**HPTN 084 Training Scenarios Pregnancy with Answers**
**24-25 January 2023**
**Hilton Hotel, Sandton**

**PREGNANCY**

**Scenario 1**

A participant has missed her CAB LA injections for 16 weeks and is found to be pregnant at her first visit since. She returns in the 4c week 32 window. What do you do?

*Answer:*

- Confirm pregnancy – note timeframe can be same day,
- Offer the pregnancy substudy
    - If pregnancy unanticipated give her time to think through pregnancy decision – visit can be split
        - If she agrees to 4d consent for substudy, product choice CAB/TDF and samples for her and infant.
            - If yes to CAB in pregnancy, contact CMC regarding re-load requirements.
                - >7.5 weeks from last visit target date Re-load will be needed. Give injection and then schedule for next visit in 4 weeks to coincide with 4d.
        - The visit can be completed in the 4c week 32 folder but all 4d day 0 procedures should be completed.
        - Counsel participant that ANC care can be provided at study visits but delivery will need to be planned at a delivery site
            - Can conduct ANC required procedures as clinical care procedures based on national guidelines
        - Schedule an ultrasound to occur at estimated 12 weeks gestation.
        - During follow-up confirm delivery plans with participant
    - If no to 4d, document reasons for declining, refer to ANC and follow up per 4c and collect outcome data.

**Scenario 2**

A participant is in Step 4c OLE1 receiving CAB LA tests positive for pregnancy when re-consenting for Protocol Version 4 (OLE 2). Do you offer participation in the pregnancy/infant sub-study? What would you do at this visit?

*Answer:* Yes, she is eligible for 4d if she is on CAB in step 6 because she has had prior exposure to CAB.

Next steps

- Confirm pregnancy – note timeframe can be same day,
- Offer the pregnancy substudy
    - If pregnancy unanticipated give her time to think through pregnancy decision – visit can be split
        - Offer consent for the pregnancy substudy (4d). If she agrees to 4d consent for substudy, product choice CAB/TDF and samples for her and infant.
        - The visit can be completed in the 4c week 32 folder but all 4d day 0 procedures should be completed.
        - Counsel participant that ANC care can be provided at study visits but delivery will need to be planned at a delivery site
            - Can conduct ANC required procedures as clinical care procedures based on national guidelines
            - If yes to CAB in pregnancy, provide CAB injection
            - Schedule an ultrasound to occur at estimated 12 weeks gestation.
            - During follow-up confirm delivery plans with participant
        - If no to 4d, document reasons for declining, refer to ANC and follow up per 4c and collect outcome data.
    - If she declines sub-study despite prior CAB exposure, she will be followed up in step 5
    - Pregnancy outcome data must be collected.

**Scenario 3**

A participant comes in for pregnancy Week 24 in OLE 1 and you just received all approvals for protocol version 4. What do you do?

*Answer:*

- Re-consent her for v4,
    - Complete Informed Consent Version 4 CRF in the Product Choice folder.
- Confirm whether changes to pregnancy consents regarding infant sample collections.
- Complete Step 4 d Week 24 visits procedures per version 4.0.

**Scenario 4**

A participant miscarries at Step 4d Week 16. What do you do?

Answer:

- Complete a medical assessment to determine whether miscarriage in progress or complete and manage accordingly
    - Determine whether further medical/surgical management required and report any hospitalization
- Counsel / refer her as needed over her loss.
- Complete the with pregnancy outcome- OLE CRF *w obtainable outcome of 'spontaneous abortion'* (For all pregnancies reported, positive pregnancy test >1day, a Pregnancy outcome is required).
- Confirm her product choice in OLE 1 (it may have changed for pregnancy)
- She may return to non-pregnant follow-up
    - In this case return to Step 4c where she was at the last visit PLUS the 16 weeks on the pregnancy substudy (so if she were at Week 8 in 4c she would now be at Week 24 in 4d). Either 4c - Step 4c
    - Step 6 depending on when pregnancy occurred – consult with CMC regarding transition to step 6
    - Indicate on DOV-Pregnancy-OLE schedule change.

**Scenario 5 (Still in OLE1 at the time of miscarriage)**

A participant had first positive pregnancy test at the first OLE1 visit on 21 November 2022. Her LMP was 1 October 2022 and the estimated gestational age is 7 weeks. She consented for the pregnancy and infant sub-study and CAB use in pregnancy. Visit 4b was conducted on that date and four weeks later on 19 December she transitioned to the 4d week 8 visit. By January of 2023 she had miscarried.

What do you do?

Answer:

- At transition she was already 7 weeks pregnant.
- To manage visit schedules she was slotted into the next injection window after 4b i.e. 4d week 8.
- Confirm no active bleeding and no RPOC
- Counsel her re her loss
- Document pregnancy outcome
    - Complete the with pregnancy outcome- OLE CRF *w obtainable outcome of 'spontaneous abortion'* (For all pregnancies reported, positive pregnancy test >1day, a Pregnancy outcome is required).
- As she miscarried, and step 4C follow up not complete she can return to Step 4c SOE.
    - Confirm pregnancy test negative
    - Her step 4c visit windows should be calculated based on the 4b visit date (date of entry into OLE1).
    - Indicate on DOV-Pregnancy-OLE schedule change.

**Scenario 6 (In OLE2 at the time of the miscarriage)**

A participant had her first OLE visit on 1 February 2022 and elected to use CAB LA. Step 4b was conducted on 1 Feb 2022 and 4c week 0 on 1 March 2022. She had a positive pregnancy test while in OLE1 on 1 October 2022. She consented for the pregnancy and infant sub-study and CAB use in pregnancy and transitioned to the 4d SOE. She has a stillbirth on 28 May 2023. Protocol 4.0 is now in use at your site.

What do you do?

*Answer:*

- Document pregnancy outcome
- Report any SAE e.g. hospital admission
- Confirm pregnancy test negative
- Confirm her product preferences
    - If she chooses TDF/FTC she goes to step 5
    - If she still wants CAB, she can potentially continue on step 6 assuming reconsent
    - Consult CMC re step 6 who will consider the following
        - Under version 4, if she was non-pregnant and continued to step 6 she would still be in step 6 (around week 56/64) therefore it is feasible for her to return to step 6
            - Had she completed step 4c (and not been pregnant) the week 56 visit of step 6 would have been 28 March 2023, and week 64 would be 23 May 2023. (based off 4b injection start date)
        - She therefore returns to week 64 Step 6 on CAB

**Scenario 7**

A participant comes into clinic at step 5, Week 36 of OLE1. Her initial randomization arm was TDF/FTC. She had transitioned to step 5 due to a grade 3 ALT elevation. At her step 5, week 36 visit, she tests positive for pregnancy. The pregnancy is confirmed that day by a second test. The participant never took CAB LA and has been on Step 5 and taking TDF/FTC.
How should she be managed?
*Answer:*

- Participant is not eligible for step 4d – no prior CAB exposure
- At week 36, complete the following CRF
    - Positive pregnancy test results-OLE form, indicating she does not qualify for Pregnancy sub-study.
    - Pregnancy Report-OLE and
    - Pregnancy History Form.
    - Continue to follow until Week 48 of OL1
    - Collect samples per Step 5 SOE, confirm pregnancy same day
- Notify CMC
- Refer to local obstetrician/healthcare provider for pregnancy management
- At Week 48, transition off of study to local PrEP services
- For all pregnancies reported, positive pregnancy test >1day, a Pregnancy outcome is required.
- Make arrangements to follow up with participant about pregnancy outcome where feasible

**Scenario 8**

A participant comes into clinic at Step 4c Week 36 of the first Open Label period (OLE1) i.e. interim visit for suspected pregnancy. She has always attended her study visits. At her interim visit, she tests positive for pregnancy. The pregnancy is confirmed that day by a second test. The participant took CAB LA during the blinded part of the study, but chose TDF/FTC for OL1 and has been followed on step 4c.

How should she be managed?

*Answer:*

- She is eligible for step 4d given prior exposure to CAB during the blinded period
- Counsel the participant re pregnancy sub-study
- If she is ambivalent, visit can be split to give her time to think through her options
- Notify CMC
- If she accepts 4d, confirm consent for sub-study, for preferred product in pregnancy and infant sample collection
- If she selects CAB, she will require a re-load given >8 weeks since last target injection date
- If she declines 4d, she should be followed up in step 4c (only 2 visits in OLE1 remaining). Pregnancy outcome data is still required even if she gets to the end of 4c and option to transition to step 5 under protocol version 4 not available. Contact the CMC to discuss further management.
- If/once version 4 approved at site she should be followed up on step 5 to ensure PrEP coverage during pregnancy and follow up to pregnancy outcome since PPT was exposed to CAB LA
- Ensure that she is linked to ANC care as part of study visits and/or at local health care provider

Version 4active at site. Is Participant is eligible for OLE2 at the end of pregnancy

She should be followed up on step 5

Can she choose TDF/FTC or CAB LA at the end of pregnancy?

She completes follow up at end of step 5

What CRFs need to be completed at the Week 36 visit?

- On the Pregnancy test results-OLE form Indicate: positive results, she qualifies for 4d and if she decides to participate in 4d. Complete Pregnancy Report-OLE and Pregnancy History Form.

What samples should be collected?

IV testing, pregnancy as noted above, CBC, Chemistry Alb BUN Creatinine ALT AST tbili, syphilis CTNG trich, urine protein and glucose, Plasma and DBS Storage (if an interim visit contact management alias list).

**Scenario 9**

A participant comes into clinic at Step 4c Week 24 of the first Open Label period (OLE1). She has always attended her study visits. At her Week 24 visit, she tests positive for pregnancy. The pregnancy is confirmed that day by a second test. The participant took CAB LA during the blinded part of the study, and continued on CAB LA for OL1 and has been followed on Step 4c.

How should she be managed?

*Answer:*

- Participant is eligible for 4d given prior CAB exposure
- Counsel the participant about 4d
- If participant is ambivalent/wants to discuss with family, allow for split visit and conduct consent and 4d procedures at a subsequent interim visit
- If she chooses 4d, document consent for sub-study, product choice in pregnancy, and consent for sample collection in mother and infant
- If she consents to CAB in pregnancy offer injection and continue follow up on step 4d
- If she declines 4d, continue follow up in 4c but discontinue injections as no Cab injections can be given during pregnancy without consent.

What CRFs need to be completed at the Week 24 visit?

Complete required wk 24 CRFs. Also ensure positive results are entered on the pregnancy test results-OLE form, indicating she qualifies for Pregnancy sub-study. Pregnancy Report-OLE and Pregnancy History Form. *If she consents for the substudy, then 4d day 0 CRFS must be completed in addition to the wk 24 CRFs.*

For all pregnancies reported, positive pregnancy test >1day, a Pregnancy outcome is required at subsequent visit.

What samples should be collected?

HIV testing, pregnancy as noted above, CBC, Chemistry Alb BUN Creatinine ALT AST tbili, syphilis CTNG trich, urine protein and glucose, Plasma and DBS Storage

**Scenario 10**

A participant on Step 4d, who is taking TDF/FTC, presents to her Week 4 post-partum visit. She wants to switch to CAB LA. She has no previous lab or clinical indications preventing her from switching.

How should she be managed?

*Answer:*

- Assume participant has had prior CAB exposure because she is on 4d
- Assume that for the pregnancy she opted to take TDF/FTC; she can return to CAB post-partum if she chooses
- Contact CMC who can advise re re-starting CAB
- Last target injection date likely to >8 weeks so re-load required
- CMC likely to guide to provide an injection at week 4 and then resume 8 weekly injections from week 8 post-partum
- Continue follow up on 4d schedule

What CRFs need to be completed at the Week 4 visit?

DOV-Pregnancy OLE CRF: 1) indicate CAB LA as current product given 2) complete oral CAB question re # bottles dispensed 3) Indicate product hold. Complete Product Hold CRF for TDF/FTC.

What samples should be collected?

Collect rapid HIV, instrument HIV, VL and plasma / DBS storage and breast milk collection / storage

**Scenario 11**

A participant on Step 5 during OL2 (i.e. version 4 approved at site) is taking TDF/FTC, presents to her Week 12 visit. She tests positive for pregnancy. The test is confirmed on a second sample. The participant received one CAB LA injection during OL1 before she decided to discontinue CAB LA.

How should she be managed?

**Answer**

- Participant is eligible for step 4d because of prior CAB exposure
- Counsel her regarding 4d
- If she is ambivalent, allow for a split visit and complete step 5 procedures (dispense enough TDF/FTC product until next visit)
- If she consents to 4d,
    - complete 4d procedures and document consent for substudy, product choice, and sample collection for infant and mother
    - follow on 4d schedule
    - unlikely to want CAB injections based on past history but would need a reload potentially
- if declines step 4d, continue on step 5 per version 4
- Ensure adequate ANC and alignment of visits with study visits where possible
- Collect outcome data given prior CAB exposure
  - Consult with CMC.

What CRFs need to be completed at the Week 4 visit? (DM to fill in)

Complete required wk 4 CRFs. Ensure positive results are entered on the pregnancy test results-OLE form, indicating she qualifies for Pregnancy sub-study. Pregnancy Report-OLE and Pregnancy History Form should also be completed. *If she consents for the substudy, Complete Consent Pregnancy Infant Substudy CRF; 4d day 0 procedures (and CRFS) must be completed in addition to the wk 4 CRFs.*

What samples should be collected?

Collect rapid HIV, instrument HIV, VL, plasma / DBS storage

**Pregnancy Scenario 12**

Participant initially randomized to CAB LA entered OLE1 on 1 March 2022 and elected to continue CAB LA and a 4c week 0 visit was conducted on that date. She is pregnant at the 4c week 32 visit on 11 October 2022 and transitioned to step 4d. She delivers on 17 June 2023 and completes the 48 weeks of infant follow-up on 18 May 2024. How do you proceed?

Is this participant eligible for step 6 at the end of pregnancy or is the end of study participation for her?

*Answer:*

- Step 4c starts 1 March 2022
- If non-pregnant she could have continued into step 6 in March 2023
- Step 6 would have ended March 2024
- Contact CMC regarding step 6 continuation
    - CMC would consider timelines above and follow up of non-pregnant participants at site
    - In this instance she would have completed study follow up (may>Mar 2024) and can be transitioned to local HIV prevention services