Px Wire A Quarterly Update on HIV Prevention Research | Vol. 10 No. 2 | April–June 2017 | AVAC Global Advocacy for HIV Prevention

AVAC's Take

New trials, new terms, new times

Talking about biomedical HIV research used to be as easy as . . . 1, 2, 3. A product started in a small Phase I safety trial, moved to a bigger Phase II trial for expanded safety, and then on to a Phase III efficacy trial to see if it actually worked. It was a tidy framework, and it worked well enough—for a while. But the real world is a messy, complicated place. And that's where prevention research happens. About a decade ago, the HIV prevention field started talking about Phase IIb trials, which aren't licensure trials but do provide "proof-of-concept"—a hint or indication that a candidate works.

Beginning in 2006, trials of new biomedical strategies started to show efficacy and the world got even more complicated—in a good way. The new strategies changed prevention programs and prevention research. Countries and communities are adapting and inventing new approaches to delivering these tools, like oral PrEP and voluntary medical male circumcision (VMMC). And the research field is grappling with how these new approaches impact HIV prevention trial design.

Adjustments must be made on (at least) two fronts. First, once something is introduced in a country (whether PrEP as a pilot program or VMMC as a national campaign), that strategy has to be considered for inclusion in the standard package of prevention services offered to every participant who joins a trial. What gets added when? The UNAIDS/WHO guidance document on ethical considerations in biomedical HIV prevention trials states that "New HIV risk-reduction methods should be added . . . as they are scientifically validated or as they are approved by relevant authorities." But that doesn't settle the question entirely. The wording allows the possibility that a tool could be added before local approval.

Second, some new strategies may be part of the design of the trial. When a strategy is included in the trial design and used as an active comparison to the experimental product, it's not a background option, but rather a key part of a trial designed to find out whether the experimental product is better or as good as the existing option. How does that work? This issue of *Px Wire*—including the centerspread—is your guide to the evolving world of HIV prevention trial design. —*AVAC*

Next-Generation PrEP Trials

The age of "active controls"

A medicine you get only every two months to reduce HIV risk sounds like a great deal for some people. This could be an option in the future, but only if two big efficacy trials of long-acting injectable cabotegravir (CAB-LA) find that one shot of this long-acting antiretroviral in the buttocks every eight weeks shields trial participants from HIV.

The first of two efficacy trials, HPTN 083, launched in December 2016. It tests injectable CAB-LA as PrEP among

At A Glance

Long-Acting Injectable PrEP Efficacy Trials (May 2017)

Trial	Product	Design	Funders	Size	Population	Status	Location
HPTN 083	Cabotegravir injection every two months	Double-dummy/ double-blind Phase IIb/III efficacy trial	NIAID, ViiV Healthcare, Bill & Melinda Gates Foundation	4,500	HIV-negative men and transgender women who have sex with men	Launched December 2016	40 sites in Argentina, Brazil, Peru, South Africa, Thailand, USA, Vietnam
HPTN 084				3,200	HIV-negative sexually active women	Potential start in second half of 2017	20 sites in seven countries in East and Southern Africa

Continues on back >

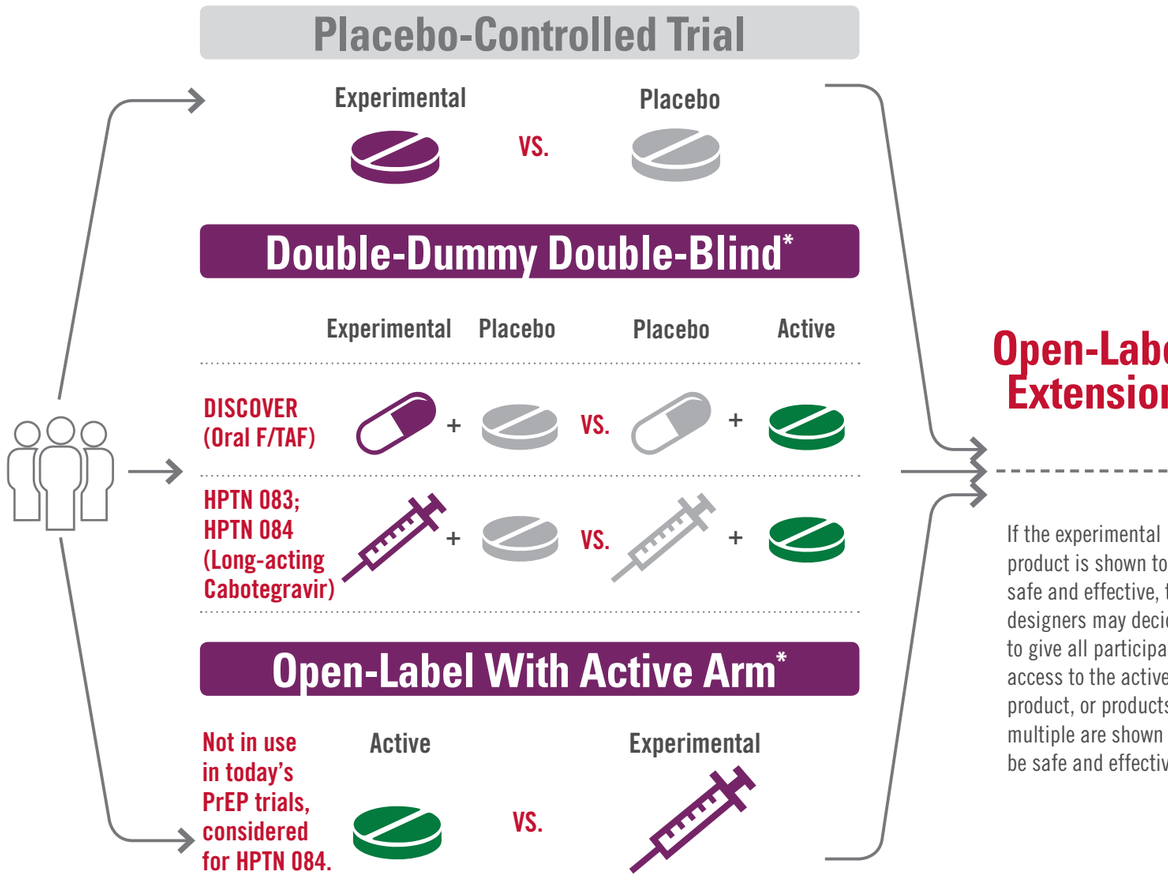
AVAC
Global Advocacy for HIV Prevention

An Advocate's Guide to Research Terms in the Post-Placebo Era

There are more biomedical strategies available for HIV prevention than ever before. Daily oral PrEP is rolling out in countries around the world. Voluntary medical male circumcision continues to be scaled up. And antiretroviral treatment (ART) for people living with HIV is available "on demand" in many countries. Effective ART is good for people's health and can help reduce the risk of passing on the virus.

At the same time, research is continuing. Today's ARV-based prevention tools require high levels of adherence (e.g., taking a pill every day). Additional tools like a vaccine or a long-acting form of PrEP would be important additions.

Today's trials have to test these new tools—and meet ethical standards by providing participants with the best available prevention package. This means something different now that PrEP is rolling out. This graphic and the accompanying lexicon showcase some of the new trial designs and terms used to talk about trial design.



All of these designs are randomized, meaning that participants are assigned to a study arm by chance. This protects against bias, whether the particpant knows what he or she is receiving or not.

Placebo · Experimental product · Safe and effective product · * Trials with active control arm

HIV Prevention Trial Lexicon

- **Active arm [of a trial]** is the group of participants receiving a proven or experimental strategy. There can be one or more active arms in a trial. There can be an "active control" arm (see below) or an "active experimental arm". The difference is whether the efficacy of the active strategy is known or not. Outcomes (like rates of HIV or rates of pregnancy) in people in the experimental active arm are compared to outcomes in people in the control arm.
- **Active control arm [of a trial]** is usually a group of trial participants who are receiving a known effective strategy or intervention that participants in the experimental arm are not receiving. For example, in trials of long-acting injectable PrEP, people in the active control arm are receiving daily oral PrEP, a known effective strategy.
- **Blinded trials** are ones in which the participants don't know what they are receiving. A **double-blinded** trial is one in which neither the participants nor the trial team know which participants are receiving the experimental product and which ones are receiving something else—either a placebo or another product. Blinding protects against bias. If participants or trial staff know who is getting the active experimental product they might act differently. Participants who know they got the experimental product might take more risks if they believe the experimental product provides protection; people who got the placebo might use more condoms.
- **Control arm [of a trial]** is the group of participants that are not receiving the experimental product or strategy. This group receives the same prevention package (see below) as the experimental arm.
    - **Double-dummy double-blind trials** are a way to compare two strategies that can't be made to look identical, without revealing who's receiving what. Imagine a trial seeking to compare an injection and a pill. They don't look alike, right? In a double-dummy double-blind trial design, all of the participants would get both a pill and an injection. One group of participants would get an active pill and a dummy injection; the others would get an active injection and a dummy pill. Neither the staff nor the participants would know who had which active strategy.
    - **Dummys** are the same thing as placebos. A dummy version of an experimental product looks exactly like that product (e.g., vaccine, injection, infusion, pill or ring) except that it doesn't have any active ingredient. Examples include a sugar pill or a saline injection or a ring without any drug inside it.
    - **Non-inferiority trials** are trials that are designed to show that a new method (Product A) works as well as a method that has previously been shown to work (Product B). If A doesn't meet or exceed B's effectiveness, it is considered inferior. This doesn't mean it isn't effective, just that it is not better than the existing product.
    - **Open-label [trial]** is a trial in which both participants and trial staff know who is receiving what. Trials of voluntary medical male circumcision were open-label in that trial staff and participants knew who had undergone the procedure immediately and who had been assigned to the delayed surgery arm.
    - **Open-label extension (OLE) trial** is a study that usually follows directly from an efficacy trial that showed the product was successful in reducing HIV risk. In OLEs, trial participants from both the active and placebo arm and, sometimes, members of their communities, get the chance to use the active product. Everyone knows what they are receiving and knows that the product worked in the efficacy trial.
- A trial's **prevention package** is the set of tools and services all participants receive, no matter which arm of the trial they are in. (In HIV prevention trials, all participants in both the control and active arms receive male and female condoms, counseling, HIV and STI testing and treatment and may receive other services like harm reduction, referrals for voluntary medical male circumcision, PrEP, etc.)
- **Superiority trials** are trials that are designed to show that a method (Product A) is more effective than placebo, or sometimes, to show that a new method (product A) is more effective than an already-existing method (Product B). A superiority trial is designed to find out whether Product A is more effective than placebo (or Product B) in enrolled participants, and the trial makes every effort to ensure the products are used correctly and consistently.

> *Continued from front*

men who have sex with men (MSM) and transgender women. A companion study among women—HPTN 084—is due to start later this year. Both of these trials have a design that's known as "double-dummy double-blind". Each is designed to compare CAB-LA to daily oral PrEP. HPTN 083 is a "non-inferiority trial" and HPTN 084 is a "superiority" trial. Do these terms sound familiar? They might not. (See the centerspread for a lexicon and illustrations.) The advent of daily oral PrEP as a WHO-recommended prevention strategy has propelled changes in trials of other prevention strategies.

Why? While the comparison isn't exact—and the history is controversial—consider research on prevention of vertical transmission of HIV. Once a lengthy regimen of AZT showed efficacy, another trial that sought to test a simpler strategy—single doses of nevirapine for the mother and newborn—came under intense scrutiny for a design that included a placebo arm, an arm with proven efficacy (the AZT regimen) and an arm with a regimen with unproven efficacy (short-course nevirapine). Many stakeholders felt that a placebo arm was unethical, and it was ultimately dropped. The trial did test an unproven and proven strategy head-to-head, even as some stakeholders also raised concerns about asking some women to use an unproven strategy when a proven one existed. The rationale was, in part, that less complex strategies were needed. The trial went on and ultimately found efficacy, providing an additional, valuable option for prevention of vertical transmission, as well as lessons about the difficulties of post-placebo trial design.

Similar issues are in play with PrEP today. Daily oral PrEP is effective when taken correctly and consistently. But additional options are needed, such as an injection. Both oral and injectable PrEP are designed to be used on their own. So a trial with "background" oral PrEP given to all participants isn't a great option, as injectable-oral PrEP combos are not in the works.

HPTN 084, the planned trial of CAB-LA in African women, is an example of the complexities of trials in the post-placebo era. It was originally designed as an open-label study (see centerfold). In this design, some women would have been randomly assigned to receive daily oral PrEP, others to receive the injection. With this design, researchers hoped that women randomized to receive oral PrEP would use it more consistently than women did in some of the PrEP efficacy trials. In some of those trials, women's adherence was quite low, perhaps because they did not know whether they were receiving an active product, or whether that product worked. (However, there is now evidence from PrEP projects that women can and will take daily oral PrEP consistently.) Each group would have known what they were receiving and been counseled accordingly.

Regulatory authorities raised concerns about the open-label design and the possibility that it would introduce bias into the research. When participants aren't blinded and know what they are receiving, they may change their behaviors in ways that impact the validity of the results (e.g., if women receiving oral PrEP who understood that it was a proven tool increased their risk behaviors or women receiving the experimental injection increased condom usage). In both open-label and blinded trials, people are assigned to study arms by chance. The difference is that in blinded trials participants don't find out what they are receiving. The argument for this design is that it offers a more fair comparison of two options versus unblinded trials.

Regulators' concerns were discussed within the scientific community and in a community consultation that AVAC helped to organize with the HPTN 084 trial team. There was rich discussion in these meetings about the trial design. Ultimately, the HPTN 084 design changed to the double-dummy double-blind design (same as HPTN 083). The DISCOVER trial of a different drug being tested for oral PrEP, F/TAF, is also using this design. Time will tell whether future trials of PrEP strategies can utilize such a design.

It's complex territory, and AVAC will continue to work with our partners in research and civil society to ensure that the trial designs are ethical, the goals well understood, and the outcomes on track to achieve the ultimate goal—a sustained end to epidemic levels of new HIV infections worldwide.

About AVAC

AVAC works to accelerate the development and global delivery of HIV prevention tools. To receive regular updates via email sign up at *www.avac.org/signup.*

423 West 127th St., 4th Floor • New York, NY 10027 USA
Telephone +1 212 796 6423 • *www.avac.org*