When Can We Expect PrEP 2.0?

What does the future hold for new pre-exposure prophylaxis (PrEP) against HIV, including long-acting injectables and less toxic drugs?

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After a decidedly slow start, the use of Truvada (tenofovir/emtricitabine) as pre-exposure prophylaxis (PrEP) to prevent HIV is on a roll among men who have sex with men (MSM) in the United States.

Data from Gilead Sciences, which manufactures Truvada, suggest that U.S. PrEP prescriptions more than tripled between 2014 and 2015, with MSM the apparent primary adopters of an HIV prevention method that the U.S. Food and Drug Administration (FDA) approved in July 2012. New York State Medicaid data have indicated a more than four-fold upswing in PrEP prescriptions during that period, from 303 to 1,330. And a study that surveyed MSM attendants of the Seattle Pride Parade found that the proportion of those at high risk for HIV who reported ever taking PrEP increased from 5 percent in 2012 to 31 percent in 2015, with 23 percent of the overall group currently on Truvada.

A very rough, and likely low-ball, estimate suggests that about 22,000 Americans were on PrEP at the beginning of 2015, including perhaps 4,000 in San Francisco.

The open-label extension of the global iPrEx study, published in July 2014, estimated that taking four to seven tablets of Truvada per week (PrEP is intended for daily use) offers maximum percent protection against HIV among MSM; this likely means lowering HIV risk by more than 99 percent. In fact, in all of the studies of PrEP among MSM, no one contracted the virus who was apparently taking Truvada at least four times a week.

How well MSM will adhere to the daily Truvada regimen in the real world, and thus how well PrEP will reduce transmission on a wide scale, remains an open question. On average, adherence was quite poor in the initial iPrEx study, published in 2010, and in its open-label extension, or OLE. (However, the American participants in iPrEx OLE did apparently adhere well.)

More recent research casts a hopeful light on the adherence front, suggesting that PrEP may have considerable power to reverse the rising HIV incidence rate seen in recent years among American MSM. The PROUD study, in which MSM received PrEP prescriptions from English sexual health clinics, found that Truvada lowered the group's HIV rate by 86 percent. The high population-level

effectiveness of PrEP in this study implies that these very high-risk men were adhering quite well. Then there's the news that none of the more than 600 MSM receiving PrEP at a Kaiser Permanente clinic in San Francisco have contracted HIV, despite the fact that the group has had a very high rate of sexually transmitted infections. And in a study of PrEP among a group of high-risk MSM and trans women in San Francisco, Washington, DC, and Miami, about 80 to 86 percent of the participants took Truvada at least four days a week. The study saw a very low HIV rate.

All of these indications of PrEP's potential for public health-level success notwithstanding, researchers are still fast at work developing new methods for the so-called biomedical prevention of HIV. The PrEP of the future may look much like birth control does today, with an array of options for individuals to choose from, including multiple oral medications, long-acting injectable PrEP, a long-term implant placed under the skin (known as a subdermal implant), and even long-acting PrEP that uses antibodies rather than antiretroviral (ARV) medications.

Chatter among PrEP enthusiasts may suggest that at least one of these advancements is imminent. But the fact is that at least several years will likely pass before Truvada as PrEP has any company. Holding back these developments is the inescapable fact that the clinical trials process that is required before researchers can submit a new form of PrEP to the U.S. Food and Drug Administration is a slow one, with each of the three phases requiring a greater amount of time than the last. Phase III trials typically run for several years. And then the FDA's subsequent review process tacks on many more months before an ultimate approval, should an OK from the federal government actually come.

Jim Pickett, director of prevention advocacy at AIDS Foundation of Chicago, expresses frustration with common misperceptions that a long-acting injectable PrEP in particular is around the corner.

"Folks who are sort of waiting on the sidelines for long-acting PrEP options will have a long wait before something is on the market and available," he says. "No one should be under the illusion, or delusion, that this method is coming to a pharmacy near you anytime soon."

So what's in the PrEP pipeline? How much longer do we have to wait?

The randomized, double-blind, placebo-controlled Phase II NEXT-PrEP study, just wrapping up this month, has tested the safety and tolerability of four combinations of three different ARVs as PrEP among 600 at-risk MSM and women in the United States. The drugs studied include Selzentry (maraviroc) and the two components of Truvada, Viread (tenofovir) and Emtriva (emtricitabine). Each participant has been instructed to take three pills each day for 48 weeks, a regimen that includes one or two placebo pills, depending on how many active drugs the study member has been randomized to take. The active drugs in each of the four study arms include: Selzentry; Selzentry and Emtriva; Selzentry and Viread; and Viread and Emtriva (in other words, Truvada, but taken as two separate pills).

This study will not test how well these combinations work as HIV prevention; that's the task of a possible subsequent Phase III trial, which, as is typical, would include a much larger pool of

participants. Rather, the study will primarily look at side effects. Since Truvada has been shown to reduce bone mineral density and to raise the risk of a reduction in kidney function, the researchers will see if Selzentry offers a safer option on these fronts. The researchers will also test rectal and vaginal tissue and secretion concentrations of the study drugs to anticipate how well they will work in preventing HIV.

Outside of the chance for a potentially favorable side effect profile for Selzentry compared with Truvada, using Selzentry for PrEP may have upsides when considering the potential for drug resistance. Research suggests that those who do become HIV positive while taking Truvada as PrEP only rarely develop resistance to the drug. (To develop drug resistance, individuals on PrEP likely have to be taking Truvada sporadically or not at all when they contract the virus and then start taking the tablet more frequently and for a considerable period after seroconverting.) For those who do develop resistance to the tenofovir component of Truvada, HIV treatment options narrow significantly; tenofovir is the most widely prescribed ARV, taken by over 80 percent of Americans treated for the virus. Selzentry, on the other hand, is much less commonly used by people with HIV, so developing resistance to that drug would be less consequential.

The NEXT-PrEP investigators plan to present their findings at the Conference on Retroviruses and Opportunistic Infections (CROI) in Boston in February 2016.

Another possible answer to Truvada's potential negative effects on bone mineral density and kidney function may be in a new take on tenofovir Gilead has recently developed. Truvada contains a form of the HIV medication tenofovir that is called tenofovir disoproxil fumarate, or TDF. In November, the FDA approved Genvoya (elvitegravir/cobicistat/emtricitabine/tenofovir alafenamide), the first combination tablet to include a version of tenofovir known as TAF, which research has shown is less toxic to bones and kidneys than TDF. In April, Gilead applied for FDA approval of a Truvada 2.0 of sorts that includes TAF instead of TDF; an approval for use in treating HIV—not for PrEP—is expected in the coming months.

The science looking into whether a TAF-inclusive version Truvada will actually work as PrEP is only in the very early stages. There is no guarantee, especially considering the fact that the body metabolizes TAF and TDF differently, that the updated Truvada will actually work as PrEP. According to Gilead spokesperson Ryan McKeel, there hasn't yet been any research in humans of TAF-inclusive Truvada as PrEP, just an animal study and ongoing laboratory research into the drug's ability to penetrate human tissue.

"Gilead will evaluate these data in order to determine next steps," McKeel says of the preliminary research findings.

Until there are solid answers about TAF-inclusive Truvada's effectiveness as PrEP, Mitchell Warren, executive director of the global HIV advocacy organization AVAC, cautions physicians against prescribing the drug off-label as PrEP once it has received (and presuming it does receive) FDA approval as a treatment for HIV.

“Once a product’s in the public domain and available, even for another indication, the opportunity to do something that we don’t fully understand is something we need to be monitoring very carefully, and advocating that [medical] practice follows evidence, not opinion,” Warren says.

Looking beyond PrEP that’s taken orally, Tim Horn, HIV project director at Treatment Action Group, says that a reformulated tenofovir gel for use as a rectal microbicide against the virus “is certainly a product to watch.”

The two-year Phase II MTN-017 trial of the gel wrapped up in mid-2015. The study investigators plan to release their first results at CROI in February.

Then there is the exciting prospect of a long-acting injectable PrEP. Recently, news came down the pike that a dual-ARV, long-acting injectable treatment, given every four or eight weeks in a Phase IIb trial, suppressed HIV as well as a standard oral ARV regimen. This finding has stoked excitement for long-acting ARVs’ potential use as PrEP. Scientists are already hot on the trial, and are currently conducting Phase II trials to investigate how well each of these two long-acting ARVs, Janssen’s Edurant (rilpivirine) and ViiV Healthcare’s investigational cabotegravir, may work individually as PrEP.

A shot of long-acting PrEP given in the gluteus muscle by a clinician every three months (the same interval between clinic visits that those taking PrEP must follow in order to maintain the Truvada prescription) could help solve the medication adherence problems that threaten to lower PrEP’s effectiveness among those taking daily oral Truvada.

According to John Pottage, MD, chief scientific and medical officer at ViiV, the company has projected a May 2016 start for a Phase III trial of long-acting cabotegravir as PrEP for MSM. The investigators are still working out the dosing schedule, but according to Pottage the shots will likely be given to participants every two or three months. The goal is to finish that study by 2019 and then apply to the FDA, which would hopefully bring an approval for the new HIV prevention method in 2020.

Participants in the Phase III trial will be required to start with a four-week course of oral cabotegravir before switching to the injections. This isn’t to build up drug levels, but to test for side effects; once a long-acting injectable is in the body, there’s no getting it out, and it can remain for several months.

“Administering a drug that lingers in the body for very long periods of time, without an antidote available, comes with very important safety considerations,” Horn says.

“So far the side effect profile looks good,” Pottage says of cabotegravir, “but it’s still the early days” of research into the drug.

The lingering effects of injectables also raise the risk of drug resistance during the months after an individual discontinues the injections. Eventually, the drug will dissipate to levels that are too low

to provide full protection against HIV but may still be high enough to prompt the development of drug resistance if someone contracts the virus during that window. Pottage says a possible way to buffer against drug resistance development is to give individuals who have stopped the injectable ARV a daily oral version of the drug until the injectable's "tail" has petered out enough to eliminate the risk of emerging drug resistance. This strategy raises the question, however, of how well those who received PrEP as an injection would ultimately adhere to a subsequent oral regimen, especially if the reason these individuals opted for the injectable was because they weren't able to take a pill every day.

A potential alternative to injectables could be a subdermal implant, likely placed inside of the upper arm. A recent study in beagle dogs found that a matchstick-sized device that was filled with TAF delivered high levels of tenofovir to immune cells over a 40-day period. A device like this could possibly provide effective PrEP prevention for months, perhaps even years. But implantable PrEP won't be available anytime soon; even the earliest human trials of this technology won't begin for at least another two to four years.

A major question about an injectable or implantable PrEP that requires infrequent administration is how this scheduling would affect the regular STI testing that individuals currently taking Truvada for HIV prevention typically receive. As the thinking goes, if people take greater sexual risks as a result of taking PrEP, frequent testing may mitigate the spread of STIs to others. (The CDC advises that people on PrEP undergo tests for STIs twice a year, but some clinicians may run these tests at each of the quarterly clinic visits that are required to maintain a PrEP prescription.) That benefit could be lost if people on PrEP didn't need to visit a clinic as often as every three months.

Looking far into the future, the National Institutes of Health (NIH) recently announced a partnership with GSK (GlaxoSmithKline) to research the use of so-called broadly neutralizing antibodies (BNAs) for both HIV care and prevention. These are naturally occurring antibodies, including one known as VRC01, that are highly effective at neutralizing a wide array of strains of the virus. The goal is to use combinations of the BNAs to broaden their potency even further.

According to Anthony S. Fauci, MD, director of the National Institute of Allergy and Infectious Diseases, a division of the NIH, BNAs can be manipulated to persist in the body for so long that their use as PrEP may only require injections every four or six months. GSK and the NIH are in the process of designing Phase I trials.

In the meantime, in the oft-repeated words of Robert M. Grant, MD, MPH, a professor at the University of California, San Francisco, who was the head of the iPrEx study, today's Truvada as PrEP "works if you take it."

Warren is concerned that there are those at high risk for HIV who may opt not to take Truvada because they would rather wait for another form of PrEP to come along. He joins Jim Pickett in stressing that these individuals will be waiting for a while.

"There is no certainty at all that we will have anything new within the next five years," Warren

says of advancements in PrEP technologies. “Maybe we will have several new products. Maybe in a decade we’ll have a partially effective vaccine. I hope we do. But people should not be making their individual risk calculations based on products they hope for.”

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