Letter of Amendment #1 to:

HPTN 084: A Phase 3 Double Blind Safety and Efficacy Study of Long-Acting Injectable Cabotegravir Compared to Daily Oral TDF/FTC for Pre-Exposure Prophylaxis in HIV-Uninfected Women

Version 3.0, 12 August 2021

DAIDS Document ID: 38070
IND # 122, 744

LoA #1, v1.0, FINAL, 24 September 2021

Instructions to the Study Sites from the Sponsor

The following information impacts the HPTN 084 study and must be forwarded to all responsible Institutional Review Boards (IRBs)/Ethics Committees (ECs) and any other required regulatory authorities as soon as possible for their information, review and approval. This Letter of Amendment (LOA) must be approved all required regulatory authorities before implementation.

The following information may also impact the sample informed consent. Your IRB/EC will be responsible for determining the process of informing subjects of the contents of this letter of amendment.

The HPTN 084 protocol will be fully amended in the future and will include the modifications outlined in this LOA.

Text appearing below in highlighted **bold** will be added, and text appearing in highlighted ~~strike-through~~ will be deleted.

Summary of Revisions and Rationale

1. Revision 1: Consent forms for the qualitative sub-study for partners and providers have been added; they were erroneously omitted from protocol version 3.0.
2. Revision 2: A footnote to clarify the timing of the fetal ultrasound has been added to the Schedule of Evaluations for "Appendix VIII: Schedule of Evaluations for Step 4d- Procedures for Pregnant/Breastfeeding Participants."
3. Revision 3: A typographical error in the Schedule of Evaluations for "Appendix VIII: Schedule of Evaluations for Step 4d- Procedures for Pregnant/Breastfeeding Participants" has been corrected and a clarifying footnote has been added.
4. Revision 4: Typographical errors in the footnotes for the Schedule of Evaluations for "Appendix VIII: VIII: Schedule of Evaluations for Step 5- Procedures for Participants Taking OL TDF/FTC for 48 Weeks after Premature CAB LA discontinuation" have been corrected.
5. Revision 5: Outdated text from "Section 8.0 (NOT MODIFIED FROM THE MAIN PROTOCOL), 8.1 Ethical Review" was removed.
6. Revision 6: Minor typographical errors were corrected in the consent form in the section titled "What happens next?"
7. Revision 7: In Section 5.14, "Pregnancies, Confirmed Pregnancies" wording was changed to eliminate potential confusion during implementation.
8. Revision 8: Text has been added to the main consent form for participants in the Pregnancy and Infant sub-study clarifying PrEP options from Week 24 post-partum and beyond.
9. Revision 9: Clarifying text has been added to Section 5.16, "Acceptability Assessments, Qualitative Sub-Study."

Implementation

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. An LoA registration notification from the DAIDS PRO is not required prior to implementing the LoA. Please file this LoA, all associated IRB/EC and regulatory entity correspondence, and all correspondence with the DAIDS PRO in your essential document files for HPTN 084.

Protocol Signature Page

HPTN 084

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I will conduct this study in accordance with the provisions of this protocol and all applicable protocol-related documents. I agree to conduct this study in compliance with United States (US) Health and Human Service regulations (45 CFR 46); applicable US Food and Drug Administration regulations; standards of the International Conference on Harmonization Guideline for Good Clinical Practice (E6); Institutional Review Board/Ethics Committee determinations; all applicable in-country, state, and local laws and regulations; and other applicable requirements (e.g., US National Institutes of Health, Division of AIDS) and institutional policies.

Name of Investigator of Record	**Signature of Investigator of Record**	**Date**

1. Revision 1: Consent forms for the qualitative sub-study for partners and providers have been added; they were erroneously omitted from protocol version 3.0.

Sample Qualitative Informed Consent Form for Male Partners
HPTN 084

A Phase 3 Double Blind Safety and Efficacy Study of Long-Acting Injectable Cabotegravir Compared to Daily Oral TDF/FTC for Pre-Exposure Prophylaxis in HIV-Uninfected Women DAIDS Document ID # 38070
Version 3.0, 12 August 2021

GENERAL OVERVIEW

Your partner has taken part in a clinical trial called HPTN 084. This study compared the effectiveness of taking an injection of cabotegravir every two months to daily use of oral PrEP/Truvada to prevent HIV. It found that injectable CAB LA was very effective in preventing HIV. Women who participated in the study can now choose to use CAB LA, the Truvada daily oral pill, or no method at all.

You have been invited – on your partner's recommendation to take part in a qualitative substudy. The goal of the substudy is to understand how women, their partners and other community members feel about injectable CAB LA and HIV PrEP in general. This qualitative substudy is being conducted in four of the HPTN 084 sites in Africa. It will include a total of 80-110 women, 20-24 male partners, 20-24 providers and other key stakeholders in communities where the trial has been conducted.

The interview with male partners will be led by a trained and experienced interviewer. We are interested in learning about your thoughts, opinions, and experiences with your partner's trial participation. For example, we would like to know your role in decisions related to study participation. We would also like to know what you think about the injections (shots) and about the oral pills, including the benefits and risks, questions about taking these products during pregnancy, and the impact of your partner's participation in the study on your relationship. We hope that the information learned from this study will help us to better understand what kind of HIV prevention options women, men and couples prefer.

What happens if you do not want to join the qualitative interviews?
You can choose not to be interviewed. Your participation is completely your choice.

What will happen if you do want to join the qualitative interview study?
If you decide to join the qualitative interview study, you will be contacted by a study team member to arrange the interview. Interviews will be conducted in-person in a private setting, if unable to meet in person the interview may be conducted by phone. The interview will take approximately 60 minutes.

The information that you share during the qualitative interview will be treated confidentially. We will not share any information you provide with your partner. The interview will be audio-recorded to help assure that we get the best understanding possible from each discussion. This recording will be used to make a written transcript of the interview. The recording and transcript will only have a Participant ID number. No identifying information will be included in the written transcript.

We hope that you will be comfortable answering all of the questions and talking openly and honestly. But, please keep in mind that you do not have to answer any of the questions. You may stop participating completely at any time.

Information about your partner, who is participating in this study, will remain confidential and will not be shared with you.

What are the potential benefits?
You will not receive any direct benefit from being in the qualitative interview; however, you or others in your community may benefit from this study later. The information gathered during this study may help make more HIV prevention options available. This may be beneficial to you and your community.

What are the possible risks or discomforts?
The questions we will ask you may make you feel uncomfortable. Your partner or others may not like for you to talk about the study and how it affects your home life. We hope that the qualitative interview procedures described above will minimize your discomfort when discussing sensitive topics. However, the greatest risk may involve your privacy and confidentiality. Additional steps that the study team has taken to protect your privacy are described below.

How will your privacy be protected?
Every effort will be made to keep your personal information confidential. Your personal information (name, address, phone number) will be protected by the research clinic. Your name, and anything else that might identify you personally, will not be used in any publication of information about this study.

Information from the qualitative substudy may be reviewed by institutions who are helping to fund or implement the trial. However, no personal information will be shared. Information from these qualitative interviews will only be described in general ways. The sponsor of the study (US National Institutes of Health (NIH) their representatives), US FDA, US Department of Health and Human Services (DHHS), Office of Human Research Protection (OHRP) and other government and local, US and International regulatory entities, authorized representatives of US NIH and/or its contractors, [insert names of applicable IRBs/ECs/other local review bodies as applicable] IRB, study staff, study monitors, and companies that makes the study drug (ViiV Healthcare and Gilead Sciences, Inc.). We cannot guarantee absolute confidentiality.

A description of this study will be available on www.ClinicalTrials.gov, as required by US law. This web site will not include information that can identify you. At most, the web site will include a summary of the results. You can search this web site at any time.

What are the alternatives to participating in this study?
You do not have to participate in the interviews.

Reasons why you may be withdrawn from the study without your consent
Your participation in the interview may be ended early without your consent for the following reasons:
• The research study, or the qualitative part of the research study, is stopped or canceled.
• The study staff feels that participating in the interview would be harmful to you.

What happens if you are injured by this research?
It is unlikely that you will be injured as a result of taking part in a qualitative interview. If you are injured, the [institution] will give you the treatment needed for your injuries. You [*will/will not*] have to pay for this treatment. You will be told where you can get additional treatment for your injuries. There is no program to pay money or give other forms of compensation for such injuries through the United States NIH. You do not give up any legal rights by signing this consent form.

Who can you contact if you have any questions?
We are happy to answer any questions that you may have. It may be that you have questions about your

rights as a participant in this qualitative substudy, or that you think you have been injured because you were in this study. In this case you can contact [insert name of the investigator or other study staff] at [insert telephone number and physical address].

If you have any questions or concerns about whether you should join this study, or your rights as a research participant, you should contact [insert name or title of person on the IRB/EC or other organization appropriate for the site] at [insert physical address and telephone number].

What is the cost of study participation?
There is no cost to you for being in this study. You will receive [insert local amount] for your time, effort, and travel to and from the clinic for each study visit.

SIGNATURE PAGE

PRINCIPAL INVESTIGATOR: *[Insert Name*]
PHONE: [Insert Number]

Study Participation
If you have read this consent form, or had it read and explained to you, and you understand the information, and you voluntarily agree to join the study, please sign your name or make your mark below.

_____ Participant Name (print)	_____ Participant Signature	_____ Date

For staff: I have explained the purpose of the screening to the volunteer and have answered all of their questions. To the best of my knowledge, they understand the purpose, procedures, risks and benefits of this study.

_____ Study Staff Conducting Consent Discussion (print)	_____ Study Staff Signature	_____ Date

Sample Qualitative Informed Consent Form for Healthcare Providers

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Version 3.0, 12 August 2021

GENERAL OVERVIEW

Some women from your community have participated in a clinical trial called HPTN 084. This study compared the effectiveness of taking an injection of cabotegravir every two months to daily use of oral PrEP/Truvada to prevent HIV. It found that injectable CAB LA was very effective in preventing HIV. Women who participated in the study can now choose to use CAB LA, the Truvada daily oral pill, or no method at all.

You have been invited to take part in a qualitative substudy. The goal of the substudy is to understand how women, their partners and other community members feel about injectable CAB LA and HIV PrEP in general. This qualitative substudy is being conducted in four of the HPTN 084 sites in Africa. It will include a total of 80-110 women, 20-24 male partners, 20-24 providers and other key stakeholders in communities where the trial has been conducted.

We are interested in talking with providers and other community members about HIV prevention services and providing the CAB LA injection. For example, we would like to know your role in helping men and women decide about using PrEP. We would also like to know what you think about the injections (shots) and about the oral pills. We hope that the information learned from this study will help us to better understand what kind of HIV prevention options women, men and couples prefer.

What happens if you do not want to join the qualitative interviews?
You can choose not to be interviewed. Your participation is completely your choice.

What will happen if you do want to join the qualitative interview study?
If you decide to join the qualitative interview study, you will be contacted by a study team member to arrange the interview. Interviews will be conducted in-person in a private setting, if unable to meet in person the interview may be conducted by phone. The interview will take approximately 60 minutes.

The information that you share during the qualitative interview will be treated confidentially. The interview will be audio-recorded to help assure that we get the best understanding possible from each discussion. This recording will be used to make a written transcript of the interview. The recording and transcript will only have a Participant ID number. No identifying information will be included in the written transcript.

We hope that you will be comfortable answering all of the questions and talking openly and honestly. But, please keep in mind that you do not have to answer any of the questions. You may stop participating completely at any time.

What are the potential benefits?
You will not receive any direct benefit from being in the qualitative interview; however, you or others in your community may benefit from this study later. The information gathered during this study may help make more HIV prevention options available. This may be beneficial to you and your community.

What are the possible risks or discomforts?
The questions we will ask you may make you feel uncomfortable. We hope that the qualitative interview procedures described above will minimize your discomfort when discussing sensitive topics. However, the greatest risk may involve your privacy and confidentiality. Additional steps that the study team has taken to protect your privacy are described below.

How will your privacy be protected?
Every effort will be made to keep your personal information confidential. Your personal information (name, address, phone number) will be protected by the research clinic. Your name, and anything else that might identify you personally, will not be used in any publication of information about this study.

Information from the qualitative substudy may be reviewed by institutions who are helping to fund or implement the trial. However, no personal information will be shared. Information from these qualitative interviews will only be described in general ways. The sponsor of the study (US National Institutes of Health (NIH) their representatives), US FDA, US Department of Health and Human Services (DHHS), Office of Human Research Protection (OHRP) and other government and local, US and International regulatory entities, authorized representatives of US NIH and/or its contractors, [insert names of applicable IRBs/ECs/other local review bodies as applicable] IRB, study staff, study monitors, and companies that makes the study drug (ViiV Healthcare and Gilead Sciences, Inc.). We cannot guarantee absolute confidentiality.

A description of this study will be available on www.ClinicalTrials.gov, as required by US law. This web site will not include information that can identify you. At most, the web site will include a summary of the results. You can search this web site at any time.

What are the alternatives to participating in this study?
You do not have to participate in the interviews.

Reasons why you may be withdrawn from the study without your consent
Your participation in the interview may be ended early without your consent for the following reasons:
• The research study, or the qualitative part of the research study, is stopped or canceled.
• The study staff feels that participating in the interview would be harmful to you.

What happens if you are injured by this research?
It is unlikely that you will be injured as a result of taking part in a qualitative interview. If you are injured, the [institution] will give you the treatment needed for your injuries. You [*will/will not*] have to pay for this treatment. You will be told where you can get additional treatment for your injuries. There is no program to pay money or give other forms of compensation for such injuries through the United States NIH. You do not give up any legal rights by signing this consent form.

Who can you contact if you have any questions?
We are happy to answer any questions that you may have. It may be that you have questions about your rights as a participant in this qualitative substudy, or that you think you have been injured because you were in this study. In this case you can contact [insert name of the investigator or other study staff] at [insert telephone number and physical address].

If you have any questions or concerns about whether you should join this study, or your rights as a research participant, you should contact [insert name or title of person on the IRB/EC or other organization appropriate for the site] at [insert physical address and telephone number].

What is the cost of study participation?
There is no cost to you for being in this study. You will receive [insert local amount] for your time, effort, and travel to and from the clinic for each study visit.

SIGNATURE PAGE

PRINCIPAL INVESTIGATOR: *[Insert Name*]
PHONE: [Insert Number]

Study Participation
If you have read this consent form, or had it read and explained to you, and you understand the information, and you voluntarily agree to join the study, please sign your name or make your mark below.

_____ Participant Name (print)	_____ Participant Signature	_____ Date

For staff: I have explained the purpose of the screening to the volunteer and have answered all of their questions. To the best of my knowledge, they understand the purpose, procedures, risks and benefits of this study.

_____ Study Staff Conducting Consent Discussion (print)	_____ Study Staff Signature	_____ Date

2. Revision 2: A footnote to clarify the timing of the fetal ultrasound has been added to the Schedule of Evaluations for "Appendix VIII: Schedule of Evaluations for Step 4d- Procedures for Pregnant/Breastfeeding Participants."

including antenatal assessment per SOC	X	X	X	X	X	X	X	X	X	X	X				X						X
Ultrasound or refer to ultrasound[15]				X																	
Blood collection	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X

"[15] **Ultrasound is required once in the first trimester to ensure optimal fetal dating. This choice of ultrasound date within the schedule of events would align to estimated gestational age at the time of pregnancy identification. Ideally the ultrasound should be completed by Week 12.**"

3. Revision 3: A typographical error in the Schedule of Evaluations for "Appendix VIII: Schedule of Evaluations for Step 4d- Procedures for Pregnant/Breastfeeding Participants" has been corrected. An "X" was added to Week 40 for the row titled "Dispense/administer study product, as is appropriate." It was inadvertently omitted. In addition, a clarifying footnote has been added.

Contraceptive counseling																	X	X	X	X	X	X
Dispense/administer study product, as is appropriate[16]	X		X		X		X		X		X						X	X	X	X	X	X
ISR Assessment, only for																						

Clarifying Footnote:

"[16] **After delivery of an infant, study participants will only receive CAB LA up to and including the visit at Week 24. After the Week 24 visit, participants may choose to either transition to TDF/FTC or to a local PrEP program."**

4. Revision 4: Typographical errors in the footnotes for the Schedule of Evaluations for "Appendix VIII: VIII: Schedule of Evaluations for Step 5- Procedures for Participants Taking OL TDF/FTC for 48 Weeks after Premature CAB LA discontinuation" have been corrected. A footnote "1" was added to the "Clinical Evaluations & Procedures" for "Urine Collection." A footnote, "7," was removed from the column titled "Step 5, Day 0."

TDF/FTC for 48 Weeks after Premature

Time in Step 5	Step 5, Day 0*	S V
ADMINISTRATIVE, BEHAVIORAL, REGULATO		
Locator information	X	
Acceptability assessment	X	
Behavioral assessment (if done in last 4 weeks, skip D0 and start at W12)	X	
HIV prevention counseling	X	
Offer condoms	X	
CLINICAL EVALUATIONS & PROCEDURES		
Medical history, concomitant medications, targeted physical exam (with pulse, BP, weight and BMI calculated at each visit)	X	
Blood collection	X	
Urine collection[1]	X[7]	
Vaginal swab collection[1]	X[7]	
Adherence counseling[2]	X	
Dispense pills to all participants	X	
LOCAL LABORATORY EVALUATIONS & P		
HIV testing[3]	X	
HIV viral load testing[4]	X	
Pregnancy testing[5]	X	
Chemistry testing[6]	X	
Liver function testing[7]	X	
Syphilis testing	X[7]	
GC/CT and TV testing[1]	X[7]	
Plasma storage[8,9]	X	
DBS storage[9]	X	

FOOTNOTES FOR Step 5 SOE

5. Revision 5: Outdated text from "Section 8.0 (NOT MODIFIED FROM THE MAIN PROTOCOL), 8.1 Ethical Review" was removed.

~~This protocol and the template informed consent form contained in Appendix IV and any subsequent modifications will be reviewed and approved by the HPTN Scientific Review Committee (SRC) and~~

~~DAIDS Prevention Science Review Committee (PSRC) with respect to scientific content and compliance with applicable research and human subjects regulations.~~

6. Revision 6: Minor typographical errors were corrected in the amended consent form in the section titled "What happens next?"

   "What happens next?
   We'd like to offer you the chance to continue taking CAB LA or TDF/FTC for the next 48 weeks. We want to learn more about women's HIV prevention choices now that we know that CAB LA is safe and works to prevent HIV. We also want to learn more about CAB LA use during pregnancy and breastfeeding. In the next part of the study, the "open-label" part of the study you will be able to:

   - Stay on CAB LA if you are already on it
   - Stay on TDF/FTC if you are already on it
   - Switch to CAB LA if you are on TDF/FTC and it is safe for you to do so
   - Start or re-start CAB LA if you have been on the annual visit schedule and it is deemed safe for you to take CAB LA
   - Stop ~~from~~ CAB LA **and switch** to TDF/FTC **to cover the tail**

   If you think you are no longer at risk for HIV, you may stop both study product**s**. We'd still like you to come for study visits for 48 weeks. Study staff will take with you and help you to decide whether you are at risk for HIV and still need to take pre-exposure prophylaxis or PrEP (either oral or injectable) to prevent HIV."

7. Revision 7: In Section 5.14, "Pregnancies, Confirmed Pregnancies," wording was changed to eliminate potential confusion during implementation. Sites may enroll a pregnant woman into the Pregnancy and Infant sub-study without waiting for a confirmation test two weeks after the original test.

   "5.14 Pregnancy
   Confirmed Pregnancies
   Participants with a positive pregnancy test will require **a second** confirmation ~~of~~ pregnancy test ~~at a subsequent visit at least TWO weeks later~~. All pregnancies that occur during the course of the study must be reported to the CMC within seven days of site awareness (either upon confirmation by urine or blood pregnancy testing during a study visit or as reported by the participant between study visits). Site staff will refer to their SOP for detailed management."

8. Revision 8: Text has been added to the main consent form for participants in the Pregnancy and Infant sub-study clarifying PrEP options from Week 24 post-partum and beyond. Participants may choose to take TDF/FTC or may choose to access CAB LA at a local access program for study participants. Text was edited in "Study activities for women who become pregnant," "After Delivery."

   "-If you choose to take CAB LA injections during breastfeeding, we will check the injection location carefully at Week 8 ~~and Week 48~~. **Your last CAB LA injection through the study will be given 24 weeks after delivery. If you wish to continue taking HIV prevention medications at that point, we will offer you the choice of either taking TDF/FTC through the study or we will refer to you a local access program for CAB LA."**

9. Revision 9: Clarifying text has been added to Section 5.16, "Acceptability Assessments, Qualitative Sub-Study."

   "Several additional activities will be conducted within the qualitative sub-study, including interviews with male partners and other key informants and up to two participatory workshops. As is appropriate, separate informed consent will be collected.

   1. In each site, a total of 5-6 male partners of qualitative sub-study participants will be invited to participate in a qualitative interview. The qualitative study team in each site will identify sub-study participants who represent different product-related experiences and who would be interested/willing to facilitate their partner's engagement in the study. **Women participants will be provided with palm cards that describe the purpose of partner interviews and provide contact information through which the male partner can indicate his interest in participation.** Male partner interviews will explore disclosure and/or couple decision-making about trial participation and product use, perceived risks and benefits of injectable and oral PrEP use, questions about product use during pregnancy, use by a partner, and impact of trial participation on couple relationship. **Male partner interviews will be conducted in-person and in a private mutually agreed upon setting – most likely at the clinic when acceptable and feasible, or they may be conducted by phone or virtually. Any in-person interviews will follow standard COVID-19 protocol that are being implemented, including socially distanced seating and use of face masks for the interviewer and male partner participant.**

   2. In each site, a total of 5-6 community-based healthcare providers and/or other key informants (CBO stakeholders or others) will be invited to participate in a qualitative interview to explore perceptions about CAB LA and other PrEP modalities, required information, tools and strategies to integrate delivery of CAB LA into other services, and perspectives about how to increase demand for and uptake of injectable and oral PrEP within different populations (e.g., adolescents and young women, pregnant and breastfeeding women etc). **Providers and other stakeholders will be purposively recruited to represent the various healthcare settings through which CAB LA may potentially be introduced, including primary health care clinics, antenatal clinics, HIV/STI clinics or other venues. Brochures describing the HPTN 084 study and findings as well as the purpose of the provider interview will be distributed to potential healthcare and CBO venues. When feasible, provider interviews will be conducted face-to-face in a private space at the healthcare/stakeholder's place of employment. Face-to-face interviews will follow COVID-19 mitigation strategies, including socially distanced seating and use of face masks for the interviewer and the healthcare provider/stakeholder. When this is not feasible (due to lack of private space or because of COVID-19 conditions), the interview may be conducted by phone.**

   3. Finally, teams in each site will convene one to two participatory workshops that include a mix of participants who represent target end-user group(s), providers and community representatives. They will review findings from the qualitative sub-study, make use of design strategies (e.g., personnas, journey maps, scenario development); and draft potential messages and/or strategies that support uptake, use and/or transitions between PrEP products, including CAB LA. **It is anticipated that the workshops may be conducted in a hybrid manner, with some in-person participation – when feasible – and some participants joining by internet. Standard mitigation strategies will be implemented to maintain safety of the workshop participants and implementers.**