

# Treatment ISSUES

## Next steps for PrEP: Getting a proven prevention option to the people who need it

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Pre-exposure prophylaxis, or PrEP, for HIV prevention has garnered a lot of attention over the last several years, beginning with the positive results from the iPrEx trial in men who have sex with men (MSM) reported in late 2010.<sup>1</sup> Since then, the field has seen both positive and flat results from other trials, leading to a regulatory and normative movement that is helping to chart the way for PrEP access for those who can use it as an HIV prevention option.

In July 2012, the U.S. Food and Drug Administration (FDA) approved the HIV treatment drug Truvada for use as a once-a-day prevention option for HIV-negative men and women. This was the first time an antiretroviral (ARV) treatment drug had been approved to reduce the risk of HIV infection via sexual exposure and the only FDA-approved option via this mode of transmission since the approval of the female condom in 1993. Around the time of the FDA decision, the World Health Organization (WHO) issued guidelines for countries planning PrEP demonstration projects. These demonstration projects will look at how daily PrEP might be used in different real-world settings, when people know they are taking an intervention that works as opposed to in a clinical trial when it's not clear an intervention works and a portion of participants get a placebo. While these moves from regulatory and normative agencies signal the significance of PrEP as an important HIV prevention option, recent clinical trial data suggest that a daily pill-taking approach for PrEP may not work for everyone at risk. So how can Truvada as PrEP best be used? What do recent trial data mean for research, investment, and public health policy? Advocates, researchers, funders, and policy makers alike are trying to understand what these trial results are telling us and find the best way forward to make PrEP available to men and women who can and will use it.

### Recent Results

At the 20th Conference on Retroviruses and Opportunistic Infections (CROI), researchers from the VOICE trial—a study that involved over 5,000 women in South Africa, Uganda and Zimbabwe—presented the results from the study. The data showed that none of three interventions tested in VOICE—daily oral tenofovir, daily oral Truvada (TDF/FTC), and daily 1% vaginal tenofovir gel—provid-

ed additional protection against HIV in this study, likely because few of the women in the trial used the products as directed.<sup>2</sup>

The data from VOICE show that there is still much to be learned about what people want and need for HIV prevention options. This notion was reinforced with recently-published data from a pilot project in young Black men who have sex with men in Chicago that, among other things, looked at adherence to a daily PrEP regimen. The study showed that these young gay men also struggled to adhere to daily PrEP with “being away from home” cited as the most common reason individuals had difficulty taking their pills regularly.<sup>3</sup>

### PrEP Basics and Large-Scale Trial Results

Pre-exposure prophylaxis, or PrEP, is a strategy that involves use of antiretroviral medications (ARVs) to reduce the risk of HIV infection in HIV-negative people. Many different types of PrEP have been considered or are being studied. These include daily pill-taking, use of long-lasting ARV injections, or less-than-daily (intermittent) dosing. In addition, ARV-based microbicides, such as vaginal or rectal gels or vaginal rings with varying dosing schedules, are being studied.

The first PrEP proof-of-concept came from the multinational iPrEx trial in MSM and transgender women, which showed that daily Truvada was effective at reducing risk. That result was confirmed in the Partners PrEP and TDF2 studies, which took place in heterosexual serodiscordant couples (one partner HIV-positive, the other HIV-negative) and in heterosexual men and women, respectively. The FEM-PrEP study of daily Truvada in young women and the VOICE study of daily Truvada (as well as daily oral tenofovir and daily 1% tenofovir gel) were unable to show effect due to lack of adherence to the study products.

All of the efficacy data to date are from trials looking to reduce HIV risk via sexual transmission. There is one trial of daily oral tenofovir among injecting drug users in Thailand. Results from this study are expected later in 2013.

## PrEP in the Real World

Daily oral Truvada is FDA-approved to reduce the risk of contracting HIV via sexual exposure in HIV-negative women and men. The data that led to this approval came from several HIV prevention clinical trials and these data are clear: those who are able to take daily oral Truvada reduce their risk of getting HIV. Importantly, the FDA considered the data from the FEM-PrEP trial, particularly as it related to women’s lack of adherence or their inability to take PrEP as prescribed, in making the decision to approve Truvada for men and women at risk of HIV in the US. What is not yet clear is how PrEP will work in the real world.

We know that some women and men report an interest in using PrEP if it’s safe, effective and affordable. PrEP acceptability studies among gay men and women have shown that many see PrEP as a viable option, at least when asked about it as a possible option.<sup>4,5</sup> But information on so-called real-world risk remains quite limited, as does information on how men and women might actually use daily PrEP.

Adherence to the daily dosing schedule varies greatly across the randomized controlled PrEP trials (see table below). Researchers are attempting to better understand what motivates some trial participants to use PrEP and what barriers might prevent other participants from using the products. To augment the data gathered from clinical trials and open-label extension studies, which provide active PrEP (no placebos) to trial participants in a follow-up study, researchers are also designing demonstration projects and pilot programs that can help determine how to deliver daily oral Truvada to those who can most benefit from it, and what level of support may be needed for

*Researchers are attempting to better understand what motivates some trial participants to use PrEP and what are barriers to adherence for others.*

### PrEP Works...If You Take It

Trial	Efficacy	Adherence
CAPRISA 004 <sup>6</sup>	1% tenofovir gel: 39%	51%
iPrEx <sup>7</sup>	Oral daily Truvada: 42%	51%
Partners PrEP <sup>8</sup>	Oral daily tenofovir: 67% Oral daily Truvada: 75%	83% 81%
TDF2 <sup>9</sup>	Oral daily Truvada: 62%	81%
FEM-PrEP <sup>10</sup>	Oral daily Truvada: No Protection	24%
VOICE <sup>2</sup>	TFV gel: No protection Oral daily tenofovir: No protection Oral daily Truvada: No protection	23% 28% 29%

*The point estimate of efficacy for each study is listed and adherence estimates were determined by measuring drug levels from participant samples collected at varying time points.*

women and men who decide to use PrEP as a prevention option.

Some advocates are concerned that there is not a clear agenda for PrEP demonstration projects that will provide the range of answers needed for moving PrEP forward as a viable prevention option. Advocacy around this began ahead of FDA approval when a range of HIV and health advocates worked together to try and define a broad demonstration project agenda for populations at risk, including both women and men.<sup>11</sup> More recently, a coalition of HIV and women’s health advocates released a statement calling on U.S. government agencies to coordinate a PrEP agenda to quickly and accurately answer questions about how PrEP can be made available to women in the U.S., particularly given that none of the key PrEP trials among women included U.S. women.<sup>12</sup>

### Truvada as PrEP in the U.S.

The price of Truvada in the U.S. (about \$1,467 a month)<sup>13</sup> is a major concern for PrEP access, but there has been some movement to make PrEP more affordable. Currently, some individuals in the U.S. seeking to use PrEP have been able to receive reimbursement from their private healthcare insurers, and some insurance companies

have indicated a willingness to pay for Truvada as PrEP. Anecdotal evidence shows that some state Medicaid programs have reimbursed for PrEP use, although this is not widespread. (It is also unclear whether such Medicaid

payment is the result of policy or the result of confusion because Medicaid already reimburses for Truvada when part of an antiretroviral treatment regimen for HIV-positive individuals.) Under the Affordable Care Act, certain prevention measures (such as routine HIV testing) can be designated essential and automatically exempt from cost or co-payment. To be deemed essential, the prevention measure must be graded highly by the U.S. Prevention Services Task Force, but there has been no evaluation to date of Truvada as a prevention measure.

Gilead, the manufacturer of Truvada, has instituted a PrEP Medication Assistance Program, which is available to assist eligible lower-income HIV-negative adults in the U.S. who do not have private insurance (income eligibility goes up to five times the U.S. federal poverty level).<sup>14</sup> However, Gilead’s program covers only the cost of the drugs and not the related clinical visits. Those who use PrEP need to closely monitor their overall health and frequently get tested for HIV.

Groups like the Fair Pricing Coalition—a group of activists who advocate with the pharmaceutical industry regarding the price of HIV and hepatitis drugs—are working on lowering the cost of Truvada, as well as additional free tests and benefits for PrEP users. Gilead has already committed to providing free condoms and reimbursement for testing for those initiating Truvada as PrEP.

## Emerging and Potential HIV Prevention Technologies



### Truvada as PrEP Outside the U.S.

While some international groups have drafted guidelines for the use of daily Truvada as PrEP, it is noteworthy that no regulatory authority other than the U.S. FDA has approved daily Truvada as PrEP. As a result, PrEP access outside of the U.S. varies greatly.

Truvada, and its generic equivalent (TDF/FTC), are used as part of combination therapy to treat HIV/AIDS in some resource-limited and middle-income countries, and certain partners of Gilead in India and South Africa have the right to manufacture and sell generic versions of Gilead products in some developing countries. Under these agreements, Gilead receives a small royalty on product sales based on the generic price, which is as low as \$9.00 a month in some countries.<sup>15</sup> Notably, Truvada is not licensed and therefore not available as HIV treatment in some countries, including Peru, where the majority of iPrEx trial participants came from. There are advocates working towards access to Truvada for both treatment and prevention.

While the generic price is often quite low, a PrEP program would also need to include regular HIV and other testing. Truvada is also used as an HIV treatment in Europe and other developed countries, where pricing is comparable to the U.S.

Gilead has said that it is in discussions with a number of other international regulatory agencies about moving forward with Truvada licensure for PrEP. To date, the company has not filed for licensure outside the U.S.

### Next Steps in the U.S. and Globally

Even with FDA approval of Truvada as PrEP in the U.S., there is no clear pathway, and no defined timeline, for moving towards PrEP implementation domestically—although there has been some movement. The U.S. Centers for Disease Control and Prevention (CDC) has issued interim guidance documents on the use of PrEP for gay men<sup>16</sup> and for heterosexual men and women<sup>17</sup> and is working on Public Health Service Guidelines for PrEP. In addition, as part of the Risk Evaluation and Mitigation Strategy (REMS) that was part of the U.S. FDA approval of Truvada as PrEP, Gilead was required to develop training guides for healthcare providers, safety information sheets,

a medication guide, and other materials. But community leaders report that there is still a need for outreach and education aimed at healthcare providers whose patients are among those who may benefit from PrEP. At the same time, demonstration projects and pilot programs will provide additional information and data to help guide broader PrEP implementation programs.

In resource-limited settings, specifically sub-Saharan Africa, the trajectory for PrEP implementation is much less clear. PrEP and ARV-based microbicide trials have taken place in several countries, including Botswana, Kenya, South Africa, Uganda and Zimbabwe. Proposed PrEP demonstration projects in these countries will help inform World

Health Organization (WHO) guidelines on PrEP in resource-limited countries, expected to be released in 2015. The WHO guidelines would potentially pave the way for some countries to include PrEP programs in their national response to

HIV. Yet many questions would still need to be answered, including how programs would be funded and what policies would need to be developed for PrEP access in countries with waiting lists for HIV treatment programs.

In some middle-income countries where trials took place, including Brazil, Peru, and Thailand, PrEP is still a long way from being included in national guidelines or programs for HIV prevention.

### From Daily PrEP to a Range of Options

Adherence to the daily dosing of Truvada as PrEP has been an issue in the trials to date. Adherence to any daily medication can be difficult for many people, and especially for young people, who are often those most in need of new HIV prevention options. Researchers are, therefore, looking at a range of new options that may be less dependent on adherence and may be easier and more desirable for people to use. These include different delivery mechanisms, such as vaginal rings and injections, and less-than-daily dosing schedules for pills or gels (see images above). Researchers are also looking at rectal microbicides, which could be used by anyone at risk via anal sex. Researchers are also considering products for women that would combine an anti-HIV drug with a contraceptive; these products in development are being referred to as “multi-purpose prevention technologies”. The goal is to

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provide a range of options that would work for those most in need of new HIV prevention options.

### An Urgent Need for New Prevention Options

Incidence rates are still incredibly high among those most at risk in the U.S. and around the world. The VOICE trial showed a very high rate of HIV infections among young, unmarried women in the trial—5.7% among all the women in the trial and 8.8 % among unmarried women under the age of 25 in South Africa.<sup>2</sup> We have also seen very high rates of HIV infection among young black gay men in the U.S. Recent CDC data show that over the past three years, new HIV diagnoses among young black gay men in the U.S. increased by 48%.<sup>18</sup>

The bottom line for PrEP is that men and women need new prevention options that they can—and want—to use. For some people, that is a daily oral pill. But, as VOICE and other trials have shown, that may not be the right option for many other people. PrEP trials have taught us that biomedical tools have to work outside of the lab and within the complex realities of people's lives. The challenge is finding that marriage of need and desire to suit men's and women's lives, and then providing access to the right products at the right time. HIV prevention and research advocates, community leaders, and healthcare providers will be grappling with this challenge for the foreseeable future.

For more information on PrEP, please visit [www.cdc.gov/hiv/prep](http://www.cdc.gov/hiv/prep), [www.prepwatch.org](http://www.prepwatch.org), or [www.avac.org/prep](http://www.avac.org/prep).

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