PrEP Works: The Little Blue Pill That Could

The results are in—pre-exposure prophylaxis (PrEP) works. The strategy, which involves having people take the daily HIV treatment Truvada to prevent becoming infected with HIV, cut transmission on average by up to 73 percent when taken correctly. While experts are celebrating the news, they are also cautioning that the road from research to rollout of PrEP could be long and complicated.

November 23, 2010 By David Evans

November 23 will likely go down as a pivotal day in the history of the AIDS epidemic. On this day, researchers published data in The New England Journal of Medicine (NEJM) proving that daily use of the antiretroviral (ARV) drug Truvada (tenofovir and emtricitabine) by HIV negative people cuts new infections by at least 44 percent That small blue tablet, which only needs to be taken once per day, is going to have a very big future in HIV prevention.

Activists have been anxiously awaiting the results of this first clinical trial, which tested the strategy of taking a pill to prevent infection, called pre-exposure prophylaxis (PrEP). They'd been buoyed by positive studies of PrEP in monkeys and the good outcome from the recent trial of tenofovir gel in women reported at the International AIDS Conference in Vienna in the summer of 2010. That trial found that intermittent use of a tenofovir vaginal gel cut infections by up to 54 percent in the women who used the gel most regularly.

There have been plenty of dashed hopes, however, during the past two decades of AIDS research, and despite good early data there was no certainty that PrEP would work as expected. Now the results are in for the first PrEP study, called the Preexposure Prophylaxis Initiative (iPrEx).

In the men and transgender women in the study who took daily Truvada—all of whom had reported high levels of unprotected receptive anal intercourse before enrolling—new infections were cut by 44 percent compared with those who received a placebo. What's more, in those who reported using Truvada religiously—meaning at least 90 percent of doses were taken correctly each month—PrEP cut new infections by 73 percent. Experts in the field of prevention have reacted with both jubilation and caution.

"This has been a landmark year for HIV prevention research," said Yasmin Halima, director of the Global Campaign for Microbicides. "We now have proof of concept that both topical gels and oral pills have potential to work in preventing HIV among those at highest risk."

In an editorial in the NEJM that accompanied the study results, Nelson L. Michael, MD, PhD, from the U.S. Military HIV Research Program in Rockville, Maryland, sounded a more cautious note. While acknowledging the magnitude of the finding, Michael warned against a headlong rush to roll out the strategy.

First, while Truvada showed at least moderate efficacy against infection in people whose primary risk factor was receptive anal intercourse, we don't yet know how well it will work in people whose primary risk is vaginal sex or intravenous drug use. Also, though there were relatively few side effects, the actual number of serious side effects might have been underestimated given that the proportion of people actually taking Truvada regularly was lower than hoped.

Lastly, the considerable cost of Truvada is magnified by the fact that people taking it will require much more intensive and frequent care and follow-up than those not taking the drug. Deciding how to implement PrEP and how to pay for it are going to require some difficult and complex negotiations among activists, researchers, government officials and policy makers.

Making Sense of the Numbers

Researchers screened nearly 5,000 men who have sex with men (MSM) and transgender women for iPrEx, ultimately enrolling 2,499. Though it was an international trial, most of the participants were Latino and resided in either Peru or Ecuador. Most were in their early 20s, and all of the participants were born male, though 1 percent identified as female. A substantial number, 41 percent, reported having exchanged sex for money or drugs in the six months before enrollment.

The participants were randomized to take either Truvada or a placebo once daily. Drugs were dispensed every four weeks, at which time the participants also received safer-sex and adherence counseling, condoms, rapid HIV tests, adherence evaluations and surveys of their HIV risk practices. Physical exams and blood chemistry were also taken regularly.

Ultimately, 100 participants in the study contracted HIV, 36 in the Truvada group and 64 in the placebo group, a difference of 44 percent. This average reduction in HIV infection risk of 43.8% includes all study participants—even those who did not take the daily pill consistently. When the adherence was factored in, those who reported 90 percent or greater adherence were 73 percent less likely to become infected if they took Truvada.

One of the biggest concerns about using Truvada as PrEP is the risk that someone taking it to prevent infection could end up developing virus that is resistant to the drug if they do become infected, thereby reducing their roster of available treatments. Though none of the participants who became infected after starting the study developed Truvada resistance, this wasn't the case for two people who later turned out to have been in the earliest stages of infection before the trial started. Their infections were missed during the screening period, because they didn't have HIV antibodies yet.

Truvada was well tolerated. People taking Truvada were a bit more likely to report having nausea, and they were also more likely to have elevations in proteins that signal potential kidney damage.

Overall, however, the rates of both of these side effects were extremely low, and when a person had to go off the study drug for elevations in kidney proteins, his or her levels subsequently normalized. Michael notes, however, that the participant's true adherence was much lower than their reported adherence, so that the study might have underestimated the risk for serious kidney problems.

One important note about adherence: Though most study participants reported taking their pills as prescribed on a regular basis, subsequent measures of Truvada levels in the blood and inside of cells told a different story. Specifically, the components in Truvada could only be detected in blood or cells in 9 percent of those who became infected and in only 51 percent of those who remained uninfected.

There is both good and bad news to be derived from these results. When the iPrEx research team compared the infection rate based on having detectable Truvada levels in cells or blood, those with adequate blood and cellular levels were 92 percent less likely to become infected than those with no detectable drug.

On the other hand, the discrepancy between self-reported adherence and the true adherence, as measured by blood and cell levels, was exceptionally large. This means that not only will adherence potentially be a big issue, but it will also significantly complicate how to determine whether people are actually adhering to their regimens as there is a strong likelihood that what they report to their providers might not in fact be the reality.

Michael hypothesizes that the poor adherence might be due to the fact that the study participants were warned that they might receive a placebo and that even if they got Truvada, it might not work. Other studies suggest that people are more likely to adhere to a medication if they believe it will help them.

While belief in Truvada's efficacy might boost adherence, it could reduce condom use, a phenomenon called risk compensation. In this study, people's condom use actually went up during the trial. Further studies will now be needed to determine whether people who know they are getting Truvada, and understand it's prevention potential, will subsequently forgo other prevention methods.

Real World Implications

As positive as these results are, and as welcome as it is to have another "arrow" in the prevention "quiver" as Michael put it in his NEJM editorial, the way ahead is filled with unknowns.

There's a very big difference between the real world implications of the iPrEx results and the results from the tenofovir vaginal gel study reported earlier this year—the vaginal gel won't be made available until researchers can confirm its protective effect and work out some of the complications in assessing adherence and rolling it out. Truvada, however, is already approved in most countries around the globe, and provided that a person can score a prescription and pay for it, he or she could start taking that little blue pill today.

This has the Centers for Disease Control and Prevention (CDC) in Atlanta concerned. They will be weighing the study results and the cautionary flags it raised, along with demands by activists calling for a rapid rollout of confirmatory studies and studies to determine how to best make Truvada available to those who need it most.

Though Truvada PrEP worked fairly well for people engaged in receptive unprotected anal intercourse, it might have different efficacy in people whose primary risk is vaginal sex or intravenous drug use, though the results bode well for women whose transmission risk is vaginal sex.

Also, the drug proved most effective in people reporting the highest level of risk. Thus, should providers write a script for any of their MSM or transgender patients who report ongoing unprotected anal intercourse, or should they first refer them to prevention specialists, who can help them lower that risk, before offering Truvada?

Another unanswered question is how frequently people who go on PrEP should be tested and monitored for HIV and potential Truvada side effects, and how we should monitor their adherence to the drug. If they have adherence challenges, what interventions will help the most? If people have persistent adherence problems, despite interventions, should they be taken off PrEP?

All of these questions and more must be answered, not only for the purposes of developing the best medical guidelines for the use of PrEP, but also for the purposes of determining how to pay for the treatment in those who need it. While some people have the resources to pay for PrEP out of pocket, most don't. The retail price for a one-month supply of Truvada on one online pharmacy is more than $1,000.

Mitchell Warren, the executive director of the AIDS Vaccine Advocacy Coalition, in New York City, warns that we shouldn't wait too long to answer these questions. "It's a result that requires immediate action," Warren said. "Moreover, gay men and others at risk of HIV need to give crucial input and have influence on what the next steps for this new intervention might be.

"There is a global imperative to act on the results with ambitious, carefully prioritized research and implementation agendas, including strategic demonstration projects," Warren continued.

The CDC says it is primed to respond. The agency indicates that it will be developing clinical guidelines as quickly as possible to help providers assess who will most benefit from PrEP and how people should be monitored if they are prescribed Truvada for prevention. Moreover, the CDC also says that it will be developing fact sheets directed toward MSM about PrEP and its place in the prevention toolbox. It is also committing to call together public and private insurers to assess how PrEP could be paid for.

The CDC is also committed to learning more about PrEP as quickly as possible. The agency indicates it is interested in "demonstration projects in clinics serving MSM to assess feasibility, acceptability and the impact of PrEP in real-world settings."

A Light at the End of the Tunnel

As the CDC, the community and other stakeholders discuss how to pay for PrEP, Kevin Frost, the chief executive officer of amfAR, The Foundation for AIDS Research, applauds the investment in HIV research that resulted in the iPrEx study, and he hopes for continued support to answer the questions that remain. “Today’s announcement demonstrates that research is absolutely essential to our domestic and global response to HIV/AIDS,” he said. “Even in this difficult economic environment, investments in research continue to be validated. If we’re serious about controlling this epidemic, we need to continue to make those investments.”

Warren is also concerned about funding implications, saying: “As we move toward potential PrEP implementation, it is critical to remember that millions of HIV-positive people around the world, including thousands in the United States, lack access to the HIV treatment they need, which is often the same drug used in this trial.”

Despite the limitations and the unanswered questions, Halima, from the Global Campaign for Microbicides, felt it is important to also focus on the good news, saying that at long last “there is light at the end of the long HIV prevention research tunnel.”
