PODCAST TRANSCRIPT

What's All the Fuss About F/TAF? A Call for Action in 2020

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Jeanne Baron: [00:00:02] You're listening to *Px Pulse*, a regular podcast bringing you fresh voices on critical issues facing HIV prevention research today.

Jeanne Baron: [00:00:24] Since 2012, an oral drug called TDF/FTC (brand name Truvada, or TDF for short) has been approved for HIV prevention. Known widely as PrEP, in these seven years since approval the field has learned a great deal about its very high effectiveness if you take it, and about persistent challenges in actually delivering PrEP to the people who need it. Now Truvada's maker Gilead has a new version of PrEP—brand name Descovy. Both the original PrEP and the new one include a drug called emtricitabine, but they have different versions of another drug called Tenofovir. Descovy (or TAF/FTC) we call F/TAF, or TAF for short. Its approval by the FDA in October has triggered a cascade of comment and criticism, new challenges and some important opportunities. Here to help explain some of the impact from this development and its implications is AVAC Executive Director, Mitchell Warren.

Mitchell Warren: [00:01:23] Hello there.

Jeanne Baron: [00:01:24] Hello. So, Mitchell, what prompted Gilead to make such a significant investment when Truvada (or TDF) works, if you take it?

Mitchell Warren: [00:01:34] Well, I think what's important to start is to understand what these drugs are. In TDF (or Truvada)—the PrEP we've known for a number of years included one form of Tenofovir, and F/TAF includes a slightly different form of Tenofovir, but the basic drugs are the same. What makes TAF different than TDF is that you need less drug to get into the pill, to get into the body and get what we think are protective levels. So the F/TAF pill is

considerably smaller. It has much less active drug and therefore its manufacturing cost is much lower as well. And it may be why some of the side effects that you get with TDF don't appear with TAF.

Mitchell Warren: [00:02:16] So, there was a rationale to want to know if this was a drug that was a viable alternative. It was approved first for treatment and then Gilead, the company that makes it, decided to do the Discover trial amongst gay men and other men who have sex with men and transgender women having sex with men. That trial result came out earlier this year, and it showed what we call statistically 'noninferiority', which basically means F/TAF for PrEP is no better than, but similar to TDF for PrEP. But, the two drugs have slightly different side effect profiles.

Jeanne Baron: [00:02:53] What are the different side effects?

Mitchell Warren: [00:02:55] So it's really important to keep in mind every drug has side effects—that's to state the obvious. We've known from the beginning (since Tenofovir's been around) there were issues about kidneys and bone density, for some people.

Jeanne Baron: [00:03:08] Over a long time of exposure. But not [for] everybody, just some people.

Mitchell Warren: [00:03:13] Many people take Tenofovir very happily without those side effects. But it can happen. The flip side of that, though, is that with TAF, it appears that there are issues of both weight gain and unhealthy cholesterol that may be a side effect with TAF. And again, it's much earlier days, [with] fewer people on them. These are trade offs. No drug is perfectly safe. These are trade offs. And there is an attempt that overstates TAF's benefits both its efficacy benefits and its safety profile, we think.

Mitchell Warren: [00:03:44] We want to be very clear as advocates to stay true to the data. TAF is noninferior and it has a different side effect profile. Individuals on PrEP should be having the conversation with their provider: 'is this the better choice for me?' And if the answer is, 'you have some kidney issues. You

might want to switch,' perhaps TAF is better. But if you are happily taking TDF/FTC for PrEP right now, there is no reason (either because of safety or efficacy) to switch.

Jeanne Baron: [00:04:14] So the data shows that it works as well as Truvada (or TDF). And I'm still trying to get at 'where was the need?' The challenge with PrEP now has been about rollout, implementation, getting PrEP to the people who need it. We know rollout has been picking up speed, but there are still fewer than 400,000 people globally on PrEP, according to AVAC's PrEP Tracker (which we update quarterly). And we also saw there were still 1.7 million new infections [in 2018], so we know that the prevention is not happening at scale.

So in your ideal world, can F/TAF play a role in overcoming these barriers?

Mitchell Warren: [00:04:52] The ideal picture is one that has many more prevention options. We know that people want choices. So by having F/TAF for PrEP, we are not actually expanding our method mix considerably. We basically are swapping one daily pill for another. If it's cheaper, if it's smaller, if it has different side effects that may work for some people, there is good merit to wanting to think about having this additional option. But many of the challenges with scaling up oral PrEP programs are not because of the pill itself.

Mitchell Warren: [00:05:24] So, we need to make sure that we are not fooling ourselves in trying to reduce the number of new infections considerably simply by introducing F/TAF. The good news is there's a very robust pipeline of other methods—the vaginal ring, an injectable, implants, a vaccine, an antibody. That's what expands our method mix. In the short term, though, if we can find a pill that is smaller and cheaper and still safe and effective, that's a good thing. But there's much we don't know about F/TAF.

Jeanne Baron: [00:05:50] Right, the data are only on men who have sex with men (MSM for short) and transgender women. There is a big population that needs prevention

missing.

Mitchell Warren: [00:06:01] Absolutely. Prevention needs to be for everybody who needs it. And right now, according to the label and according to the data, F/TAF for PrEP is not applicable to cisgender women who are at risk.

Jeanne Baron: [00:06:12] Let me just stop you right there. So the approval for TAF came out in early October from the FDA. It now has a label for anyone over 35 kg (that's roughly 77 pounds). That label's an effort to make this product available to adolescents, but what does it mean that the label also says not for those who engage in 'receptive, vaginal sex'? How did it happen that women got left out? [Women are] a vital population to reach.

Mitchell Warren: [00:06:43] The idea of doing a trial like Discover in cisgender women is very complicated. If you go back in the last decade, the trials that have shown us that oral PrEP with TDF worked so well—up to 90 percent efficacy came from three trials, all in MSM and transgender women. There is even more data in women from more trials than in MSM, but the results are so disparate. We have evidence in cisgender women that show it is very effective, much like in MSM. But we also have a number of studies that showed no effect at all. Now, many of us would argue we know from the analysis of those trials that that very low efficacy, or no efficacy in a couple of trials, was due to adherence, not due to the drug itself (so how well people took it).

Jeanne Baron: [00:07:29] We know TDF (Truvada) works if you take it for men and women. But the body of data from past trials showing that efficacy in women is more complicated than the data is for men and transgender women.

Mitchell Warren: [00:07:44] That is exactly right. It makes the trial pretty unfeasible to do because it would take tens of thousands of participants.

Jeanne Baron: [00:07:51] With a traditional trial design.

Mitchell Warren: Yes. So there became this breakdown, this stalemate, of how to study this

[00:07:53] product in women. And very sadly, the regulators and the company took a decision without consultation, but amongst themselves, to not have that efficacy trial of TAF in women and instead look to see if there was some pharmacologic measure they could bridge between the efficacy trials in men and maybe it would work in women. And it did not work. The data were not strong enough.

Jeanne Baron: [00:08:31] So there's been a lot of criticism out there that this wasn't just one person's failure, or Gilead's failure alone. There also was a failure among regulators all along the way to figure out a trial design that would work.

Mitchell Warren: [00:08:47] Yes, there's failure on the company to develop it and do the appropriate studies. [There's] failure on the regulators to require it. But one of the red flags, I think, for all of us going forward as advocates is that we knew, at least conceptually, some of this was happening and we all didn't engage as aggressively as we need to. Not only about the trial design, but what is the full package, the full suite of studies that need to be done so we're going to get a product approved for all populations who might need it. We are now a number of years behind this product (F/TAF) being approved for women. As discussions go forward, as decisions get made, we need to ensure that they don't happen only between the product developer and the regulator.

Jeanne Baron: [00:09:35] You're calling for a high level—a gold standard—of community engagement, of Good Participatory Practice when it comes to figuring out exactly how you're going to measure efficacy in this trial.

Mitchell Warren: [00:09:49] You're hearing me right, because trials have results. And sometimes they are crystal clear. And more often than not, they are confusing to interpret. And our experience at AVAC with many partners, is that when you can engage stakeholders early in the process and then throughout the conduct, navigating through the complexity of the results, and most importantly, figuring out what to do with that result is best done with stakeholders who've been part of that process throughout. I do not want

to be in a place where in 2024 or 2025 when this trial finishes, it's only then that we're beginning to say, 'well, did you think about that? How did you make that comparison?' We need to agree to the terms of engagement at the outset.

Jeanne Baron: [00:10:38] And now we come to the trial that's being designed as we speak. The FDA, when they approved TAF, came along with a subsequent postmarketing requirement setting out the terms around which this trial must be conducted. That happened in very early October. Back in 2016, they said 'we don't know how to design this trial without involving something like 20,000 women.' Now they're proposing a trial with a much smaller number, perhaps some few thousand women. What problem did they solve?

Mitchell Warren: [00:11:07] The FDA has said they're willing to consider innovative trial designs. And we all know we need to be innovative in our trial designs because we are in a very different world going into 2020—incidence is declining. So, can you compare F/TAF (the new product) to a background incidence—a background rate of new infections? And this has been something that's been discussed for a number of years as a potential trial design that would streamline and perhaps make trials still ethical, but shorter in timeframe, perhaps smaller, maybe less expensive. And the trial designs have historically been rejected.

Jeanne Baron: [00:11:44] Rejected in HIV prevention research. Just focusing in on using background incidence as a control, what's the concern?

Mitchell Warren: [00:11:54] It's harder to design and harder to analyze the data. So, people didn't do them. The beautiful part about a controlled trial is that you are randomizing not only between which drug they get, but also people's behaviors would be equally distributed because you've done a thorough randomization.

Jeanne Baron: [00:12:10] A thorough randomization between groups that are then compared. One group, so to speak, that gets something new and one group that doesn't.

When you compare them, it's an apples to apples comparison because they've been randomized the same way. It's more complex to establish an apples to apples comparison in a trial using a background incidence, because that background rate of new infections is derived from a community or from a source that was not randomized exactly the same way as that group that's testing the new drug, just for an example.

Mitchell Warren: [00:12:43] Exactly. Many trials, if you look when they report results, the demographics look similar between the two arms, their risk behaviors look similar, because we've randomized all of that. We don't get that in quite the same way if we're using a background incidence measure—that's why this is innovative. But we need that, because we need to know if F/TAF works in women.

Jeanne Baron: [00:13:06] We're going to be following the progress of F/TAF and the trial design as it takes shape in the months to come. Drugmaker Gilead says it's committed to engaging with civil society and community. Advocates must come together to make sure this commitment is fulfilled. What do you want Gilead to know? And what do you want to know from Gilead? We want to hear from you. Write to avac@avac.org and find more information on the *Px Pulse* page at avac.org/px-pulse.

Jeanne Baron: [00:13:39] You've been listening to *Px Pulse*, recorded in the New York City studios of the Radio Foundation and The Relic Room. Our theme music was composed by Alexie Stevens. Our engineer is Sam Bair.