In May and July 2020, the world learned new data from HPTN 083, a study of long-acting injectable cabotegravir (CAB-LA) for HIV prevention. This update summarizes the findings, unanswered questions and next steps.

### Top-Line Findings to Date

- A trial called HPTN 083 that tested a PrEP strategy of one month of daily oral cabotegravir (CAB), followed by injections every two months of CAB-LA, was found to be safe and effective in preventing HIV in cisgender men who have sex with men (MSM) and transgender women. The HPTN 084 study of CAB-LA among cisgender women is ongoing.
- Participants in both study arms—those who received CAB-LA and those who received daily oral TDF/FTC—had low rates of HIV infection compared to the trial’s estimates of incidence in these populations in the absence of PrEP use.
- Rates of HIV infection were significantly lower in participants who received CAB-LA compared to those who received daily oral TDF/FTC. The difference in infection rates support the conclusion that CAB-LA is “superior” to oral TDF/FTC in terms of HIV risk reduction.
- Importantly, data on individual adherence to daily oral PrEP among participants who acquired HIV are not yet available. The study has not determined whether CAB-LA is inherently more effective than daily oral PrEP, or whether the difference in infection rates between arms has to do with product use, and potentially low adherence, in people taking daily oral PrEP.
- The trial is seeking to learn more about factors that impacted HIV acquisition in participants in the CAB-LA arm: three of whom acquired HIV during the oral lead-in phase; five despite continuous, on-time CAB injections; and five in participants who had a prolonged hiatus from CAB.

### Top-Line Advocacy Messages and Questions

- **Adherence still matters—a lot.** HPTN 083 can’t tell (yet) whether differences between product are inherent to the products, or the way that people used them.
- **“Superiority” is a statistical term used in the context of clinical trial design and results analysis.** The term doesn’t reflect which method might work best in different peoples’ lives.
- Each of the two PrEP methods were safe and effective in the study, and each method has unique characteristics. Informed choice is key.
- **Access planning must now accelerate and expand the availability of all PrEP strategies with multi-month prescriptions and self-testing where feasible for oral PrEP, to support and expand continued use in COVID-19 contexts.** Introduction of daily oral PrEP was slow on many levels—now is the time to pick up the pace and close access gaps for all PrEP options.
- As the PrEP field expands beyond oral TDF/FTC to include oral TAF/FTC, the dapivirine vaginal ring and CAB-LA, it is essential to provide clear messages supporting daily oral TDF/FTC as a highly effective, available and urgently needed option. Oral TDF/FTC is currently the only PrEP option widely approved and well understood in terms of the relationship between blood drug levels and infection, requirements for safe initiation and discontinuation, side effects, long-term safety, use in people who inject drugs (PWID) and more.
- **No one can be left behind.** With data gaps re: daily oral TAF/FTC for cisgender women, and an ongoing trial in cisgender women for CAB-LA, it will be essential to map PrEP access and messages for all people at risk, including women in all their diversities as well as key populations.
### What is CAB-LA?

Cabotegravir is an antiretroviral developed by ViiV Healthcare and formulated as an injectable for long-lasting pre-exposure prophylaxis (PrEP). It is an integrase inhibitor, the same class of drugs that includes the widely-used ARV dolutegravir. Injectable cabotegravir in combination with injectable rilpivirine has been developed as a treatment option to maintain virologic suppression in people who first were able to suppress virus levels on oral antiretrovirals. It has been approved for treatment use in Canada and is currently under regulatory review with the US Food and Drug Administration. This document focuses on CAB-LA as PrEP.

### Where are the CAB-LA trials for prevention happening, and in what populations?

There are two large-scale efficacy trials testing CAB-LA—HPTN 083 and HPTN 084—as well as smaller sub-studies that gather additional data from adolescents, who were not included in the original studies. See table below.

HPTN 083 is ongoing in 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. Recruiting a younger and more diverse participant population—a specific goal of the study team—is to be applauded. Similar efforts can and must be funded and prioritized across HIV prevention trials.

HPTN 084 is ongoing with nearly 3,200 cisgender women at sites in Botswana, Eswatini, Kenya, Malawi, South Africa, Uganda and Zimbabwe.

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<thead>
<tr>
<th>Ongoing CAB-LA Trials At-A-Glance</th>
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<tr>
<th>Trials</th>
<th>Design/Trial Questions</th>
<th># of Participants</th>
<th>Population</th>
<th>Countries</th>
<th>Status</th>
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<tbody>
<tr>
<td>HPTN 083</td>
<td>Non-inferiority design; comparing once-daily oral TDF/FTC to bimonthly injectable cabotegravir</td>
<td>4,570</td>
<td>Cisgender gay men and other men who have sex with men (MSM); transgender women</td>
<td>Argentina, Brazil, Peru, South Africa, Thailand, US, Vietnam</td>
<td>Unblinded May 2020 following an interim review by the independent DSMB; ongoing.</td>
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<td>Started December 2016</td>
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<tr>
<td>HPTN 084</td>
<td>Superiority design; comparing once-daily oral TDF/FTC to bimonthly injectable cabotegravir</td>
<td>3,200</td>
<td>Cisgender women</td>
<td>Botswana, Eswatini, Kenya, Malawi, South Africa, Uganda, Zimbabwe</td>
<td>95 percent enrolled, with the next DSMB review expected in November 2020; ongoing.</td>
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<td>Started November 2017</td>
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<th>Ongoing Substudies</th>
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<tr>
<th>Trials</th>
<th>Description</th>
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<tr>
<td>HPTN 083-01</td>
<td>Single-arm, non-comparative study that evaluates the safety, tolerability and acceptability of CAB-LA among adolescent males and transgender women. Participants receive oral CAB for 5 weeks, followed by 29 weeks on CAB-LA, then quarterly visits for 48 weeks after final injection. Total study duration per participant will be approximately 21 months.</td>
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<td>HPTN 083-02</td>
<td>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.</td>
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<tr>
<td>HPTN 084-01</td>
<td>Single-arm, non-comparative study that evaluates the safety, tolerability and acceptability of CAB-LA among adolescent females. Participants receive oral CAB for 5 weeks, followed by 34 weeks on CAB-LA, then quarterly visits for 48 weeks after final injection. Total study duration per participant will be approximately 21 months.</td>
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<tr>
<td>HPTN 084-02</td>
<td>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.</td>
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<tr>
<td>HPTN 084-03</td>
<td>Assessment of drug-drug interactions between CAB-LA and contraceptives.</td>
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<td>IMPAACT 2026</td>
<td>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 living with HIV during and after pregnancy.</td>
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Efficacy Study Design

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<thead>
<tr>
<th>Screening day and informed consent</th>
<th>STEP 1</th>
<th>STEP 2</th>
<th>STEP 3</th>
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<tbody>
<tr>
<td></td>
<td>Every day for 5 weeks</td>
<td>Every 2 months for approximately 3 years</td>
<td>Every day for 1 year</td>
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<tr>
<td><strong>Group A</strong></td>
<td>CAB</td>
<td>TDF/FTC</td>
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<tr>
<td><strong>Group B</strong></td>
<td>CAB</td>
<td>TDF/FTC</td>
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Participants are randomized to either CAB-LA (Group A) or oral TDF/FTC (Group B) study arms. In Step 1 Group A receives an active CAB tablet and placebo TDF/FTC tablet for the first 5 weeks. If the CAB tablet is safe and well-tolerated, participants continue to Step 2 where they receive an active CAB injection and continue the TDF/FTC placebo pill. Group B receives a placebo CAB tablet and active TDF/FTC for the first five weeks. In Step 2, participants receive placebo injections and active TDF/FTC. Any participant who stops CAB injections, either due to personal choice or when done with the three-year follow-up, is offered oral TDF/FTC for a year.

What questions is HPTN 083 designed to answer?

HPTN 083 was designed as a non-inferiority study evaluating two primary questions:

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

A non-inferiority trial is designed to compare two products, asking if the experimental product is just as safe and effective as an approved product. As part of the trial design, statisticians and regulators set criteria for whether the experimental product is not worse than (not inferior to) or better than (superior to) a proven strategy.
What data have been shared from HPTN 083 to date?

**Efficacy**

On May 14, 2020, the HPTN 083 trial’s Data and Safety Monitoring Board (DSMB) met to evaluate data on participant safety, study conduct and progress, and efficacy. Each time a DSMB meets, it makes a recommendation to the study team to either continue per protocol, modify or terminate a study.

After reviewing the data, the DSMB recommended that all HPTN 083 trial participants be told which active drug (CAB-LA or TDF/FTC) they were receiving, that the placebo products be dropped from the study, and to give participants the option to choose either product through the end of the study, as soon as sufficient CAB-LA drug supply is delivered to study sites.

On July 7, 2020, at the AIDS 2020 conference, the HPTN 083 trial team presented a more extensive analysis of the interim study data. A total of 52 participants have HIV infections to date, 13 participants acquired HIV in the CAB-LA arm (incidence rate 0.41%) and 39 participants acquired HIV in the TDF/FTC arm (incidence rate 1.22%). The hazard ratio for the CAB-LA versus TDF/FTC arms is 0.34 (95% CI 0.18-0.62), corresponding to a 66 percent reduction in incident HIV infections in study participants randomized to receive CAB-LA compared to TDF/FTC. This finding met pre-specified criteria for concluding that CAB-LA was superior to daily oral PrEP in reducing HIV risk amongst the trial populations. Importantly, data on adherence to daily oral PrEP among participants who acquired HIV are not yet available. The study has not determined whether CAB-LA is inherently more effective than daily oral PrEP, or whether the differences in infection rates between arms has to do with product use, and potentially low adherence, in people taking daily oral PrEP.

**Safety**

CAB-LA and oral TDF/FTC were both safe and well-tolerated. Injection-site reactions, raised body temperature, fever, nasopharyngitis 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 TDF/FTC. 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 to discontinue—about 2 percent of those receiving active CAB-LA stopped injections.

**Rates of other sexually transmitted infections**

Participants in both arms of HPTN 083 had high rates of other sexually transmitted infections, including newly-diagnosed syphilis, chlamydia and gonorrhea during the course of the trial. This is consistent with STI rates seen in the context of oral PrEP use in trials as well as outside of a clinical trial context. This finding reinforces the need for all PrEP strategies to be delivered in the context of comprehensive, integrated packages of services including counseling, basic healthcare, contraception and sexual and reproductive health services, and linkages to HIV treatment and care as needed.

**Role of adherence**

A substudy of 400 people randomly-selected from the TDF/FTC 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 TDF/FTC arm who acquired HIV during the trial are not yet available; they are currently being analyzed. Three of the thirteen participants 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. Adherence to CAB-LA is known, since participants received the injection at the study sites.
What is, or should be, happening now?

- ViV has confirmed that they are beginning the process of compiling information for US FDA regulatory review for a prevention indication, and they have stated their preference to have data from both HPTN 083 and 084 to apply for a broad label for use. The timing for a formal regulatory submission and whether this would or could happen before HPTN 084 results are available is not yet clear.

- AVAC’s advocacy team and partners, including COMPASS, CASPR, Advocacy Fellows and others, are working to develop priorities, scenarios, questions and a common advocacy agenda. Community input on how PrEP products are described, considered for licensure and introduction, programmed, purchased and situated in national primary prevention efforts will be an important focus of this agenda.

- The Biomedical Prevention Implementation Collaborative (BioPIC) is advancing planning for well-designed, well-timed, and well-funded product introduction, and supporting global and country decision-makers in this effort. Funded by the Bill & Melinda Gates Foundation as part of the AVAC and CHAI HIV Prevention Market Manager project, BioPIC is spearheading an overall introduction strategy. Central to this strategy will be an operational research agenda, to find out how health systems can be strengthened to deliver CAB-LA, should it be approved for use; to establish how best to support community and individual access to and demand for CAB-LA; and to learn what the product and the programs to deliver it might cost, and which funders might support this. BioPIC is also exploring how this approach can be adapted to jumpstart planning for other HIV biomedical prevention products in development.

- WHO and UNAIDS, both of which are participating in BioPIC, must work together to lead development of clear messages, access plans and scale-up plans for PrEP programs, emphasizing the need for informed choice.

What about cisgender women and the HPTN 084 trial?

There are no efficacy data yet for CAB-LA in cisgender women—a trial in that population, HPTN 084, is ongoing. During the May 2020 DSMB meeting, the data from both HPTN 083 and HPTN 084 were reviewed. At the time, HPTN 083 had collected approximately 50 percent of its data, while HPTN 084 had about 25 percent of its data. (HPTN 084 started about a year later than 083, and was temporarily delayed due to safety issues with dolutegravir, a related drug.) The DSMB review in May saw no safety concerns in HPTN 084, and the DSMB recommended that it continue per protocol. The next DSMB review for HPTN 084 is scheduled for November 2020.

What is the difference between a non-inferiority and superiority trial and why the difference between HPTN 083 and HPTN 084 trials?

A non-inferiority trial has pre-specified criteria to determine whether one product is “not worse than” another. A superiority trial determines whether one product is more effective than another. One trial can seek to measure both non-inferiority and superiority.

HPTN 083 and HPTN 084 both have the same double-dummy double-blind design comparing oral TDF/FTC to CAB-LA (figure on p. 3). HPTN 084 was always planned to evaluate superiority—not because of 083. HPTN 084 data will be evaluated to see if the criteria for superiority were met; the trial also has pre-specified criteria for evaluating non-inferiority.
Cumulative data from previous clinical trials show that daily oral TDF/FTC is over 90 percent effective in MSM and transgender women, i.e., it’s very effective. When testing a new product against a very effective one, as is the case with HPTN 083, it can be very difficult to show that the new product is better. As a result, the statistical analysis for 083 was designed to look for non-inferiority—that CAB-LA is as good as or no worse than oral TDF/FTC. Given the high effectiveness of oral TDF/FTC in the HPTN 083 trial population, this “no worse than” result would be a strong one.

Discussions about the trial design of HPTN 084 involved extensive dialogue with women, allies, the clinical trial team, ethicists and regulatory authorities. One key issue was how to use prior trial data in cisgender women to set statistical “rules” for determining non-inferiority or superiority. Looking at then-available data from previous studies, some trial data showed oral PrEP to be highly effective among cisgender women, other data did not. It’s important to note that those data came from trials where women didn’t use the product consistently—so the measurement was of “effectiveness” (how the product works with imperfect use) versus “efficacy” (how the product works with correct, consistent use). Based on these discussions, HPTN 084 was designed to investigate if CAB-LA would result in superior efficacy to oral TDF/FTC in the study population of cisgender women.

What do HPTN 083 data mean for ongoing HIV prevention trials?

The WHO/UNAIDS *Ethical considerations in biomedical HIV prevention trials*, in its Guidance Point on standard of prevention states that, “New HIV-risk-reduction methods should be added, based on consultation among all research stakeholders including the community, as they are scientifically validated or as they are approved by relevant authorities.”

Previous HIV prevention trials have included newly proven HIV prevention options as part of the standard of prevention—the package of intervention every participant in HIV prevention trial receives to help reduce their risk of HIV—in some cases even before widely available, e.g., voluntary medical male circumcision (VMMC) and oral PrEP. In both cases, those interventions were already available for off-label use even before they were introduced in national programs. CAB-LA is still an investigational product and not available outside the context of a clinical trial. This will likely be the starting point for decisions about CAB-LA, and activists and advocates will, as always, need to guide decisions.

Does HPTN 083 provide insight into how a CAB-based PrEP strategy compares to TAF/FTC?

No. TAF/FTC (also known as F/TAF) is another tenofovir-based oral PrEP strategy, currently approved for daily PrEP in the US for people at risk of HIV, excluding those at risk via vaginal sex. The data from TDF/FTC and HPTN 083 can’t be extrapolated to a comparison with TAF/FTC.
Both HPTN 083 and HPTN 084 have an oral lead-in phase—will that be a requirement for CAB-LA use?

Long-acting injectables for some people is an alternative to daily pill-taking for HIV prevention. Given the investigational nature of the product, participants in the active CAB-LA arms took an oral form of cabotegravir for five weeks before receiving their first injection. This allowed researchers to look for any unexpected adverse events or reactions to the product before giving participants a long-acting injection.

The HPTN 083 trial team states that the oral lead-in will continue to be required for participants in HPTN 083 who now have the option to switch from oral to injectable PrEP—and vice versa. Whether an oral lead-in will be recommended by regulators remains to be seen. The trial team has said that, “The study will continue analyzing the safety data on the oral lead-in period from participants who switch from TDF/FTC to the regimen containing CAB-LA. At the time of the release of study results in July 2020, discussions are ongoing about the risks and benefits of an oral lead-in.”

What is “the tail”?

In HPTN 083 and 084, CAB-LA is given every two months. This dosing schedule is designed to maintain drug levels that protect against HIV infection. When injections are discontinued, the drug remains in the body, at declining levels, for some time. This “tail” of active but declining drug in the body may not be protective. If drug levels insufficient to protect against HIV linger, and an individual becomes infected, the risk of developing drug resistant HIV is a worry but the actual risk of resistance is not clear. HPTN 083 trial participants are given daily oral TDF/FTC to “cover the tail” for 48 weeks after they stop injections, if they consider themselves to be at risk.

Understanding the clinical relevance of the tail—what it means for resistance, drug-drug interactions, fertility, pregnancy and breastfeeding is essential. It will also be critical to understand the durability of self-assessments of risk—when a person stops injections and decides he or she does not need additional oral PrEP, does that align with their actual risk over the next 48 weeks in which the tail appears to persist. The data on the “tail phase” from HPTN 083 and 084 will begin to provide evidence to answer some of these questions; additional qualitative research will be critical, as will centralized registries to monitor and survey tail-phase experience. Ongoing surveillance of individuals discontinuing must continue if CAB-LA is approved and rolled out.

What if CAB-LA has different safety and efficacy data in HPTN 084 participants?

It is critical to test products in the people who will use them. The ongoing HPTN 084 trial will provide insights and information on how the product works in the lives and bodies of cisgender women. If there are differences in safety, efficacy or side effects, it will be essential to develop clear, consistent messages. With daily oral PrEP, different numbers of doses are needed to achieve protection in anal and vaginal sex. The latter requires a longer period of daily adherence to achieve protection. Public health messages must reflect these differences. If there are differences in the effects of CAB-LA, it will also be essential to learn from and integrate with contraceptive programming—promote and program all PrEP products, and never preselect or cut costs by emphasizing a single product. Choice is crucial.
WHAT CAN ADVOCATES DO NOW?

• **Talk to your community.** What do the results mean for them? Understanding specific questions and concerns will help frame advocacy priorities. Help communities understand the results of 083, the significance of CAB-LA as an experimental long-acting product that is currently only available in the context of a clinical trial, the regulatory process, the potential scenarios for HPTN 084, and the importance of scaling up oral PrEP programs in the meantime.

• **Demand funding, targets and innovation to support equitable oral PrEP access—with modifications for COVID-19 contexts.** The best-understood, proven strategy 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 for planned and ongoing research to ensure communication, access and continued work meet your needs.

RESOURCES

- Resource page on HPTN 083 trial design 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, July 8, 2020
- A Conversation About Long-Acting PrEP for Cisgender Women, featuring Sinead Delany-Moretiwe, HPTN 084 Study Chair and Awelani Neluonde, CAB Member, July 2020
- A Conversation About Long-Acting PrEP for MSM & Transgender Women, featuring Raphael Landovitz, HPTN 083 Study Chair and Jessica Salzwedel of AVAC, 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, BioPIC is designed to close the gap between research and rollout for CAB-LA and future products.
- Testing Long-Acting PrEP, Easier Said Than Done, Px Pulse podcast, October 2017, researcher and statistician Deborah Donnell describes the two different design approaches to the trials testing long-acting cabotegravir.
- Px Wire: A Quarterly Update on HIV Prevention Research, April–June 2017, AVAC, issue offers 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”.

ABOUT AVAC

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.