Clarification Memo #2 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 #2: April 2, 2020

Summary of Clarifications

All HPTN 083 sites were sent an email on Friday, March 13, 2020, regarding general guidance for HPTN 083 participants in follow-up during the global COVID-19 pandemic. This guidance appears again in this Clarification Memo (CM), as well as other guidance.

This CM is being issued to safeguard the health and well-being of HPTN 083 study participants in the context of circulating severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) and the associated coronavirus disease (COVID-19) pandemic.

As the study Sponsor, the Division of AIDS (DAIDS) has determined that this CM should be implemented immediately upon issuance. Consistent with United States Food and Drug Administration guidance, institutional review board/ethics committee (IRB/EC) approval of this CM is not required by the Division of AIDS prior to implementation. However, given the context of the COVID-19 pandemic and the importance of the guidance provided in this CM, sites should submit this CM to IRBs/ECs/other regulatory entities for their information or, if required by the IRBs/ECs/other regulatory entities, for their review and approval.

The purpose of this CM is to provide operational flexibility for conducting study visits and procedures when needed to ensure ongoing access to study drug when possible and to prioritize the conduct of clinically and scientifically important procedures and evaluations when possible.

Implementation of this CM is expected to be time-limited in relation to the COVID-19 pandemic. In consultation with HPTN Network leadership and the study Sponsor, the HPTN 083 Protocol Team will determine when, in the future, the guidance provided in this CM is no longer applicable. When such a determination is made, study sites will be formally notified and instructed to inform their IRBs/ECs.

Please file this CM and any applicable IRB/EC correspondence in your essential document files for HPTN 083.

Implementation

This CM provides operational guidance to study sites from the HPTN 083 Protocol Team. The Protocol Team acknowledges that the extent to which site operations may be disrupted by the COVID-19 pandemic may vary across sites and over time. **All sites should follow applicable government, health authority, and institutional policies with respect to conduct of study visits and procedures, with utmost importance placed on the health and well-being of study participants and study staff.** Site investigators should continue to follow current protocol specifications for communication with the Protocol Team and/or Clinical Management Committee and should contact the protocol team leadership with any questions or concerns regarding this CM or management of study participants.

PRIORITIZATION OF STUDY VISIT PROCEDURES

- Sites with full capacity to conduct study visits in-person at the study clinic should continue to do so in full compliance with the protocol.
- Sites with limited capacity to conduct in-person study visits should prioritize assessments as determined by the site Investigator of Record (IoR) (e.g., urgent safety testing, HIV testing, provision of study product, etc.).
- Sites with no capacity to conduct in-person visits may conduct telephonic or video-based assessments remotely at the discretion of the IoR (and following all institutional approval requirements), and may include targeted medical history (including ascertainment of AEs), HIV and adherence counseling, interviewer-administered surveys, etc. The content of these visits should be determined by the site IoR.

  Note: If locally available, feasible, and at the discretion of the IoR, home HIV self-tests can be sourced and distributed to participants for participant use, and results demonstrated by video or photo-sharing to study sites as corroborative evidence of testing and test results. Such photos should be placed in the participant research record. Absence of home-testing results will NOT be considered a protocol deviation, nor reportable.
- Sites that are able may also conduct study visits — in full or in part — off-site if permitted by applicable government, health authority, and institutional policies. This is including but not limited to home-based visits. Where this option is permitted, site staff should communicate with participants to determine in advance where and when such visits will take place, with adequate protections for safety, privacy, and confidentiality. Off-site visit procedures should be conducted by site staff who are adequately qualified and trained to conduct the procedures, as determined by the site Investigator of Record (IoR), with attention paid to occupational health, biohazard containment, and specimen and data chain of custody. These staff should also be adequately qualified and trained to immediately assess and/or manage any adverse events or social impacts that may occur during the visits. If adverse events requiring further evaluation or management are identified during an off-site visit, staff conducting the visit should arrange for appropriate clinical management, in consultation with the IoR or designee as needed**. NOTE: Step 2 BLINDED study product cannot be provided at an off-site visit.**

GUIDANCE FOR STEP 1, STEP 2 AND STEP 3

Guidance was provided via email to Investigators of Record and Study Coordinators on March 13, 2020. Additional guidance is provided where noted.

Guidance sent via email on March 13, 2020 - For participants in Step 1 (at sites that have ongoing enrollment activities): We anticipate that continuation on daily blinded oral study product would be appropriate – meaning, for participants that cannot report for the Week 2 or Week 4 visit, study product would continue, and where possible, study product potentially shipped or couriered to participants directly from PAB DAIDS established site pharmacies. If this is not feasible, participants should be instructed to protect themselves against HIV infection and exposure by all means available to them until they can return to study participation, and participants should document as carefully as possible the dates of exhaustion of their Step 1 study product medication supplies. Investigators of Record should use their clinical judgement regarding ongoing dispensation of oral study product in these extraordinary circumstances absent interim safety monitoring.

Guidance sent via email on March 13, 2020 - For participants in Step 2: Oral study products cannot be dispensed absent an injection given if both are due, and the same advice above would apply - that participants should protect themselves against HIV infection and exposure by all means available to them until they can return to study participation.

New guidance for Step 2 in this CM:

All sites should emphasize multi-modal HIV prevention activities – including social distancing, HIV status discussion, condom use, PEP and PrEP clinical services, HIV and STI testing (and treatment), clean needle use (if applicable), and other locally available in -person and/or on-line HIV prevention resources.

In the event that a site can no longer provide blinded Study Product in Step 2:

Sites that are able may provide PrEP services through NON-STUDY clinical services, or through referral to PrEP services as a bridging mechanism while study product injections are unable to be administered. Participants should return blinded oral study products if this is pursued. Participants should be instructed to store their blinded oral study product bottle supply safely at home until the participant is able to return the blinded oral study product bottle at the next scheduled study visit.

For sites that are not be able to provide PrEP services through NON-STUDY clinical services: In consultation with the Division of AIDS, the protocol team is investigating the availability and timing for the provision of open-label oral TDF/FTC study product as a bridging mechanism while study product injections are unable to be administered. Neither the availability nor the timing of when additional open-label oral TDF/FTC study product may be available is known at this time. As such, sites should prioritize leveraging local resources in the event that a bridging mechanism is necessary. Participants leveraging NON-STUDY clinical services that may include PrEP or in the future event that oral TDF/FTC bridging is able to be made available via the study protocol (additional information will be sent if/when this is confirmed), should remain in Step 2 of the protocol. Additional guidance will be sent at the time of implementation regarding documentation of HIV testing at the time of bridging for such participants.

Guidance sent via email on March 13, 2020 - For participants in Step 3: We anticipate that continuation on daily unblinded oral study product would be appropriate; (if oral study product is ongoing for that participant) – meaning, for participants that cannot report for the quarterly visits, study product would continue, and where possible, study product potentially shipped or couriered to participants directly from PAB DAIDS established site

pharmacies. If this is not feasible, participants should be instructed to protect themselves against HIV infection and exposure by all means available to them until they can return to study participation, and participants should document as carefully as possible the dates of exhaustion of their Step 3 study product medication supplies. Investigators of Record should use their clinical judgement regarding ongoing dispensation of oral study product in these extraordinary circumstances absent interim safety monitoring, given known previous creatinine clearance and adherence reported trajectories.

New guidance for Step 3 in this CM: It is acceptable to provide a 3-month supply plus 1 additional month for overage for each quarterly dispensation (again, provided quarterly only if the IoR determines ongoing dispensation is acceptable as stated above).

Guidance sent via email on March 13, 2020 - For those on annual follow-up: Annual visits should be delayed until study conduct can be resumed at the site, even if this pushes a final visit date past the 3-years-post-enrollment date.

STUDY PRODUCT CONSIDERATIONS

- For emergency cases, the *Pharmacy Guidelines and Instructions for DAIDS Clinical Trials Networks* permits shipment or courier of oral study product from the site directly to participants. The pharmacist should refer to the section on "Shipping Study Product to a Participant" in this manual for detailed procedures. If this method is to be implemented, each site pharmacist must develop appropriate procedures for the shipment or courier of oral study product to identified participant in accordance with these guidelines and must include appropriately documented chain of custody. This method should only be used if permissible per local institutional and IRB/EC policies.

- All questions related to study product management should be directed to Katie Shin – kashin@niaid.nih.gov.

DOCUMENTATION

- Site-specific contingency plans, and the implementation thereof, should be documented in essential document files for HPTN 083.
- Participant-specific documentation should be entered in participant study charts in real-time to the extent possible.
- Specific guidance regarding coding visits and instructions therein is forthcoming from SCHARP in a separate communication to all sites.
- In consultation with the Division of AIDS, the HPTN Network is developing comprehensive guidance for documenting and/or reporting protocol deviations that may occur due to limited site capacity to conduct study visits or procedures during the COVID-19 pandemic. Once this Network-level guidance is available, it will be provided in a separate communication to all sites.