Clarification Memo #3 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
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Summary of Revisions and Rationale

Clarification Memo (CM) #1, dated February 10, 2020, contains some inconsistencies as well as inadvertently omits some further clarifications. CM #2, dated April 02, 2020, was issued to provide emergent operational guidance for study conduct during the COVID-19 pandemic and does not contain any clarifications to CM #1. In order to clarify and correct the inconsistencies contained in CM #1, CM #3 replaces CM #1 in full, and the two items that appeared in CM #1 are included again below, with some further clarifications to other items as noted.

The following is the summary and rationale of the four revisions contained in this CM:

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; however, some procedures in 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, allowing the reader to refer to only one column for the requirements of this visit in Appendix IB. The relevant footnotes for this visit contained in Appendix IC have also been deleted and moved to Appendix IB. Additionally, and new to CM #3, the "Note" in Section 5.8 of the protocol inadvertently omitted additional exceptions to some of the procedures and testing required for the Week 153/Day 0 visit. These are now added to Section 5.8 of the protocol, as well as to Appendix IB and IC accordingly. Also new to CM #3 is the clarification of an exploratory objective to be consistent with the Informed Consent Form. Finally, the clarifications stated in CM #1 for Section 9.2.1 are the same in CM #3.

The clarifications are listed here in order of appearance in the protocol:

1. An exploratory objective in the Schema and Section 2.4 is clarified to state that other infections can be analyzed to be consistent with language included in Appendix IV: Sample Screening and Enrollment Informed Consent Form.

2. Additional exceptions to procedures and testing required for the Week 153/Day 0 visit in the "Note" at the end of Section 5.8 of the protocol were inadvertently omitted in Version 3.0 of the protocol. The additional exceptions are now included in the "Note" as further clarification.

3. 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 a recommendation from the Multinational DSMB.

4. The procedures for the last visit in Step 2 (Week 153) and the first visit of Step 3 (Day 0) are combined as one visit in Protocol Version 3.0, and are outlined in Section 5.8 of the protocol, including further clarifications under the "Note" in Section 5.8 (referenced in item #1 above). These procedures were also outlined in Appendices IB and IC (Schedule of Evaluations and Procedures for Step 2 and Step 3, respectively); however, additional discrepancies were noted in these appendices. 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 new footnotes have been added to Appendix IB, including for the additional exceptions for testing for the Week 153/Day 0 visit as referenced in item # 1 above.

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: Only one objective is impacted and is depicted below in the two protocol sections in which it appears.

Schema, Exploratory Objectives:

- To perform secondary laboratory assessments that may include evaluation of factors related to HIV infection, hepatitis infection, or ~~sexually transmitted infections (STIs)~~ **other infections**; antiretroviral (ARV) drug use; pharmacogenomics; characterization of HIV in infected participants; and evaluation of laboratory assays related to the study objectives

2.4 Exploratory Objectives

- To perform secondary laboratory assessments that may include evaluation of factors related to HIV infection, hepatitis infection, or ~~sexually transmitted infections (STIs)~~ **other infections**; antiretroviral (ARV) drug use; pharmacogenomics; characterization of HIV in infected participants; and evaluation of laboratory assays related to the study objectives

Clarification 2: Only the "Note" at the bottom of Section 5.8 of Version 3.0 the protocol is depicted below.

NOTE: If a participant in Step 2 transitions prematurely to Step 3, or misses the Week 153 visit **for any reason**, **or if the Week 153 visit already occurred under Version 2.0 of the protocol and the participant now needs to move to Step 3 under Version 3.0 of the protocol,** the procedures listed above will be performed as part of the last visit of Step 2 (whenever that occurs)/Day 0 of Step 3 to the extent possible. All assessments are identical to Week 153/Day 0 listed above with the following exceptions:

- Behavioral assessment – do not administer if done within the last month before entering Step 3. **Refer to SSP Sections 6 and 13 and SSP Appendix III – Schedule of Forms.**
- Acceptability assessment (not listed above) – this should be administered at this visit if it was not done in the last 6 months before entering Step 3. **Refer to SSP Sections 6 and 13 and SSP Appendix III – Schedule of Forms.**
- Urine collection and testing for GC/CT – do not collect/do not perform test if testing occurred within 3 months prior to entering Step 3
- Rectal swab collection and testing for GC/CT – do not collect/do not perform test if testing occurred within 3 months prior to entering Step 3
- Syphilis testing – do not perform test if testing occurred within 3 months prior to entering Step 3
- **ECG – do not perform procedure if done within 3 months prior to entering Step 3**
- **Urine collection for urinalysis – do not collect/do not perform test if testing occurred within 3 months prior to entering Step 3**
- **HCV – do not perform test if testing occurred within 3 months prior to entering Step 3**

As mentioned above, any scenarios that do not fit into these exceptions or any other questions about the requirements for the last day of Step 2/first day of Step 3 (Week 153/Day 0), whenever that visit may occur, should be directed to the CMC.

Clarification 3:

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 4:

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 at Week 153, the first day of Step 3 begins at Week 153 and is also considered Day 0 of Step 3. The timeline for Step 3 continues whether or not a participant attends the Week 153/Day 0 visit or any subsequent visits.**

For participants who are already beyond Week 153 of Step 2 in their follow-up schedule, the timeline for Step 3 begins 8 weeks following their last injection and continues whether or not a participant attends the Day 0 visit or subsequent visits.

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.). 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.

Per Section 5.8 of the protocol, note the following:

- **Do not perform the following tests/procedures if they occurred within the last three months prior to either prematurely transitioning to Step 3, or the Week 153/Day 0 visit was missed for any reason, or if the Week 153 visit already occurred under Version 2.0 of the protocol and the participant now needs to move to Step 3 under Version 3.0 of the protocol: ECG; urine collection for urinalysis and GC/CT testing; rectal swab for GC/CT testing; HCV testing; and syphilis testing, and perform these requirements only at Weeks 24 and 48 (except for HCV testing, which is not required at Weeks 24 and 48). Refer to Appendix IC.**

- **For participants who either prematurely transition to Step 3, or the Week 153/Day 0 visit was missed for any reason, or if the Week 153 visit already occurred under Version 2.0 of the protocol and the participant now needs to move to Step 3 under Version 3.0 of the protocol, administer the acceptability assessment at the Week 153/Day 0 visit (whenever it occurs) as the final assessment if not done in the previous 6 months prior to transitioning, to include a brief preference assessment.**
- **Regarding the behavioral assessment, for participants who either prematurely transition to Step 3, or the Week 153/Day 0 visit was missed for any reason, or if the Week 153 visit already occurred under Version 2.0 of the protocol and the participant now needs to move to Step 3 under Version 3.0 of the protocol, do not administer at Week 153 and instead administer the behavioral assessment at Week 12 if it was done within the last month prior to transitioning, (see Appendix IC).**

[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[31]	~~X~~[1]		X		X
Dispense pills	~~X~~	X	X	X	
LOCAL LABORATORY EVALUATIONS & PROCEDURES					
HIV testing[42]	~~X~~	X	X	X	X
Chemistry testing[53]			X		X
Liver function tests[64]			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. If the behavioral assessment was not done at Day 0, administer at Week 12.** ~~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~~

[31] 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.