Clarification Memo # 1 to:

HPTN 083: A Phase 2b/3 Double Blind Safety and Efficacy Study of Injectable Cabotegravir Compared to Daily Oral Tenofovir Disoproxil Fumarate/Emtricitabine (TDF/FTC), For Pre-Exposure Prophylaxis in HIV-Uninfected Cisgender Men and Transgender Women who have Sex with Men

Protocol Version 3.0, October 31, 2019
DAIDS Document ID: 20725
IND # 122, 744

Final Date of CM # 1: February 10, 2020

Summary of Revisions and Rationale

1. Section 9.2.1 of the protocol has been clarified to state that resistance testing performed by the HPTN Laboratory Center or designee will be performed periodically throughout the study, per the following recommendation of the Multinational DSMB Meeting held on May 9, 2019:

   "Resistance testing in real time should be performed on any breakthrough infections, and results should be provided to the site PI to take appropriate action."

2. The procedures for the last visit in Step 2, which is Week 153, and the first visit of Step 3, which is Day 0, are combined as one visit in Protocol Version 3.0, and are outlined in Section 5.8 of the protocol and also in both Appendix IB and IC. The procedures for the Week 153/Day 0 visit are correctly outlined in Section 5.8 of the protocol and in Appendix IB. However, some procedures from Section 5.8 were inadvertently not also listed in the column for Week 153/Day 0 in Appendix IC. In order to provide further clarity and avoid confusion, the Week 153/Day 0 column in Appendix IC is removed. Additionally, for further clarity, the relevant footnotes from Appendix IC have been moved to Appendix IB, and a new footnote has been added to Appendix IB.

   Note: As outlined in Section 5.8 of the protocol, if the Week 153 visit is missed or has already occurred or passed at the time Version 3.0 of the protocol is approved and implemented at a site, the final visit of Step 2/first visit of Step 3 will take place at the next visit the participant attends, and any procedures required for the Week 153/Day 0 visit not already required at the next visit the participant attends will be performed.

Implementation

The clarifications included in this memorandum have been approved by the Division of AIDS (DAIDS) Medical Officer. Sites should submit the memorandum to local Investigational Review Board (IRB)/Ethics Committee (EC)/other regulatory entity for information purposes as required.

None of the corrections in this memorandum impact the sample informed consent form, and the benefit-to-risk ratio for participants is not affected in any way.

Text appearing below in highlighted **bold** outlines the correction. The text appearing in highlighted ~~strike-through~~ deletes the error.

Clarification 1:

9.2.1 Virology

The HPTN LC will perform QA testing, including testing to determine HIV infection status in selected cases. Additional assays may be performed at the HPTN LC or a laboratory designated by the HPTN LC. This testing may include the following tests for participants who acquire HIV infection: HIV viral load, HIV resistance testing, HIV subtyping, and other tests to characterize HIV viruses and/or the host response to HIV infection. Results will not be returned to the sites or study participants, with the exception of HIV testing (if results obtained at the HPTN LC do not agree with site results).

Resistance testing will be performed at the HPTN LC or a laboratory designated by the HPTN LC. This testing will be performed ~~retrospectively at the end of~~ **periodically during** the study. Results of this testing will not be returned to study sites. Because real-time resistance testing may be needed for clinical management in the event of HIV infection, each site will have an SOP as to how they will accomplish real-time local or regional resistance testing to assist with clinical decision making; separate specimens should be collected for that testing.

Clarification 2:

Appendix IB: Schedule of Procedures and Evaluations - Step 2 – Blinded Injections + Blinded Daily Oral Pills

WEEKS (shaded column = injection/ dispense pills visit)	5	6	9	10	17	19	25	27	33	35	41	43	49	51	57	59	65	67	73	75	81	83	89	91	97	99	105	107	113	115	121	123	129	131	137	139	145	147	Week 153/ Day 0*
Locator Information	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
HIV Counseling	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Condoms and lubricant	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Acceptability Assessment					X						X						X						X												X				
Behavioral Assessment	X		X		X		X		X		X		X		X				X				X				X				X				X				X
Adherence Counseling	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
History, concomitant medications, physical exam	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Weight, blood pressure, pulse data entry to Medidata Rave	X		X		X		X		X		X		X		X		X		X		X		X		X		X		X		X		X		X		X
ECG															X												X												X
DXA (subset only, 175 per arm)[1]															X												X											
Blood Collection	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Urine collection for urinalysis testing															X												X												X
Urine collection for GC/CT testing									X						X						X						X						X						X
Rectal swab for GC/CT testing[2]									X						X						X						X						X						X
Injection/Dispense pills	X		X		X		X		X		X		X		X		X		X		X		X		X		X		X		X		X		X		X		X[8]
ISR evaluation		X		X		X		X		X		X		X		X		X		X		X		X		X		X		X		X		X		X		X

WEEKS (shaded column = injection/ dispense pills visit)	5	6	9	10	17	19	25	27	33	35	41	43	49	51	57	59	65	67	73	75	81	83	89	91	97	99	105	107	113	115	121	123	129	131	137	139	145	147	Week 153/ Day 0*
HIV testing[3]	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
HCV testing[4]															X												X												X
CBC with differential		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Chemistry testing[5]		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Liver function tests[6]		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Fasting glucose and fasting lipid profile[7]															X												X											
Syphilis serologic testing									X						X						X						X						X						X
Urine GC/CT testing									X						X						X						X						X						X
Rectal swab GC/CT									X						X						X						X						X						X
Urinalysis															X												X												X
Plasma storage	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
DBS storage			X		X		X		X		X		X		X		X		X		X		X		X		X		X		X		X		X		X

FOOTNOTES FOR APPENDIX IB

*~~See Appendix IC and corresponding footnotes for Step 3 Day 0~~ **For participants who transition to Step 3 prematurely, the timeline for Day 0 begins 8 weeks after that participant's last injection, even if the participant does not report to the Day 0 visit (or the Week 12 visit, etc.). The timeline for Step 3 continues whether or not a participant attends visits. Sites may contact the CMC for questions regarding participants who transition to Step 3 prematurely who are then subsequently missing, though it is not required to do so. For participants who transition to Step 3 at Week 153, the first day of Step 3 begins at Week 153 and is also considered Day 0 of Step 3. Additionally, skip Day 0 rectal swab for GC/CT if testing has occurred within last 3 months of Day 0 and do only at Weeks 24 and 48 (refer to Appendix IC). Finally, administer the acceptability assessment at Day 0 as final assessment if not done in the previous 6 months on Step 2, to include a brief preference assessment**

[1] To include dietary calcium and Vitamin D assessment

[2] If testing cannot be performed at the local laboratory, testing at another laboratory will be considered (see SSP Manual).

[3] The HIV testing algorithm is provided in Appendices IE-G and the SSP Manual. If HIV rapid testing is indicated, this testing may be performed in the clinic or the laboratory.

[4] Testing does not need to be repeated if infection was documented at a prior visit. HCV Ab testing is required.

[5] Required chemistry testing: BUN/Urea, creatinine, CPK, calcium, phosphorous, glucose, amylase, and lipase.

[6] Required LFTs: AST, ALT, total bilirubin, and alkaline phosphatase.

[7] Required for lipid profile: Total cholesterol, HDL, triglycerides, and LDL (either calculated or measured). Participants should have fasted for at least 8 hours, preferably 12 hours, prior to sample collection

[8] Per Section 5.8 of Protocol V3.0 and Appendix IB, the last injection in Step 2 will occur at the Week 145 visit. An injection will not be administered at the Step 2 Week 153/Step 3 Day 0 visit; any remaining blinded oral study product will be collected from the participant, and open-label TDF/FTC will be dispensed.

Appendix IC: Schedule of Procedures and Evaluations - Step 3 – Open Label Daily Oral TDF/FTC Post-Last Injection

Procedures*	~~Week 153/ Day0*~~	Week 12	Week 24	Week 36	Week 48
ADMINISTRATIVE, BEHAVIORAL, REGULATORY					
Locator Information	~~X~~	X	X	X	X
HIV Counseling	~~X~~	X	X	X	X
Offer Condoms and lubricant	~~X~~	X	X	X	X
Acceptability Assessment[2]	~~X~~				
Behavioral Assessment ~~(if done in last 4 weeks, skip D0 and start at W12)~~	~~X~~		X		X
Adherence Counseling	~~X~~	X	X	X	
CLINICAL EVALUATIONS & PROCEDURES					
History, concomitant medications, physical exam	~~X~~	X	X	X	X
Weight, blood pressure, pulse data entry to Medidata Rave	~~X~~	X	X	X	X
Blood Collection	~~X~~	X	X	X	X
Urine collection for GC/CT testing	~~X~~[1]		X		X
Rectal swab for GC/CT testing[3~~1~~]	~~X~~[1]		X		X
Dispense pills	~~X~~	X	X	X	
LOCAL LABORATORY EVALUATIONS & PROCEDURES					
HIV testing[4~~2~~]	~~X~~	X	X	X	X
Chemistry testing[5~~3~~]			X		X
Liver function tests[6~~4~~]			X		X
Syphilis serologic testing	~~X~~[1]		X		X
Urine GC/CT testing	~~X~~[1]		X		X
Rectal swab GC/CT testing	~~X~~[1]		X		X
Plasma storage	~~X~~	X	X	X	X

FOOTNOTES FOR APPENDIX IC

***See Week 153/Day 0 of Appendix IB for Step 3 Day 0 procedures.** ~~For participants who transition to Step 3 prematurely, the timeline for Day 0 begins 8 weeks after that participant's last injection, even if the participant does not report to the Day 0 visit (or the Week 12 visit, etc.). The timeline for Step 3 continues whether or not a participant attends visits. Sites may contact the CMC for questions regarding participants who transition to Step 3 prematurely who are then subsequently missing, though it is not required to do so. For participants who transition to Step 3 at Week 153, the first day of Step 3 begins at Week 153 and is also considered Day 0 of Step 3.~~

[1] ~~Skip Day 0 if testing has occurred within last 3 months of Day 0 and do only at Weeks 24 and 48.~~

[2] ~~Administer acceptability assessment at Day 0 as final assessment if not done in the previous 6 months on Step 2, to include a brief preference assessment~~

[3~~1~~] If testing cannot be performed at the local laboratory, testing at another laboratory will be considered (see SSP Manual).

[42] The HIV testing algorithm is provided in Appendices IE-G and the SSP Manual. If HIV rapid testing is indicated, this testing may be performed in the clinic or the laboratory.
[53] Required chemistry testing: BUN/Urea, creatinine, CPK, calcium, phosphorous, glucose, amylase, and lipase.
[64] Required LFTs: AST, ALT, total bilirubin, and alkaline phosphatase.