

HPTN 084: Tips and Lessons Learned

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).

General non-clinical questions should be directed to (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.

When referring to the protocol, first reference **Appendix VIII- Procedures for Offering Open Label (OL) Cabotegravir** to find out if any of the main sections of the protocol has modifications.

Table of Contents

Open-label Extension Q&As.....	2
Pregnancy and infants	2
Post-trial access	4
Alternate schedules	4
Data Management	4
Lab related queries	4
OLE Lessons Learned from Sites	5
Previous Tips and Hints.....	6
Missed Visits or Injections	6
CPK, Liver Function, other laboratory testing/ results	6
Data Management	6
Audits.....	7
Other.....	7

HPTN 084: Tips and Lessons Learned

Open-label Extension Q&As

- **Will participants on CAB LA and who choose to take TDF/FTC in Step 4 move to Step 5 eventually?**

No, people who take TDF/FTC during version 3.0, will be followed according to Step 4c for 48 weeks. Contact the CMC with any questions.

- **How should sites handle cases when a participant has an AE ongoing under V2.0, but under V3.0 those same labs are not protocol specified?**

Note: If a participant has an AE ongoing under V2.0, but under V3.0 those same labs are not protocol specified, the site should still request those labs as part of clinical care purposes to ensure the AE resolves (returns to baseline) or stabilizes.

Pregnancy and infants

- **What will happen to women who get pregnant while in the study and do not want to join the sub-study?**

If a PPT is taking CAB LA and wants to keep taking CAB LA, then she is required to join the sub-study for additional safety monitoring. CAB LA is not licensed in the 084 countries and there is limited data on safety and pregnancy. She will receive additional monitoring during her pregnancy and of her and her infant during follow-up.

If she has previously taken CAB LA- then she is eligible for the sub-study and can join EVEN IF she wants to keep taking TDF/FTC during pregnancy. She will receive additional monitoring during her pregnancy and of her and her infant during follow-up.

If a PPT becomes pregnant on the OLE and is taking TDF/FTC she will continue to be followed in Step 4c UNLESS she previously had ANY CAB LA exposure. Pregnancy outcome data will still be collected in these participants at 12 months.

For participants transitioning from HPTN 084-01, the same approach would apply for the first two situations. The OLE is for 084-01 participants who wish to continue CAB, so scenario 3 would not apply. Contact the CMC if in doubt.

- **Has the sponsor factored in the costs for where participants will be delivering from?**

The study is not paying for delivery of or care for infants. Women who wish to participate in the pregnancy sub-study will have study visits/ evaluations listed in the Schedule of Evaluations. However, sites must work with local providers and include referrals in their pregnancy SOP.

- **We are collecting infant plasma at delivery and 6 visits thereafter. Within how many hours of delivery do we collect the blood sample and cord blood storage? Or should it be collected at birth?**

It should be done immediately or as soon as possible.

HPTN 084: Tips and Lessons Learned

- **To what extent will sites treat infants who are sick? This has budgetary implications as sites will provide some medications. Is there a plan to reimburse sites? Children get quite a good number of adverse events, and it is inevitable mothers will bring in children when sick.**

Sites should refer to their conmeds budget to help in this case if they are able. Obviously, we are not the primary, but you may assist if you can, or refer for free or reduced assistance.

- **For the sake of accessing participant data during delivery, is there a medical release form available or recommended for this study?**

We expect sites to partner with providers for the ability to obtain information ahead of time- very similar to how we collect information on SAEs. The site-specific pregnancy SOP should reflect this information and how you will collect samples/ be notified of delivery occurring/ obtain medical release, etc.

- **Under the current protocol, participants that give birth remain on the pregnancy schedule until they have stopped breastfeeding, do these participants qualify for the Pregnancy sub-study in OLE?**

Participants with prior exposure to CAB are eligible for the sub-study. Participants in the TDF/FTC arm who want to take CAB during pregnancy are also eligible for the sub-study. Refer to the cheat sheet in the SSP and contact the CMC so that we can know more about 1) their original study arm 2) whether they want to take CAB in pregnancy and 3) where they are in pregnancy, so that the CMC can guide on the transition arrangements.

If they have delivered already they could choose whether they want CAB or TDF/FTC in Step 4c (unless they need 4a and 4b).

- **How far apart should the two pregnancy tests be conducted?**

This is one of the big changes between versions 2 and 3. We did pregnancy testing 4 weeks apart in version 2 because we had to unblind those who were pregnant, and we wanted to avoid unblinding if there was an early termination. For version 3 all we are looking for is a confirmation. This could be on the same day (if needed) if you can manage logistically with 2 separate specimens at 2 different time points.

- **What will happen to participants who get pregnant at 48 weeks (Step 4c)?**

The protocol allows for inclusion of pregnant women in the sub-study up to 8 weeks after week 48. Then follow procedures as described about inclusion in pregnancy and infant study based on 1) original randomized group 2) preference for CAB in pregnancy. Contact the CMC.

- **ISR data- Why are we are not collecting it in Step 4 but it is collected in the pregnancy sub-study.**

We had not specified ISR visits in Version 3 (like the 1 week follow-up ISR visits in Version 2) except in the pregnancy sub-study. However, you should solicit all AE information at visits. Because it is not specified does not mean that you should not query for this information at study visits and record AEs if they occur. We are tracking ISR in pregnancy because we had not tracked that specific information previously and want to compare ISR rates in pregnant vs. non-pregnant state.

HPTN 084: Tips and Lessons Learned

Post-trial access

- **What are plans for post-trial access if CAB is not approved via national programs?**

We have had active conversations with ViiV since the beginning of the study and they have done a nice job on trying to plan for post-trial access. There are plans to modify the protocol and provide CAB LA to participants for an additional 48 weeks (making it 96 total). ViiV is committed to providing CAB to women who need it until it is available in-country.

Alternate schedules

- **Who of the participants currently on Open Label Truvada schedule or Annual visit schedule is eligible or not eligible for OLE?**

The main contraindication to the OLE is if you had an AE that led to discontinuation of study product for either arm or those taking contraindicated medications to study products. Contact the CMC for advice.

- **Participants who are currently on an annual schedule- if they are not eligible for the OLE will we continue to follow them annually?**

During the trial we were all blinded and to ensure there was not some differential drop-off between the arms we kept everyone on study to measure primary endpoint. Now that the endpoint is known we no longer have a need for those to stay in annual testing.

Data Management

- **In case of multiple births such as twins or triplets, how are we to input multiple infant PTIDs on a CRF?**

An infant PTID must be created for each infant and a log line should be submitted with each infant PTID on the Pregnancy Outcome CRF.

Lab related queries

- **Is there a reason why albumin was introduced and some testing like lipase are not being done under 3.0?**

In version 2 we were looking at adverse events and collecting large amounts of data to see whether there were differences in the two treatment arms and at this point in time we have not seen significant glucose, lipase or calcium differences in the two arms. There is no need for intensive monitoring of the safety of CAB at this point in time.

- **Should a 4 ml, 5ml tube or a 6ml tube be utilized for Protocol Version 3 collection?**

Please contact the HPTN LC regarding tube sizes because there are specific requirements on anticoagulants used for plasma storage (K2 spray dried EDTA). The LC will guide you in the correct anticoagulant and you may need to use a variety of tubes to get a 20 mL collection for plasma storage. For the safety testing, always check with the local laboratory regarding the specific requirements. Ensure that the consent form has some leeway regarding the volume ie if you need to draw a 6 mL in place of a 4 mL tube. As long as we can get the volume of plasma needed for the storage requirements in the SSP you may use any of these tubes depending on availability.

Additional note: For the contraception sub-study it doesn't matter if the woman has changed her contraception method- we just need her to consent to collect samples.

HPTN 084: Tips and Lessons Learned

OLE Lessons Learned from Sites

- **When in doubt, contact the CMC**

- **Plan for transitions**

Refer to Appendix 9B of the HPTN 084 SSP- HPTN 084 Cheat Sheet for Transitioning PPTs from V2.0 to V3.0.

- **Communication between team members is important**

One site convened daily check-ins during the first few weeks after activation to discuss clinic flow and review what did and did not work. This helped troubleshoot regularly.

- **Manage expectations of participants as the duration of the visits were significantly increased.**

One site had to decrease daily bookings to accommodate longer visits.

One site suggested having enough refreshments for participants.

- **One site changed their clinic flow to this and found that it worked well:**

- Participant and the nurse review the ICF, and the nurse takes vital signs.
- Clinician does contraception counseling, medical history and physical examination and counsels on product of choice.
- Counselor does pre-testing counseling and the CASI.
- Nurse draws blood.

- **One site said conducting Group ICF information sessions has been helpful.**

- **One site is using stickers on their participant files to alert everyone in the clinic to what the participant has chosen.**

HPTN 084: Tips and Lessons Learned

Previous Tips and Hints

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.
- Consider printing out the Schedule of Visits 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.

CPK, Liver Function, other laboratory testing/ results

- Contact 084mgmt@hptn.org for questions about lab redraws.
- A participant had a grade 2 platelets result of 81,000 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 because this may affect the ability to provide injections. Participants with plts <50,000 may not be able to receive injections.
- 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 ensuring 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.

Data Management

- 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 calculations:

HPTN 084: Tips and Lessons Learned

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

- 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.

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 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.

Other

- One site is conducting mock visits to make sure it has thought through everything before participants come in.
- 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. Check the prohibited meds list as some antacids may contain prohibited medication. Always contact the CMC if you have any doubts.

HPTN 084: Tips and Lessons Learned

- 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 (if the second part of the split visit occurs >7 days), and sample storage) and pregnancy testing must be repeated on the day the participant returns for product.