Questions from the Q&A session with sites on 20 January 2022

1. **Do you plan to communicate to participants about FDA approval of CAB LA for PrEP?**
   Yes. The team wrote a Dear Participant Letter and sent it to sites on 06Jan2022. It is also posted on the HPTN website https://www.hptn.org/research/studies/hptn084. Sites should be sharing this Dear Participant Letter with participants.

2. **How exactly do we roll out the reconsenting? Do we batch participants and bring them in, or do we re-consent them as they come in for their prior scheduled visits?**
   Participants will consent to version 3 at their next scheduled study visit. You do not have to bring all participants in at once.

3. **Is there an assessment of understanding for the new ICF?**
   Yes, there is an assessment of understanding in the SSP in Section 4 (Table 4-1).

4. **Participants are allowed to change the product choice before 24 weeks into the OLE. What if after this period a participant requests a change? What happens then?**
   Participants on CAB can discontinue CAB after 24 weeks and will be followed in Step 5.

   Participants who have opted for TDF/FTC will not have a chance to change to CAB after 24 weeks as the protocol currently stands. This is because of the available follow up time (24 weeks) and the time frames to achieve CAB initiation (4 weeks OLI, 4 weeks loading dose), gives limited time on CAB. This may be revised if the follow up time is extended.

5. **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.

<u>Pregnancy and infants</u>

6. **The v3.0 amendment ICF template you provided includes a section with pertinent pregnancy information. Where in the ICF is a signature page for pregnant women?**
   The ICF does have signature lines for this. Scroll all the way through the ICF.

7. **Step 4d states that pregnant and breastfeeding mothers who decline to be on CAB LA will be offered OL Truvada. Our site did not receive Step 3 OL Truvada as we were far off from transitioning into Step 3 at the time of unblinding. Therefore, we have two types of Truvada available for the study; the OL Truvada used in v2.0 of the protocol and the two label Truvada which was used during the blinded part of the study. We would like to get guidance as to which Truvada to use for the pregnant and breastfeeding women who decline to be on CAB LA**
   The SSP Section 8 (V2.2, 09Dec2021) was updated to allow for the provision of either blinded or unblinded TDF/FTC so long as it is NOT placebo. This same language is included in the current Section 8, V3.0, 04Jan2022.

8. **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.

9. **Where will the cord blood and breastmilk be processed?**
   Processing will take place at the LC. Work with local providers to ensure that staff are available at time of delivery.

10. **Will the infants be brought in every two weeks for blood draw?**
    No. Refer to the Schedule of Evaluations Step 4d for the timepoints.

11. **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.

12. **'Study activities for women who become pregnant' section of the protocol v3.0 template ICF contains many additional procedures on pregnancy, delivery, after delivery, breastfeeding and infant follow up. Our site is not participating in any HPTN 084 sub-study. At what point in the study are participants enrolled into the mother-infant sub-study? How different are the procedures for mother-infant sub-study different from the procedures outlined in the v3.0 ICFs?**
    As a point of clarification, for the v3.0 protocol, the long-acting contraceptive requirement has been removed. Participants at all sites will likely become pregnant and thus all sites will be managing pregnant women and should provide a pregnancy management plan or SOP. Depending on the PPTs product exposure, they will either be followed according to Step 4c or according to Step 4d. Sites should review the protocol and develop the Pregnancy Management SOP.

13. **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.

14. **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.

15. **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.

16. **Are we generating infant PTIDS even if the infant is not participating in the sub-study?**
    If the participant's infant is participating in the sub-study yes. If not participating in the sub-study there is no additional data beyond routine being collected other than the pregnancy outcome.

17. **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).

18. **What will happen to pregnant women who join the sub-study and miscarry?**
    You will report a pregnancy outcome. Contact the CMC so that we can make a decision based on where they are on follow-up how we will continue. Most likely we would revert to 4c.

19. **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.

20. **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.

21. 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.

Post trial access

22. Post-study drug availability is limited to a small group. Why are we not providing Truvada to all eligible participants after study ends? HPTN 083 Step 4 participants who move to Step 5 are offered Truvada in America. Why is it different from HPTN 084?

Post trial access for CAB requirements are being met through the current OLE. There may be an additional 48 weeks of OLE on either product (96 total). After this 96 week period post-trial, participants will be referred to local national programs for TDF/FTC or CAB (if available). If CAB is not available, ViiV is committed to working with sites on a per participant basis to try to maintain access of CAB until locally available. Anyone on CAB who discontinues CAB prematurely is offered TDF/FTC for 48 weeks as a benefit of the study. Truvada is already approved as PrEP in the countries working on 084 and is part of the standard of prevention. Therefore, it is reasonable after the trial to refer participants to national PrEP programs for ongoing PrEP access.

23. 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. ViiV is committed to providing CAB to women who need it until it is available in-country.

Alternate schedules

24. What is the plan for chronic defaulters, will they be terminated in Step 4 or we await study end?

For those who are lost to follow up, sites will have the opportunity to reach out to them now that we know the product is effective and one regulatory body has approved CAB so they may wish to re-engage in the study. Participants cannot be un-terminated. Those with AEs due to product of course could not continue on study and should be terminated. Not everyone will be eligible for the OLE. If there are any questions reach out to the CMC.

25. After version 3 Protocol entry, can those on TDF/FTC switch to Step 4a and 4b?

No participant will stay in follow-up on protocol version 2.0.

If a participant was in the TDF/FTC arm, she has a choice to take TDF/FTC or CAB in the OLE. If they wish to stay on TDF/FTC they can go straight to 4c as there is no need for 4a or b (injection visits).

For participants who are on OL TDF/FTC because of premature CAB d/c they can be followed in step 4c until completion of the 48 weeks OLT. They will not be able to transition to CAB if their reason for CAB d/c was a safety reason.

If they are OLT for non-LARC use, they could transition through steps 4a/b if they wish to start CAB.

26. **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.

27. **Will participants who are currently on Open label have an opportunity to be consented for protocol version 3.0?**
    If they qualify (no contraindications). Contact the CMC.

28. **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

29. **Do we have a new CRF completion guideline for OLE?**
    Yes, it is posted on Atlas and Data Communique 14 was also released from the SDMC concerning the OLE.

30. **Will retired CRFs in Medidata rave be locked or they will be active?**
    They will remain locked with the exception of a few that will be re-opened. Refer to Data Communique 14.

31. **Will the Data Management team be providing visit scheduling tools?**
    Yes; these are available in Atlas.

32. **When will the new forms be activated in Rave?**
    The new forms are currently active.

33. **When will the training database be available so that site staff can begin to practice before activation?**
    It is currently available.

34. **How do I record in the database a participant that does not choose to join the OLE?**
    The Product Choice form documents this detail and must be completed for all PTIDS.

35. **How do I get the Albumin lab to stop appearing as overdue?**
    Please ignore this overdue icon, this will be corrected in the next migration.

36. **Where do I find CASI translations and the Certificate of Translation documents?**
    These are posted on ATLAS, under the Documents section.

37. 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

38. 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.

39. Using schwarz equation to calculate GFR for 084-01 do we change to Cockcroft-Gault in 084?

Post-hoc clarification for sites that are doing HPTN 084-01: we added a note to the SSP to clarify that participants who initiated the trial on 084-01 using the Schwartz equation will have creatinine clearance assessed per Schwartz equation at follow up visits.

40. 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.