Letter of Amendment # 3 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
Protocol Version 1.0, dated 2 March 2017
DAIDS Document ID: 38070
IND #: 122,744

Final Letter of Amendment Version: 31 May 2018

Summary of Revisions and Rationale

Recent information has been made available regarding Dolutegravir (DTG), which is an integrase inhibitor in the same class of pharmaceuticals as cabotegravir (CAB), the study drug under investigation in HPTN084.

This information involving the use of DTG in pregnancy is from the Botswana NICHD-funded Tsepamo Birth Outcomes Surveillance Study. This study was designed to evaluate adverse birth outcomes by maternal HIV status and ART regimen, and to determine whether there is an increased risk of neural tube defects (NTDs) among infants exposed to efavirenz (EFV) from conception. Reports and photographs (where available) of major abnormalities were reviewed by an experienced medical geneticist who was blinded to exposure information. During a preliminary unscheduled analysis of the Tsepamo data collected between August 15, 2014 and May 1, 2018 (which was undertaken at the request of colleagues who were preparing for a WHO meeting), the investigators found 4 cases of neural tube defects in babies of 426 women who became pregnant while taking DTG (prevalence 0.9%). This rate compares to a 0.1% risk of neural tube defects in infants born to women taking other antiretroviral medicines at the time of conception.

Accordingly, the US NIH Multinational DSMB has met and advised that all women in HPTN 084 must be on an effective long-acting method of contraception as a precaution. In addition, any participants who become pregnant will be offered early monitoring, using ultrasound and if necessary referral for biochemical blood testing, to assess whether neural tube defects (NTD) may be present, and managed in accordance with national guidelines.

Implementation

The information contained in this Letter of Amendment (LoA) impacts the HPTN 084 study, including the study informed consent form(s), and must be submitted to site Institutional Review Boards (IRBs) and/or Ethics Committees (ECs) as soon as possible for 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. Note that required approvals of protocol Version 1.0, LoA #1, LoA #2 and LoA #3 must be obtained before initiating this study.

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.

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 084.

If the HPTN 084 protocol is fully amended in the future, this LoA 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.

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
FINAL, Version 1.0, dated 2 March 2017
DAIDS Document ID: 38070

A Study of the HIV Prevention Trials Network (HPTN)

Letter of Amendment #3, Dated: 31 May 2018

LETTER OF AMENDMENT SIGNATURE PAGE

I will conduct the 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 U.S. 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.

I have read and understand the information in this protocol and will ensure that all associates, colleagues, and employees assisting in the conduct of the study are informed about the obligations incurred by their contribution to the study.

_____ _____
Signature of Investigator of Record **Date (MM/DD/YYYY)**

_____
Name of Investigator of Record (print name)

Revision 1-Related Changes: Protocol Updates in Response to FDA Request

Revision 1, Change 1) Information on DTG, pregnancy, and corresponding changes to procedures for HPTN 084:

1.0 Introduction

1.7.1 Dolutegravir and Pregnancy

Dolutegravir (DTG) is an integrase inhibitor in the same class of pharmaceuticals as CAB. Thus far, limited safety or efficacy data for DTG in pregnancy in humans have been published or presented.
In May 2018, WHO and several other regulatory agencies released advisories regarding the safety of dolutegravir in early pregnancy[50]

This was based on information received from the Botswana NICHD-funded Tsepamo Birth Outcomes Surveillance Study, the largest body of data related to birth outcomes following the use of DTG in pregnancy. This study was designed to evaluate adverse birth outcomes by maternal HIV status and ART regimen, and to determine whether there is an increased risk of neural tube defects (NTDs) among infants exposed to efavirenz (EFV) from conception. Botswana's HIV program moved to universal ART with DTG/TDF/FTC in first line for patients starting ART (including pregnant women) in May of 2016 (women already on other regimens were not switched to DTG). The previous first-line regimen was EFV/TDF/FTC. Almost all women on DTG-based and EFV-based ART took these drugs in combination with TDF/FTC. More than 95% of women in Botswana deliver in a hospital, and obstetric records were available for >99% of women. The Tsepamo surveillance study is conducted at 8 of the largest public maternity wards across Botswana (representing ~45% of the total births in the country). Research assistants' abstract exposure data from the maternity card for all consecutive in-hospital deliveries (both HIV-infected and HIV-uninfected women). Each newborn, whether stillborn or live-born, undergoes a systematic infant surface examination that is completed by trained nurse midwives. Reports and photographs (where available) of major abnormalities are reviewed by an experienced medical geneticist who is blinded to exposure information. During a preliminary unscheduled analysis of the Tsepamo data collected between August 15, 2014 and May 1, 2018, which was undertaken at the request of colleagues who were preparing for a WHO meeting, the investigators found 4 cases of neural tube defects in babies of 426 women who became pregnant while taking DTG (prevalence 0.9%). This rate compares to a 0.1% risk of neural tube defects in infants born to women taking other antiretroviral medicines at the time of conception. Data is expected on the pregnancy outcomes of an additional 600 women in the Tsepamo study who were taking DTG around the time of conception. More data are also expected to be forth coming from other studies of DTG in pregnancy. These data will provide more information on the safety of DTG for women of childbearing age.

Cabotegravir is not dolutegravir. While these medications share a common molecular backbone, and have a similar mechanism of activity, they are separate chemical compounds and have differences in antiviral activity, pharmacokinetics, metabolism and drug-drug interactions. It is not known if the safety signal identified with dolutegravir will be observed with cabotegravir. Cabotegravir was evaluated in a complete package of reproductive toxicology studies, including embryofetal development studies, and no safety findings suggestive of teratogenesis or neural tube defects were identified in the December 2017 version of the Investigator's Brochure. Nevertheless, given limited experience with use of cabotegravir in pregnancy women of

reproductive potential are required to adopt highly reliable means of contraception during participation and throughout long term follow up phases of studies following exposure to CAB LA.

Revision 1, Change 2)
3.1 Inclusion Criteria

- ~~If of reproductive potential, women~~ **Have documented evidence of surgical sterilization, OR documented evidence of no uterus (e.g., hysterectomy), OR** must agree to use a reliable form of **long acting** contraception, during the trial and for 52 weeks after stopping the long acting injectable, or 30 days after stopping oral study product, from the list below:
    - Intrauterine device (IUD) or intrauterine system (IUS) that meets <1% failure rate as stated in the product label
    - Hormone-based contraceptive that meets <1% failure rate when used consistently and correctly as stated in the product label **(implants or injectables only; this excludes combined oral contraception)**

Revision 1, Change 3)
3.2 Exclusion Criteria

- **If potentially able to conceive, unwilling to adhere to long acting contraception (IUD/IUS, injection, or implant) with a <1% failure rate when used consistently and correctly as stated in the product package insert/ manufacturer's guidelines**

Revision 1, Change 4)
5.3 Step 1, Oral Run-in Phase: Safety Visits

Oral Run-in Safety Visits at Weeks 2 and 4

All HIV test results from previous visits and at least one HIV test result from the current visit must be available and reviewed. If any of these tests is reactive/positive, study drug must be discontinued and procedures in Section 5.11 will be followed.

If of reproductive potential, **adequate contraception should be confirmed and** a pregnancy test must be conducted and the result from the current visit (same day) must be viewed. If the participant is not pregnant, the site will follow the SOE for the visit. If a participant tests positive for pregnancy, see Section 5.14.

Investigators should contact the CMC at 084cmc@hptn.org if a participant has missed her contraception, has a missed or delayed week 4 visit, or has not had sufficient oral drug exposure during the four-week oral run-in period to transition to step 2.

Revision 1, Change 5)
5.14 Pregnancy

Because CAB and CAB LA are investigational agents, women may not enroll if they are pregnant or desire to become pregnant. Receipt of study product by participants requires use of an effective method of contraception as outlined in Section 3.1. Participants should be encouraged to delay pregnancy for at least ~~48~~ **52** weeks following discontinuation of IM dosing. All participants must also use male or female condoms for prevention of HIV and other STIs. Study staff will provide contraceptive counseling to enrolled participants throughout the duration of study participation and will facilitate

access to contraceptive services through direct service delivery and/or active referrals to local service providers for methods that cannot be provided on-site. **Study staff should confirm adequate contraception with one of the study approved contraceptive methods (see section 3.1) at each visit. Where adequate contraception cannot be confirmed, and in the opinion of the investigator early pregnancy cannot be excluded, then the investigator should contact the HPTN 084 CMC at 084cmc@hptn.org for further guidance regarding the administration of study injections.**
A four-week supply of open label TDF/FTC should be administered during the first positive pregnancy test. No injections should be given if there is a positive pregnancy test.

All participants who are pregnant must be referred for an Ultrasound and evaluation by an obstetric specialist at about 12-14 weeks gestational age, for other testing, counseling, and management. Further biochemical blood test may be done as indicated. All findings and outcomes will be collected and reported.

Refer to procedures in Appendix Id.

Revision 1, Change 6)

5.15 Participants who discontinue long acting contraception
All participants who are not currently pregnant and potentially able to conceive and decide to discontinue long acting contraception for any reason will be immediately placed onto open label TDF/FTC and follow procedures detailed in Appendix Ic. If she completes 48 weeks of TDF/FTC and study follow-up is ongoing she may be required to be followed up at least annually for HIV testing.

If the participant conceives, she should follow procedures for pregnant participants (see section 5.14).

Participants who complete pregnancy and cease breastfeeding may resume open-label study product and visits according to Appendix Ib, provided they agree to use an approved contraceptive method (either injection, implant or IUD/IUS). If participants decline to use an approved contraceptive method, they will be given open-label TDF/FTC and followed for the remainder of their study period. Once a participant has completed 48 weeks of TDF/FTC after her last CAB LA/placebo injection and study follow-up is ongoing she may be required to be followed up at least annually for HIV testing.

In all cases contact the HPTN 084 CMC at 084cmc@hptn.org

Revision 1, Change 7)
REFERENCES
[50]http://www.ema.europa.eu/ema/index.jsp?curl=pages/news_and_events/news/2018/05/news_detail_002956.jsp&mid=WC0b01ac058004d5c1

Revision 1, Change 8)
Appendix Ia: Schedule of Evaluations- Screening and Step 1, Oral Run-in Phase

	Screening	DAY	WEEK 2	WEEK 4

		0/Enrollment		
Adherence counseling/**contraception counseling**[13]/pill count (pill count Weeks 2 and 4 only)		X	X	X

[13] Refer to the SSP Manual.

Revision 1, Change 9)
Appendix Ib: Schedule of Evaluations - Step 2, Injection Phase

WEEKS in Study (shaded column = injection/ dispense pills visit)	5	6	9	13	17	21	25	33	41	42	49	57	65	73	81	89	97	105	113	121	129	137	145	153	161	169	177	185
Adherence counseling / **contraception counseling**[11]	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X

[11] Refer to the SSP Manual.

Revision 1, Change 10)
Appendix Ic: Schedule of Evaluations - Step 3, Follow-up Phase

Time in Step 3	**Step 3, Day 0***	**Step 3, Week 12**	**Step 3, Week 24**	**Step 3, Week 36**	**Step 3, Week 48**
Adherence counseling/ **contraception counseling**[8] for all participants	X	X	X	X	

[8] Refer to the SSP Manual.

Revision 1, Change 11)
Appendix Id: Schedule of Evaluations for Pregnant Participants

WEEKS in Study	**4 weeks after first positive pregnancy test**	**Quarterly Visit 1 (12 weeks since first positive pregnancy test)**	**Quarterly Visit 2 (24 weeks since first positive pregnancy test)**	**Quarterly Visit 3 (36 weeks since first positive pregnancy test)**
ADMINISTRATIVE, BEHAVIORAL, REGULATORY				
Locator information	**X**	**X**	**X**	**X**
HIV prevention	**X**	**X**	**X**	**X**

counseling				
Condoms per local SOC	**X**	**X**	**X**	**X**
Acceptability assessment		**X**		
Behavioral assessment		**X**		**X**
CLINICAL EVALUATIONS & PROCEDURES				
Adherence counseling	**X**	**X**	**X**	**X**
Dispense TDF/FTC to all participants	**X**	**X**	**X**	**X**
Medical history, concomitant medications, targeted physical exam		**X**	**X**	**X**
Blood collection	**X**	**X**	**X**	**X**
Urine collection	**X**	**X**	**X**	**X**
Vaginal swab collection[1]		**X**		**X**
LOCAL LABORATORY EVALUATIONS & PROCEDURES				
HIV testing[2]	**X**	**X**	**X**	**X**
Pregnancy testing[3]	**X**			
Chemistry testing[4]			**X**	
Liver function testing[5]			**X**	
Syphilis testing	**X[7]**		**X**	
Vaginal GC/CT and TV testing[2]	**X**	**X**	**X**	
Plasma storage[6]	**X**	**X**	**X**	**X**
DBS storage	**X**	**X**	**X**	**X**

FOOTNOTES FOR APPENDIX Id

[1] GC/CT NAAT testing may be performed using urine or a vaginal swab; TV testing is performed using a vaginal swab.

[2] The HIV testing algorithm is provided in the SSP Manual. If HIV rapid testing is indicated, this testing may be performed in the clinic or the laboratory. At least one HIV test must be available the same day as sample collection and before product is administered.

[3] Pregnancy testing may be performed in the clinic or the laboratory. Results must be available the same day as sample collection and before product is administered. Testing may be performed using a urine, plasma, or serum sample. The assay used for pregnancy testing must have a limit of detection of 25 mIU/mL or lower. Pregnancy testing is not required at subsequent visits if a positive result is obtained and the participant is still pregnant. If the confirmatory pregnancy test is positive, the participant is referred for an Ultrasound and evaluation by an obstetric specialist at about 12-14 weeks gestational age, for other testing, counseling, and management. Further biochemical blood testing may be done as indicated. All findings and outcomes will be collected and reported.

[4] BUN/urea, creatinine, CPK, calcium, phosphorous, glucose, amylase, and lipase.

[5] AST, ALT, TBili, and alkaline phosphatase.

[6] Stored plasma will be used for Quality Assurance testing and other assessments at the HPTN LC (see Section 9). Assessments will be performed retrospectively; results will not be returned to study sites or participants, except as noted in Section 9.0.

[7] If not done within 4 weeks of initial positive pregnancy test

Revision 1, Change 12)

Appendix IV: Sample Screening and Enrollment Informed Consent Form

Screening Visit Activities

- Test you for pregancy *[site insert sample type, blood vs. urine]* and talk to you about your plans in the next years for becoming pregnant **as well as available forms of long acting contraception. We will require proof of contraception if you have received it elsewhere.**

Step 1 Visit Activities

Step 1: Enrollment Visit (Week 0) Activities

- **Talk with you about long term contraception. If you are not currently using implants, injectables or intrauterine devices to prevent pregnancy we will offer them to you in the clinic or refer you for services. We will require proof of contraception if you have received it elsewhere. If you are receiving a long-acting injectable contraceptive, we will also require proof that you received your most recent dose.**
-

Step 1: Weeks 2 and 4 Visit Activities

- **Talk with you about long term contraception. If you are not currently using implants, injectables or intrauterine devices to prevent pregnancy we will offer them to you in the clinic or refer you for services. We will require proof of contraception if you have received it elsewhere. If you are receiving a long-acting injectable contraceptive, we will also require proof that you received your most recent dose.**

Step 2: CAB LA Injection or TDF/FTC Dispensing Visit Activities

These visits will take place at Weeks 9, 17, 25, 33, 41, 49, 57, 65, 73, 81, 89, 97, 105, 113, 121, 129, 137, 145, 153, 161, 169, 177, 185. [*Note: Sites may remove Week numbers in the text if easier to depict it in a table or refer to the Schedule of Procedures and Evaluations*].

- **Talk with you about long term contraception. If you are not currently using implants, injectables or intrauterine devices to prevent pregnancy we will offer them to you in the clinic or refer you for services. We will require proof of contraception if you have received it elsewhere. If you are receiving a long-acting injectable contraceptive, we will also require proof that you received your most recent dose.**

Step 2: Weeks 6, 13, 21 and 42 Safety Visit Activities

- **Talk with you about long term contraception. If you are not currently using implants, injectables or intrauterine devices to prevent pregnancy we will offer them to you in the clinic or refer you for services. We will require proof of contraception if you have received it elsewhere. If you are receiving a long-acting injectable contraceptive, we will also require proof that you received your most recent dose.**

Step 3 Visit Activities

Step 3: Follow-up Visits

- **Talk with you about long term contraception. If you are not currently using injectables or intrauterine devices to prevent pregnancy we will offer them to you in the clinic or refer you for services. We will require proof of contraception if you have received it elsewhere. If you are receiving a long-acting injectable contraceptive, we will also require proof that you received your most recent dose.**

PREGNANCY

To participate in this study, you must agree not to become pregnant. You must agree to use a reliable form of **long acting** contraception **(either injectables, implants or IUD/IUS)** during the trial and for 52 weeks after stopping injections, or for 30 days after stopping oral study product. **If you have received your contraception at another site which is not this study clinic, we may ask you to provide proof that you are on an effective long-acting contraceptive method.**

We have some early information as of May 2018 from a different ongoing study being done in Botswana with dolutegravir (DTG), a medicine that is similar to but not the same as cabotegravir (CAB), the medicine being studied in HPTN 084. In that study, women living with HIV were taking DTG for treatment of HIV infection. Some of the women who became pregnant while taking DTG had babies with birth defects of the spinal cord and the brain. This is a <u>new, unexpected finding</u>. Researchers are currently gathering more information and trying to understand if DTG caused the babies' birth defects. We don't have the answer yet.

Here are some things that we do know:

- **In the Botswana study, 4 out of 426 women taking DTG <u>before</u> they got pregnant had babies with the nervous system birth defects. This means that about 1 out of every 100 babies were born with these problems.**
- **This is about 10 times more than expected compared to babies who were born to women taking other HIV treatment drugs in the same study.**
- **There are about 600 more women in the Botswana study who were taking DTG around the time they became pregnant that have not given birth yet. All of those babies will be born between now and February 2019. Those women and their babies will be carefully monitored and this will give us more information about the safety of DTG in pregnancy.**

We share this information with you so that you can decide if you want to continue your participation in the HPTN 084 study. We do not know if CAB can cause birth defects in babies. When we have more information, we will share that with you. We will also let you know if we decide to make any changes to HPTN 084.

If you are currently enrolled in HPTN 084 and do not wish to continue to receive injections, or do not wish to utilize long acting forms of contraception, we will offer you 48 weeks of open label TDF/FTC.

If you become pregnant while on HPTN 084 we will refer you for an Ultrasound and evaluation by an obstetric specialist approximately 12 weeks into your pregnancy so that we can examine the health of your unborn baby. Ultrasound imaging uses sound waves and allows an inside view of soft tissues and body cavities without the use of invasive techniques. There is no evidence that any

danger occurs from doing an ultrasound during pregnancy. If the ultrasound shows anything unusual we will refer you for further care.

Once your pregnancy has ended and you have completed breastfeeding you may resume taking the study product you were allocated to (injection OR pills) and resume your previous visit schedule, provided that you agree to use an approved long-acting contraceptive method. If you do not wish to use an approved long-acting contraceptive method, then we will ask you to continue taking open-label TDF/FTC for up to 48 weeks after your last CAB LA injection and attending quarterly study visits. After that we will ask to see you at least once a year for HIV testing until the study has ended.

Revision 1, Change 13)
Appendix IV: Qualitative Informed Consent Form

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. If you participate in a focus group discussion, we will assign you a number instead of using your real name.

Your records may be reviewed by the sponsor of the study (US National Institutes of Health (NIH) their representatives), US FDA, US Department of Heath and Human Services (DHHS), Office of Human Research Protection (OHRP) and other government and ~~regulatory authorities~~ 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.).