HPTN 084 Study-Specific Procedures Manual Overview and Version Control

Section Number	Section Title	Current Version Number	Current Version Date	Updates and Comments
1	Introduction	3.0	04Jan2022	Updates for Version 3.0 • Minor editorial changes, referenced OLE throughout, updated LOC staff and phone numbers, updated links to DAIDS resources • Section 1.4 (Investigator Responsibilities): Clarified that a new 1572 is not needed for the OLE, added text regarding IoR responsibilities • Section 1.5.5 (Protocol Registration for OLE): Updated for OLE requirements. • Added HPTN 084 OLE (Protocol Version 3.0) Study-Specific Activation Checklist
2	Protocol	3.1	26Apr2022	Updates for Version 3.1 • Added LOA#2 and LOA#3 to V3.0 Protocol Updates for Version 3.0 • Added V3.0 Protocol and LoA#1 and CM#1 to V3.0 Protocol
3	Document Requirements	3.1	15Aug2022	Updates for Version 3.1 • Section 3.4.1.12: Added protocol deviation category (physical assessment deviation) Updates for Version 3.0 • Throughout removed text and tables that are not specific to the OLE, added references to the DAIDS Score Manual and updated links to DAIDS reference documents. Removed reference to the DAIDS Clinical Research policy on Critical Events. • Section 3.3.3.1 (Clinic Notes): Removed example clinic note for screening visit. • Table 3-1a- Updated for the OLE • Table 3-1b- Added new CRFs to table • Section 3.4.1.12 (Other): Added an example of a deviation that would fall under the 'other' deviation category. • Section 3.4.2 (Protocol Deviations During the COVID-19 Pandemic): Added a note about missed assessments due to COVID.
4	Continuation in Protocol Version 3.0 (OLE)	3.1	26Apr2022	Updates for Version 3.1 • Participants cannot be un-terminated. Clarified that participants who permanently discontinued study product under Step 2 or Step 3 of the protocol, but are otherwise eligible for injectable CAB, may be eligible to restart study product under Version 3.0. Updates for Version 3.0 • Updated to align with the OLE.

Section Number	Section Title	Current Version Number	Current Version Date	Updates and Comments

				• Section 4.2 (Continuation in Protocol V3.0): Added text about transitions to the OLE and how to unterminate participants who are eligible to transition to the OLE and have previously been terminated.
				• Section 4.2.1 (Informed Consent Process): Added text around administering the addendum to the main consent form to document participants' continued participation.
				• Table 4-1: HPTN 084 OLE Version 3.0 Sample IC Assessment Tool
				  o Added questions related to the OLE
				• Table 4-3 (Sample Screening and Enrollment Log):
				  o Added column for OLE.

5	Study Procedures Overview	3.0	04Jan2022	Updates for Version 3.0 • Added text related to the OLE. Removed language that is no longer applicable, added reference to the Score Manual

6	Visit Checklists	3.1	26Apr2022	Updates for Version 3.1
				• Step 4c correction- added albumin to chemistry panel bullet
				• Schedule of additional procedures for women with reactive/ positive HIV tests
				  o Correction- added DBS storage.
				  o During the OLE, both the CMC and HIV alias should be contacted about any HIV reactive or positive tests.
				• Step 4d- added text clarifications to rows for ultrasounds, medical history and breast milk collection
				• Step 4d- LoA#2:
				  o ISR Assessment- Removed from Week 48 post-partum
				  o Plasma Storage- Added at Weeks 40
				  o DBS for women on TDF/FTC- Removed "except week 40"- now collected at Week 40. For clarity text now reads "all visits; delivery and post-partum except weeks 2, 32, 40, 48.
				  o Infant HIV testing (if mother has one or more reactive/ positive HIV test)- delivery and all post-partum visits
				  o Infant DBS- delivery and all visits
				  o Infant plasma storage- Added Weeks 32 & 40
				• Step 4d- LoA#3: Added infant AE assessment

Section Number	Section Title	Current Version Number	Current Version Date	Updates and Comments
				Updates for Version 3.0 • Added text related to the OLE. Removed language and checklists that are no longer applicable. • Added checklists for Steps 4a, 4b, 4c, 4d, 5 • Updated checklists for reactive/positive HIV schedule
7	Participant Retention	3.0	04Jan2022	Updates for Version 3.0 • Added text related to the OLE. Removed language that is no longer applicable. • Section 7.4 (Retention Plan): As with HPTN 084 pre OLE (Version 3.0), sites are expected to retain participants with no more than 5% annual loss to follow-up. A new SOP is not required for the OLE, but sites may wish to modify their existing plan if necessary.
8	Study Product Considerations	3.0	04Jan2022	Updates for Version 3.0 • Added Appendix 8b: Specific Updates to SSP Section 8 in relation to issuance of unblinded study products in when implementing Appendix VIII, HPTN 084 Protocol Version 3.0. • Relabeled HPTN 084 Record of Dispensation of Participant-Specific Study Product to Non-Pharmacy Staff to Appendix 8c (and throughout this section). • Relabeled HPTN 084 Record of Return of Participant-Specific Study Product by Non-Pharmacy Staff to Appendix 8d (and throughout this section).

9	Clinical Considerations	3.1	26Apr2022	Updates for Version 3.1
				• Section 9.2 (Participant-Reported Medical History during Follow up:
				  o Removed HIV RNA text related to screening/enrollment. Added OLE HIV RNA reference.
				• Section 9.2.1 (Medical History at Follow-up Visits):
				  o Baseline refers to the timepoint at which the participant enrolled in the original blinded trial.
				• Section 9.2.5 (Adverse Events)
				  o For infant AEs, refer to section 10.3.1 Considerations for Infants in Step 4d
				• Section 9.2.7 (Injection site reaction (ISR) assessment)
				  o Note: Step 4d has specific ISR reporting requirements.
				  o For infant AEs, refer to section 10.3.1 Considerations for Infants in Step 4d
				• Section 9.2.8 (Concomitant medications)

Section Number	Section Title	Current Version Number	Current Version Date	Updates and Comments
				○ Participants who seroconvert and start ART need to have their ART documented in the CM log. For infants, do not record concomitant medications on the CM log; however, they should be documented in the source documentation. • Section 9.4 (Specimen Collection) ○ Added note about creatine clearance equation for HPTN 084-01 participants. • Section 9.5 (Clinical Management Committee) ○ Added note- Due to the relaxed contraceptive requirements under the OLE, sites will no longer need to report to the CMC cases when a participant's LARC is delayed. • Section 9.7 (HIV Considerations During Study Conduct) ○ During the OLE, both the CMC and HIV alias should be contacted about any HIV reactive or positive tests. Added note about SOE. • Section 9.9 Tuberculosis ○ If TB treatment is required contact the CMC for guidance. • Section 9.10 Pregnancy ○ Pregnancy must be confirmed on two separate samples. Added some clarifications to this section including that each site must have a pregnancy SOP in place. • Toxicity Management Diagrams ○ Specified that these diagrams only apply to direct recipients of study product. • Appendix 9A: Added rows for treatment assignments during the blinded trial/OLE • Appendix 9B: OLE Cheat Sheet- added that participants are permitted to change contraceptive method in contraceptive sub-study. Updates for Version 3.0 • Throughout made this section specific to the OLE including the toxicity management diagrams, including removing language around enrollment, Step 1 and Step 2, pre-exiting conditions, and blinding/unblinding, LARC. Removed section on Hepatitis B and Hepatitis C testing • Section 9.4.6 (Neurologic Symptoms): Changed the wording in the neurologic symptoms section. It is now not required to actively assess neurologic systems; however, these symptoms will be assessed as part of the targeted physical exam as needed. • Added Appendix 9b: HPTN 084 Cheat Sheet for Transitioning PPTs from V2.0 to V3.0.

Section Number	Section Title	Current Version Number	Current Version Date	Updates and Comments

10	Adverse Event Reporting and Safety Monitoring	3.2	03Jun2022	Updates for Version 3.2
				Section 10.6
				• A sentence was added to clarify that if a participant has an AE ongoing under the version 2.0 protocol but under the 3.0 protocol 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.
				Updates for Version 3.1
				• Added Section 10.3.1 Considerations for Infants in Step 4d
				  • Added details around infant AE collection
				• Section 10.5: (AE Relationship to Study Product)
				  • Added reference to Steps 4-5
				• Section 10.6: (Reporting AEs to the HPTN SDMC)
				  • Added note about which AEs are reported to the database
				• Table 10-1: Reference Guide for Reporting AEs and EAEs
				  • Added reference to infant AEs
				Updates for Version 3.0
				• Throughout made specific to the OLE, including removing references to placebo.
				• Section 10.6 (Reporting AEs to the HPTN SDMC): Added note about HIV seroconversion. It is not in of itself an AE. However, symptoms related to HIV could be categorized as an AE

11	Laboratory and Specimen Management Procedures	3.1	26Apr2022	Updates for Version 3.1 Table 11-7: SOE- Step 4a • Removed “if not done in 4a” from row for CBC and Fasting Lipid Profile; this was a typo. Table 11-9: SOE- Step 4c • Added footnote #5 “only for those who did not have this collected in steps 4a and 4b” to Week 0 Xs for CBC and Chemistry testing. Renumbered remaining footnotes. • Corrected fasting lipid collection timepoints (only done at Week 48) Table 11-10: SOE- Step 4d • Added plasma and DBS storage to Week 40.

Section Number	Section Title	Current Version Number	Current Version Date	Updates and Comments
				• Added timepoints for infant testing (if mother has one or more reactive/ positive HIV test result) and DBS storage • Added timepoints for infant plasma storage • Added a clarification to footnotes 11 and 12. Section 11.3.5: Creatine Clearance: For participants who join from the HPTN 084-01 protocol, calculated creatinine clearance will be performed using the Modified Bedside Schwartz Equation. Section 11.8: Breast Milk collection and processing for OLE ppts Store at 4°C. Clarified that 2 to 8°C is acceptable. Updates for Version 3.0 • Section 11.1 (Overview): Updated links for universal precautions • Section 11.2.4 (Use of the LDMS): Updated contact information for LDMS and added information that should be provided to the LDMS user support when submitting questions. Added text around Specimen Data Quality Check (SDQC) reports and removed outdated language. The one-week requirement to resolve discrepancies has been removed. • Section 11.3 (Protocol related testing and sample collection): Breast milk and Cord blood collection should be according to manufacturer recommendations and local regulations and be included in your SOPs. Added collection instructions for Cord blood, infant collections and breast milk at the end of this section. • Section 11.3.1 (OLE samples): Added section for Open label (OL) Cabotegravir samples. • Added Tables: 11-7, 11-8, 11-9, 11-10, 11-11 and 11-12 (added Albumin and removed some chemistry tests) • Section 11.3.2 (HIV Testing): Added RNA must be collected and performed at all visits • Figure 11-3: Added a new HIV algorithm image for follow up visits which includes collecting and performing RNA at all visits. • Section 11.4 (Plasma Processing for Storage Main Study): Specified that this section now relates to the Main Study • Section 11.5 (Plasma Processing for IC storage): Under LDMS Specimen Code for Plasma Storage. PL1= Plasma, Single Spun (used to say Plasma, Double Spun)

Section Number	Section Title	Current Version Number	Current Version Date	Updates and Comments
				• Section 11.8 (Breast Milk collection and processing for OL participants): Added breast milk collection and processing for OL participants. • Section 11.9 (Cord Blood collection and processing for OL participants): Added cord blood collection and processing for OL participants. • Section 11.10 (Infant Blood collection and processing for OLE participants): Added infant blood and processing for OL participants. • Sections 11.11.5-11.11.7: Added instructions for breast milk, cord blood and infant blood • Section 11.13 (Shipping of Samples to the HPTN LC): Added cord blood, breast milk and infant plasma; in addition to Paul Richardson contact Estelle Piwowar-Manning with questions; removed reference "To Be Shipped" boxes; notify the LC via email Estelle Piwowar-Manning (epiwowa@jhmi.edu) when shipment is ready to be picked up. DBS cards can now be shipped as requested versus on the set schedule.
12	Counseling Considerations	3.1	26Apr2022	Updates for Version 3.1 • Added rows Added Decisional Balance Worksheet for OLE as Appendix 12-A Updates for Version 3.0 • Throughout made specific to the OLE. • Added Decisional Balance Worksheet for OLE as Appendix 12-A
13	Data Management	3.2	15Aug2022	Updates for Version 3.2 • Updated HPTN 084 SDMC Staff table with Debbie Landis and Jennifer Schille as new Data Managers. Removed Priyanka Agarwal. • In Table 13-2, corrected OLE Visit Codes in Step 5. Updates for Version 3.1 • Updated HPTN 084 SDMC Staff table with Sophie Hasan as new Clinical Safety Associate. • Corrections to Table 13-2: HPTN 084 OL Visit Codes, Target Days, and Visit Windows Updates for Version 3.0 • Added table 13-2: HPTN 084 Open Label (OL)Visit Codes, Target Days, and Visit Windows • Section 13.5 (Types of Visits): Removed section on Alternate Schedules • Added rows for the OLE to Appendix 13A: HPTN084 Schedule for Forms

Section Number	Section Title	Current Version Number	Current Version Date	Updates and Comments
14	CASI	3.0	04Jan2022	Updates for Version 3.0 There were no changes to the main chapter. An updated CASI was added as Appendix 14A.
15	Reporting Plan	3.0	04Jan2022	Updates for Version 3.0 Only the footer was updated as per updated version of the SSP manual. No other edits were made.
16	Data Communiqués	3.0	04Jan2022	Updates for Version 3.0 Only the footer was updated as per updated version of the SSP manual. No other edits were made.
17	COVID-19 Measures	3.0	04Jan2022	Updates for Version 3.0 • Added text related to the OLE.
Appx I	Guidance for the management of discordant/ discrepant HIV test results	2.1	16Nov2021	This is a new version of this document