

FINAL Letter of Amendment # 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

Version 1.0, February 2, 2016

DAIDS Document ID: 20725

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Final Version of LoA # 1: 24 May 2016

The information contained in this Letter of Amendment (LoA) impacts the HPTN 083 study, including the study informed consent forms, and must be submitted to site Institutional Review Boards (IRBs) and/or Ethics Committees (ECs) as soon as possible for their review and approval. Approval must also be obtained from site regulatory entities if applicable per the policies and procedures of the regulatory entities. All IRB/EC and regulatory entity requirements must be followed and all required approvals of **both** protocol Version 1.0 **and** this LoA must be obtained before initiating this study. Likewise, all participants must provide written informed consent for this study using site-specific informed consent forms that correspond to this LoA.

Upon receiving IRB/EC approval, and approval of any other applicable regulatory entities, study sites must submit a LoA registration packet to the DAIDS Protocol Registration Office (DAIDS PRO) at the Regulatory Support Center (RSC). Sites will receive a registration notification for the LoA after the DAIDS PRO verifies that all required registration documents have been received and are complete. This notification must be received prior to implementation of this LoA. Receipt of this notification, as well as an initial registration notification for protocol Version 1.0, will be confirmed as part of the site-specific study activation process for this study.

Please file this LoA, all associated IRB/EC and regulatory entity correspondence, and all correspondence with the DAIDS PRO in your essential documents files for HPTN 083.

If the HPTN 083 protocol is fully amended in the future, this Letter of Amendment will be incorporated into the next version. Text appearing below in highlighted **bold** will be added, and text appearing in highlighted **strike-through** will be deleted.

Summary of Revisions and Rationale

Revision 1: Drs. Adeyeye, Burns, Phanuphak and Scott have been added to the protocol team roster. Drs. Adeyeye and Burns are the Division of AIDS Medical Officers for the study. Dr. Phanuphak serves as a representative for the three sites in Thailand, and Dr. Scott is an investigator at the Bridge HIV site in San Francisco, CA, and is leading the SexPro assessment (see below). Dr. Elharrar has been removed from the protocol roster as she is no longer employed at the Division of AIDS. The email address for Dr. Fields has been updated.

Revision 2: The picture of the overview of the study design and randomization scheme toward the front of the protocol (just before Section 1.0) mistakenly lists Week 29 as a study visit in the study. The picture is corrected to list it as Week 27 instead of Week 29.

Revisions 3 a - c:

- Revision 3a removes erroneous text in Section 1.4.
- Revision 3b corrects the text in Section 1.11 regarding the injection schedule – it is listed as quarterly; this has been corrected to state that the injections will be given at two time points 4 weeks apart and every 8 weeks thereafter.
- Revision 3c adds a new Section 1.14 as the study will utilize a web-based tool at screening at North and South American sites for estimating a personalized HIV risk score using a tool called SexPro. This tool will provide additional precision for enrolling the highest risk participants in to the study. The new section adds pertinent information related to the SexPro web-based tool.

Revision 4: The behavioral risk inclusion criterion in Section 3.1 has been updated to include a risk behavior score based on the SexPro web-based tool *for North American sites only*. Additionally, the word “on” was inadvertently left out of the risk criterion.

Revision 5: Two exclusion criteria have been modified and one criterion has been added to Section 3.2 as follows:

- The criterion regarding known allergies to the study products has been revised to specifically mention allergy to egg or soy products, which are components of the Intralipid product, which serves as placebo for the injectable cabotegravir study product.
- The criterion regarding buttock implants has been modified to include non-surgically placed silicone implants since the study is taking place in regions where this type of implant is commonly used by transgender women.
- A QTc criterion is added as an exclusion criterion since it is an assessment used for stopping study product during the course of the study.

Revision 6: The SexPro assessment has been added to Section 5.1, which is the listing of procedures to be performed at screening.

Revision 7: The window for performing the DXA as listed in Section 5.2 has been corrected to match the wording in the sample informed consent (it is correct in the sample informed consent).

Revision 8: The first tertiary endpoint in Section 7.5.3 is updated to remove pill counts as a measurement of adherence in Step 2. Pill counts are only being performed in Step 1 of the study.

Revision 9: The references in Section 11 have been updated to add citations related to SexPro.

Revision 10: The SexPro assessment has been added to the Schedule of Evaluations for screening.

Revision 11: Dried blood spots has been added for collection at the time of HIV seroconversion.

Revision 12: The QTc criteria in Appendix III is updated to remove the “B” which signifies the Bazett’s formula, the standard clinical correction formula. The study allows flexibility for sites regarding which clinical correction formula to use (e.g., Bazett’s or the Fridericia correction formula may be used during the study, as long as the same measurement type is used throughout the study for a given participant).

Revisions 13 a-e: The sample informed consent form in Appendix IV has been updated as follows:

- Revision 13a corrects the length of time someone may be in Step 2 of the study
- Revision 13b removes urine test results as confirmation of eligibility since no urine testing is performed at screening (note: the body of the protocol is correct)
- Revision 13c adds the SexPro assessment and additional information about the purpose of the DXA subset
- Revision 13d adds information about the fact that bone changes are reversible when TDF/FTC is stopped (based on new information presented at the Conference on Retroviruses and Opportunistic Infections [CROI] in February, 2016), as well as to remove an incorrect and redundant sentence and fix the spelling of a word
- Revision 13e adds information about the potential risks of Intralipid (used as placebo for CAB LA), which was inadvertently not included during protocol development

IMPLEMENTATION

Revision 1 **Protocol Team Roster**

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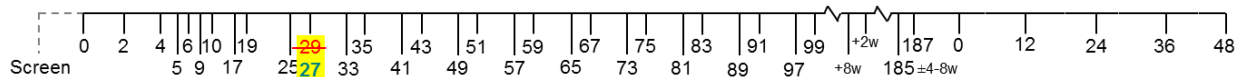
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Revision 2 OVERVIEW OF STUDY DESIGN AND RANDOMIZATION SCHEME

Note: Only the relevant portion of the corrected scheme is depicted.



Revision 3a Section 1.4 Clinical Experience to Date: Oral CAB and CAB LA

Note: Only the relevant portion of the section is depicted, which is the 4th paragraph down from the beginning of Section 1.4.

Injection site reactions (ISR) occurred in the majority of participants following IM (76% with any ISR) dosing, however, the reactions were mild and moderate (overall ISR Grade 2: 14% in IM without any Grade 3 or 4 ISRs).⁴⁹ ISRs related to CAB LA injection were common but generally mild (IM: 86%, SC: 99%) with no Grade 3 ISR AEs in Phase 1 studies. The most frequent ISRs for IM dosing were pain (71%), erythema (9%) and nodules (7%) (C-2013). Median IM ISR durations were approximately 5 days for pain and erythema, and approximately 22 days for nodules.⁴⁹

Note: Only the relevant portion of the section is depicted, which is the 1st paragraph down from the beginning of Section 1.11.

It is clear that the effectiveness of daily oral TDF/FTC is tightly correlated with adherence. Therefore, a critical component of the comparison between daily oral TDF/FTC and CAB LA will be participants' ability/willingness to take a daily pill compared to a clinic-administered injection ~~on a quarterly schedule~~ **at two time points 4 weeks apart followed by every 8 weeks thereafter.** To evaluate the clinical applicability of this difference, the study will provide adherence support at baseline and at all follow-up visits for all participants in a manualized/standardized fashion commensurate with an intervention that could be easily implemented in diverse clinical settings. Any participant who has self-reported or actual returned pill-count evidence of challenges with adherence to AT MINIMUM the level of 4 doses weekly will be provided an individualized adherence intervention designed to problem-solve individual barriers to adherence.

Revision 3c **Section 1.14: Rationale For Web-Based Sexual Health Promotion Score During Screening**

SexPro is a web-based tool that provides participants with a sexual health promotion score. The SexPro score was developed to estimate short-term HIV acquisition risk using data from several large cohorts of MSM in the United States and South America.⁸⁰⁻⁸⁴ Different models were developed for North and South America, based on data from these two populations. In particular, these models reflect differences in demographic and substance use effects on HIV acquisition, and required tradeoffs between goodness of fit and delivering interpretable risk information. From this, two separate SexPro interfaces were created: one for North American MSM (available in English and Spanish), and one for South American MSM (in Spanish and Portuguese). Participants answer a brief questionnaire including age, race/ethnicity (US only), behavioral risk factors, substance use, and history of sexually transmitted diseases (gonorrhea, chlamydia, and syphilis) which are used to calculate their personalized HIV risk score reflecting their likelihood of HIV acquisition at six months. Scores range from 1 (highest risk) to 20 (lowest risk) based upon a positive sexual health promotion framing. The SexPro score for the North American model has been subsequently validated in two contemporary longitudinal cohorts of MSM – HPTN 061 and HVTN 505 – and shows good model fit, especially among Black MSM in HPTN 061. A SexPro score of 16 or lower showed good sensitivity (75.4%) and specificity (51.8%) in HVTN 505. All HIV seroconversions in HPTN 061 occurred below this value; this cut-off was chosen to identify MSM at high risk for HIV infection, and to maximize sensitivity of the tool for Black MSM in the US. The SexPro score, using a score cut-off of 16 or lower, will be used in addition to the current behavioral risk inclusion criteria for the US-based cohort; participants who do not qualify on the basis of the current behavioral risk will be eligible with a risk score of 16 or lower. This recognizes that young men of color in the US are at risk of acquiring HIV with less self-reported risk than older white men. SexPro will also be administered to MSM outside of US, but will not be used as part of the inclusion criteria, as this has not yet been validated in separate cohorts.

Revision 4 Section 3.1: Inclusion Criteria

Note: Only the relevant portion of this section is depicted.

- At high risk for sexually acquiring HIV infection based **on** self-report of at least one of the following:
 - Any condomless receptive anal intercourse in the 6 months prior to enrollment (condomless anal intercourse within a monogamous HIV seronegative concordant relationship does not meet this criterion)
 - More than five partners in the 6 months prior to enrollment (regardless of condom use and HIV serostatus, as reported by the enrollee)
 - Any stimulant drug use in the 6 months prior to enrollment
 - Rectal or urethral gonorrhea or chlamydia or incident syphilis in the 6 months prior to enrollment
 - **SexPro score of ≤ 16 (US sites only)**

Revision 5 Section 3.2: Exclusion Criteria

Note: Only the relevant portion of this section is depicted.

- Known or suspected allergy to study product components (active or placebo), **including egg or soy products (egg and soy products are contained in Intralipid)**
- Surgically-placed **or injected silicone/industrial product** buttock implants, per self-report
- Alcohol or substance use that, in the opinion of the study investigator, would jeopardize the safety of the participant on study (e.g., provided by self-report, or found upon medical history and examination or in available medical records).
- History of seizure disorder, per self-report
- **QTc interval (B or F) > 500 msec**

Revision 6 Section 5.1: Screening

Note: Only the relevant portion of this section is depicted.

Administrative, Behavioral, and Regulatory Procedures

- Informed consent
- **Administer SexPro assessment (US only for inclusion purposes; South American sites only for data collection purposes currently)**
- Locator information
- HIV counseling
- Offer condoms and lubricant

Revision 7 Section 5.2: Step 1: Week 0 – Enrollment

Note: Only the relevant portion of this section is depicted.

Clinical Procedures

- Complete medical history and complete physical exam, including concomitant medications (may be performed during screening at the discretion of the Investigator of Record or their designee)
- DXA (only if part of BMD subset, and may be performed -14 30 days/+ 14 7 days of enrollment), and dietary calcium and Vitamin D assessment

Revision 8 Section 7.5.3: Tertiary Endpoints

Note: Only the relevant portion of this section is depicted.

- Adherence to study product during step 2: For CAB-LA/Placebo CAB-LA scheduled injections received; for TDF/FTC/Placebo TDF/FTC pill dispensing, pill counts

Revision 9 Section 11: REFERENCES

Note: Only the references being added are depicted.

80. Koblin BA, Chesney MA, Husnik MJ, et al. High-risk behaviors among men who have sex with men in 6 US cities: baseline data from the EXPLORE Study. Am J Public Health 2003;93:926-32.

81. Koblin BA, Mayer KH, Noonan E, et al. Sexual risk behaviors, circumcision status and pre-existing immunity to adenovirus type 5 among men who have sex with men participating in a randomized HIV-1 vaccine efficacy trial: Step Study. J Acquir Immune Defic Syndr 2012.

82. Bartholow BN, Goli V, Ackers M, et al. Demographic and behavioral contextual risk groups among men who have sex with men participating in a phase 3 HIV vaccine efficacy trial: implications for HIV prevention and behavioral/biomedical intervention trials. J Acquir Immune Defic Syndr 2006;43:594-602.

83. Buchbinder SP, Vittinghoff E, Heagerty PJ, et al. Sexual Risk, Nitrite Inhalant Use, and Lack of Circumcision Associated With HIV Seroconversion in Men Who Have Sex With Men in the United States. J Acquir Immune Defic Syndr 2005;39:82-9.

84. Sanchez J, Lama JR, Peinado J, et al. High HIV and ulcerative sexually transmitted infection incidence estimates among men who have sex with men in Peru: awaiting for an effective preventive intervention. J Acquir Immune Defic Syndr 2009;51 Suppl 1:S47-51.

Revision 10 Appendix Ia: Schedule of Procedures and Evaluations – Screening; Step 1 – Blinded Daily Oral Pills

Note: Only the relevant section of the screening Schedule of Procedures and Evaluations is depicted.

Appendix Ia: Schedule of Procedures and Evaluations – Screening; Step 1 – Blinded Daily Oral Pills

	Screening	Step 1		
		DAY 0/Enrollment	WEEK 2	WEEK 4
ADMINISTRATIVE, BEHAVIORAL, REGULATORY				
Informed consent	X			
SexPro assessment (US sites only for inclusion; South American sites only for data collection)	X			
Locator information	X	X	X	X
Demographic information		X		
Randomization		X		
HIV counseling	X	X	X	X
Offer condoms and lubricant	X	X	X	X
Baseline acceptability assessment		X		
Baseline behavioral assessment		X		
Adherence counseling/pill count (Pill count Week 2 and 4 only)		X	X	X

Revision 11 Appendix II: Schedule for Additional Procedures for Enrolled Participants who have a Reactive or Positive HIV Test Result (including HIV confirmatory visit)

	HIV Confirmation Visit	Week 12	Week 24	Week 36	Week 48 ⁶
ADMINISTRATIVE, BEHAVIORAL, REGULATORY					
Locator information	X	X	X	X	X
Offer condoms and lubricant	X	X	X	X	X
HIV counseling	X				
CLINICAL EVALUATIONS AND PROCEDURES					
History, con meds, physical exam	X	X	X	X	X
Blood collection	X	X	X	X	X
LOCAL LABORATORY EVALUATIONS					
HIV testing ¹	X				
CD4 cell count	X		X		X
HIV viral load testing	X		X		X
HIV resistance testing ²	X				
Chemistry testing ³		X	X	X	X
Liver function testing ⁴		X	X	X	X
Plasma storage ⁵	X	X	X	X	X
DBS storage	X				

Revision 12 Guidance on Toxicity Management for Specified Toxicities - QTc – Criteria for Permanent Discontinuation of Study Product

Note: Only the relevant section of the screening Schedule of Procedures and Evaluations is depicted.

A participant that meets either criterion below will have study product stopped, but will remain in study follow-up. The QT **(QTc)** correction formula used to determine study product discontinuation should be the same one used throughout the study. **For example, either Bazett’s (QTcB) or Fridericia (QTcF) correction formula may be used, as long as the same formula is used throughout for a given participant.**

- QTc~~B~~ > 550 msec, OR
- Change from baseline: QTc~~B~~ > 60 msec

Revision 13a Appendix IV: Sample Screening and Enrollment Informed Consent Form

Note: Only the relevant section of the ICF is depicted below from the “STUDY GROUPS” section of the consent form.

Group A – this group gets real CAB pills and injections:

- Step 1: Real CAB pill AND placebo pill for TDF/FTC (2 pills total) every day for 5 weeks
- Step 2: Real CAB injections given as one shot, then another shot a month later, and then every 2 months after that AND placebo pill for TDF/FTC every day up to **four three** and half years
- Step 3: Real TDF/FTC pill every day for about a year, then move to local HIV prevention services

Group B – this group gets real TDF/FTC pills:

- Step 1: Real TDF/FTC pill AND placebo pill for CAB (2 pills total) every day for 5 weeks
- Step 2: Placebo CAB injection AND real TDF/FTC pill everyday up to **four three** and a half years
- Step 3: Real TDF/FTC pill every day for about a year, then move to local HIV prevention services

Revision 13b Appendix IV: Sample Screening and Enrollment Informed Consent Form

Note: Only the relevant portion under the STUDY PROCEDURES, Screening Visit section of the consent form is depicted.

Confirmation of Eligibility:

Once all the results of the screening tests are known, the following will happen within 45 days after screening:

- You will be told your test results and what they mean.
- If you have a positive HIV, hepatitis B or C test you will not be eligible for the study, and you will be referred for the appropriate medical care (*sites to add specifics about this here as necessary*).
- If you are negative for HIV but the results from the other blood **or urine** tests show that you might have some health problems, you may not be eligible for the study. Study staff will refer you to available sources of medical care and other services you may need. Later, if these problems resolve, you may be able to come back to find out if you are eligible at that time.

Note: Only the relevant portion of the Screening Visit section of the consent form is depicted.

Screening Visit

Your screening visit may occur after you read, discuss, understand, and sign this form, or will we schedule it for you at another time. We will help you understand the form and answer your questions before you sign this form. The procedures done for the screening visit will take about [site to fill in time required], and may be done at one or more visits.

At this visit, the study staff will:

- Ask you where you live and other questions about you, your medical health, your sexual practices, including if you are at a higher risk of getting HIV, and whether you use alcohol or drugs. [Sites in US to add this here: We will ask you to answer some additional questions about sexual practices using an assessment called SexPro, which may provide additional information about your HIV risk, and whether this study is appropriate for you.] [Sites in South America to add this here: We will ask you to answer some additional questions about sexual practices using an assessment called SexPro, which may provide additional information about your HIV risk.]
- Give you a brief physical exam to make sure you are healthy.
- Talk with you about HIV and ways to protect yourself from getting it and offer condoms and lubricant.
- Have an electrocardiogram (ECG) scan, which is a test to monitor your heart.
- Collect ~XX mL (about x teaspoons) of blood for HIV testing, Hepatitis B and C testing, to check your general health, to check the health of your liver, and for storage for study-related testing.
- [Sites participating in the DXA substudy to include this:] We may ask you to be a part of a group that gets bone mineral density-energy x-ray absorptimetry (DXA) scans. A DXA scan is a special kind of x-ray using a small amount of radiation, allowing the doctor to see parts of the body better than a regular x-ray. We know that TDF/FTC may cause thinning or softening of bones in some people. We want to see whether there are changes to your bones during the study, and the DXA scan lets us evaluate your bones. We want to see if this is different between the TDF/FTC and CAB treatments. The scan will be done at the Enrollment visit (this visit), and 2 other times during the study (Weeks 57 and 105).

Note: Only the relevant portion of the RISKS AND/OR DISCOMFORTS portion of the consent form is depicted.

Side effects of TDF/FTC include:

Lactic acidosis (elevated lactic acid levels in the blood) and severe hepatomegaly (enlarged liver) with steatosis (fatty liver) that may result in liver failure, other complications or death have been reported with the use of antiretroviral nucleoside analogues alone or in combination. The liver complications and death have been seen more often in women on these drug regimens. Some nonspecific symptoms that might indicate lactic acidosis include: unexplained weight loss, stomach discomfort, nausea, vomiting, fatigue, cramps, muscle pain, weakness, dizziness and shortness of breath.

Other side effects include:

~~The following side effects have been associated with the use of tenofovir:~~

- Upset stomach (nausea), vomiting, gas, loose or watery stools
- Abdominal pain
- Generalized weakness
- Dizziness
- Depression
- Headache
- Shortness of breath
- Increased cough
- Runny nose
- Allergic reaction: symptoms may include fever, rash, itching, upset stomach, vomiting, loose or watery stools, abdominal pain, achiness, shortness of breath, a general feeling of illness or a potentially serious swelling of the face, lips, and/or tongue.
- Skin darkening of the palms of hands and/or soles (bottom) of feet
- Bone pain and bone changes such as thinning and softening which may increase the risk of breakage **(this side effect goes away after stopping TDF/FTC)**

Note: Only the new paragraph is depicted below, and should be placed directly after the side effects of TDF/FTC and before the side effects of Blood Draws.

Side effects of Intralipid when used as an intramuscular injection placebo include headache, anxiety, insomnia, vomiting, nausea, constipation, extremity pain, agitation, diarrhea, sedation, nasopharyngitis, upper respiratory infection, cough, urinary tract infection, decreased weight, and increased muscle tone.

When Intralipid is given as an intravenous infusion (into a vein directly) for nutrition, the following side effects have been reported (note that these side effects have not been reported when Intralipid is administered through an intramuscular injection):

Immediate or early adverse reactions, each of which has been reported to occur in clinical trials less than 1% of the time: trouble breathing, blue appearance to the skin at where the injection was given, allergic reactions, elevated levels of fat in your blood, increased chances of getting blood clots, nausea, vomiting, headache, flushing, increase in temperature, sweating, sleepiness, pain in the chest and back, slight pressure over the eyes, dizziness, and irritation at the site of the infusion;

Delayed adverse reactions such as: large liver, yellowing of the skin and eyes, large spleen, low blood cell counts, increases in liver function tests, and overloading syndrome (seizures, fever, increase in white blood count, large liver, large spleen, and shock).