The iPrEx Results: Lifting Hopes, Raising Questions

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Thanksgiving week was a truly auspicious time for results to be released from the first clinical trial evaluating the use of antiretroviral treatment to prevent HIV infection among gay men and transgenders. There was much to be thankful for: Data from the iPrEx study showed that taking once-daily tenofovir/emtricitabine (Truvada), as part of a comprehensive HIV prevention package, reduced new infections by about 44%.

Thirty years into an epidemic disproportionately affecting gay men and other men who have sex with men, there is finally a study showing the efficacy of an HIV prevention strategy tested specifically in that population. Moreover, iPrEx proved the concept of pre-exposure prophylaxis (PrEP)—taking antiretroviral drugs *before* exposure to HIV—as a way to avoid infection.

The iPrEx study involved nearly 2,500 healthy, "high risk" gay men, transgender women, and other men who have sex with men, and took place in 11 sites in Peru, Ecuador, Brazil, South Africa, Thailand, and the United States (San Francisco and Boston). Participants were randomly assigned to take either one tablet of Truvada (a combination of tenofovir and emtricitabine) or a placebo once a day. Both study groups also received comprehensive HIV prevention information and services, including condom counseling and screening and treatment of sexually transmitted infections. (See "News Briefs," page 4, for details on the study design and outcomes.)

The results of the iPrEx study not only demonstrated that PrEP was effective in reducing HIV infection, but that it also appeared to work best among participants who used the study drug consistently. Compared with the placebo group, 50% fewer HIV infections occurred among participants who reported taking Truvada half the time, and 73% fewer infections occurred among those who reported taking the study drug on 90% or more days.

Blood levels of Truvada were compared in 34 people who acquired HIV during the trial and 43 people who remained HIV negative. Among those taking Truvada, the drug was detected in less than 10% of people who became infected and about half of those who remained HIV negative. This suggests that drug level in the blood was a good predictor of protection from HIV infection. So, taking the pill consistently makes a real difference.

But it is important to note that only about half of the iPrEx participants actually took their pills daily as prescribed by study protocol. As has been true in other HIV prevention trials, adherence—taking the study product as prescribed—is a core issue in determining whether and how well something works. Many people have difficulty taking a pill once a day every day, so it will be important to see whether *knowing* the actual efficacy of the pill makes a difference in how diligent people are in taking it. (Participants in the iPrEx study did not know whether they were taking Truvada or the placebo.)

The iPrEx study also showed that PrEP with Truvada was generally safe and well tolerated. Researchers found no differences in serious side effects between the Truvada and placebo groups, and those side effects that did occur—such as nausea and unintentional weight loss—were infrequent and mild. This is similar to

For more information about the promise of PrEP and other antiretroviral drug–based approaches to HIV prevention, see "Is HIV Treatment HIV Prevention?" in the Summer/Fall 2009 issue of *BETA*.

what has been found in previous PrEP safety studies and among HIV positive people taking Truvada as part of their treatment regimen.

Fortunately, very little drug resistance was seen in the iPrEx study. No resistance mutations to the tenofovir component of Truvada developed. Resistance to emtricitabine occurred among only two participants taking the study drug, and it turned out that these individuals already had HIV when they enrolled in the trial. (Their infections were too recent to be detected by the HIV antibody tests administered at enrollment.)

One very important finding from the iPrEx study was that, overall, participants in both the Truvada and the placebo arms reduced their HIV-associated behavioral risk during the trial period by increasing their condom use and decreasing their number of sex partners. This finding speaks to the impact of the comprehensive HIV prevention counseling provided during the study. It also raises the question of how much of the reduction in HIV infections observed was actually a result of the study drug and how much may have been due to behavioral risk reduction.

The efficacy of PrEP, although partial (that is, not reducing risk of HIV infection by 100%), raises a host of scientific, clinical, programmatic, and policy questions that are being pursued by U.S. and global researchers, advocates, policy makers, and funders. On the research front, a number of PrEP studies are underway or planned that will assess the efficacy of PrEP administered in different ways and among different populations. Most immediately, an 18-month open-label study of Truvada PrEP, which will provide the drug to any HIV negative participants in the original iPrEx study who wish to join, will begin early next year and is expected to provide more information about safety, efficacy, and pill-taking behavior among those who now know what they are taking and how it appears to work.

Other PrEP efficacy trials are underway around the world (see table, page 49). Additional studies designed to assess the safety and acceptability of oral tenofovir, oral tenofovir/emtricitabine (Truvada), and vaginally applied tenofovir gel as PrEP are also ongoing in diverse populations, including female sex workers and young men who have sex with men. These studies are testing different methods for delivering PrEP drugs (such as vaginal or rectal application), as well as intermittent dosing (twice weekly and after sex); results are expected beginning in early 2011. The ultimate goal of all of these studies is to develop safe, effective, and feasible strategies for HIV prevention that will have the greatest public health impact globally.

But feasibility must be tested outside the rarified context of controlled research studies. That is why a number of organizations are looking to develop demonstration projects in places like San Francisco, where the iPrEx study findings are particularly relevant because of the disproportionate impact of HIV on gay men. These projects would help determine the best strategies for delivering PrEP, maximizing adherence to the PrEP regimen, and assessing the cost-effectiveness of this approach. A qualitative component of these projects would also tell us how individuals do or do not incorporate a new practice (daily or intermittent pill-taking) into their lives and the meanings they bring to that process, and how this influences the effectiveness of PrEP at an individual and community level.

Meanwhile, it is likely that some people will begin asking their health care providers whether they are candidates for taking PrEP based on the iPrEx study results and their sense of their own risk for HIV infection (for example, if they are HIV negative and in a "serodiscordant" partnership with someone who has HIV). The Centers for Disease Control and Prevention (CDC) plans to provide a guidance document to help health care providers make sound clinical decisions with their clients on a case-by-case basis. However, it is currently the consensus of the public heath community that no one should "try this at home" at this point, and that all sexually active people should be advised to continue using condoms for prevention of HIV and other sexually transmitted infections, since condoms remain the most effective tool we have.

On the policy and advocacy front, much attention is focused on issues of pricing and availability of

The "standard of prevention" for any biomedical trial of an HIV prevention strategy includes counseling about HIV risk and safer sex, testing and treatment for any sexually transmitted infections, and access to free condoms.

While this comprehensive HIV prevention package is ethically necessary, it does complicate the interpretation of study results. Researchers may have difficulty determining how much of a reduction in HIV infections was due to the study product and how much was a result of counseling, condom access, etc.

For an in-depth look at this and other quandaries in prevention research, see "Confronting the 'Evidence' in Evidence-Based HIV Prevention: Current Scientific and Political Challenges" in the Summer 2008 issue of *BETA*.

PrEP. In the U.S., the annual cost of Truvada when purchased at market rate is about $12,000 to $14,000 per individual. Some countries that have negotiated agreements with Truvada's developer, Gilead Sciences, are able to produce generic versions at a much lower cost, but this is not the case in the U.S. Moreover, the pills are not the only things that come with a price tag; to be an effective HIV prevention strategy, PrEP must be accompanied by regular HIV testing, monitoring for side effects, and adherence counseling.

At a time when many HIV positive people in the U.S. and globally still lack access to lifesaving antiretroviral treatment, many people wonder whether it is ethical to provide these same drugs to HIV negative people who have other HIV prevention options. Some also worry that the costs associated with providing PrEP will threaten access to HIV treatment through public programs, such as the AIDS Drug Assistance Program (ADAP), whose funding already is tenuous.

Most of us engaged in AIDS advocacy do not believe that HIV prevention and HIV treatment should be pitted against each other. The best way to ensure that all HIV positive people have access to optimal care and treatment is to reduce the number of people who become infected in the first place. As more HIV positive people around the world survive into midlife and older age because of better and more tolerable antiretroviral therapy, the costs attendant with their care and treatment—including treatment for co-morbidities such as cancer and heart, liver, and bone disease—are becoming insurmountable. Funds for HIV/AIDS treatment and care will go further if fewer people acquire the virus.

efficacy: the capacity of a drug or other intervention to produce a desired effect under ideal research conditions, such as in a controlled trial.

effectiveness: the capacity to produce a desired effect under "real world" conditions, such as in a given community or population.

We also must be sure that PrEP does not become something only available to people who can afford it, thereby heightening class-associated disparities that already exist in HIV epidemics and in health care systems in the U.S. and elsewhere. This means we must advocate for reduced drug prices for both HIV prevention (PrEP) and HIV treatment, and for equitable health care delivery systems.

Finally, we must ensure that advances in science, like PrEP, continue to happen, by advocating for a robust research enterprise, particularly at the National Institutes of Health (NIH), whose initial funding made the iPrEx study possible. Most other promising HIV prevention studies—biomedical, behavioral, and social—also depend on support from the NIH, whose budget is currently under threat in these tight economic times.

But this is no time to cut research funding. The recent development of the first U.S. National HIV/AIDS Strategy, whose three main goals are reducing new HIV infections, ensuring access to care and treatment for all HIV positive people, and reducing HIV-associated health disparities, makes clear the need to identify the most effective and efficient strategies to target limited funds. Research is essential to identifying and optimizing those strategies, and to determining whether PrEP is one of them.

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ONGOING PREP EFFICACY TRIALS

Trial and Intervention	Location(s)	Study Population	Results Expected
Bangkok Tenofovir Study *Daily oral tenofovir*	Thailand	Injecting drug users	Early 2012
iPrEx extension study *Daily oral Truvada*	Brazil, Ecuador, Peru, South Africa, Thailand, United States	Men who have sex with men (including male-to-female transgenders)	Mid- to late 2012
Partners PrEP *Daily oral tenofovir; daily oral Truvada*	Kenya, Uganda	Serodiscordant heterosexual couples	Early 2013
VOICE *Daily oral tenofovir; daily oral Truvada; daily topical tenofovir gel*	South Africa, Uganda, Zambia, Zimbabwe	Women	Early 2013
FEM-PrEP *Daily oral Truvada*	Kenya, South Africa, Tanzania, Zimbabwe	Women	Mid- to late 2013