PrEP: A Possible Approval Like No Other

March 29, 2011 By Tim Horn

In early March, AIDS Healthcare Foundation began a paid advertisement campaign urging Gilead Sciences to refrain from seeking approval from the U.S. Food and Drug Administration for Truvada for use of the combination tablet as HIV prevention, in an approach known as pre-exposure prophylaxis, or PrEP. The ads were met by an outcry from the community. One prominent organization, the HIV Prevention Justice Alliance, issued a sign-on letter, dated March 16, urging the FDA "to examine the study results of PrEP rather than playing to speculation and fear."

While I agree that PrEP should be considered as an option in the HIV prevention toolkit and would ultimately support an effort by Gilead to expand Truvada's labeling to include PrEP--should the company petition the FDA for approval--I am also of the mind that a green light from the FDA should not be met with the rush-to-treatment that typically follows approval of a drug.

Given how little we know about the safe application of PrEP in a real-world setting--read: outside of a clinical trial--not to mention the expense of a comprehensive prevention program that includes PrEP, I think more feasibility studies need to take place before we consider a widespread HIV prevention program involving PrEP.

Here's what we do know:

PrEP is effective in one population of at-risk individuals: men who have sex with men (MSM). The iPrEx clinical trial, sponsored by the National Institute of Allergy and Infection Diseases (NIAID) of the U.S. National Institutes of Health (NIH) and co-funded by the Bill & Melinda Gates Foundation, involved a large sample size (approximately 2,500) of MSMs. The study, which had sound design and statistical analysis, proved Truvada use resulted in significantly fewer infections compared with those using a placebo.

What is less clear, however, is how effective PrEP--and all that is required for it to be safe and have maximum efficacy, including frequent HIV testing, blood tests before PrEP is prescribed as well as during treatment (to monitor for side effects), and strong adherence support--will be in the real world. A breakthrough in HIV prevention science it may be, but a simple pill to ward off the scourge of our times it is not. On this point, I agree with AHF.

The iPrEx study demonstrated that there were 44 percent fewer HIV infections among those who were assigned to take Truvada for an average of 1.2 years according to the original results published November 23, 2010, in the *New England Journal of Medicine* (*NEJM*). And according to follow-up data reported by Robert Grant, MD, of the Gladstone Institute of Virology and Immunology in San Francsico at the 18th Conference on Retroviruses and Opportunistic Infections, this efficacy rate was basically sustained out for almost two years of PrEP (42 percent fewer HIV infections were documented among those assigned to the PrEP arm for up to 144 weeks).

AIDS Healthcare Foundation argues that the 44 percent efficacy rate--and likely the longer-term 42 percent efficacy rate--"is much too low to merit approval." Even advocates who already support Truvada PrEP admit that the overall efficacy rate isn't exactly outstanding.

What has been a major talking point by PrEP proponents, however, is the fact that iPrEx volunteers who

actually took their Truvada as prescribed likely did much better than average. According to the *NEJM* report, there were 73 percent fewer HIV infections among those who took their Truvada 90 percent or more of the time as measured by pill counting and self-reports, compared with those who received placebo. Even more telling are data involving Truvada levels in blood and cell samples provided by patients--proof positive of adherence. In those with detectable levels of Truvada, there was a 92-95 percent reduction in the risk of contracting HIV.

Additional data from iPrEx, reported at CROI, optimistically pointed out that the drug detection rate was high among those participating in the study at sites in San Francisco and Boston, the two United States cities selected to participate in the clinical trial. In these two cities, Truvada was detected in 97 percent of patients randomized to Truvada.

What is important to understand when considering the data, however, are the small numbers of people involved in these "subgroup analyses." Consider the fact that drug levels were tested in *less than 5 percent* of those who received Truvada, out of 1,251 who initially randomized to receive the drug. Additionally, if we're only looking at adherence rates among those in the United States--and there's no doubting that excellent adherence was associated with near-perfect efficacy--consider the fact that *less than 10 percent* of the overall iPrEx study population were from either Boston or San Francisco.

To my knowledge, we've never approved a drug, or developed new public health strategies, based on cherry-picked numbers. While the iPrEx study's rosy subset analysis will undoubtedly pique the interest of FDA reviewers, the agency has a long history of being primarily concerned with overall study results, as it is tasked with safeguarding the public against the worst possible outcomes. This means seriously weighing the worst outcomes--the risk of new HIV infections and the possible development of drug resistance as a result of poor adherence in the real world--against the best possible outcomes associated with excellent adherence.

Virtually everyone working in HIV/AIDS treatment advocacy has, at one time or another, been dazzled by a drug that showed early promise, but there's generally agreement that approval isn't merited until additional studies have been conducted to help us learn as much as we possibly can. There is a big difference between what happens in drug trials, and what happens outside of them. When considering the use of Truvada as PrEP, even if the FDA only approves the drug for MSM in the United States, we still have much more to learn.

For example, we still don't know if the high efficacy rates among predominantly white gay and bisexual men in affluent cities like Boston and San Francisco will be seen in poorer cities, such as Oakland and Baltimore, homes to a large number of disenfranchised black and Latino MSM.

We also have no idea if Truvada can be used intermittently, for example, taken only before potentially risky sexual activity. And, if so, what is the time span for which the drug must be taken prior (and potentially after) sexual activity.

While iPrEx successfully answered some important fundamental questions regarding the safety and efficacy of PrEP in MSM, it did not answer a number of questions critical to other groups for whom PrEP could potentially prove effective.

For example, will PrEP's safety and efficacy prove comparable in women and injection drug users? We won't know this until a clinical trial exploring Viread as PrEP for injection drug users are reported in 2012 and a study exploring Truvada as PrEP in heterosexual men and women are reported a year later.

The iPrEx study had many safeguards in place--rapid HIV testing and adherence counseling every four weeks and frequently laboratory testing to look for adverse effects--to maximize efficacy and to ensure that those who tested positive while on treatment or experienced serious side effects (fortunately, there weren't any) stopped PrEP as quickly as possible. Is such an intensive approach necessary outside of the clinical trial setting to maximize benefits and minimize risks? If yes, are health care systems in the U.S. (not to mention the rest of the world) financed and staffed adequately to offer up such comprehensive

preventive medicine? And at what cost? Truvada alone is $36 a day--add in regular HIV testing, lab tests and adherence counseling and the price tag, per person, becomes a hefty one indeed.
Consider the following from George Carter of the Foundation of Integrative AIDS Research, which is based on iPrEx data and economic considerations:

*It will require treating at least 45 people over a year to prevent one infection: economies of scale notwithstanding, from some source or another a minimum of $146/pt/year * 44 patients or US$6,570 to prevent one infection per year or in the places where Gilead happily charges whatever they want, we'll give a mid-range $12,000/pt/year * 45 = US$540,000/pt/year to prevent a single infection. And that is just the (arbitrary and vicious) cost of the DRUG! A* [quality-adjusted life year] *analysis of physician, nurse and outreach time and costs will add substantially to that per patient cost.*

All of this said, resisting FDA approval of Truvada as PrEP is futile. Truvada is widely available and extensively used for the treatment of HIV and, if anecdotal reports are to be believed, already being prescribed and used "off label" as PrEP. What's more, the U.S. Centers for Disease Control and Prevention (CDC) has already issued interim guidelines on the use of Truvada as PrEP, recognizing that, unlike experimental drugs only available through clinical trials, there's little standing in the way of Truvada PrEP prescriptions.
My hope is that a potential approval will allow Gilead--which stands to make a good chunk of change, given its considerable potential market expansion with PrEP along with the fact that iPrEx (and other efficacy studies) aren't being funded by the company--and health agencies to address the numerous outstanding questions regarding the safety and efficacy of PrEP in diverse at-risk populations and to develop sound educational and support programming to at-risk individuals and health care providers hoping to use Truvada for the prevention of HIV.
Ideally, we'd have much of this settled before a drug becomes commercially available, like we do with experimental agents for the treatment of HIV. But in this case, there's no returning the genie from

whence she came--Truvada can be gotten with a prescription, by anybody, and the results of iPrEx, while limited, are compelling in their suggestion that Truvada can be an effective agent when used as part of a comprehensive prevention strategy.

This is where I disagree with AHF. The real fight isn't in holding up the FDA's approval of Truvada as PrEP, but in holding Gilead's (and the government's) feet to the fire to ensure that Truvada is not only safe and effective in the real world, but actually accessible and affordable to communities that will need it most.
