HPTN 083 Study-Specific Procedures Manual
(Version 3.0)
Overview and Version Control

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

1	Introduction	3.0	12 December 2019	Updates for Version 3.0:
				• Section 1.2: Updated to reflect current staff.
				• Section 1.4: Updated the link to the US Food and Drug Administration's Information Sheet Guidance.
				• Section 1.5.4: Updated Table 1-1 to reflect approvals required and provide clarification on local regulatory authorities or IRB/EC approvals.
				• Section 1.5.5: Updated to:
				  • Provide the current link to the DAIDS Protocol Registration Policy and Procedure Manual.
				  • To provide clarification on protocol registration.
				• Section 1.6: Updated to revise the link to the DAIDS Protocol Registration Policy and Procedure Manual.

2	Protocol	3.1	12 February 2020	Updates for Version 3.0: • Updated to add Protocol Version 3.0. Updates for Version 3.1: • Updated to add Clarification Memo #1 to Version 3.0 of the Protocol.

3	Document Requirements	3.1	12 February 2020	Updates for Version 3.0:
				• Section 3.2: Updated the link to the DAIDS Protocol Registration Policy and Procedure Manual.
				• Section 3.3.3.3: Updated to clarify the process of updating Table 3-1.
				• Section 3.3.3.4: Updated to:
				  • Revise Version 2.0 references to Version 3.0.
				  • Include additional HPTN LOC Research Specialist as a contact person.
				  • Include clarifications to the eligibility criteria.
				• Section 3.4: Updated to:
				  • Revise a reference to the HPTN Manual of Operations.
				  • Define study product overdose.

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				• Include clarification that clinical-related deviations are determined by the CMC. • To prevent unblinding in consulting and reporting pharmacy-related deviations. • Revise minor grammatical errors. • Add clarification on determining if a protocol deviation is a critical event. • Section 3.5: Updated to: • Reflect current requirements for maintaining study-related records. • List completed activities that mark completion of a clinical research study. <u>Updates for Version 3.1</u>: • Section 3.4: Updated to indicate sites don't need to contact Marybeth and Kaila for known reportable deviation.
4	Recruitment, Screening and Enrollment	3.0	12 December 2019	<u>Updates for Version 3.0:</u> • Section 4.2: Updated to: • Reflect changes in enrollment and accrual period. • Clarify that screening and enrollment is provided on the portal. • Section 4.5: Updated to: • Clarify pre-screening activities. • Include the email of the HPTN LOC Research Specialist. • Section 4.7: Updated to revise screening procedures for participants currently using oral Truvada. • Section 4.8: Updated to include procedures performed at the enrollment visit.

5	Study Procedures	3.0	12 December 2019	Updates for Version 3.0:
				• Section 5.2: Updated to:
				  • Revise the number of years a participant is in annual follow-up per Version 3.0 of the protocol.
				  • Revise Step 2 visits per Version 3.0 of the protocol.
				  • Clarify when participants will be unblinded.
				  • Include instructions for determining when participants attend annual visits.
				  • Include clarification of when participants begin step 3 after completing 3 years of follow-up in Step 2.
				  • Provide details on transitioning participants to local HIV services.
				• Section 5.3: Updated to:
				  • Clarify instructions for visits outside of the target window.
				  • Clarify instructions for missed or late visits.
				  • Provide guidance on conducting merged visits.
				• Section 5.3.1: Updated to:
				  • Include additional procedures for a secondary objective.
				  • Include the procedures completed at the final visit of Step 2.
				  • Include the procedures completed at the final visit of Step 2 for participants that prematurely transition to Step 3.
				  • Include the procedures completed at the follow-up visit for participants that do not transition to Step 2.
				  • Include the procedures completed at the follow-up visit for participants that prematurely end Step 2.
				  • Include cases in which the participant should be withdrawn from the study.
				  • Include the procedures for participants that withdraw consent.
				  • Include the procedures for participants that can no longer receive injections.
				  • Include recommendations concerning study product.
				  • Clarify procedures for participants in the DXA subset.
				• Section 5.4: Updated to:
				  • Revise a reference to another section.
				  • Reference Appendix II.
				Section 5.5: Updated to: Include additional information on transferring participants from one site to another.

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6	Visit Checklist	3.2	27 February 2020	Updates for Version 3.0:
				• Section 6.4: Updated to:
				  • Provide guidance on the creatine clearance eligibility criteria.
				  • Clarify eligibility criteria on Grade 3 or higher laboratory abnormalities.
				  • Include a note on participation in HIV vaccine trials.
				  • Specify Week 0 is also Day 0.
				  • Include an additional enrollment procedure.
				  • Include an additional Week 5 visit procedure.
				  • Include additional produces in the remaining injection visits for Step 2.
				  • Include an additional procedure in Step 3.
				Updates for Version 3.1:
				• Section 6.4: Updated to:
				  • Remove safety visits after week 147 during Step 2.
				  • Remove injection visit week 153 from procedures during Step 2.
				  • Remove week 129 visit from Administer Step 2 CASI procedure.
				  • Include weeks 65, 81, and 121 and remove week 145 from Interviewer-Administered: Follow-up 1.
				  • Include a new section describing procedures at week 153, last day of Step 2/Day 0, First Visit of Step 3.
				  • Remove Day 0 from all procedures in Step 3.
				  • Include Week 12 for Administering Step 3 CASI.
				  • Update the protocol section to reference for Step 3.
				  • Remove outdate notes about blood collection for Procedures for Enrolled Participants who Seroconvert.
				Updates for Version 3.2
				  • The visit checklist for Week 153 and Step 3 were updated to add a note on when CASI should be done at Week 12.

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7	Participant Retention	3.0	12 December 2019	Updates for Version 3.0: • Section 7.2: Updated to: Revise the definition of retention. • Section 7.7: Updated to: Revised the length of time a participant has annual visits. • Section 7.8: Updated to: • Include details for annual follow-up for different situations. Include guidance for procedures when participants withdraw from the study.

8	Study Product	3.0	12 December 2019	Updates for Version 3.0:
				• Sections (8.2-8.6, 8.7, 8.7-8.7.2, 8.7.4, 8.8.1, 8.8.4, 8.8.5) were removed. All section numbering was updated after section 8.1.
				• Section 8.1.3: Updated to remove outdated section references and add clarifying language.
				• Section 8.1.6: Updated to:
				  • Revise the visits within Step 2.
				  • Update a reference to an appendix.
				  • Updated to include a note clarifying the last visit of step 2.
				• Section 8.1.7: Updated to clarify study visits for participants.
				• Section 8.8.3: Updated to provide details on emergency unblinding.

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

9	Clinical Considerations	3.1	12 February 2020	Updates for Version 3.0:
				• Section 9.1: Updated to: Revise a reference to another section within the SSP.
				• Section 9.2.1: Updated to:
				  • Specify enrollment as the randomization point.
				  • Include a note about abnormal laboratory values.
				• Section 9.2.4: Updated to: Include details about taking the study product.
				• Section 9.3.2: Updated to:
				  • Specify when height and weight measurements are taken.
				  • Include a reference to another section.
				• Section 9.3.3: Updated to:
				  • Include a reference to another section.
				  • Include examples of vital signs.
				• Section 9.3.4: New Sub-section to section 9. All sub-section numbers increased by one after this section.
				• Section 9.3.5.4: Updated to:
				  • Adjust the weeks ISRs are captured.
				  • Include the updated section number to reference.
				  • Instructions for documenting interventions to mitigate ISRs.
				• Section 9.4.1: Revised to organize the information for clarity purposes. Some information about consideration of administering precautionary and prohibited medications was move to new section 9.4.2.
				• Section 9.4.2: New Sub-section to provide guidance on co-administration of precautionary and prohibited medications.
				• Section 9.6: Updated to:
				  • Include a reference to another section.

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				• Include clarification on creatine clearance.
				• Section 9.9: Updated to:
				  • To reference Appendix II.
				  • Include a clarification on reactive/positive HIV test results.
				• Section 9.9: Updated to:
				  • Include a reference to appendix III.
				  • Include a template for emailing the 083HIV email alias.
				• Section 9.10.1: Updated to: Include clarifications for procedures regarding Hepatitis testing.
				• Section 9.11: Updated to: New sub-section to Section 9. All section numbers increased by one after this section.
				• Section 9.12: Updated to:
				  • Revise the procedures for the BMD subset.
				  • Update the table numbering.
				• Toxicity Management Diagrams were updated per Version 3 of the protocol.
				<u>Updates for Version 3.1:</u>
				• Toxicity Management Diagrams slides updated:
				  • ALT Open-label Phase: To clarify guidance refers to participants who discontinued product use during Step 2
				  • ALT Considerations: include guidance regarding product management for participants that acquire HBV infection during study follow-up.
				  • Creatinine Phosphokinase Grade 3: Updated to remove consultation with CMC if retesting does not result in Grade 3 AE.
				  • Creatinine Phosphokinase Grade 4: Updated to add guidance if CK or CPK is persistent asymptomatic Grade 4 elevation.
				  • QTc: Updated to specify which prolonged QT intervals warrant obtaining two additional ECG.

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10	Adverse Event Reporting and Safety Monitoring	3.0	12 December 2019	Updates for Version 3.0:
				• Section 10.1: Updated to revise dates and versions of the listed materials.
				• Section 10.3: Updated to include an updated URL.
				• Section 10.4: Updated to:
				  • Revise the title of a referenced material.
				  • Include an updated Toxicity Table.
				• Section 10.5: Revised to include the updated name of the CRF section referenced.
				• Section 10.6: Updated to clarify the reporting of adverse events.
				• Section 10.7.1: Updated to provide clarifications on reporting injection side reactions and post injection adverse events.
				• Section 10.7.3: New sub-section to Section 10. All section numbers increased by one.
				• Section 10.7.4: Updated to provide instructions for laboratory values from any non-HPTN Laboratory Center.
				• Section 10.9: Updated to:
				  • Include an updated URL.
				  • Clarify what is reported to DAIDS.
				• Section 10.11: New sub-section to Section 10. All section numbers increased by one.
				• Section 10.12: New sub-section to Section 10. All section numbers increased by one.
				Section 10.13: Updated to clarify which organization will send the Product Safety Information

11	Laboratory and Specimen Management Procedures	3.0	12 December 2019	Updates for Version 3.0:
				• Section: 11.3: Updated to:
				  • Reflect the changes to annual follow-up in Version 3.0 of the protocol.
				  • Add clarifications for merged study visits.
				  • Add a description of the proper transportation container for handling samples.
				  • Table 11-4 is revised to reflect changes to annual follow-up in Version 3.0 of the protocol.
				• Section 11.3.1: Updated to:
				  • Clarify the description of TAT for HIV testing.
				  • Add details for reporting HIV testing results
				  • Clarify the retention of sample for HIV rapid testing
				  • Add contact requirements for contacting the 083 seroconversion committee
				  • Clarify requirements for participants with a reactive or positive HIV test.
				  • Provide instructions for split visits.
				  • Revise the approximation of time a participant spends in Step 2.
				  • Clarify instructions for the Confirmation visit.
				• Section 11.3.5: Updated to clarify procedures for lipid testing.
				• Section 11.3.6: Updated to: Clarified retention requirements of urine specimens.
				• Section 11.4 Updated to:
				  • Add guidance on proper plasma levels in a cryovial.
				  • Clarify when to use a biological safety cabinet
				• Section 11.5.1: Updated to: Revise supplier information
				• Section 11.5.2: Updated to:
				  • Clarify the requirement for using a biological safety cabinet
				  • Revise the temperatures for DBS drying
				• Section 11.6: Updated to: Clarify the requirement for using a biological safety cabinet during plasma processing
				• Section 11.7: Updated to:
				  • Clarify requirements for shipping samples
				Add possible returning shipper information

12	Counseling Considerations	3.0	12 December 2019	Updates for Version 3.0:

Section Number	Section Title	Current Version Number	Version Date	Updates and Comments
				• Section 12.2: Updated to clarify instructions that study products should not be shared. • Section 12.4: Updated to include clarification on counseling for oral product use. • Section 12.7: Updated to revise section references.

13	Data Management	3.0	12 December 2019	Updates for Version 3.0:
				• Section 13.1: Updated the alias email address.
				• Section 13.3: Updated to:
				  • Clarify what coding queries may be used for.
				  • Clarify the query management and resolution process.
				  • Include instructions on electronic signatures by investigators.

				• Section 13.4.2: Updated to clarify who is able to access information on participant randomization.
				• Section 13.5: Updated to
				  • Clarify when visits can be completed.
				  • Revise Table 13-1 per Version 3.0 of the protocol.
				• Section 13.6: Updated to remove unnecessary language.
				• Section 13.7.2: Updated to include a reference to another section of the SSP.
				• Section 13.7.3: Updated to add clarification for split visits.
				• Section 13.7.4: Updated to provide clarification on interim visits.
				• Section 13.7.4.1: Updated to:
				  • Include additional visit codes.
				  • Provide an additional example.
				• Section 13.7.5: Updated to provide guidance on participants in Step 2.
				• Section 13.8: New sub-section to Section 13. All section numbers increased by one.
				• Section 13.9: Updated to remove a refence to documents that have moved.
				• Section 13.11: Updated to revise procedures for QC review of Step 2.

14	Computer Assisted Self-Interview (CASI)	3.0	12 December 2019	Only the footer was updated as per updated version of the SSP manual. No other edits were made.
15	Reporting Plan	3.1	12 February 2020	Updates for Version 3.0

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				Only the footer was updated as per updated version of the SSP manual. No other edits were made. Updates for Version 3.1 Only the footer was updated to correct the number of pages from 5 to 6.
16	Data Communiqués	3.1	12 February 2020	Updates for Version 3.0 • New section to the SSP manual. Version number reflects the version of the manual. Updates for Version 3.1 • Included Data Communiqué #4.
	Appendix I: DXA Scans	3.0	12 December 2019	Only the footer was updated as per updated version of the SSP manual. No other edits were made.
	Appendix IIa: Record of Dispensation	3.0	12 December 2019	Only the footer was updated as per updated version of the SSP manual. No other edits were made.
	Appendix IIb: record of Return	3.0	12 December 2019	Only the footer was updated as per updated version of the SSP manual. No other edits were made.
	Appendix III: Schedule of Forms	3.2	27 February 2020	Updates for Version 3.0: • "Vital signs" was added to each table. • Clarifications were added for sites to follow based on their approval status on Version 3.0 of the protocol. • Additional procedures and clarifications were included in the table for Step 3. Updates for Version 3.1 • Include a note on SMSQs for Step 3 Open Label Oral Day 0. Updates for Version 3.2: • Table for Step 3 was updated to add a note on when CASI should be done at Week 12.
	Appendix IV: Participant Transfer and Receipt Process	3.0	12 December 2019	Only the footer was updated as per updated version of the SSP manual. No other edits were made.

Section Number	Section Title	Current Version Number	Version Date	Updates and Comments
	Appendix V: Guidance for management of "discordant/discrepant' HIV testing results	3.0	12 December 2019	Only the footer was updated as per updated version of the SSP manual. No other edits were made.
	Appendix VI: Emergency Unblinding by CRS IoR for Medical Reasons	3.0	12 December 2019	Only the footer was updated as per updated version of the SSP manual. No other edits were made.

	Appendix VII: SSP Manual Updates Per LoA #1 to Version 3.0 of the Protocol	3.1	1 September 2020	Updates for Version 3.1:
				• Section 1.2.1: Updated to add LoA #3
				• Section 1.2.5:
				  • Updated to clarify communication with the pharmacy once a participant has been unblinded.
				  • Updated to correct instructions for Step 3 product dispensation
				• Section 1.2.6: Updated to clarify requirements for completing the injection site reaction
				• Section 1.2.10:
				  • Updated to correct visit windows
				  • Updated to clarify requirement for completing post-exercise assessments
				• Section 1.2.11: Updated to add Data Communique #9
				• Table A: Schedule of Procedures and Evaluations: Updated to clarify procedures performed at injection visits
				• Visit checklists: Updated to include a note of when the injection site reaction and post-exercise assessments are required.
				• A new section added: HPTN 083 Adherence Counseling Updates

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Section Number	Section Title	Current Version Number	Version Date	Updates and Comments
1	Introduction	2.0	27 August 2018	Updates for Version 2.0: • Section 1.5.2: Updated to add information about site-specific ICF review following initial version. • Table 1-1: Updated to include behavioral assessments and CRFs • Section 1.5.5: Updated to add local regulatory authority as required approval for protocol registration. • Table 1-2: Updated the name of the Centro de Pesquisas Clínicas IC-HCFMUSP CRS
2	Protocol	2.0	27 August 2018	Updates for Version 2.0: • Updated to add Protocol Version 2.0

3	Document Requirements	2.0	27 August 2018	Updates for Version 2.0:
				• Some sections were updated to correct spelling and change wording for clarity.
				• Section 3.2: Updated to:
				  • Clarify that original and subsequent versions of the FDA Form 1572 and protocol registration documents must be filed as part of the essential documents.
				  • Specify all key staff listed in FDA form 1572 must complete the financial disclosure forms
				  • Specify documentation of training required to be filed
				  • Specify that sites may choose how to file CRFs
				• Section 3.3.3.4: Information on completion of eligibility criteria checklist was added.
				• Table 3-2: Updated to include language from Version 2.0 of the protocol about the calculated creatinine clearance and Grade 3 or higher laboratory abnormalities
				• Section 3.3.4: Updated to include language regarding safeguarding participant's confidentiality when sending documents outside the clinic
				• Section 3.4: Updated to:
				  • Include examples of reportable protocol deviations
				  • Text was rearranged and formatted for clarity purposes, including organizing text by order of events when a site identifies a protocol deviation.

Section Number	Section Title	Current Version Number	Version Date	Updates and Comments
				• Add reminder that if an unblinding happens to not include any information in the email which would unblind any additional individuals.
4	Recruitment, Screening, and Enrollment	2.0	27 August 2018	Updates for Version 2.0 • Section 4.5: Updated to add requirements and guidance for use of an eligibility checklist to confirm a participant's eligibility. • Section 4.7: Updated to add language informing sites to obtain IRB approval before use of SexPro, and to include target visit window for the BMD subset at enrollment. • Section 4.8: Updated to add information how to handle erroneous randomizations.

5	Study Procedures Overview	2.0	27 August 2018	Updates for Version 2.0
				• In a number of areas, the section was adjusted to clarify instruction about transitioning participants to annual follow up who don't complete the expected study procedures
				• Section 5.3: Updated to add:
				  • Guidance and examples for handling split visits, some types of missed visits, and out-of-target-window visits.
				  • Language from Version 2.0 of the protocol regarding communication with the CMC for out of window visits.
				• Section 5.3.1: Updated to add:
				  • Guidance on how to handle situations in which a participant cannot read the CASI questionnaire
				  • Language from Version 2.0 of the protocol regarding transition to Step 2 for participants with less than 50% adherence.
				  • Language from Version 2.0 of the protocol regarding for participant withdrawal and early termination.
				  • Wording was edited for clarity on expectations for the number of bottles of study product to dispense under certain circumstances.
				  • Matching language from Version 2.0 of the protocol regarding amount of product dispensation.
				  • Information was added on how to handle DXA scans in the case of premature transition to Stage 3.
				  • Language per Version 2.0 of the protocol on DXA scan windows during follow-up.

Section Number	Section Title	Current Version Number	Version Date	Updates and Comments
				• Section 5.5: Updated to provide guidance on situations when a participant moves away from study site and edited to specify that participants will not be withdrawn from the study for moving away from study sites.
6	Visit Checklists	2.0	27 August 2018	Updates for Version 2.0: • Section 6:3: Minor editing for clarity. • Section 6.4: Eligibility Checklist Template updated to include language from Version 2.0 of the protocol about the calculated creatinine clearance and Grade 3 or higher laboratory abnormalities.
7	Participant Retention	2.0	27 August 2018	Updates for Version 2.0: • Several areas were edited to correct spelling or change wording for clarity. Also, "for HIV testing" was deleted throughout the section when referring to annual study visits. • Section 7.8: Language was added to match the protocol regarding participant withdraw from study.
8	Study Product Considerations	2.0	27 August 2018	Updates for Version 2.0: • Several areas of the section were updated to correct spelling, change wording for clarity, update use of acronyms. • Section 8.3: Revised wording describing the study product regimens for the various steps of the study was revised for clarity and to add some additional details. • Section 8.4: Updated contact information for the Protocol Pharmacist at DAIDS/PAB. • Section 8.5.1: Information updated about the needles available from the CRPMC, and to modify the instructions to sites for completing the drug supply statement and ordering supplies from CRPMC. • Section 8.6: Update to instruction regarding accountability records and for returning or destroying drug, depending on location of site (in or out of U.S.) • Section 8.6.1: Updated to give revised instructions on how to document drug chain of custody including drug returned to the pharmacy after dispensation • Section 8.7.1: Updated the storage temperature to 30 C for oral CAB/CAB placebo and additional instructions on storage conditions. Text added to indicate that CAB injectable suspension to be stored in vials.

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				• Section 8.7.3: Updated to clarify that at dispensation, tear-off labels from oral product bottles can be attached to whichever participant-specific pharmacy record the site is using.
				• Section 8.7.4: Updated to:
				  • Clarify the volume of CAB LA injectable product should be prepared for use in an injection
				  • Modify instructions to describe how to load the product into the syringe depending on the volume contained in the vials in use at the site.
				  • Add guidance for the storage temperature range for a prepared syringe of CAB LA (or placebo) and for pharmacy staff to be certain to deliver the full dose volume, considering the residual amount of product in the needle after administration.
				  • Add language regarding needle size.
				  • Instructions for syringe management after loading with placebo were modified to account for different site procedures, i.e. whether the administration needle is added in the pharmacy or the clinic.
				• Section 8.7.5: Updated to add instruction about maintaining syringes with injectable product at room temperature.
				• Section 8.7.6: Updated information about the amount of product to dispense during Step 1.
				• Section 8.7.8: Updated to add guidance about ensuring that a participant always has an adequate supply of study product. Text added to note that injections are IM.
				• Section 8.7.9: Updated to add that oral product should be dispensed in original bottles and language revised re: guidance on when to transition to Step 3.
				• Section 8.8.2: Updated per Version 2.0 of the protocol for participants with less than 50% adherence to study product at Week 4.
				• Section 8.7.8: Updated to add guidance about ensuring that participant always has an adequate supply of study product.
				• Section 8.7.9: Updated to add that oral product should be dispensed in original bottles and language revised re: guidance on when to transition to Step 3.

Section Number	Section Title	Current Version Number	Version Date	Updates and Comments
				• Section 8.8.2: Updated to add language amount of product dispensation, instructions to participants about management of their oral medication; assessment of participants' remaining medication to guide dispensation of new bottles; and when to dispense oral product at a given visit, depending on whether the participant receives an injection. • Section 8.8.3: Updated to clarify labeling instructions to indicate that product is to be dispensed blinded in Steps 1 & 2 and open label in Step 3, and that a participant-specific label must be put on product prepared for dispensing. • Section 8.8.6: Updated to add information on emergency unblinding
9	Clinical Considerations	2.0	27 August 2018	Updates for Version 2.0 • Section 9.3.2: Language was added to clarify that BMI is to be calculated at baseline and that needle gauges other than those listed may be used. • Section 9.3.4.6: Stipulation made that medical marijuana use will not be captured in the concomitant medications log. • Section 9.3.4.7: Edited for clarity on which drugs are not to be concomitantly administered and which drugs could be used with caution. • Section 9.4: It was clarified that BMI may be re-calculated after baseline if participant has had a significant change in weight. • Section 9.5: Updated per Version 2.0 of the protocol regarding creatinine clearance assessment, management, and reporting. • Section 9.6: Language was modified to include a Medical Safety Physician on the CMC. • Section 9.7.3: Updated per Version 2.0 of the protocol regarding CMC contact due to positive syphilis results. And language from Version 2.0 of the protocol was added regarding reporting of STIs. • Section 9.7.4: Updated to match language in Version 2.0 of the protocol regarding eligibility for participants with hepatitis results that were not negative. • Section 9.8: Updated to include information on DXA subset procedures and study windows. Also, language was added to match Version 2.0 of the protocol on BMD subset procedures and windows.

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10	Adverse Event Reporting and Safety Monitoring	2.0	27 August 2018	Updates for Version 2.0
				• Section 10.3: Updated the link to the DAIDS Toxicity Table.
				• Section 10.4: Further guidance was added on AE severity grading.
				• Section 10.6: Guidance was added regarding where to include information when completing an AE form and distinguishing conditions from procedures for reporting purposes.
				• Section 10.7: A new section with four sub-sections was added providing guidance for:
				  • 10.7.1- Reporting of injection and post-injection reactions/AEs
				  • 10.7.2- Reporting procedure-related AEs. Also, language was added per Version 2.0 of the protocol on STI reporting.
				  • 10.7.3- Reporting laboratory AEs
				  • 10.7.4- Reporting recurrent AEs
				• Sections numbers after 10.7 have changed to a number ahead. For example, Section 10.8 is now 10.9
				• Section 10.9: Updated the link to the DAIDS EAE manual and added additional instructions for reporting AEs that require expedited reporting.

11	Laboratory and Specimen Management Procedures	2.0	27 August 2018	Updates for Version 2.0 • Section 11.3: Clarification added that test results from a single visit cannot be used for multiple visits if more than one visit is performed on the same day. • Section 11.3.1: Additional text added to clarify that plasma storage is required every time HIV testing is performed if not limited by the informed consent. • Section 11.4: Text added to indicate that plasma storage volume of 1.8mL is approximate and that a precision pipette need not be used for this task. The type of cryovial used for plasma storage was clarified. LDMS coding reminders were added for appropriate code use and notification.

Section Number	Section Title	Current Version Number	Version Date	Updates and Comments
				• Section 11.5.2: DBS processing temperature restrictions per testing laboratory notice updated. LDMS coding reminders added for appropriate code use and notification. The storage temperature for whole blood prior to the creation of DBS was updated. Updates and clarification added to the instructions for the environmental drying requirements for the DBS cards. Clarification added regarding the checking of humidity indicators. • Section 11.6: Text added to clarify storage volume requirements for whole blood for pharmacogenomics testing. LDMS coding reminders added for appropriate code use and notification.
12	Counseling Considerations	2.0	27 August 2018	Updates for Version 2.0 • Section 12.3.2: Wording regarding pill counts modified slightly for clarity, and a reference to Table 9-1 was removed.
13	Data Management	2.0	27 August 2018	Updates for Version 2.0 • Section 13.2: Updated email address for Medidata Rave access assistance. • Section 13.3: Updated personnel to contact with manual data queries and reformatting the section on query management and resolution for greater clarity. An instruction was added for situations when "Site from System" queries appear in Medidata Rave. Information and guidance was added about reports that sites can access through Medidata Rave for Open Queries and AEs unresolved ≥30 days. • Section 13.4.1: List of screening visit forms requiring Rave entry was updated to include Inclusion/Exclusion form and a small tweak to wording made for clarity. • Section 13.4.2: Guidance was added regarding HIV testing and Inclusion/Exclusion form completion steps required prior to enrollment. Language was added to indicate the time zone used for the randomization CRF. A reminder to confirm all necessary items are complete and correct before randomizing was added. • Section 13.4.3: Slight changes were made to instructions for entry of data into Medidata Rave when data is first collected elsewhere and for AEs/EAEs. • Section 13.5: Language was removed that had required contacting the CMC for injection visits inside the allowable visit window but outside the target window. Table 13.1 in this section was revised to include allowable visit windows.

Section Number	Section Title	Current Version Number	Version Date	Updates and Comments
				• Section 13.6: Language was added to clarify expectations for the timing of injections, and how to handle late injections and late safety visits following an injection. • Section 13.7: A reference was added to Section 5.3 of the SSP for information on visit types. • Section 13.7.2: A reference was added to Section 5.3 of the SSP for information on missed visits and language edited to clarify other aspects of missed visits/ • Section 13.7.3: A reference was added to Section 5.3 of the SSP for information on spit visits • Section 13.7.4: Language was added to define an interim visit and to further elaborate conditions under which an interim visit code must be assigned. Language about transitioning to yearly HIV testing visit was removed. • Section 13.7.5: Language was added regarding expectations for annual visits. • Section 13.8: The schedule of forms was expanded to include "CASI surveys" and a note included regarding differences in nomenclature between this SSP section and the protocol.
14	Computer Assisted Self-Interview (CASI)	2.0	27 August 2018	New section to the SSP manual. Version number reflects version of the manual.
15	Reporting Plan	2.0	27 August 2018	New section to the SSP manual. Version number reflects version of the manual.
	Appendix 1: DXA Scans	2.0	27 August 2018	Only the footer was updated as per updated version of the SSP manual. No other edits were made.
	Appendix IIa: Record of Dispensation	2.0	27 August 2018	Only the footer was updated as per updated version of the SSP manual. No other edits were made.
	Appendix IIb: Record of Return	2.0	27 August 2018	Only the footer was updated as per updated version of the SSP manual. No other edits were made.
	Appendix III: Schedule of Forms	2.0	27 August 2018	<u>Updates for Version 2.0</u> • Screening Visit Forms and Surveys Table: Inclusion/Exclusion forms added. • Step 1 Forms and Surveys Table: Items in the table were reordered to be listed alphabetically and the CASI survey was added to the list. • Step 2 Oral and Injections weeks 5-43 Forms and Surveys Table: CASI survey administration was added to the schedule of visits.

Section Number	Section Title	Current Version Number	Version Date	Updates and Comments
				• Step 2 Oral and Injections weeks 49-91 Forms and Surveys Table: CASI survey administration was added to the visit schedule and Vitamin D and Calcium Assessment was removed the schedule for Week 57. • Step 2 Oral and Injections weeks 97-139 Forms and Surveys Table: CASI survey administration was added to the visit schedule and Vitamin D, and Calcium Assessment was removed the schedule for Week 105. • Step 2 Oral and Injections weeks 145-187 Forms and Surveys Table: CASI survey administration was added to the schedule of visits • Step 3 Open Label Oral Forms and Surveys Table: Lead electrocardiogram was removed from week 24 and CASI survey administration was added • Additional/As Needed CRFs Table: This list was reformatted into table form and the Yearly Visit form was added. • Description of Survey Information was updated so that the language more closely mirrored what was in the protocol.
	Appendix IV: Participant Transfer and Receipt Process	2.0	27 August 2018	Only the footer was updated as per updated version of the SSP manual. No other edits were made.
	Appendix V: Guidance for the management of "discordant/discrepant" HIV testing results	2.0	27 August 2018	Only the footer was updated as per updated version of the SSP manual. No other edits were made.
	Appendix VI: Emergency Unblinding by CRS IoR for Medical Reasons	2.0	27 August 2018	Only the footer was updated as per updated version of the SSP manual. No other edits were made.

HPTN 083 Study-Specific Procedures Manual
(Version 1.0)
Overview and Version Control

Section Number	Section Title	Current Version Number	Version Date	Updates and Comments
1	Introduction	1.2	16 January 2018	Updates for Version 1.1: • Section 1.2: Protocol Pharmacist contact information was updated • Table 1-2: updated to delete the India site Updates for Version 1.2 • Section 1.2: Updated to add LOC Community Programs Managers contact information • Table 1-2: updated to delete the Miami site
2	Protocol	1.1	16 January 2018	Updates for Version 1.1: • Updated to add CM #1, CM #2, and LoA #4

3	Document Requirements	1.6	22 May 2018	Updates for Version 1.1:
				• Table 3.2: platelet count value updated to remove an extra "0"
				Updates for Version 1.2:
				• Links to DAIDS documents were updated throughout the section
				• Table 3-2: Note added to the HIV eligibility entry to emphasize testing window for HIV RNA test
				• Table 3-2: Note added to the history of seizure entry to emphasize that report of any seizure is exclusionary
				Updates for Version 1.3:
				• Table 3-2: updated to delete inhaled nitrates as an exclusionary stimulant drug
				• Section 3.4 updates include:
				  • Who sites need to contact in case of a protocol deviation
				  • Updates to instructions on submitting protocol deviations
				  • Updates to the process for informing the 083PD@hptn.org team of the deviation
				Updates for Version 1.4:
				• Section 3.2: Minor update to correct discrepancy in table 3-1 numbering
				• Table 3-1: Minor update to instructions
				• Table 3-2: HIV related eligibility criteria was updated to include listing of required HIV testing at screening

Section Number	Section Title	Current Version Number	Version Date	Updates and Comments
				• Section 3.4: Updated to add clarity to the deviation language as well as to add one additional example of reportable protocol deviations Updates for Version 1.5: • Section 3.4: Updated to include instruction on format to use when emailing the 083PD@hptn.org team Updates for Version 1.6 • Section 3.2: Update timeframe for updates to staff CV to match DAIDS requirements • Section 3.3.3.4: Updated to clarify use of eligibility checklist • Section 3.4: Updated to clarify reporting of deviation trends, and to add location of the critical event form

4	Recruitment, Screening, and Enrollment	1.3	16 January 2018	Updates for Version 1.1:
				• Section 4.7 was updated to include:
				  • Information on printing of SexPro outcome page
				  • Guidance on use of PrEP by potential participants
				  • Guidance on use of PEP during screening period
				Updates for Version 1.2:
				• Section 4.7 was updated to include an entry to emphasize that report of any seizure is exclusionary
				• Section 4.8 was updated to specify who to contact in case a participant wants to discontinue study participation directly or soon after randomization.
				Updates for Version 1.3:
				• Section 4.7: Updated to add reference to Protocol Appendix IE and to list the required HIV tests at screening.
				• Section 4.8: Updated to clarify information regarding split Enrollment visit

5	Study Procedures Overview	1.5	22 May 2018	Updates for Version 1.1: • Section 5.3.1, second bullet was updated to correct when samples are collected. Updates for Version 1.2: • Section 5.4 was updated to include a statement to remind sites to follow the HIV testing algorithm during follow-up. • Section 5.5:

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

				• Listing of who should be notified in case of a participant transfer was updated to specify protocol-specific contacts.
				• Link to DAIDS SOP was updated.
				Updates for Version 1.3:
				• Section 5.3 was updated include considerations for missed visits.
				• Section 5.5 was updated to correct the process for participant transfer.
				Updates for Version 1.4:
				• Table of content: deleted listing of Section 5.6
				• Throughout the section language related to transition to annual HIV testing visits updated to match LoA#4
				• Section 5.2: Updated to include reference to protocol and new Appendix Id.
				• Section 5.3:
				  ○ Rearranged for clarity purposes
				  ○ Language referencing target and allowable windows added
				  ○ Missed visit information updated to match language in LoA#4
				• Section 5.4: Updated to add references to new Protocol Appendix Id and SSP Appendix V.
				• Section 5.5: Updated to clarify that transfer process is the same for temporary and permanent transfers.
				• Section 5.6: Deleted since process is the same for temporary and permanent transfers.
				Updates for Version 1.5:
				• Section 5.3: To clarify exact timing when to contact CMC for missed safety visit
				• Section 5.3.1: To add information on participants who prematurely move to Step 3, participant withdraw, and information on dispensation of study product.

6	Visit Checklists	1.7	16 January 2018	Updates for Version 1.1: • Visit checklists updated to include timing of behavioral and acceptability assessments per most recent schedule of forms. Updates for Version 1.2: • Section 6.3 was updated to clarify procedures taking place before enrollment. Updates for Version 1.3:

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

				• Visit checklist template for *Step 2 (Remaining Injection Visits)* was updated to correct the weeks that syphilis serology sample is collected
				<u>Updates for Version 1.4:</u>
				• Eligibility checklist for screening:
				  • Note added to the HIV eligibility entry to emphasize testing window for HIV RNA test
				  • Text added to the history of seizure entry to emphasize that report of any seizure is exclusionary
				<u>Updates for Version 1.5:</u>
				• Eligibility Checklist was updated to delete inhaled nitrates as an exclusionary stimulant drug
				<u>Updates for Version 1.6:</u>
				• Eligibility Checklist was updated to correct the timing HIV test results are resulted and confirmed non-reactive, as per Clarification Memo #1.
				<u>Updates for Version 1.7:</u>
				• Section 6.1: updated include that use of checklists is strongly recommended and sites can modify as needed.
				• Section 6.3, third bullet: updated to include information for sites that conduct split Enrollment visit
				• Section 6.4:
				  ○ Eligibility checklist: Updated to include all required HIV tests and signatures prior to enrollment and dispensation of study product. Also, statement at the end of the checklist updated to explain meaning of signatures and who needs to sign.
				  ○ All other visit checklists updated to include required HIV tests.
				  ○ Step 1: Enrollment, Week 0: Updated to include note regarding enrollment for sites with slit Enrollment visit
				  ○ New sample visit checklist for Procedures for Annual HIV Testing Visits has been added

7	Participant Retention	1.2	22 May 2018	<u>Updates for Version 1.1:</u>

Section Number	Section Title	Current Version Number	Version Date	Updates and Comments
				• Section 7.7, 23rd bullet: updated to include reference to the Annual HIV testing visit for participants that wish to discontinue study participation. • Section 7.8: Updated to add requirement for transition to Annual HIV testing visit. Updates for Version 1.2: • Section 7.8: To add information on considerations related to participant withdrawal to maintain ITT analysis.
8	Study Product Considerations	1.0	8 December 2016	
9	Clinical Considerations	1.5	2 July 2018	Updates for Version 1.1: • Section 9.4: updated to include the link to injection instructions in Thai • Section 9.5: updated to include guidance on timing of lipid profile sample collection if participant is not fasting at enrollment visit. Updates for Version 1.2: • Section 9.2.5: updated to provide clarification on documentation of ongoing conditions at enrollment. • Section 9.3.4.7: Note added regarding to explain reason there is no distinction between Truvada's precautionary and prohibited medications • Section 9.4: updated to include the link to injection instructions in Portuguese, Spanish, and Vietnamese Updates for Version 1.3: • Section 9.7.1: Corrected to permanently discontinue study product once HIV infection is confirmed during Step 1. Updates for Version 1.4: • Section 9.1: Updated to include new Protocol Appendix Id • Section 9.2.4: Added regular or low dose of ASA is not exclusionary. Also added language to the acute HIV infection information at enrollment for sites that do split visit, per LoA#4. • Section 9.2.6: Bullet added with guidance for participants that report issues swallowing tablets. • Section 9.3.2: Updated information on needle size • Section 9.3.4.1: AE grading and reporting updated per LoA#4 • Section 9.3.4.3: AE reporting updated per LoA#4

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

				• Section 9.3.4.7: Cabotegravir prohibited medications updated for clarity.
				• Section 9.4: Updated links to instruction videos of ventrogluteal injections. Also added bullet to include information about not holding injection if participant took oral product on the day of Week 5 visit.
				• Section 9.7.1: Updated to include reference to Appendices IE-1G of the protocol and Appendix V of the SSP.
				• Toxicity Management Diagrams: Updated per LoA#4
				
				<u>Updates for Version 1.5:</u>
				• Section 9.3.2: Updated needle size to include 1" needles
				• Section 9.3.4.4: Updated to include information on definition and reporting of an ISR
				• Section 9.3.4.7:
				  ○ Notes were added to clarify co-administration of immunomodulators, NSAIDS, and drugs eliminated by active tubular secretion
				  ○ Table 9-1 was added to provide NSAID Dose Levels
				  ○ Two notes were added to provide guidance regarding CMC consultation for specific situations when PEP or PrEP is used. Also, guidance was added in the event a new needle is needed or if the needle malfunctions
				• Section 9.4: To remove links of injection videos were deleted and a new location and password was added.
				• Section 9.5: To add clarification of use of creatinine clearance calculation for TWG
				• Section 9.6: Information was added to the sample format for communication with the CMC.
				• Section 9.7.3: To add information on positive/reactive syphilis testing

10	Adverse Event Reporting and Safety Monitoring	1.2	22 May 2018	<u>Updates for Version 1.1:</u> • Section 10.1 and 10.3: Tox table reference updated per LoA#4 • Section 10.6: AE reporting requirements updated per LoA#4 • Section 10.8: For clarity, updated to add "at the same time" to ALT > 3x ULN AND total bilirubin > 2x ULN SAE reporting requirement. • Table 10-1: Reporting requirements updated per LoA#4 <u>Updates for Version 1.2:</u>

Section Number	Section Title	Current Version Number	Version Date	Updates and Comments
				• Section 10.3: Updated to add information on ISR reporting. • Section 10.6: To update instructions on documentation of severity increase of an AE to match CRF language

11	Laboratory and Specimen Management Procedures	1.3	16 January 2018	Updates for Version 1.1:
				• Section titles 11.3 – 11.10 – formatting corrected to 11.2.1 – 11.8.
				• Pages 11-4 to 11-5 - spacing updated for LDMS label example explanation
				• Pages 11-12 to 11-13 - table 11-2 – footnotes updated to be page specific (start at #1 not #26)
				• Page 11-21 – break added to start plasma processing on new page
				• Figures 11.4 and 11.5 updated to reflect 1 DBS card storage instead of 2 [display of 10 sub-aliquots changed to 5 sub-aliquots]
				Updates for Version 1.2:
				• Header and figure numbers updated throughout the section due to additional information.
				• Section 11.2.4: updated to include information about the use of web LDMS.
				• Section 11.2.5: updated to include requirement for responding to LDMS reconciliation reports within 1 week of receipt.
				• Table 11-2: corrected to remove the requirement for 25 OH Vitamin D at follow up visits.
				• Table 11-3 footnote numbering corrected to 3.
				• Section 11.3.2: updated to clarify that HBcAb total is required and that there is no exception to the enrollment criteria which excludes participants with a positive HBsAg and/or HCV antibody.
				• Section 11.3.7: corrected to indicate Syphilis results from the enrollment visit are not required prior to enrollment.
				• Section 11.4:
				  ○ updated to include additional allowable LDMS condition codes for plasma storage.
				  ○ updated to clarify how plasma aliquots should be created from the LDMS.
				• Section 11.5.2:
				  ○ updated to include additional allowable LDMS condition codes for DBS storage.

Section Number	Section Title	Current Version Number	Version Date	Updates and Comments
				○ updated to clarify how DBS aliquots should be created from the LDMS. • Figures 11-4 to 11-18 have been included as example screenshots for the entry of stored samples into the both the PC and Web based LDMS systems. • Section 11.6: updated to clarify how whole blood for pharmacogenomic testing should be entered into LDMS and additional storage/shipping instructions. • Section 11.7: updated to clarify sample shipment instructions. • Section 11.7.4: updated to remove text included in error. <u>Updates for Version 1.3:</u> • Section 11.1: updated to include Aurora location where DBS are shipped and tested • Section 11.2: Visit code reference to SSP section 13 added • Section 11.2.5: Primary Specimen report production updated to "upon request" for 083 • Section 11.3: ○ Testing tables and titles updated for addition of LoA#4 Annual Follow-up procedures ○ Annual follow-up situations (as described in LoA#4) added to written descriptions for Step 1, 2, and 3 completions or discontinuations ○ Blood draw volumes updated to "approximately 20mL" ○ LC notification for missed Pharmacogenomic sample collections added ○ Table 11-4 added: Annual follow-up HIV testing (as described in LoA #4) ○ Table 11-4 and 11-5 references updated throughout document to match new table and table shift • Section 11.3.5: Fasting lipid profile sample collection for returning participants updated to specific optimal 72-hour collection • Section 11.4: Blood draw volumes updated to "approximately 20mL" • Section 11.5.2: ○ Drying time of DBS updated to include the need of LDMS comments when over 16 hours ○ Use of heat sources not allowed for DBS drying added

Section Number	Section Title	Current Version Number	Version Date	Updates and Comments
				○ Indicator cards and desiccant use specified for after "the DBS card is dried and ready for freezer storage." ○ Commenting in LDMS for changes of humidity cards or desiccant packs added ○ Page 11-28 duplicate sentence removed • Section 11.7, Whole Blood: Sentence separated from header to match document formatting
12	Counseling Considerations	1.4	22 May 2018	Updates for Version 1.1: • Section 12.3.1: Oral product instructions updated to revise guidance if a dose is missed and to include additional information about product storage by participants. Updates for Version 1.2: • Section 12.3.1 was updated to include a note regarding the appearance of Turvada tablets in the study • Section 12.3.4: Statement that log in to the HPTN website is necessary to access the counseling manual. Updates for Version 1.3: • Section 12.2: Updated to include reference to Protocol Appendix 1E • Section 12.3.1: Updated to include guidance about slitting pills • Section 12.3.2: Updated to include guidance about product use on the day of Week 5 Visit. Updates for Version 1.4: • Section 12.3.1: To add pictures of oral study product and minor editorial update • Section 12.3.2: To add information on product use counseling at the enrollment visit to minimize misunderstanding of product use.
13	Data Managment	1.0	8 December 2016	
	Appendix 1: DXA Scans	1.1	22 February 2017	Updates for Version 1.1: • Updated to clarify that array mode should be used for all scans
	Appendix IIa: Record of Dispensation	1.0	5 October 2016	
	Appendix IIb: Record of Return	1.0	5 October 2016	
	Appendix III: Schedule of Forms	1.0	6 February 2017	

Section Number	Section Title	Current Version Number	Version Date	Updates and Comments
	Appendix IV: Participant Transfer and Receipt Process	1.0	2 June 2017	
	Appendix V: Guidance for the management of "discordant/discrepant" HIV testing results	1.1	9 January 2018	
	Appendix VI: Emergency Unblinding by CRS IoR for Medical Reasons	1.1	26 July 2018	Updates for Version 1.1: • Updated to add clarity to the process for emergency unblinding and that it will be performed only in extremely rare and urgent medical emergency cases. • Updated to add the use of the MediData system as the primary emergency unblinding method, which is to be performed by the IoR or designee. • Updated to state that emergency unblinding by the site pharmacist is the back-up procedure in cases where the MediData system is unable to be used, and to include additional instructions for that process.