

## HPTN 084: Tips and Lessons Learned from 084 Sites

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](mailto:084CMC@hptn.org)).

General non-clinical questions and Protocol Deviation questions\* should be directed to ([084mgmt@hptn.org](mailto:084mgmt@hptn.org)). Staff members from the HPTN LOC, HPTN Statistical and Data Management Center (SDMC), HPTN Laboratory Center (LC), and Pharmacy Affairs Branch (PAB) will receive the email. Emails with questions will be responded to by the most appropriate HPTN representative.

\*Sites only need to contact [084mgmt@hptn.org](mailto:084mgmt@hptn.org) if they are not sure if something is a deviation, and are no longer required to write to the protocol deviation email alias list.

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### 1. Missed Visits or Injections

- It has taken close to an hour for injectable product preparation; be sure to plan for any pharmacy-related delays for Injection Visits.
- Refer to your site's Pharmacy Establishment Plan (PEP) which outlines how the site Pharmacist of Record (PoR) will dispense study products- whether to a clinician, or directly to a participant. Both are acceptable so long as the clinician and participant remain BLINDED (unless unblinding has occurred for safety or pregnancy).
- Late or missed Week 4 and week 5 visits: Contact the CMC for guidance before you do anything!!! Participants who miss Week 4 must complete Week 4 procedures before moving to Week 5, regardless of the visit window. Week 4 is a mandatory visit, irrespective of the interval between Week 2 and Week 4 visit. The CMC will provide guidance on whether a transition to Step 2 may take place and, if so, under what circumstances. Week 5 visits are also mandatory. They can occur outside of the allowable window if the participant missed the scheduled week 5 visit date.
- Delayed or split Week 5 visits: The date of the week 5 injection resets the visit schedule from that point forward (i.e. Week 6 will always be one week after the Week 5 injection even if Week 5 is early or late). Rave calculates the remaining Step 2 visits based off Visit Date (item 1a) on the V5.0 Week 5 Date of Visit CRF. Participants technically stay in Step 2 (regardless of visit schedule) until everyone switches to Step 3.
  - Please note, this is unique for Week 5/Visit 5.0, as typically Visit Date reflects the earliest date the participant was seen for a visit. Therefore, if any assessments were completed prior to the first injection, queries may open. Please respond to indicate that the data are correct as entered.
- Consider printing out the Schedule of Visits at Enrollment and again at Week 5 and giving it to participants, so they can plan for those visits and hopefully reduce missed visits.
- The minimum allowable time between injections is 3 weeks.

### 2. Adherence

- Pill counts are only conducted at Weeks 2 and 4 (Oral Safety Visits). These pill counts are done to ensure adequate participant study product exposure before moving to injectable product. Pill counts are not formally reviewed for visits in Step 2 or Step 3.
  - Participants should be advised to bring open bottles to appointments, finish an open bottle before opening a new one, and should not combine or transfer pills between open bottles
- The protocol does not allow for a "second chance" to meet the adherence threshold after the step 1 period has elapsed.

### 3. Pregnancy/Contraception

- At the first positive pregnancy test, contact the CMC at [084cmc@hptn.org](mailto:084cmc@hptn.org).

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- If pregnancy is confirmed at 4 weeks, please ensure the procedures under SSP Section 9.15.6 Unblinding Procedures in the Event of Confirmed Pregnancy are followed.
  - Kindly note these procedures are different from those for *Emergency Unblinding for Medical Reasons* (SSP Section 9.15.1), which should occur rarely, if at all, during the study. Emergency unblinding discloses arm information to the IoR in Rave, which may be required in the setting of an urgent, potentially life-threatening clinical event. Pregnancy unblinding procedures limit information to direct treatment assignment for only the individual participant affected.
- Sites should always contact the CMC if a participant has a contraceptive coverage lapse (Refer to LoA #3)
  - If participant returns within the 1-month allowable grace period following a missed DMPA injection, or the 2-week grace period for NET-EN, sites can proceed with routine visit procedures (MUST also inform the CMC).

### 4. CPK, Liver Function, other laboratory testing/ results

- Contact [084mgmt@hptn.org](mailto:084mgmt@hptn.org) for questions about lab redraws.
- Sites can proceed with the Week 5 injection while awaiting the LDL result. Contact SDMC for any questions on eCRF completion. Try to have the participant come back within 72 hours for LDL testing (after the Week 5 visit).
- If there is a clinical indication for syphilis at the screening visit and syphilis testing is done at screening, it must be repeated at enrollment. STI positivity does not exclude enrollment. In fact, it demonstrates that the participant is high risk and a good candidate.
- If a woman is on her menses at the enrollment visit and a TV swab cannot be obtained, it should be collected as close to the enrollment visit as possible.
- The protocol inclusion and exclusion criteria were created with the goal of ensuring the safety of the participants. Therefore, laboratory values that are gradable but not exclusionary should be considered in the context of the overall health of the participant.
- A participant had a grade 2 platelets result of 81,000 at screening and the platelets were clumped/ reported as an inaccurate reflection of true platelet count.
  - This is a legitimate result from the instrument, but the lab should confirm the result on a slide review prior to releasing the result. Some instruments tend to have this happen (clumping) more frequently than others. A new draw had to be performed (Complete Blood Count or CBC). As a reminder the sites should make sure they are following appropriate mixing of the tubes when collecting as this could attribute to platelet clumping. In certain cases, another anticoagulant, citrate, may need to be used to determine just the platelet count.
  - Sites should be aware of low platelets at screening/enrollment because this may affect the ability to provide injections. Participants with plts <50,000 may not be able to receive injections.

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- Low WBC or absolute differential values should be reviewed in the laboratory following standard procedures of slide review before release.
- Low calcium values should be confirmed by the laboratory. The laboratory should also check potassium levels to determine if there is EDTA contamination in the SST/Red top tube. If so the clinic should review their blood draw practices to ensure that collections follow appropriate blood draw sequence.
- The clinic should liaise with the laboratory for any concerns with particular lab results.
- A site received a query on entering both BUN and Urea, because either BUN or UREA is required to be reported but not both. Please refer to the CCGs for additional details on entry and query response for any test that was not done.
- Original lab reports that include PTID, DOB and sex can be stored in a participant's binder versus making certified copies of originals. Check that this is in line with your site SOPs.
- Sites should complete the protocol deviation Medidata Rave CRF in cases when an HIV rapid test cannot be performed (for example, an HIV kit being out of stock) if the participant cannot be re-scheduled within the visit window.

### 5. Data Management

- Medidata Rave can be challenging to learn but, with some practice, it is easy to use.
- A PTID should be generated and assigned when a participant signs the consent. In the event she doesn't return after the first visit, she is counted as a screen out.
- Details regarding the 45-day screening to enrollment window are in SSP Section 4.7.
- For participants who screen out/screen fail:
  - The only eCRFs that are required are the following: HIV Test Results, Plasma Storage, Screening Outcome, and VOICE Risk Score. These are all located in the Screening visit folder. Please do not enter any Enrollment visit eCRFs until eligibility is determined.
  - In the event lab data are entered at screening, please disregard queries on the lab eCRFs. Sex and age are required for grading, but the Demographics eCRF, which contains these fields, is not entered until enrollment.
- At screening and enrollment any abnormal labs are considered part of the participant's Medical History and are not considered AEs.
- Data should be updated directly in the entry field using the pencil icon and not reported in the query response box. Data entered in a query response will result in a re-query.
- In the case of reloading a participant, the injection should be added to the current visit in the EDC. After the participant has been reloaded, they will return to an 8 week injection schedule. *See Data Communiqué #4 for detailed instructions.*
- For Lab eCRFs (Chemistry, Hematology, Fasting Lipids, and Liver Function) that 1) are missing lab ranges and therefore also missing calculated severity grade or 2) have errors with severity grade

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calculations: please select site name from the “Lab” drop-down menu at the top of the page to populate ranges and re-run calculations.

- On the Enrollment eCRF, check “Not applicable” for the Contraceptive Sub-study item regarding participant consent until this substudy is open and enrolling.
- CASI tips:
  - Ensure up-to-date versions of designated browsers are being used, i.e. Chrome, Firefox, Edge, or Safari, to avoid issues with the display and translations. See SSP section 14.2. *Technical Requirements* for a full list of compatible browsers.
  - Use the same assigned CASI IDs for all visits. Refer to the visit schedule to ensure the CASI being used is the intended CASI for that visit.
  - After participants complete the CASI and return tablets, staff must be careful not to click to go back into the participant’s CASI session, where it would be possible to change responses accidentally. If the participant has not already done so, as outlined in SSP Section 14.3.6., please click to “Submit” the completed survey and close the session. If the participant has stopped the survey before completion, you may also close the web browser directly to exit the session from the current page. Data from all previously completed pages will already have been submitted to the server and saved. The SDMC has been alerted to this issue. In the meantime, site staff should take care to close and not accidentally access any CASI session data.

### 6. Audits

- Be Prepared
  - Create an SOP for handling audits and inspections.
  - Prepare staff by holding trainings on audit procedures often. When an audit is announced staff should review the SOP for audits and inspections. To assist with reviewing the SOP, staff can be assigned groups to meet regularly and discuss the SOP.
  - Hold mock audits in which a staff member takes on the role of an auditor. The mock auditor should ask the staff questions to ensure the staff is prepared to answer questions appropriately. A mock audit can help the staff to think through all the necessary procedures and details. A site provided the example of being asked to show the procedure for initialing documents when multiple staff members have the same initials.
- During an Audit
  - When there is an audit (either announced or unannounced) have a space available for the auditor. This may need to be a space with a computer and internet connection, but make sure the auditor ONLY has access to information requested by the auditor.
  - Assign one staff member to be the point of contact for the auditor. This staff member should be very familiar with the study, procedures within the clinic, and the study data. Ensure that the auditor does not roam freely throughout the clinic but is confined to a

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space where there are no participant charts or study data. Information will be brought to the auditor as requested.

- Do not elaborate on any responses to questions. Yes or no are acceptable answers. If you do not know, tell the auditor you will get back to them- and do so as quickly as possible.
- Notify all staff, the protocol chairs, SCHARP, PAB, LC and DAIDS as soon as possible about an audit. These groups can help you prepare as well as be available for any questions or assistance that is needed during the audit.
- One site found creating a flow chart of procedures beneficial for the site staff to be able to quickly reference during an audit.

### 7. Other

- One site mentioned that good Community engagement is critical for recruitment.
- The initial dose of the Hep B vaccination must be given at Week 2. Subsequent doses may be given at different visits than indicated in this SOE, as long as sites follow manufacturer guideline timing. This is noted the footnote in protocol Appendix IB.
- In general, we want to avoid enrolling participants with underlying medical conditions and concomitant medications that can cause difficulty in deciding whether an adverse event should be attributed to the pre-existing condition or study product. The protocol eligibility criteria state the following: *“No medical condition that, in the opinion of the study investigator, would interfere with the conduct of the study.”* This leaves the determination regarding enrolment of participants with comorbid conditions to the discretion of the site investigator. Sites should not feel compelled to enroll a participant that they are unsure would be suitable. However, remember that this is a phase three trial and we do not want to exclude people who would benefit from PrEP. If they have co-morbid conditions that are well-controlled, then it is acceptable to enroll them if they meet all the exclusion/inclusion criteria. Consult the CMC if you are uncertain.
- One site is conducting mock visits to make sure it has thought through everything before participants come in.
- Not all participants are computer literate, so it helps to assess this at the Screening visit. If needed, additional time can be allocated to computer education at the Enrollment visit.
- In cases where a participant requests withdrawal, encourage the participant to come in for a final visit to gain a better understanding of her reasons for withdrawal. Possible issues to explore with the participant include community or family beliefs about the study as well as pressure from partner(s) to withdraw from the study. You can also propose to her the option of transitioning to the open label TDF/FTC arm of the study. Participants who prefer not to take study product can transition to the open label arm but decline to take PrEP while still remaining engaged in the study and receiving follow-up.

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- Carefully pre-screening study candidates and then having a group discussion amongst site staff (perhaps a weekly meeting) about each potential participant is helpful to avoid enrolling participants who may not be retainable. If a participant meets all inclusion/ exclusion criteria but you feel that she will not be retainable, you may invoke the “Investigator’s decision” clause in the exclusion criteria. Be careful, though, as some difficult to retain participants may also be at highest risk. Contact the CMC if you have any doubts.
- One site has suggested that women who wish to be screened for the study first be HIV-tested (after providing consent). That way, women who are HIV-infected will not need to undergo all the additional screening procedures. You could also perform pre-screening, which may include HIV rapid testing outside of the parameters of the study and would not require the long study consent. Of course, you will STILL need to perform all HIV testing procedures required at Screening when that visit does occur, making sure to obtain consent first.
- Check the prohibited meds list as some antacids may contain prohibited medication. Always contact the CMC if you have any doubts.
- Split visit at enrollment: A participant came for enrollment and completed the procedures prior to enrollment including blood draw and CASI. It was found that she was not fasting and so was informed that she would have to come in again to have the fasting blood test. She misunderstood this to mean she should leave and so left without being randomized. In instances of split Enrollment visits, both HIV rapid tests and pregnancy tests are required to be conducted on the day of randomization (so these will likely be repeated). In this case, all labs should have been repeated when the participant returned, and the HIV RNA test blood draw/ result was required to match the strict “14 day” guidelines noted in the protocol.
- Split visits can occur for a variety of reasons - such as a participant arriving too late in the day for product administration. HIV testing (rapid, ELISA and sample storage) and pregnancy testing must be repeated on the day the participant returns for product.

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### 8. CMC Query Guide

#### Standard CMC query format

Please format the subject and email in the standard CMC query format outlined in the SSP (see SSP version 2.0, Section 9.9) as it helps us log and keep track of queries.

#### Missed visits

In your initial query please include the following information:

- Last visit date
- Week 5 visit date
- LARC status (when last give, next due date).
- Presence of any unresolved AEs

This will allow us to assess if a participant can resume product and if an injection reload is needed.

Injection reloads are given when the injection is delayed by > 7.5 weeks.

#### Contraception interruption and missed contraception

Please include the following information in your initial CMC query:

- Last visit date
- Week 5 visit date
- Sexual history: **if the participant is outside of the allowable grace period for missed DMPA (4 weeks) or NET/EN (2 weeks)** we will need to know if there have been any episodes of unprotected intercourse in the preceding weeks

Note: If a participant is 1) outside of the allowable grace period for missed DMPA or NET-EN **and** 2) has had unprotected sexual intercourse since the grace period lapsed, the CMC advises that she be placed on product hold with open label TDF/FTC until early pregnancy can be ruled out.

#### Grade 3 changes in Cr or CrCl

In the initial email to the CMC we would like the following information:

History: If you can reach the participant by phone please ask about potential causes for a change in renal function. Common causes include: alcohol binge, NSAID use, con meds including antibiotic, traditional/herbal, cold/flu medications (many of which contain NSAIDS), recent illness or dehydration.

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The participant's age, and include a table with the weight, Cr/grade, CrCl/grade, and visit dates for the screening, enrolment, and two most recent visits (see below) It is not necessary to send the lab values for all visits.

Visit	Visit 1.0 (screening)	2.0 (enrolment)	Week 13	Week 17
Date	20/4/19	30/4/19	30/09/19	28/10/19
Cr (grade)	50	55	70	90 (grade 2)
CrCl (grade)	161	155	116 (grade 2)	91 (grade 3)
Weight (kg)	70	71	70	71

### **Grade 2 ALT elevation**

The SSP guidance on management of grade 2 ALT toxicity during Step 1 is to continue study product as long as the patient is not symptomatic and re-peat testing in 1 week.

If you can reach the participant by phone, we would like the following history provided In the initial email to the CMC:

- Alcohol use in the preceding two weeks. Get a detailed description of the types and volumes of alcohol consumed. Try and obtain an estimate of volumes of bottles or glasses consumed.
- New medications (ask specifically about paracetamol or cold medicines), herbal/traditional medicines and illicit drug use
- Recent illness: viral illness, malaria, etc.

When the participant returns to site for repeat testing and clinical evaluation please assess the following:

- Signs/symptoms of hepatotoxicity which can include fatigue, malaise, anorexia, jaundice, acholic stools, RUQ pain, hepatomegaly. If the participant is symptomatic, please refer for further case.

### **Grade 3 or 4 ALT elevation**

Grade 3 or 4 ALT elevation results in **permanent product discontinuation** and the participant should return to site as soon as possible for repeat testing and clinical evaluation.

If you can reach the participant by phone, we would like the following history provided In the initial email to the CMC:

- Alcohol use in the preceding two weeks. Get a detailed description of the types and volumes of alcohol consumed. Try and obtain an estimate of volumes of bottles or glasses consumed.
- New medications (ask specifically about paracetamol or cold medicines), herbal/traditional medicines and illicit drug use
- Recent illness: viral illness, malaria, etc.

When the participant returns to site for repeat testing and clinical evaluation please assess the following:

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- Signs/symptoms of hepatotoxicity which can include fatigue, malaise, anorexia, jaundice, acholic stools, RUQ pain, hepatomegaly. If the participant is symptomatic, please refer for further case.
- **If no clear cause for ALT elevation s identified by history** (i.e. alcohol binge, recent illness) please obtain the following testing in addition to repeat LFTs: RPR, urine or serum tox screen (for recreational drugs), hepatitis A IgM, Hep E IgM, Hep C antibody, CMV IgM, EBV IgM, HBsAg and HBcAb. Please also obtain an INR to measure synthetic liver function.
- Continue weekly ALT testing until grade 1 or lower