The HIV Prevention Trials Network

HPTN 084 FAQ

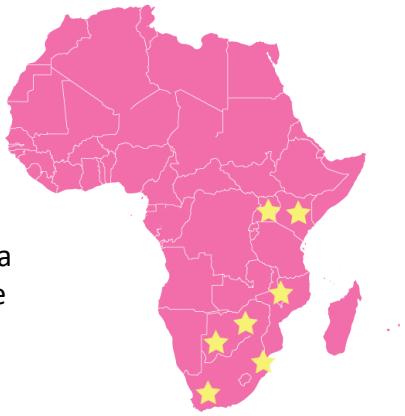
1. What is HPTN 084 (LIFE - Long-acting Injectable For the Epidemic)?

Cabotegravir Injection

Truvada Tablet

HPTN 084 (LIFE - **L**ong-acting **I**njectable **F**or the **E**pidemic) is the first study to compare the safety and efficacy of long-acting injectable cabotegravir to daily oral TDF/FTC for HIV prevention among cisgender women.

2. When and where will this study be done?



The study is taking place in Botswana, Kenya, Malawi, South Africa, Eswatini, Uganda and Zimbabwe. HPTN 084 (LIFE) started in late 2017.

3. What organizations are involved in this study?

The HPTN 084 (LIFE) study is jointly funded by the U.S. National Institute of Allergy and Infectious Diseases, part of the U. S. National Institutes of Health, Bill & Melinda Gates Foundation, and ViiV Healthcare. Study drugs are provided by ViiV Healthcare and Gilead Sciences, Inc.

4. Why is HPTN 084 (LIFE) being done?

Taking a daily pill for PrEP is an effective tool for preventing HIV; however, remembering to take a daily pill can be hard for some people, others may prefer not to take daily pill, or some people may have medical reasons that prevent them from taking a daily pill. The development of safe and effective long acting agents for HIV PrEP would increase HIV prevention choices and help those who find taking a daily pill challenging. Some people also may find periodic injections to be more discreet than daily pills. Having multiple HIV prevention methods available will give people more options to prevent HIV.

5. How many people will be in this study and who can join?

The study is enrolling about 3,200 cisgender women who are not living with HIV. Participants who join the study must be 18-45 years old and on a highly effective, long acting method of contraception including an injectable, implant or IUD/IUC. Cisgender women who have received a tubal ligation procedure (sterilization) are also eligible for the study. Cisgender women who want to become pregnant should not join this study.

6. What is cabotegravir?

Cabotegravir (CAB) is an anti-HIV drug that is being tested to see if it is safe, acceptable, and works to treat and/or prevent HIV. There are different types of anti-HIV drugs. CAB is a type of anti-HIV drug called an integrase inhibitor. Integrase inhibitors prevent HIV from making copies of itself and can reduce the amount of HIV in the body.

Two forms of CAB are being used in HPTN studies: a pill that is taken daily by mouth for 5 weeks only (known as oral CAB) and a long-acting injectable, received in clinic every two months (known as CAB LA; LA stands for “long-acting”). Since CAB can remain in the body for up to a year or more in some people, the pill is taken for five (5) weeks first to make sure there are no reactions to CAB before an injection is given.

7. What will happen during the study?

Participants who enroll in the study will be assigned at random (like flipping a coin) to either Group A or Group B. Each woman in each group will get an injection in the buttock every two months and a daily pill.

Participants in both groups will get the same number of pills and the same number of injections. Group A will get CAB pills and CAB injections plus placebo TDF/FTC pills (pills that look like TDF/FTC pills, but have no active drug).

Group B will get TDF/FTC pills and placebo CAB pills (pills that look like CAB pills, but have no active drug) and placebo CAB injections (injections that look like CAB injections, but have no active drug). Both groups go through three steps in the study and some participants could be in the study for up to 4.5 years.

Group A

This group gets CAB pills and CAB injections plus TDF/FTC **placebo pills.**

Step 1: CAB pill plus a placebo TDF/FTC pill every day for five weeks

Step 2: One singular CAB injection initially, then another injection a month later, and then every two months after that up to three and half years plus a TDF/FTC placebo pill every day

Step 3: TDF/FTC pill every day for about a year, then referred to local HIV prevention services, which may include PrEP

Group B

This group gets TDF/FTC **pills plus placebo CAB pills and placebo CAB injections.**

Step 1: TDF/FTC pill plus a placebo CAB pill every day for five weeks

Step 2: TDF/FTC pill every day plus one singular placebo CAB injection initially, then another placebo injection a month later, and then every two months after that up to three and a half years

Step 3: TDF/FTC pill every day for about a year, then referred to local HIV prevention services, which may include PrEP

8. Is the safety and efficacy of CAB being tested for HIV prevention in other populations?

Yes. A study known as HPTN 083 is the first study to compare the efficacy of CAB LA to daily oral TDF/FTC for HIV pre-exposure prophylaxis (PrEP). HPTN 083 enrolled 4,570 cisgender men and transgender women (TGW) who have sex with men at 43 sites in Argentina, Brazil, Peru, United States, South Africa, Thailand, and Vietnam. HPTN 083 started enrolling participants in December 2016.

The HPTN 083 study is jointly funded by the U.S. National Institute of Allergy and Infectious Diseases (NIAID), part of the National Institutes of Health, and ViiV Healthcare. Study drugs are provided by ViiV Healthcare and Gilead Sciences, Inc.

9. What are the other differences between HPTN 083 and HPTN 084 (LIFE)?

	HPTN 083	HPTN 084
Active Products	Long-acting injectable cabotegravir (CAB LA), oral cabotegravir (CAB), oral TDF/FTC	Long-acting injectable cabotegravir (CAB LA), oral cabotegravir (CAB), oral TDF/FTC
Populations	4,570 cisgender men and transgender women who have sex with men	3,200 (projected) cisgender women
Locations	Argentina, Brazil, Peru, South Africa, Thailand, U.S., Vietnam	Botswana, Eswatini, Kenya, Malawi, South Africa, Uganda, Zimbabwe
Start Date	December 2016	November 2017
Study Design	**Non-Inferiority of CAB LA to TDF/FTC** A non-inferiority study tests whether one drug works about the same as, but not worse than, another drug	**Superiority of CAB LA to TDF/FTC** A superiority study tests whether one drug works better than another drug
Study Steps	**STEP 1** 5 weeks of 2 daily oral pills – 1 active and 1 placebo Arm A: CAB, TDF/FTC Arm B: CAB, TDF/FTC **STEP 2** Injections every 8 weeks and daily pills for up to **3 years** TDF/FTC, TDF/FTC **STEP 3** Daily oral pills for 48 weeks TDF/FTC	**STEP 1** 5 weeks of 2 daily oral pills – 1 active and 1 placebo Arm A: CAB, TDF/FTC Arm B: CAB, TDF/FTC **STEP 2** Injections every 8 weeks and daily pills for up to **3.5 years** TDF/FTC, TDF/FTC **STEP 3** Daily oral pills for 48 weeks TDF/FTC
Study Results	The study showed **superiority** of CAB LA over oral TDF/FTC, meaning CAB LA worked better to prevent HIV infection in the population than oral TDF/FTC. There was a **66%** reduction in HIV infections in study participants provided CAB compared to TDF/FTC.	Results forthcoming upon study completion

= placebo

10. Is CAB safe?

Studies so far in people living with HIV (treatment studies) and people living without HIV (prevention studies) have shown CAB to be safe and acceptable. The most common side effects in a completed HPTN study using CAB, HPTN 077, were headache and injection site reaction.

Most recently, an independent Data and Safety Monitoring Board (DSMB) reviewed study data. The DSMB found both CAB and TDF/FTC to be safe based on data at their review. There were no safety concerns raised by the DSMB with continuing the study. The safety of both CAB and TDF/FTC will continue to be evaluated in HPTN 083 and HPTN 084 (LIFE).

11. How is HPTN ensuring the safety of HPTN 084 study participants?

Multiple people and groups will carefully look at the safety of cisgender women in HPTN 084. This study has been reviewed by regulatory authorities and research ethics committees in the U.S. and in each of the countries where the study will be conducted. The study investigators will review safety including side effects regularly. In addition, a Clinical Management Committee will help principal investigators if unexpected safety concerns arise.

An independent (has no other involvement in the study) Data and Safety Monitoring Board (DSMB) will conduct reviews of participants' safety. A DSMB is composed of clinical research experts, statisticians, ethicists, and community representatives who meet periodically during a study to review safety and efficacy data as it is gathered. A statistician who is not part of the study team presents mid-study data to the DSMB. The DSMB will tell the study team if there are new safety concerns for study participants, if there is a sign that the study is working, or if the study cannot answer one of the questions it was made to answer. If it is thought to be needed by the DSMB, the DSMB can advise that the study be ended early. Regular safety reports will also be given to regulatory and research ethics committees in each country to ensure participant safety.

In 2018, the HPTN 084 DSMB was asked to review the safety data emerging from a study of a similar drug called dolutegravir. HPTN 084 implemented additional safety measures at that time and additional data were released about dolutegravir in July of 2019.

In 2020, the HPTN 084 DSMB did not identify any safety concerns for cisgender women in HPTN 084 and recommended continuing the study as planned in order to accumulate enough data to answer the primary objective about the safety and efficacy of CAB LA among cisgender women.

12. What will happen to study participants who acquire HIV during the trial?

Study participants who acquire HIV during the study will stop receiving study drugs and will be referred to local medical providers for HIV care and treatment.

13. What HIV preventive care will study participants receive?

Study participants will be offered condoms, treatment for sexually transmitted infections (STIs), and HIV risk reduction counselling.

14. How will participants be supported to take their study medication?

Study participants will receive support from clinic staff at each visit. Staff will discuss with the study participant why it might be easy or difficult for them to take a pill every day and/or attend study visits.

15. When did HPTN 084 begin and when are results expected?

HPTN 084 began near the end of 2017. The study will last about four and a half years, with participants active in the study between one and a half and three and a half years. Results are expected in 2023.

16. Why were people talking about Dolutegravir?

Dolutegravir (DTG) is an anti-HIV treatment drug (ARV) that belongs to a group of drugs called integrase inhibitors. Integrase inhibitors prevent HIV from making copies of itself and can reduce the amount of HIV in the body. DTG comes in a pill form. Dolutegravir is only used for the treatment of HIV.

In 2018, information from a study in Botswana using DTG to treat HIV infection was released. The information showed an increase in a specific type of birth defect called a "neural tube defect" (NTD) in some babies born to mothers living with HIV while taking DTG for treatment before and during early pregnancy. The possible association between DTG and NTDs was concerning; data from more pregnancies was needed. Newer information from two large studies in Africa have shown the risks of NTDs to be much lower than what the initial information from the study in Botswana suggested in 2018.

The newer information prompted the World Health Organization (WHO) to update antiretroviral treatment (ART) recommendations in July of 2019. The WHO recommends DTG as the preferred HIV treatment option for all populations, including pregnant cisgender women and those of childbearing potential.

An NTD happens during the first four weeks of a pregnancy when the baby's spine or head do not form properly. NTDs are not common but they do occur; they usually happen when the mother has a specific vitamin deficiency (folate), has taken certain medications or there is a family history of NTDs. There is no cure for NTDs and babies who survive usually have lifelong health complications.

17. Is DTG being used in HPTN 084 (LIFE)?

No, DTG is not being used in HPTN 084 (LIFE). CAB is being used in HPTN 084. CAB and DTG are both integrase inhibitors. They are different drugs but work in a similar way. CAB is being evaluated for both HIV treatment (people living with HIV) and prevention (PrEP) of HIV, while DTG is only used for treatment of HIV.

18. What is HPTN 084 doing for participants who become pregnant in the study?

The updated recommendations from WHO regarding the use DTG will not change HPTN 084. HPTN 084 will continue with the additional safety measures that were implemented in 2018:

- Oral contraceptives are no longer permitted; participants in the study must be on an injectable contraceptive, implant or use an IUD/IUC
- Pregnancy prevention counseling efforts will be strengthened
- If a woman accidently becomes pregnant during HPTN 084 she will stop receiving study products, she will be offered TDF/FTC and referred for prenatal care including an ultrasound to look at the baby's head and spine.

19. What is Descovy®?

Descovy is a daily oral pill for PrEP that was recently approved by the U.S. Food and Drug Administration (FDA) for use among men who have sex with men and transgender women. Descovy is similar to TDF/FTC but uses a newer form of tenofovir (TDF) called tenofovir alefenamide (TAF) instead of TDF. The FDA approval is based on the DISCOVER study. This study was done in over 5,000 cisgender MSM and TGW in the U.S. and Europe. The results showed that Descovy was "non-inferior" to TDF/FTC in cisgender MSM and TGW. Non-inferior is a term that means Descovy prevented about as many HIV infections as TDF/FTC but was not worse than TDF/FTC at HIV prevention. In the U.S. Descovy may be used for HIV prevention by all methods except for vaginal sex.

20. Is Descovy® being used in HPTN 084?

No, Descovy for PrEP is not being used in HPTN 084. TDF/FTC for PrEP is being used in HPTN 084. Although Descovy is similar to TDF/FTC, there has not been a study to test how well Descovy prevents HIV infections for cisgender women who have vaginal sex. TDF/FTC is the only approved drug for PrEP for vaginal sex. For this reason, the protocol team does not plan to make changes to the trial design at this time.

21. What was the outcome of the May 2020 DSMB review for HPTN 083 and HPTN 084 (LIFE)?

HPTN 083

The DSMB reviewed HPTN 083 study data and recommended that the blinded part of the study be stopped early for successfully meeting its specified objectives. The study results showed that CAB LA, administered every eight weeks, lowered HIV incidence among cisgender men and TGW who have sex with men. A total of 50 incident HIV infections occurred in HPTN 083, with 12 incident infections in the CAB arm (incidence rate 0.38%) and 38 incident infections in the TDF/FTC arm (incidence rate 1.21%). These results demonstrate that CAB LA is highly effective in prevention of the acquisition of HIV among cisgender men and TGW. The study sponsor, the U.S. National Institute of Allergy and Infectious Diseases (NIAID), approved the decision to stop the blinded part of the study.

HPTN 084

The DSMB did not identify any safety concerns for cisgender women in HPTN 084 and recommended continuing the study as planned in order to accumulate enough data to answer the primary objective about the safety and efficacy of CAB LA among cisgender women.

22. What new information was presented at AIDS 2020?

After a more extensive analysis of the interim study data, the regimen containing CAB LA was found to be statistically superior to daily oral TDF/FTC for PrEP among the cisgender men and transgender women who have sex with men enrolled in HPTN 083. A total of 52 incident HIV infections occurred, with 13 incident infections in the CAB arm (incidence rate 0.41%) and 39 incident infections in the TDF/FTC arm (incidence rate 1.22%). The hazard ratio for the CAB versus TDF/FTC arms is 0.34 (95% CI 0.18-0.62), corresponding to a 66% reduction in incident HIV infections in study participants given CAB compared to TDF/FTC.

23. When the DSMB recommended stopping the trial, they noted that the study had crossed the stopping boundary for non-inferiority and was approaching the boundary for superiority. Why are the final findings now indicating that the regimen containing CAB-LA is superior to FTC/TDF?

The DSMB meeting on May 14, 2020 was the first formal efficacy review of data from HPTN 083. The criteria for stopping the trial early were specified to be extremely stringent, particularly at the first efficacy review, because the results would need to be strong enough to ensure HPTN 083 provided convincing evidence to support licensure of CAB LA for HIV prevention. During the May 14 meeting, the DSMB determined that the study had reached its objective – it exceeded the strength of evidence required to stop for non-inferiority at the first review.

Following the DSMB meeting, the HPTN evaluated the complete dataset using statistical methods that account for the fact that the study was stopped early based on the pre-specified interim monitoring plan. Based on this final analysis, the effect of CAB was determined to be HR=0.34 (adjusted 95% CI 18-0.62), which clearly excludes a HR of 1, meaning that CAB LA was superior to TDF/FTC (p=0.0005) for prevention of HIV acquisition. The final statistical analysis was independently reviewed by statistical experts in the field of interim monitoring of clinical trials. The pharmaceutical companies played no role in the final analysis of data, which was overseen by the study sponsor NIAID.

24. Were the medications in the studies deemed safe?

The DSMB found both CAB and TDF/FTC to be safe based on data at their review. There were no safety concerns raised by the DSMB with continuing the study. The safety of both CAB and TDF/FTC will continue to be evaluated.

25. What will happen to the participants in HPTN 083 now?

Study participants were informed of which active medication they were taking, and the study findings. Participants are being offered the opportunity to remain in the study, initially taking only the active study medication they were randomized to. Participants initially randomized to active TDF/FTC who wish to switch to CAB LA will be able to do so as soon as enough CAB LA is available for all study participants. Those who wish to continue taking daily oral TDF/FTC will be allowed to do so until the end of the originally planned blinded study (up to 3 years after enrollment). Participants who want to switch from CAB to TDF/FTC will be offered TDF/FTC for about a year after their last injection of CAB and will then be referred to locally available services.

26. Why did the DSMB recommend HPTN 084 (LIFE) continue without change?

HPTN 084 (LIFE) has not accrued enough data to determine if the study has met the primary objective. The DSMB recommended that the study continue and will continue planned reviews of study data.

The DSMB reported no safety concerns and affirmed the need to continue follow-up to ensure enough data is available to answer the study objectives. The HPTN 083 results provide important evidence that CAB LA can prevent HIV among cisgender men and TGW who have sex with men. It will be important to generate equivalent robust data among cisgender women to ensure licensure of an effective product.

27. Have plans been made to address study implementation issues that might be impacted by COVID-19?

Recognizing the challenges of COVID-19, the HPTN 084 (LIFE) study team has already developed plans to respond to the impact of the COVID-19 pandemic on study conduct. In addition, the protocol team presented their plans for handling the potential impact for COVID-19 disruption on their analysis plans. These plans have also been presented

to the FDA and will be part of an ongoing consultation with regulators on plans to protect the integrity of the HPTN 084 (LIFE) data during the COVID-19 pandemic. The DSMB will continue to monitor the trial closely during this period.

28. If CAB LA works to prevent HIV among MSM/TGW in HPTN 083, why are we unable take that result for cisgender women in HPTN 084 (LIFE)?

We do not know if CAB LA prevents HIV among cisgender women. The DSMB recommended the continuation of HPTN 084 (LIFE) and affirmed the importance of demonstrating the safety and efficacy of CAB LA among cisgender women. This is especially important given that the routes of HIV infection are different, and the drugs may behave differently among cisgender women vs cisgender men and TGW that we do not understand yet. Given that these are cisgender women of reproductive potential, it is also important to demonstrate safety in this population. The best way to learn that answer is to let HPTN 084 (LIFE) continue as planned, including regular planned DSMB reviews.

29. If CAB LA works to prevent HIV among cisgender men and TGW in HPTN 083, why are we continuing to ask cisgender women in Africa to take placebo products?

HPTN 084 (LIFE) compares two active products: TDF/FTC to CAB LA. The data from HPTN 083 provides strong evidence that CAB LA prevents HIV among cisgender men and TGW who have sex with men. In order to ensure an unbiased comparison between an oral pill and an injection among cisgender women, each product must have a matching placebo so that study staff and participants do not know whether they are taking CAB LA or TDF/FTC.

30. After HPTN 084 (LIFE) participants learn of the results in men, what happens if a woman in HPTN 084 (LIFE) does not want to take the medicines anymore because she's afraid she is getting a placebo injection?

It is the right of any participant to discontinue a clinical trial at any time for any reason. Every participant in HPTN 084 is receiving an active drug; no participants are only receiving a placebo. HPTN 084 (LIFE) was uniquely designed to compare the safety and efficacy of a long-acting injectable (CAB LA) vs a daily oral pill (TDF/FTC) among cisgender women. If participants begin to leave the trial, the trial may not be able to answer the safety and efficacy questions it was designed to answer. The HPTN 084 (LIFE) study team in conjunction with community advocates will continue to stress how important it is to stay in the trial so that they can help contribute to an answer for all cisgender women like them.

31. When will CAB LA be available for HIV PrEP?

It is too early to know when CAB LA may be available for the general public. The HPTN 084 (LIFE) study team remains committed to completing the study. After the study is completed, the regulatory approval process has several steps that need to occur first, including review and approval by the U.S. Food and Drug Administration and other regulatory agencies.

32. What are the next steps for HPTN 084 (LIFE)?

The safety and efficacy of CAB LA may not be the same in cisgender women as it is in cisgender men and TGW. HPTN 084 (LIFE) will continue to be a rigorously conducted study and collect data about the safety and efficacy of CAB LA in cisgender women under the careful review of the study team and the DSMB. Results from HPTN 083 will be shared with HPTN 084 (LIFE) study participants, investigators, and regulators involved in the study. It is of utmost importance that the efficacy and the safety of CAB LA in cisgender women be as well understood as it is for cisgender men and transgender women. Cisgender women deserve HIV prevention options that are safe, effective, and they feel comfortable using.

33. Where can I find more information?

More information on HPTN 084 can be found at www.hptn.org/research/studies/hptn084 and 084life.org.
More information about HPTN 083 can be found at www.hptn.org/research/studies/hptn083 and giveprepashot.org.