevation found at Week 26 that improved to Grade 2 at retesting. Per protocol, the CMC should be consulted for further guidance on product use.

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

Denies Alcohol, other recreational drug use

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

	Reference Ranges*	**4/6/17 W39**	**3/23/21 EntryW0**	**3/19/21 screen**
AST	10-40 U/L	812 (G4 25xULN)	15	16
ALT	9-46 U/L	225 (G3 7xULN)	15	15

**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.

6.5. Toxicity Management

Sites should regularly consult the HPTN 091 protocol Appendix II – 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 II 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.

6.6. Suspected or Confirmed HIV Infection

Section 6.4.3 and Appendix Ib of the HPTN 091 protocol and Section 8 of the SSP should be followed for any participant regarding suspected or confirmed HIV infection.

- HIV testing will be done at **all** study visits (with the exception of the GAHT Initiation Visit). Please reference HIV testing algorithms found in Section 8 of the SSP manual.
- An HIV Confirmation Visit must be scheduled for all participants who become infected at any time during the study for confirmation of HIV infection.
- For participants with confirmed HIV infection, permanently discontinue PrEP. These participants will be transitioned to local HIV-related care services. GAHT can continue.

Sites must have in place an SOP that outlines the plan for the facilitation of a participant with confirmed HIV infection into immediate suppressive ART. Sites are not responsible for the provision of ART in these cases, but are responsible for the facilitation into HIV treatment and care.

6.6.1. 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 (Section 6.2.3).

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.

6.7. Sexually Transmitted Infections (STIs)

Appendix Ia of the HPTN 091 protocol and Section 8 of the SSP should be followed for procedures regarding testing for GC/CT and syphilis. As noted in the HPTN 091 protocol, treatment for STIs will be provided per local guidelines (and may include referral for treatment).

At Enrollment and at all Follow-Up Visit (except for the GAHT initiation visit) sites should collect samples for syphilis and GC/CT testing. Please remember that for GC/CT testing, a urine sample and rectal and pharyngeal swabs need to be collected.

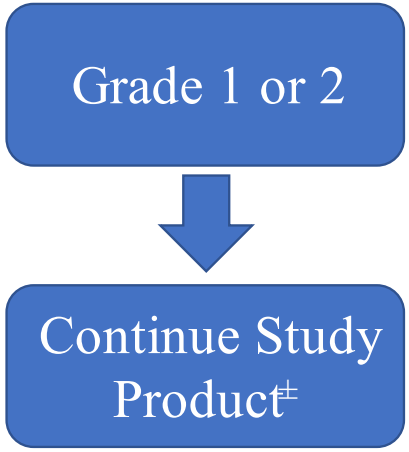
Appendix Ia of the Protocol indicates that treatment for STI will be provided at the screening visit. Since STI testing is not required at the screening visit, the treatment will be provided only if indicated per participant's symptoms. Symptomatic screening for STIs beyond what is required by the protocol will be performed at a site's discretion and costs associated may come out of each site's respective per participant study reimbursements.

When reporting sexually transmitted infections, sites need to report infections diagnosed as part of protocol-required testing for GC/CT and syphilis on the STI eCRF as well as the AE Log eCRF. All other STIs diagnosed as part of standard of care will be reported on the AE Log eCRF only.

Toxicity Management Guidance:

- Found in Appendix II of the protocol. It includes information about clinical management and product use guidelines.
- In general, the IoR/designee has the discretion to hold study product temporarily at any time if she feels that continued product use would be harmful to the participant or interfere with treatment deemed clinically necessary.
- Unless otherwise specified, the CMC needs to be consulted for guidance on resuming study product, continuing the hold temporarily, or progressing to permanent discontinuation of study product. All temporary product holds and permanent discontinuations will be documented on applicable eCRFs.
- Appendix II: Toxicity Management section is divided as follow:
  Section A: Applies to all study products – PrEP and GAHT
  General AE management
  Specific toxicities
  Section B: Management of PrEP toxicities
  Section C: Management of Hormonal Therapy Toxicities

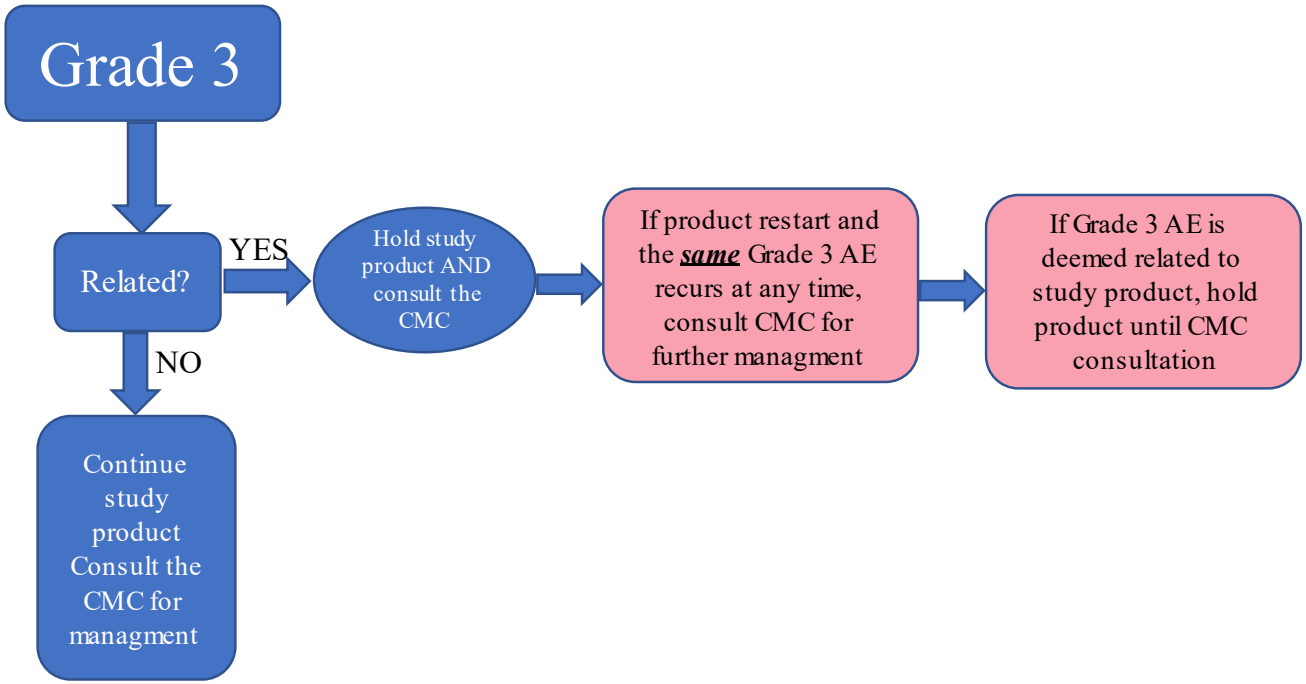
General Guidance*



±If IoR opts to hold study product, the CMC must be notified

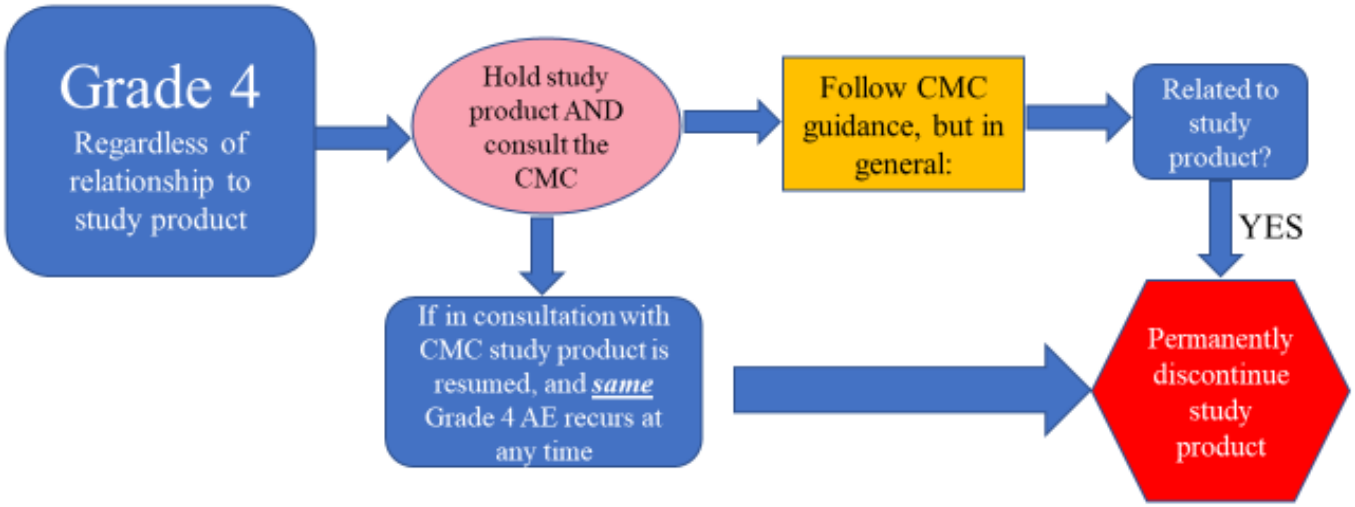
*If condition is addressed on Appendix II under Management of Specific Toxicities, follow specific guidance. This general guidance only applies to abnormalities without specific guidance in the Toxicity Management Section of the protocol.

General Guidance*



*If condition is addressed on Appendix II under Management of Specific Toxicities, follow specific guidance. This general guidance only applies to abnormalities without specific guidance in the Toxicity Management Section of the protocol.

General Guidance*

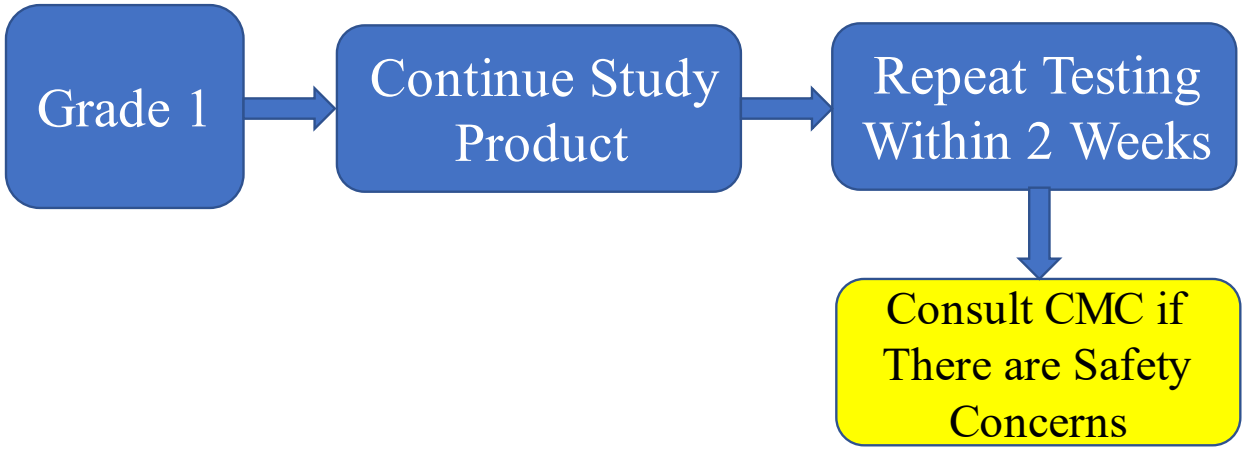


*If condition is addressed on Appendix II under Management of Specific Toxicities, follow specific guidance. This general guidance only applies to abnormalities without specific guidance in the Toxicity Management Section of the protocol.

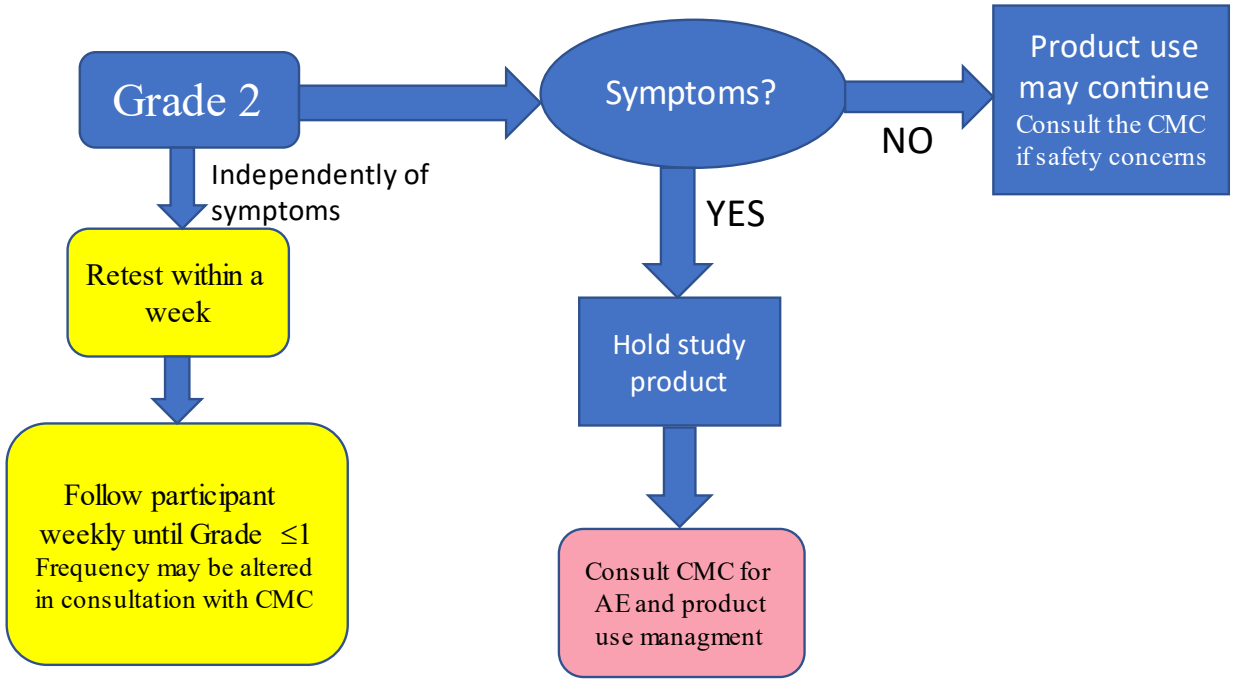
General Considerations for AST and/or ALT Elevations

- Careful assessments should be done to rule out alcohol, non -study medication - related drug toxicity, herbal medications/supplements, or viral hepatitis as the cause of elevation in AST and/or ALT of any grade.
- Carefully assess the participant for any symptoms or signs of hepatoxicity, including fatigue, malaise, anorexia and nausea, jaundice, acholic stools, right upper quadrant pain or hepatomegaly.
- If the AST and/or ALT elevation is considered most likely to be due to concomitant illness or medication, standard management, including discontinuation of the likely causative agent (if clinically indicated), should be undertaken.
- If symptoms or signs of clinical hepatitis are present, temporarily hold study product and test the participant for hepatitis (including HBsAg plus any other testing indicated by the local standard of care). If hepatitis B infection is confirmed, consult the CMC.

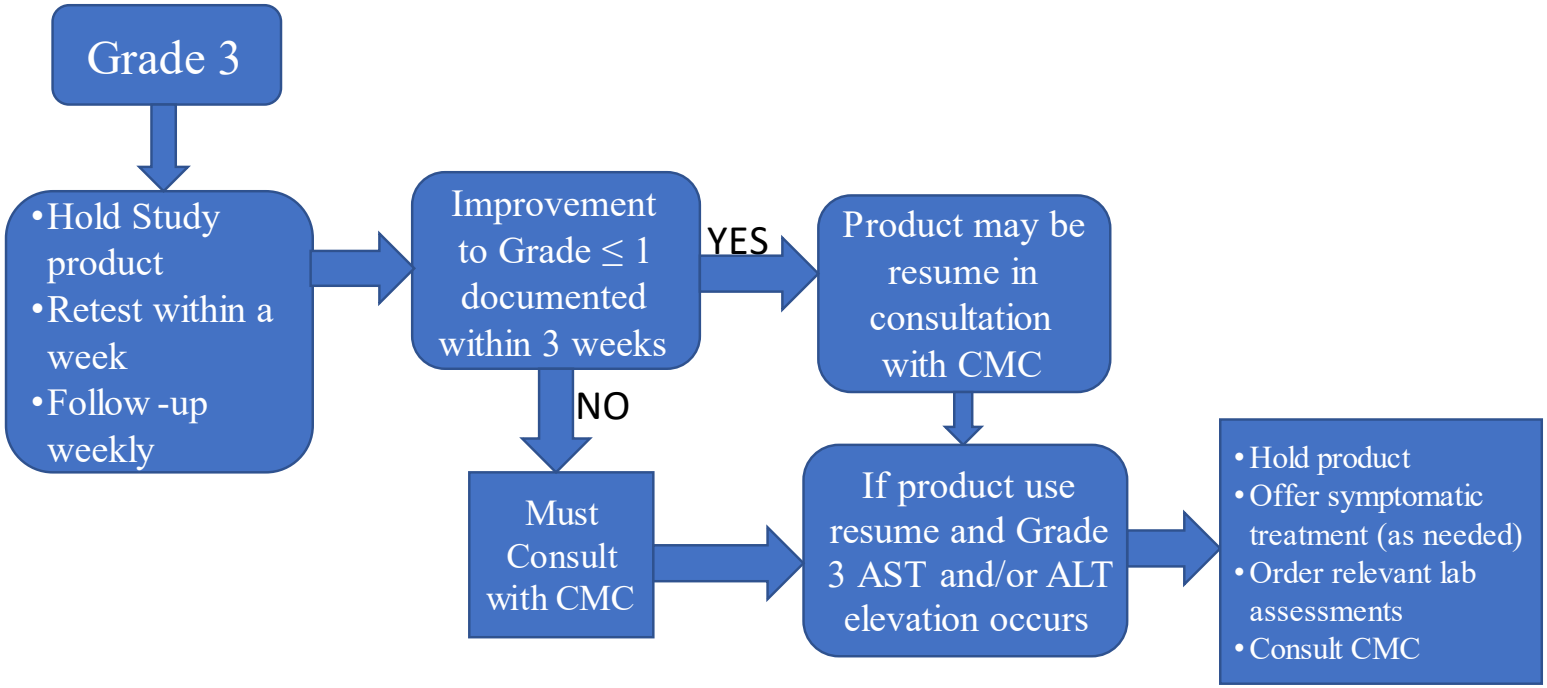
Specified Toxicities
AST and/or ALT Elevations



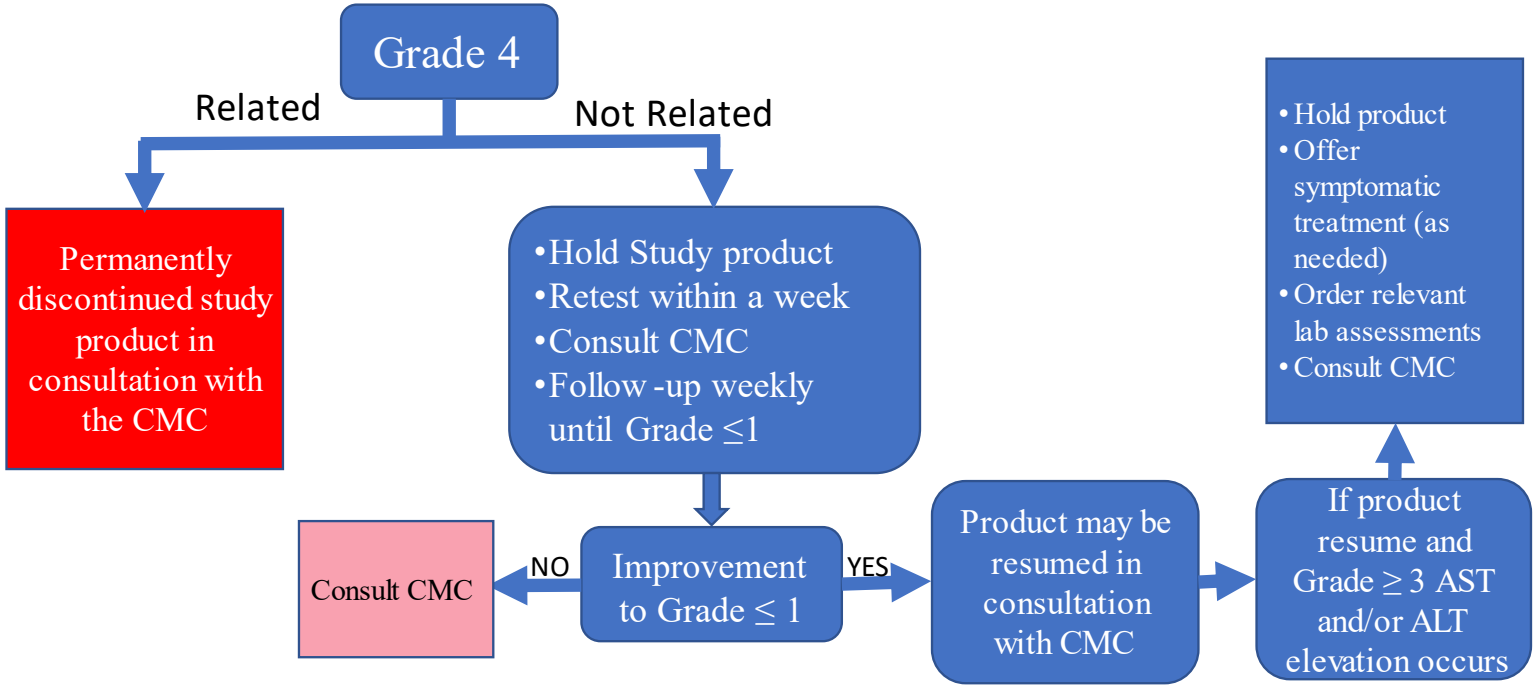
Specified Toxicities
AST and/or ALT Elevations



Specified Toxicities
AST and/or ALT Elevations

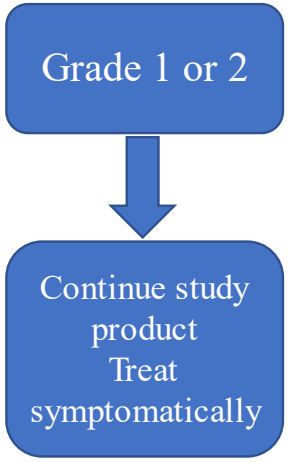


Specified Toxicities
AST and/or ALT Elevations



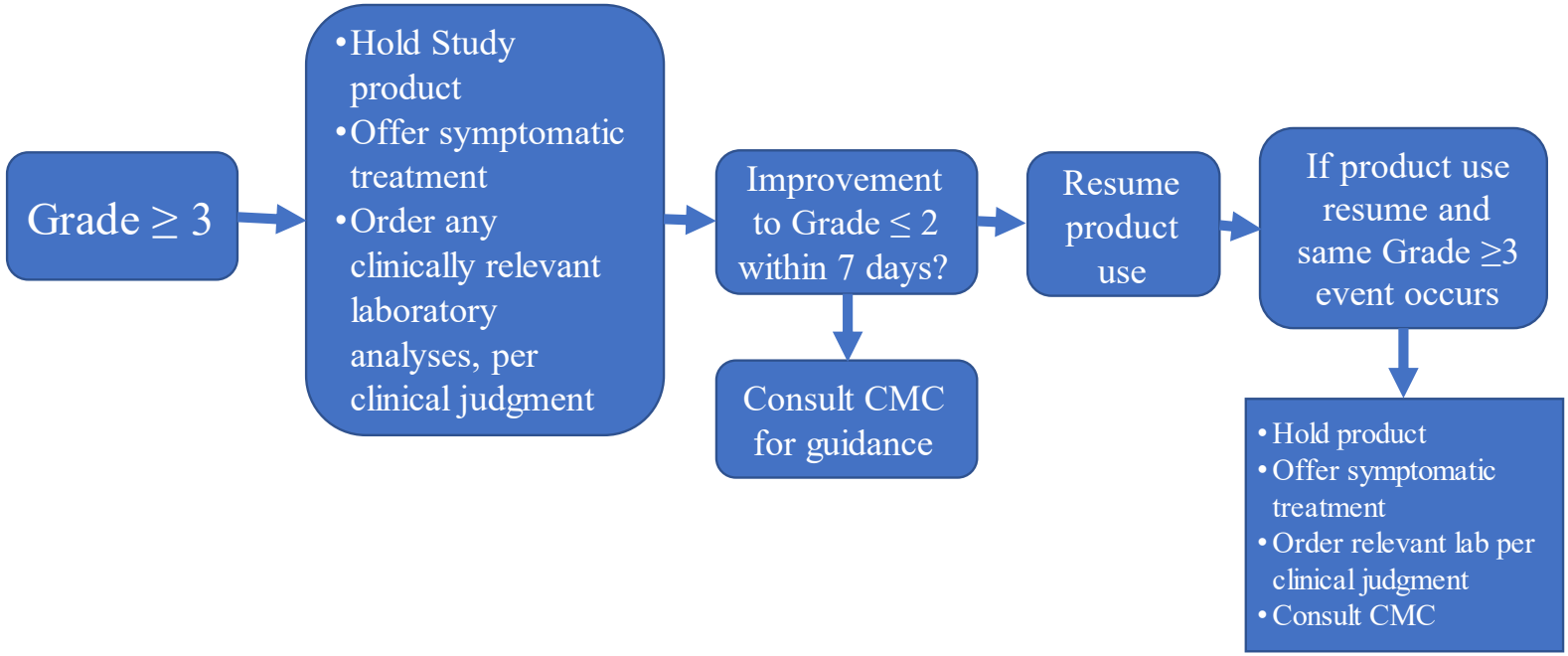
Specified Toxicities

Nausea, Vomiting, and Diarrhea*



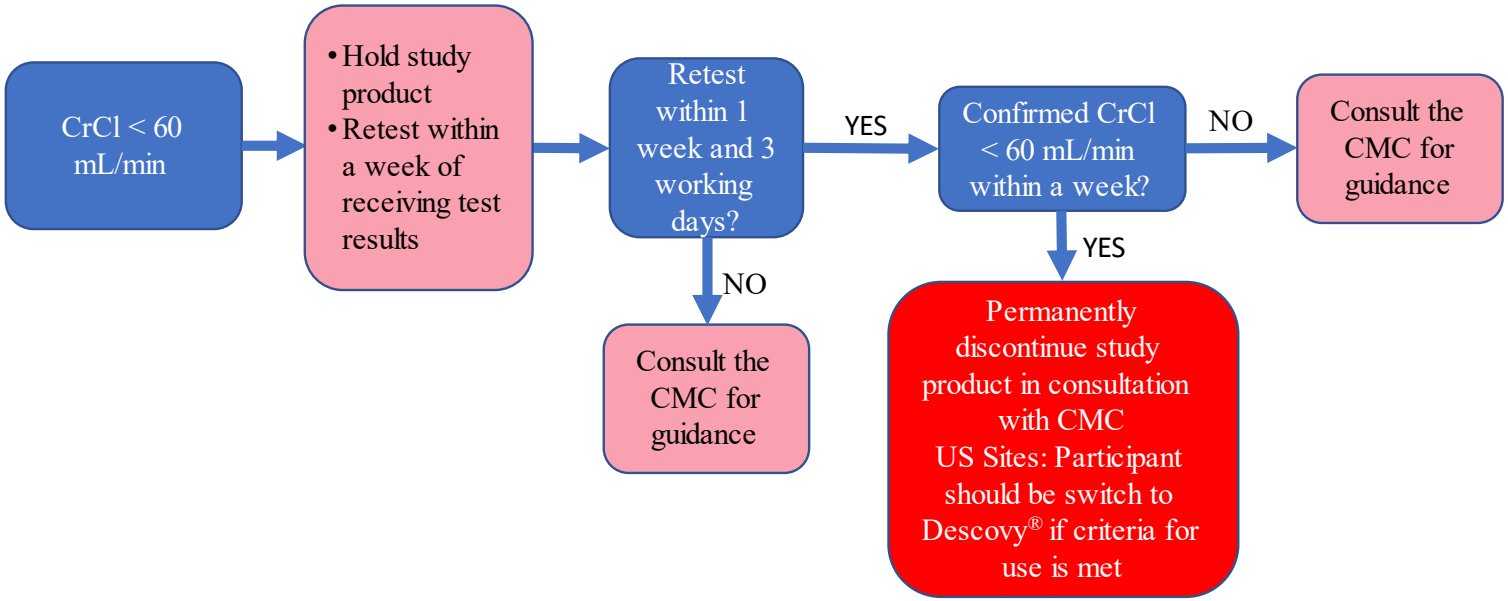
Specified PrEP Toxicities

Nausea, Vomiting, and Diarrhea*



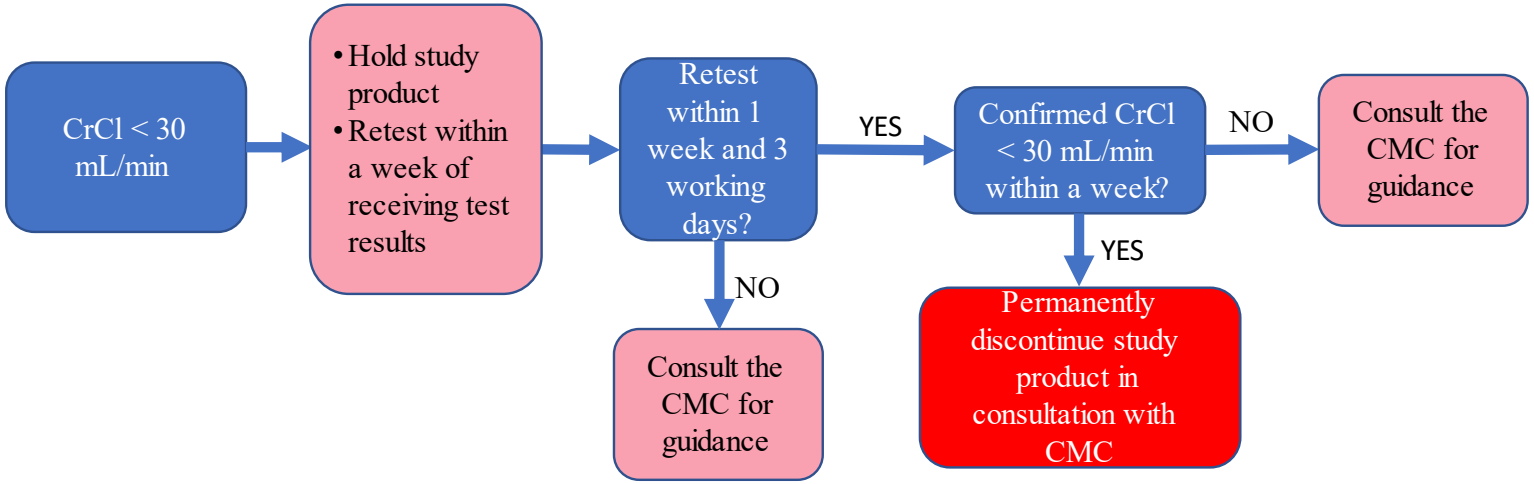
Specified PrEP Toxicities

Creatinine Clearance: Truvada ®



Specified PrEP Toxicities

Creatinine Clearance: Descovy®

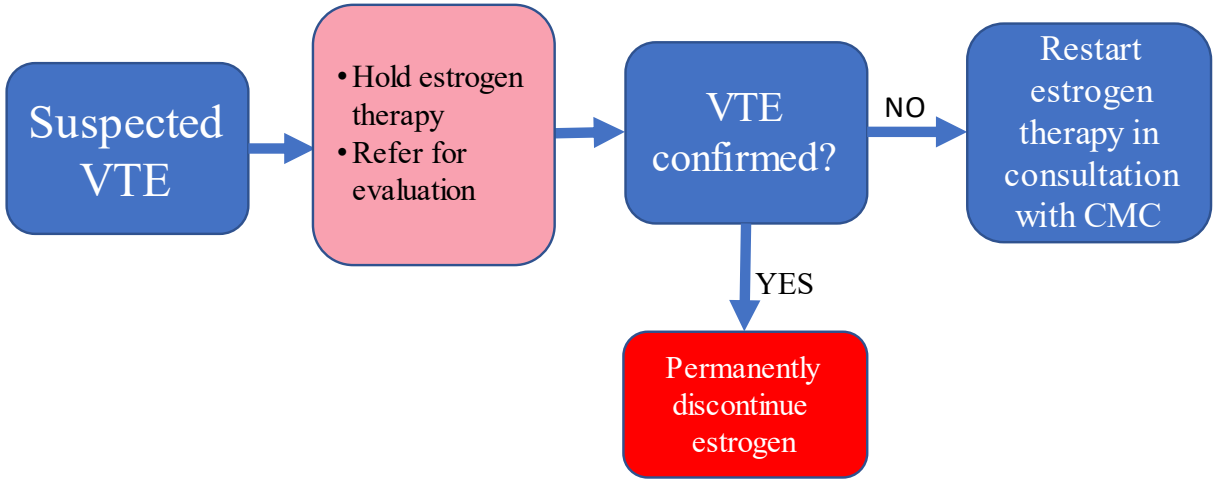


Specified PrEP Toxicities
Creatinine Clearance

- Additional Considerations:
- If clinical suspicion for renal failure exists, local medical resources with clinical expertise in renal failure must be engaged to the extent available.
- Adverse events related to creatinine clearance should be based on the assessment of BOTH the absolute creatinine clearance AND the change in creatinine clearance from baseline (Screening Visit). When gradable, only the higher grade of these two assessments should be entered on the Adverse Event e-CRF.

Specified GAHT Toxicities

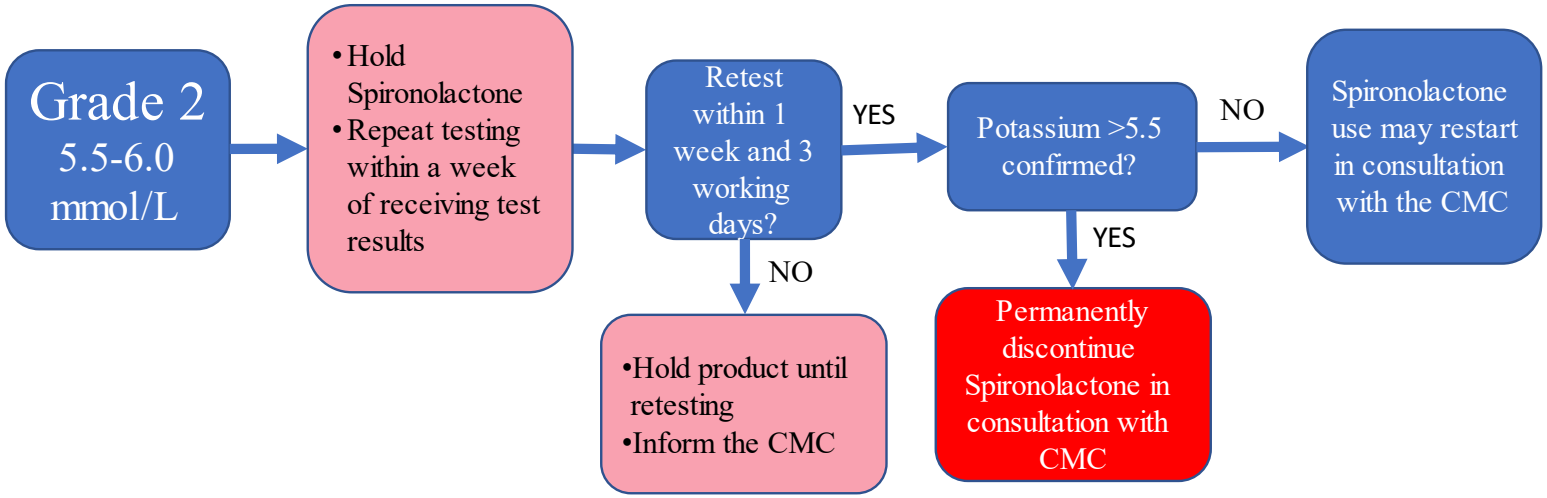
Thromboembolism (VTE)



Note: Estrogen therapy should not be administered in participants with significant risk factors for or history of venous thromboembolism. Therefore, it is important to collect detailed medical history information.

Specified GAHT Toxicities

Hyperkalemia



Note: Spironolactone is potassium -sparing diuretic and mineralocorticoid receptor antagonist that inhibits adrenal aldosterone biosynthesis and can cause elevated serum potassium.