Section 4. Continuation in Protocol Version 4.0 (OLE)

4.1 Overview of Section 4

This section provides an overview of requirements and procedures for rolling participants over into the Open Label Extension (OLE)/ Protocol Version 4.0 Additional procedure-specific details can be found in the visit checklists in SSP Section 6, and in Section 5/ Schedule of Evaluations Appendices of the Protocol.

4.2 Continuation in Protocol during the Open-Label Portions

Participants who elected to remain in follow-up after the v2.0 amendment were offered the opportunity to remain in HPTN 084 under v3.0 protocol (OLE). Similarly, eligible participants in the version 3.0 protocol are offered the option to join the v4.0 protocol amendment.

Note: Always contact the CMC for questions related to safety and study product AEs of concern for participants interested in continuing or initiating CAB LA.

4.2.1 Informed Consent Process

After receiving notification to implement Version 4.0 of the protocol, sites will administer the addendum to the main informed consent form as participants present to the site. Participants do not need to be re-consented with the ICF used for v2.0 that is contained in the defunct, main body of the original protocol. That part of the study has concluded and the information in it is not representative of the trial or participant activities. The executed form specific to amendment v4.0 will document the participant's continued participation in the study. As part of the consent discussion, sites should explain to participants the options for ongoing study participation as outlined in the Informed Consent Appendices of the Protocol.

Contact the CMC for guidance if there are other scenarios for a discussion about choice and obtaining informed consent.

Deliver All Required Information in a Manner that is Understandable to Potential Participants. If the participant is literate, give her a copy of the ICF to read. Also provide the participant with other (IRB/EC-approved) informational materials developed to

complement the ICF, if any**.** If the participant is not literate, the materials may be read to her verbatim. After the participant has read the written material (or had it read to her), verbally review the information provided. A checklist or the ICF itself may serve as a useful guide for this. For example, staff may note the main points described in each paragraph of the informed consent form and ask if the participant has questions or concerns about each point. Listen carefully to the questions or concerns expressed by the participant and discuss these thoroughly. Take as much time as needed to address each question and concern.

If the participant is illiterate, **an impartial witness must be present during the entire informed consent discussion**. The witness will be asked to sign and date the ICF to attest that the information in the consent form was accurately explained to, and apparently understood by, the participant, and that informed consent was freely given by the participant. The ICH GCP guideline identifies an "impartial" witness as a person who is independent of the study, who cannot be unfairly influenced by people involved with the study. Each site must specify its procedures for obtaining informed consent from illiterate persons in its SOP for obtaining informed consent. The SOP should define who may serve as an impartial witness to the informed consent process. It is recommended that each site seek IRB/EC review and approval of these procedures. Refer to the DAIDS Score Manual for additional information on impartial witnesses.

4.2.1.1. Assure That Informed Consent Is Obtained in A Setting Free of Coercion and Undue Influence

During the informed consent discussion, take care to not overstate the possible benefits of the amendment, nor to understate the risks. Also emphasize to the participant that medical care and other services routinely available from the clinic or hospital associated with the site will not be affected by their decision whether or not to take part in the study. Encourage the participant to take as much time as she needs — and to talk about her potential participation with others, if she chooses — before making a decision.

4.2.1.2. Confirm That the Participant Comprehends the Information

The participant must not be asked to agree to continue in the OLE portion of the trial or to sign the ICF, until she fully understands the amendment. Study staff are responsible for implementing procedures to ensure that each participant understands the risks, benefits and goals of the amendment study prior to signing the amended ICF, respectively, and undertaking any study procedures.

One approach to assessing comprehension is to use a "quiz" (either oral or written) or other assessment tool that participants complete as part of the consent process. Another approach is to use open-ended questions to ascertain participant understanding during the informed consent discussion. It is possible to incorporate a scoring system into these assessment tools and to re-review the contents of the informed consent until the potential participant can answer a certain percentage of the questions correctly. Table 4-1 includes a sample informed consent assessment tool that sites may choose to adapt for their local use. For sites that choose to adopt tools

such as those included in this section, detailed instructions for their use must be specified in the site SOP for obtaining informed consent.

Regardless of the method used to assess comprehension, if the assessment results indicate misunderstanding of certain aspects of the study, review those aspects again until the participant fully understands them. If after all possible efforts are exhausted, the participant is not able to demonstrate adequate understanding of the amendment, do not ask her to sign the ICF. Similarly, if the participant has concerns about possible adverse impacts if she were to take part in the study or indicates that she may have difficulty adhering to the study requirements, do not ask her to sign the ICF for the amendment.

4.2.1.3. Document the Process

The *DAIDS Score Manual https://www.niaid.nih.gov/research/daids-score-manual* including the section on Informed Consent of Participants provides detailed requirements and suggestions for documenting the informed consent process. https://www.niaid.nih.gov/sites/default/files/score-informed-consent.pdf. All requirements listed must be met. In order to meet some of the suggestions listed, site staff may consider the use of an informed consent "coversheet" similar to the example included in this section.

4.2.1.4. Continue the Informed Consent Process throughout the Study

Given the ongoing nature of informed consent, key elements of informed consent should also be reviewed at study follow-up visits. At these visits, study staff should review key elements of informed consent with the participant, focusing on the remainder of their study participation. For example, participants should be encouraged to ask questions as they arise and recognize that poor adherence to their study drug regimen will not affect their continued participation in the trial.

4.2.1.5. ICF Requirements for Protocol Amendments (including LoAs)

According to DAIDS policy (Protocol Registration Policy and Procedure Manual), the site's IRB/EC is/are ultimately responsible for determining whether study participants need to be re-consented for a protocol amendment. The details of re-consent for a protocol amendment will be determined based on the extent and content of the amendment, and instructions will be provided to sites in this regard, after consultation with DAIDS.

Table 4-1: 084 OLE 2 (Version 4.0 Protocol) Sample Informed Consent Assessment Tool* *(* May be adapted as needed for local use)*				
	Date: **Participant ID:**			**Staff name/initials**
		Participant's Response	Correct Answer	Notes
1	My participation in this research study is voluntary	□ True □ False	☒ True □ False	
2	During the blinded part of the study, CAB LA was found to be safe and effective in preventing HIV infection in women.	□ True □ False	☒ True □ False	
3	The purpose of the open-label extension is to learn more about women's HIV prevention choices including during pregnancy and breastfeeding.	□ True □ False	☒ True □ False	
4	This research study is part of the regular medical care offered here at [clinic name].	□ True □ False	□True ☒ False	
5	The clinic will test my blood for HIV throughout the study.	□ True □ False	☒ True □ False	
6	If I join this research study amendment, I must stay in the study for as long as the study staff says.	□ True □ False	□True ☒ False	
7	If I choose to continue Cabotegravir injections in the second open-label extension and I later decide to stop injections, I can switch to TDF/FTC to cover the tail.	□ True □ False	☒ True □ False	
8	My participation in the second open-label extension part of the study will be for 48 weeks (unless I decide to have pregnancy follow-up which will follow me for 48 weeks after birth).	□ True □ False	☒ True □ False	
9	If I fall pregnant, I will be able to choose whether I want to continue taking Cabotegravir injections.	□ True □ False	☒ True □ False	
10	If I choose to have my infant followed in the study, my infant will be monitored for 48 weeks after I give birth.	□ True □ False	☒ True □ False	
11	There are no risks in continuing to take part in this research study.	□ True □ False	□True ☒ False	
12	If I have questions between study visits, I need to write them down and bring them with me at my next appointment.	□ True □ False	□True ☒ False	*no, but it's a good idea.

Table 4-2: Sample Informed Consent Coversheet for HPTN 084 OLE 2*

Participant name:	
Date of informed consent discussion:	
Start time of informed consent discussion	
Version number/date of informed consent form used during informed consent process/discussion:	
Name of study staff person completing informed consent discussion (and this coversheet):	
In what language was informed consent obtained?	[*insert local language*] (note whether this was written and/ or verbal)
Were all participant questions answered?	☐ Yes ☐ No ⇒ Explain in Notes/Comments. ☐ NA (participant had no questions)
Did the participant accept a copy of the informed consent form (circle one option)?	☐ Yes ☐ No
End time of informed consent process/discussion:	
Notes/Comments (not documented elsewhere):	

(* May be adapted as needed for local use)

Table 4-3: Sample HPTN 084 Screening and Enrollment Log

	Participant ID	Participant Name	Date Screened	Eligible	Date of Enrollment (if not enrolled, note N/A)	If not enrolled, specify reason (include all applicable codes).	Did Participant Enroll in OLE Y/N	Staff name/ Initials
1				Y N				
2				Y N				
3				Y N				
4				Y N				
5				Y N				
6				Y N				
7				Y N				
8				Y N				
9				Y N				
10				Y N				

(*May be adapted as needed for local use. Note: There is no standard screen failure code list.)