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# Advocates' Primer on Injectable Cabotegravir for PrEP

*Trials, Approvals, Rollout and More*

Results from two large-scale efficacy trials found that injectable cabotegravir (CAB-LA), given every two months, was effective as a form of pre-exposure prophylaxis (PrEP) in preventing HIV in gay men and other men who have sex with men, transgender women who have sex with men, and cisgender women. CAB-LA was developed by ViiV Healthcare and is currently used in HIV treatment. It was approved by the US Food and Drug Administration (FDA) as the first form of injectable PrEP in December 2021. This document focuses on CAB-LA for prevention, outlining what's known and what's next for this emerging biomedical HIV prevention strategy.

## TOP-LINE FINDINGS TO DATE

- In two trials, the HIV Prevention Trials Network 083 and 084 (HPTN 083 and HPTN 084), injections of CAB-LA every two months were safe and substantially lowered HIV risk.
- In both trials, some participants received TDF/FTC as daily oral PrEP instead of CAB-LA and they also had very low rates of new HIV infections.
- Both the oral and injectable PrEP strategies worked. HPTN 084 described CAB-LA as “superior” as a statistical term derived from the specific design of this trial.
- Of the 12 infections in HPTN 083 among those receiving CAB-LA injections, four were infected at the time of enrollment but HIV tests did not detect it.
- Among the very few cases of HIV in HPTN 083, the risk of integrase-inhibitor resistant HIV was greater among those who acquired HIV while receiving on time injections compared to those who became infected during the “tail”. Three participants acquired HIV after discontinuing injections, when the active drug was slowly diminishing in the body. This period is known as the “tail”. Drug resistant mutations were not seen among those three participants. Data on this question from HPTN 084 may not be available, given the small number of infections (four) in the CAB-LA arm of the study. The small number of infections in both studies mean more data will be needed to confirm findings and gain more knowledge about the risk of drug resistance during the tail.
- CAB-LA was approved as PrEP in the US by the FDA in December 2021. ViiV also filed applications in a number of additional countries, including those that hosted the HPTN studies, with decisions expected in 2022.
- The FDA says negative results from antigen or antibody tests should be confirmed with an RNA-based test, to ensure only uninfected people begin this drug regimen. This mitigates the risk of HIV positive people using PrEP and developing HIV that is resistant to the class of treatment drugs that include cabotegravir, known as integrase inhibitors.

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## TOP-LINE ADVOCACY MESSAGES

- **Both oral PrEP and CAB-LA were safe and effective in the trials.** Each has unique characteristics, and individuals may prefer a particular PrEP method for any number of reasons. Ensuring informed choice is key. Injectable CAB-LA for PrEP is another strategy to help reduce HIV risk. For some people it will be the right one; for others, daily oral PrEP, the Dapivirine Vaginal Ring or a non-ARV-based approach will be right. And some people may choose to switch among these methods.
- **The US FDA approval of CAB-LA is a crucial milestone, and the next steps are just as critical.** Approval must be accompanied by strategic and equitable rollout. Supporting access to all forms of PrEP (injection, pill, ring) and the full range of proven prevention options requires programs that are resourced, promoted and designed to reach those who need prevention most.
- **Adherence still matters—a lot.** For CAB-LA, people will need to “adhere” to clinic visits every two months. This is particularly complex for women who may be required to visit clinics regularly for both contraceptives and CAB-LA but on different timetables. For oral PrEP, multi-month dispensing could allow less-frequent visits. The most effective and “best” product is the one that people use correctly and consistently during their periods of risk.
- **“Superiority” is a statistical term used in clinical trial design and in analyzing results.** The term doesn’t reflect which method is best for an individual.
- **Robust testing programs will be essential.** The clinical trials show CAB for PrEP provides a dramatic reduction in overall HIV incidence and similarly reduces an individual’s likelihood of becoming infected. Limited data to date show that in people on CAB-LA HIV infections can happen, and that standard HIV tests may not detect these infections at the time that they occur. In addition, as data show, a small number of people enrolled in HPTN 083 with very early stage infections that were not detected by standard HIV tests. HIV strains that are resistant to integrase inhibitors may arise in these cases. While the numbers are very small in HPTN 083, these findings suggest that CAB-LA may need to be introduced in the context of robust and feasible HIV testing strategies. An approach to testing that minimizes the risk of undetected cases will be crucial. In addition, HIV programs must be prepared to offer treatment regimens not based on an integrase inhibitor.
- **Affordable pricing is critical.** ViiV, the product developer for CAB-LA, has not yet set a price for CAB-LA outside the US, and the initial price within the US health system is exorbitant at \$3,700 per dose, or approximately \$22,000 per year, which is just above the list price for branded oral PrEP (both Descovy and Truvada) in the US. A cost-effectiveness analysis presented at the 2021 Conference on Retroviruses and Opportunistic Infections (CROI) shows that the injection must be priced in the range of generic daily F/TDF (also known as TDF/FTC or Truvada) to be considered cost effective in comparison to oral PrEP. Generic manufacturers must also be supported with investments in manufacturing technology that enable production at scale. Advocates must demand pricing transparency and a commitment to investing in choice, not just the cheapest interventions.
- **Planning for expanded access to oral PrEP strategies must accelerate.** Oral PrEP works exceptionally well for many people but remains under-utilized. Innovation in the delivery of oral PrEP is underway. In the context of COVID-19 lockdowns and restrictions, some programs have adopted multi-month prescriptions for oral PrEP, community-based pickup, and telehealth for adherence support and self-testing, where feasible. These best practices should be made standard.
- **Choice matters.** Historically, HIV programs have been siloed. As the PrEP field has expanded beyond oral F/TDF to include oral F/TAF (also known as TAF/FTC or Descovy), the Dapivirine Vaginal Ring and CAB-LA, donors and governments should make investments to integrate and strengthen health systems. Provider training, improved supply chain, effective monitoring and evaluation are pillars that must be in place to support informed choice as an increasing array of new ARV-based prevention options become available.
- **No one can be left behind.** It’s vital to expand access to PrEP among diverse populations at risk of HIV. Data and research are needed on the needs, preferences and barriers to access for diverse populations, so individuals have real choices. Clear messages must address: how best to support effective use, side effects, long-term safety, the safety of overlapping use of different forms of PrEP, use in adolescents, use in pregnant and breastfeeding people, use in people who inject drugs (PWID) and other factors that transform these options into real choices.

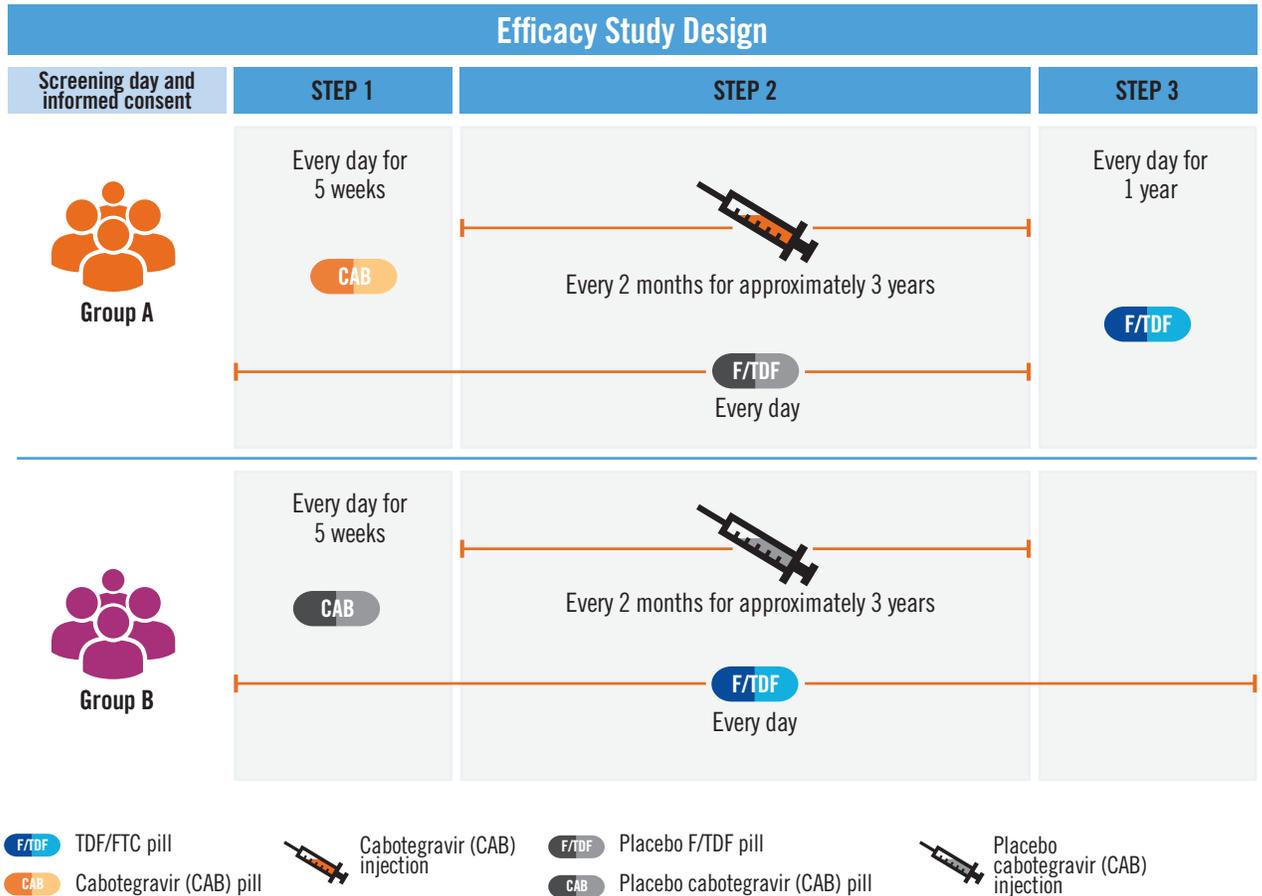
## What is CAB-LA?

Cabotegravir is an antiretroviral drug (ARV) developed by ViiV Healthcare and formulated as an injectable, administered every two months, for PrEP. It is an integrase inhibitor, the same class of drugs that includes the widely-used treatment drug dolutegravir.

Injectable cabotegravir is also used in treatment, in combination with injectable rilpivirine.

## What is the regulatory status of CAB-LA for PrEP, and ongoing advocacy for access?

On December 20, 2021, the US FDA approved cabotegravir (brand name Apretude) as PrEP for all people at risk in the US who weigh at least 35 kilograms (77 pounds). ViiV is also moving through the regulatory process for other countries, with a focus on places where the trials took place. The WHO is currently developing guidelines for CAB-LA. Additional regulatory guidance, approvals and a WHO recommendation are expected in the first half of 2022.



Participants were randomized to either CAB-LA (Group A) or oral F/TDF (Group B) study arms. In Step 1, Group A received an active tablet of cabotegravir (CAB) and placebo tablet of F/TDF for the first five weeks to establish that cabotegravir was safe and well-tolerated. In Step 2, Group A participants received an active CAB injection and continued the F/TDF placebo pill. Group B received a placebo CAB tablet and active F/TDF for the first five weeks. Any participant who stopped CAB injections, either due to personal choice or at the end of the three-year follow-up period, was offered oral F/TDF for a year.

AVAC and its partners have a range of ongoing engagements to ensure swift and ethical introduction of CAB-LA and other biomedical strategies moving through research, development and rollout. AVAC is working in coalition to ensure that donors and countries are advancing comprehensive and coordinated strategies for product introduction. Advocacy priorities to inform these strategies include: civil society involvement in the WHO's guideline development, transparent and affordable pricing, appropriate funding from PEPFAR and the Global Fund to Fight AIDS, Tuberculosis and Malaria (GFATM) and that the communities who need these strategies most are co-leading in all these efforts. As part of this work, AVAC leads the [Biomedical Prevention Implementation Collaborative \(BioPIC\)](#), convening key stakeholders to advance a common agenda for CAB-LA introduction, which will serve as a model for integrated, coordinated and expedited product introduction for this and future products.

### **When will CAB-LA be available, and what will it cost?**

The cost per dose of CAB-LA in the US is \$3,700, or \$22,000 annually, which is a substantial hurdle to broader rollout. [A cost-effectiveness analysis](#) presented at the 2021 Conference on Retroviruses and Opportunistic Infections shows that the injection must be priced in the range of generic daily F/TDF to be considered cost-effective in comparison to oral PrEP. The process for pricing should be transparent and the resulting price should support widespread use in PrEP programs in low- and lower-middle-income countries. The approach to this process should reflect a commitment to investing in choice, not just the least expensive interventions. AVAC, partners within the [CASPR](#) and [COMPASS](#) networks, current and former AVAC fellows, and other civil society allies are engaging with donors, national ministries of health and the WHO process for developing guidelines for CAB-LA to influence a host of issues related to how the product will be introduced, including price. AVAC, partners and allies are also working through the PEPFAR annual planning processes, and the strategy development process of GFATM and UNAIDS, to secure investments in prevention “platforms” that are equipped to deliver oral PrEP, injectable PrEP and the Dapivirine Vaginal Ring. This advocacy will also work to ensure transparent budget lines for each of these commodities and related program activities. Advocacy must also prioritize calls for strengthening health systems to better deliver and monitor the growing number of approved prevention options, each with their own unique benefits and challenges to individual users. These activities are ongoing, with the hope and expectation that CAB-LA and the Dapivirine Vaginal Ring could be available in multiple countries before the end of 2022.

### **How might countries, programs and individuals integrate a range of biomedical options, including oral PrEP, CAB-LA and the Dapivirine Vaginal Ring?**

Biomedical primary prevention is at a historic turning point, but only if countries and funders heed evidence-based demands that programs should emphasize choice rather than individual products.

Informed choice must guide policy and planning. It requires ambitious targets and funding for integrated contraceptive and HIV services. Informed choice will require effective testing programs and changes to overly-restrictive age-of-consent policies. And it will mean a commitment to gathering essential data now on user preferences. This data must be robust and inform future investments in a method mix for HIV prevention that truly reflects the values and desires of the communities and individuals that need prevention most.

Programs need the capacity to innovate, adapt and offer the full range of proven products. Countries, normative agencies, implementers and funders must work with civil society to meet these needs.

### **Where were the CAB-LA trials for prevention conducted and in what populations?**

Two large-scale efficacy trials, HPTN 083 and HPTN 084, are testing CAB-LA as PrEP. Smaller sub-studies are gathering additional data on the use of CAB-LA in adolescents, who were not included in the original studies. See the table below.

HPTN 083 enrolled 4,570 cisgender men who have sex with men (MSM) and transgender women at sites in the Americas, Asia and South Africa. Over 50 percent of trial participants in the US identify as Black, and 12 percent are transgender women.

Two-thirds of participants are 30 years old or younger. This study has been particularly effective at recruiting a younger and more diverse participant population. Similar efforts should be funded and prioritized across HIV prevention trials.

CAB-LA Trials At-A-Glance					
Trials	Design/Trial Questions	# of Participants	Population	Countries	Status
<b>HPTN 083</b> Started December 2016	Non-inferiority design; comparing once-daily oral TDF/FTC to bimonthly injectable cabotegravir	4,570	Cisgender gay men and other MSM; transgender women	Argentina, Brazil, Peru, South Africa, Thailand, US, Vietnam	Unblinded May 2020; follow-up through March 2022
<b>HPTN 084</b> Started November 2017	Superiority design; comparing once-daily oral TDF/FTC to bimonthly injectable cabotegravir	3,224	Cisgender women	Botswana, Eswatini, Kenya, Malawi, South Africa, Uganda, Zimbabwe	Unblinded November 2020; follow-up through May 2022

Ongoing Sub-studies	
<b>HPTN 083-01</b>	Single-arm, non-comparative study that evaluates the safety, tolerability and acceptability of CAB-LA among adolescent cisgender males and transgender females. Participants receive oral CAB for five weeks, followed by 29 weeks on CAB-LA, then quarterly visits for 48 weeks after the final injection.
<b>HPTN 083-02</b>	Evaluates potential barriers and other factors that support or inhibit adherence and clinic visits related to injectable PrEP: to learn about preferences and decision-making regarding the use of oral versus injectable PrEP and to gather explanatory qualitative data on participants' experiences in HPTN 083 to better interpret study results and guide next-generation prevention strategies.
<b>HPTN 084-01</b>	Single-arm, non-comparative study that evaluates the safety, tolerability and acceptability of CAB-LA among adolescent cisgender females. Participants receive oral CAB for five weeks, followed by 34 weeks on CAB-LA, then quarterly visits for 48 weeks after the final injection.
<b>IMPAACT 2026</b>	HPTN 084 participants who become pregnant during the study can co-enroll in a trial called IMPAACT 2026, which studies the pharmacokinetics and pharmacodynamics of antiretrovirals and anti-tuberculosis medications in women during and after pregnancy.

HPTN 084 enrolled nearly 3,200 cisgender women at sites in Botswana, Eswatini, Kenya, Malawi, South Africa, Uganda and Zimbabwe. Fifty-seven percent of participants are 18-25 years old, with an average age of 26. Fifty-five percent reported two or more partners in the past month, with 34 percent having a primary partner who is reported to be living with HIV or as having an unknown HIV status.

## What questions do HPTN 083 and 084 answer?

HPTN 083 and 084 were designed to evaluate two primary questions:

- How safe is CAB-LA delivered every two months (preceded by a month of oral cabotegravir) when compared to daily oral F/TDF?
- How effective is this method compared to daily oral F/TDF for HIV prevention?

HPTN 083 is a non-inferiority trial: a study that compares a new, experimental product (CAB-LA) and an approved product (oral PrEP with TDF/FTC) to determine whether the new product is just as safe and effective as—or “non-inferior” to—the approved product. As part of the trial design, statisticians and regulators set criteria for whether the experimental product is as good as or better than a proven strategy.

HPTN 084 is a superiority trial: a study that compares two products, asking whether the experimental product is safe and statistically more effective than an approved product.

There are additional sub-studies within HPTN 083 and 084 as well as a separate study in pregnant women that will allow researchers to gather additional information. See the table above.

## Results from HPTN 083 and 084

Trials	Total Infections	Infections in CAB-LA Arm	Infections in Oral F/TDF Arm	Hazard Ratio in CAB-LA vs. F/TDF arm
<b>HPTN 083</b>	52 Incidence 0.81%	12 Incidence 0.37%	39 Incidence 1.22%	0.31 (95% CI 0.16-0.58) 69% risk reduction
<b>HPTN 084</b>	39 Incidence 1%	3 Incidence 0.15%	36 Incidence 1.85%	0.10 (95% CI 0.04-0.27) 92% risk reduction

## Efficacy

### HPTN 083

On May 14, 2020, the study’s Data and Safety Monitoring Board (DSMB) met for a periodic evaluation of data on efficacy, participant safety, study progress and conduct. The results were trending strongly toward positive findings for safety and efficacy, and the DSMB recommended reporting the results, unblinding participants, discontinuing placebo products and offering participants the choice of either active product, CAB-LA or F/TDF, through the end of the study as soon as sufficient CAB-LA drug supply could be delivered to study sites. Advocates should monitor that this supply becomes available as soon as possible, with no unnecessary delays in access to CAB-LA for all trial participants who want it.

On August 12, 2021, the *New England Journal of Medicine* published the primary findings of HPTN 083. It reported 13 HIV infections in the CAB-LA arm (incidence rate 0.41 percent) and 39 in the F/TDF arm (incidence rate 1.22 percent). The trial team also reported on the hazard ratio, which is a comparison of the probability of an event, in this case HIV infection in one group (CAB-LA recipients) versus another group (people using daily oral F/TDF). The final calculation showed a hazard ratio of 0.34 (95 percent confidence interval of 0.18-0.62), which corresponds to a 66 percent reduction in incidence rates in study participants randomized to receive CAB-LA compared to F/TDF. This finding met the pre-specified criteria for concluding that CAB-LA was superior to daily oral PrEP in reducing HIV risk amongst the trial population.

On December 21, 2021, one day after the FDA approval of CAB-LA, the HPTN issued a press release with revised figures on the number of infections, incidence, hazard ratio and risk reduction, reflected in the table above. In guidance documents for prescribing, CAB-LA developer ViiV discusses an extended analysis of the infections in

HPTN 083, which revealed that one infection from the CAB-LA arm of the study existed but was undetected before the trial began. The revised calculations put the number of infections at 12 and the reduction in risk at 69 percent.

Among the 39 people who acquired HIV in the F/TDF arm of HPTN 083, 37 had levels of tenofovir diphosphate (a form F/TDF takes when it has been processed in the body) that were classified as suboptimal or non-adherent. The trial did not compare HIV infection rates in people adherent to daily oral PrEP compared with those receiving the injection. CAB-LA is “superior” to daily oral PrEP when people do not take PrEP pills correctly and consistently.

#### **HPTN 084**

On November 5, 2020, the study’s DSMB met for a periodic evaluation of data on efficacy, participant safety, study progress and conduct. The data showed that CAB-LA injected every two months was superior to daily F/TDF. The DSMB recommended that all trial participants be told which active drug (CAB-LA or F/TDF) they were receiving, that the placebos be dropped from the study and that participants be given the option to choose either product through the end of the study. HPTN has said that “participants taking active F/TDF who wish to use CAB-LA will be able to do so as soon as it is available.” Advocates should monitor that this supply becomes available as soon as possible, with no unnecessary delays in access to CAB-LA for all trial participants who want it.

In January 2021, trial leaders for HPTN 084 presented findings at the biennial conference, HIV Research for Prevention (R4P). These initial findings reported that 38 women acquired HIV during the trial, four in the CAB-LA study arm and 34 in the F/TDF arm. They calculated a hazard ratio for the CAB-LA versus F/TDF arms of 0.11 (95 percent confidence interval: 0.04-0.32), which corresponded to an 89 percent reduction in incidence among those who received active CAB-LA compared with those who received F/TDF. Further analysis, referred to in ViiV’s guidance documentation for prescribing, identified one infection from the CAB-LA arm that had existed, undetected, before the study began. In December 2021, the HPTN made reference to another two infections identified in the F/TDF arm of the study in a press release following FDA approval of CAB-LA. As with the 083 trial, researchers have not investigated whether the action of CAB-LA as a drug is more effective than daily oral PrEP, and differences in infection rate may reflect differences in product use and adherence.

## **Safety**

#### **HPTN 083**

CAB-LA and oral F/TDF were both safe and well-tolerated in HPTN 083. Injection-site reactions, raised body temperature, fever, swollen nasal passages and elevated blood pressure were more common in participants in the CAB-LA arm. Reduced kidney function was the most common side effect in participants receiving oral F/TDF. The most commonly cited adverse event was injection-site reactions, with 80 percent of those in the CAB-LA arm reporting at least some injection-site reaction versus 30 percent of those who received the placebo injection. This discomfort led a small percentage of participants—about two percent of those receiving active CAB-LA—to stop injections and discontinue their participation in the study.

#### **HPTN 084**

CAB-LA and oral F/TDF were also both safe and well-tolerated in HPTN 084. Mild to moderate pain or tenderness at the injection site was more common among participants in the CAB-LA arm (32 percent) as compared with those receiving the placebo injection of CAB-LA (nine percent). There were no discontinuations due to injection-site reactions. Gastrointestinal disorders and nausea were more common in the F/TDF arm.

## Rates of other sexually transmitted infections

Participants in both arms of HPTN 083 and 084 had high rates of other sexually transmitted infections, including new diagnoses of syphilis, chlamydia and gonorrhea, during the course of the trial.

This is consistent with STI rates in the context of oral PrEP use both inside and outside of clinical trials. This finding reinforces the need for all PrEP strategies to be delivered in the context of comprehensive, integrated services that include counseling, basic healthcare, contraception and other sexual and reproductive health services and linkages to HIV treatment and care as needed.

## Role of adherence

Adherence to oral PrEP in the HPTN 083 study was reasonably good. A sub-study of 372 people randomly selected from the F/TDF study arm showed that 87 percent had detectable drug levels, and 75 percent had detectable drug levels consistent with daily dosing. Adherence data on those in the F/TDF study arm who acquired HIV during the trial are being analyzed and are not yet available. Adherence to CAB-LA is known, since participants received the injection at the study sites. Three of the 12 participants who became infected in the CAB-LA arm acquired HIV during the oral lead-in phase; analysis is ongoing to understand how drug levels and other factors affected HIV risk in this arm.

HPTN 084 also conducted a sub-study on adherence, evaluating 362 participants from the arm of the study receiving F/TDF. The trial has so far reported that drug levels suggest that the study population was more adherent to F/TDF than had been anticipated, conferring even higher protection against HIV for those taking F/TDF than was planned for in the trial design. Analysis is ongoing to understand drug levels of both cabotegravir and F/TDF among those who acquired HIV.

## What adherence support was provided in each trial?

Oral PrEP adherence in both HPTN 083 and 084 was higher than has been observed in many other trials and programs. Both trials employed a model that the study teams dubbed “best real-world adherence” to support consistent and correct oral PrEP use in the study. The model draws from in-country adherence tools and is designed to be practical for clinical trial sites globally. It featured an adherence module deployed at every visit, with enhanced resources for participants who met prespecified criteria for additional support or in cases where the participant or study team thought additional support would be beneficial. This level and type of support seemed to be quite effective—above and beyond the findings related to CAB-LA—and should be adapted to support oral PrEP programs.

## What is the CAB-LA “tail”, and how will it figure into potential regulatory approval and use of CAB-LA?

The tail refers to a time period after injections have stopped and a slowly diminishing amount of cabotegravir remains in the body of someone who received CAB-LA injections. The [WHO explains](#), “these small amounts of drug may not be enough to protect against HIV infection and could result in development of drug resistant HIV following exposure during this time. It is not yet understood if this long pharmacokinetic tail will have any significant effect on drug resistance.”

Data from HPTN 083, presented at CROI in 2021, showed that resistance can occur among people taking CAB-LA but not necessarily during the tail. Among the three people who acquired HIV during the tail period, none had HIV

with genetic mutations that make it resistant to integrase inhibitors, the class of drug that includes cabotegravir. This number is too small to support conclusions about the risk of resistance, but in this handful of people, resistance didn't emerge during the tail.

When integrase inhibitor resistance did emerge in HPTN 083 participants, it was among those who acquired HIV while receiving injections on schedule. One of the people who had HIV at the time of enrollment developed resistance, as did two people who acquired HIV during the oral lead-in phase (a trial period in which individuals took the pill form of cabotegravir before receiving the injection, to ensure that the drug was well-tolerated). Two people who acquired HIV while receiving CAB-LA injections also developed integrase inhibitor resistance; two others had so little virus in their blood that the team could not get a resistance test. The take-home message—at least in the very few cases from HPTN 083—is that the risk of resistance is greater among those who acquire HIV while taking CAB-LA. There's no evidence of that risk during the tail, but the number of cases is too small to be conclusive.

For use in the US, the FDA approval requires a negative result from an FDA-approved HIV test before someone starts CAB-LA. If that negative result comes from an antigen or antibody test, it must be confirmed using an RNA-based test, which can detect HIV infection earlier than an antigen or antibody test. Early detection of infection ensures people with HIV don't continue on PrEP, which is essentially suboptimal treatment. In addition, early detection mitigates the risk of someone developing HIV that is resistant to integrase inhibitors. The FDA allows individuals to begin using CAB-LA before the RNA-based results are available. WHO testing requirements may be different. Robust yet feasible testing and screening strategies to minimize the risk of resistance will be crucial.

Part of the regulatory process will entail outlining and investing in plans and systems to monitor adverse effects and resistance (i.e., post-marketing surveillance). Advocates must demand transparency and interrogate ViiV's pharmacovigilance plans.

## **Why is the oral lead-in optional in the HPTN 083 and 084 open-label extension trials?**

Because an injection can't be removed from the body once it's administered, both HPTN 083 and 084 began with a short-acting pill of the drug that would be easy to stop taking if participants experienced a reaction. Once participants had taken the pill for about one month without adverse reactions, they switched to the injection. There were no major reactions in participants during the oral lead-in during the trials.

The final word on safety usually involves more people treated over a greater length of time than exists yet for either oral or injectable cabotegravir, and some investigators, providers or participants may not be comfortable skipping the oral lead-in. Making the oral lead-in an option is the next safe, logical step. Whether an oral lead-in will be required, recommended as an option, or eliminated by regulators, WHO or national guidelines remains to be seen. The FDA says an oral lead-in may be prescribed for approximately one month to assess tolerability.

## **CAB-LA, pregnancy and breastfeeding**

More research is needed to understand CAB-LA and the tail for women and people who are pregnant or breastfeeding. A number of participants in HPTN 084 became pregnant during the study. While no negative impacts on the health of the mothers or babies were reported, the study was not designed to answer questions about pregnancy and health. Because this trial was not large enough to detect any rare adverse events, ongoing research will be needed to determine whether CAB-LA is safe for people who are pregnant or breastfeeding. More information may come through the open-label extension studies, and any ultimate licensure for CAB-LA should include guidance for people who are pregnant or breastfeeding.

## What do HPTN 083 and HPTN 084 data mean for the standard of prevention in HIV prevention trials?

In the 2021 *Ethical Considerations in HIV Prevention Trials*, WHO and UNAIDS state that, “When new HIV prevention methods are scientifically validated and recommended by WHO, they should be added to the standard of prevention as soon as is practically possible based on consultation among relevant stakeholders, including community stakeholders.”

In February 2020, the HPTN also updated *Ethics Guidance for HIV Prevention Research*, which now states that products recommended by WHO may not be feasible to include in the standard of prevention, for example if PrEP is integrated in the design of a study arm.

HPTN guidance calls for a standard of prevention that is “pragmatic and context-specific but also aspirational.”

As WHO considers its recommendations for CAB-LA, the field must resolve how to integrate CAB-LA (as well as the Dapivirine Vaginal Ring) into trials’ standard of prevention, the package of interventions every participant in HIV prevention trials receives to help reduce their risk of HIV. Activists and advocates will, as always, need to guide decisions.

## Does either trial provide insight into how a CAB-LA-based PrEP strategy compares to F/TAF?

In October 2019, the US FDA approved a second oral PrEP drug, known as F/TAF, TAF/FTC or Descovy. This second tenofovir-based oral PrEP strategy is currently approved for daily PrEP in the US for people at risk of HIV but excludes use by those who are at risk of HIV through vaginal sex. Because HPTN 083 and 084 compared CAB-LA to oral F/TDF only, the data cannot tell us anything definitive about how CAB-LA might compare to oral PrEP with F/TAF.

## What is, or should be, happening now?

- AVAC’s advocacy team and partners, including COMPASS, CASPR, AVAC Fellows and others, are working with cisgender African women and allies to 1) hold ViiV accountable for comprehensive, ongoing community engagement; 2) ensure that PEPFAR, GFATM and UNAIDS strategies and 2022 plans include investments in the policies and programs needed to support comprehensive prevention and 3) advance an agenda that ties CAB-LA to contraceptive and sexual and reproductive health and rights programs and to the activism and priorities of LGBTQ+ and other key populations.
- The Biomedical Prevention Implementation Collaborative (BioPIC) is coordinating planning for well-designed, well-timed and well-funded product introduction. The BioPIC is supporting global and country decision-makers in this effort. Funded by the Bill & Melinda Gates Foundation, the BioPIC strategy prioritizes: strengthening health systems to deliver CAB-LA; supporting community and individual access to CAB-LA; scoping the cost of the product and programs to deliver CAB-LA and which funders might support this. The BioPIC is also adapting this approach to other HIV biomedical prevention products in development.
- WHO and UNAIDS, both of which are participating in the BioPIC, must work together to lead the development of clear messages, normative guidance and plans to scale up PrEP programs, expand access and emphasize the need for informed choice.

## WHAT CAN ADVOCATES DO NOW?

- **Talk to your community.** What do the results and FDA approval mean for your community? Understanding specific questions and concerns will help frame advocacy priorities. Help communities understand the results of HPTN 083 and 084, the potential role of injectable PrEP that is delivered every eight weeks, the regulatory process and the importance of scaling up oral PrEP in the meantime.
- **Demand funding, targets and innovation to support prevention programs that translate options into real choices.** This includes designing programs with the communities that need prevention most and gathering robust data on user preferences.
- **Call for program innovation and equitable access to the proven options that exist today.** The best understood, already proven strategy, oral PrEP, is still not available to all who need it. Multi-month prescriptions, self-testing and user-centered services are essential.
- **Hold decision-makers on CAB-LA accountable.** Is there clarity about next steps? Are there targets and milestones in place? Is there adequate funding to support rollout? How might decisions be made about who would get the product first, if it's licensed and introduced through phased rollout?
- **Work locally with research sites.** Bring your advocacy know-how to sites where research is planned or ongoing to ensure that communication, access and continued work reflect your needs and priorities.

## RESOURCES

- [Resource page on HPTN 083 trial and results](#), HPTN.
- [Resource page on HPTN 084 trial and results](#), HPTN.
- [HPTN 083 Final Results: Pre-exposure prophylaxis containing long-acting injectable cabotegravir is safe and highly effective for cisgender men and transgender women who have sex with men](#), HPTN presentation at AIDS 2020, 8 July 2020.
- [CAB-LA is a Highly Effective HIV Prevention Option; Now what?](#), *Px Pulse* podcast, December 2020.
- [A Conversation about Long-Acting PrEP for Cisgender Women](#), featuring HPTN 084 Study Chair Sinead Delany-Moretlwe and CAB Member Awelani Neluonde, July 2020.
- [A Conversation about Long-Acting PrEP for MSM & Transgender Women](#), featuring HPTN 083 Study Chair Raphael Landovitz and AVAC's Jessica Salzwedel, July 2020.
- [Biomedical Prevention Implementation Collaborative \(BioPIC\)](#), funded by the Bill & Melinda Gates Foundation as part of the AVAC and CHAI HIV Prevention Market Manager project, designed to close the gap between research and rollout for CAB-LA and future products.
- [Testing Long-Acting PrEP, Easier Said Than Done](#), featuring researcher and statistician Deborah Donnell describing the two different design approaches to the trials testing long-acting cabotegravir, *Px Pulse* podcast, October 2017.
- [An Advocate's Guide to Research Terms in the Post-Placebo Era](#), offering a guide to trial designs, a summary of long-acting PrEP trials, a lexicon of key terms for the "post-placebo era" and a handy illustration to help explain "double-dummy double-blind", *Px Wire*, AVAC, April-June 2017.



AVAC is a non-profit organization that uses education, policy analysis, advocacy and a network of global collaborations to accelerate the ethical development and global delivery of new HIV prevention options as part of a comprehensive response to the pandemic. For more information, visit [www.avac.org](http://www.avac.org).