Onward and Upward with PrEP, Cautiously

November 30, 2010 By Tim Horn

It was interesting to have been on vacation when Tsunami iPrEx--the results from an international clinical trial evaluating the safety and efficacy of Truvada as pre-exposure prophylaxis (PrEP) among 2,500 men who have sex with men and transgendered women who have sex with men--made landfall and an unparalleled number of headlines all over the world. Though I made a promise to myself that I wouldn't do a scrap of work while away, there was no escaping the cacophony of media reports suggesting that Truvada was the HIV prevention panacea we've all been waiting for. And for a brief moment in time--willfully without access to my usual sources of critical information, let alone the original iPrEx report in the *New England Journal of Medicine*, published November 23--I rather enjoyed being surrounded by nothing more than the warm, gauzy light of pumped-up and dumbed-down mainstream media reporting of this long-awaited clinical trial.

Come Monday morning, it was time to sift through the reams of print and online reports--many overweening, some overly critical--and make heads or tails of the study. It was fellow POZ blogger Joe Sonnabend, MD, a doctor and man I count as a mentor and friend, who struck the most pessimistic note with the following: "The iPrEx trial of pre-exposure prophylaxis is a failure."

While I agree with a number of points raised by Joe, I'm definitely not of the mind that the study merits such harsh criticism. In fact, I remain encouraged by the overall conclusion of the trial--that there were 44 percent fewer HIV infections among those who received PrEP compared with those who received placebo, despite the fact that risk-reduction counseling and condoms were made readily available to subjects in both groups.

But do the data constitute an HIV prevention magic bullet? No.

First and foremost, correct and consistent use of condoms is close to 100 percent effective in terms of preventing sexual transmission of HIV. Condoms are also cheap and widely available; hence the bar is already set quite high. While PrEP clearly afforded greater protection for those who received Truvada, counseling and condoms, a major problem once again reared its ugly head in the study: poor adherence.

Failure to use condoms correctly and consistently is a major reason why the HIV epidemic

continues to go unchecked--and a reason why biomedical approaches such as PrEP are being explored in the first place--and it now looks as if Truvada adherence is also a problem. Though iPrEx volunteers frequently self-reported stellar adherence, their blood levels of the tenofovir and emtricitabine in Truvada begged to differ (average drug levels were 50 percent below what they should have been). And when adherence rates are questionable in a clinical trial, where there is a great deal of structure and support available to volunteers, this does not bode well for real-world experience.

Until behavioral scientists have figured out ways to fully empower people at risk for HIV to consistently take proactive steps to protect their health, no intervention requiring regular compliance--whether it is condom use, daily PrEP or a combination of both--will substantially reduce HIV incidence rates in the U.S. or elsewhere in the world.

Second, the results of iPrEx only speak to one population of people at risk for HIV: males and transgendered females who have sex with men. These findings can't be extrapolated to other at-risk communities, notably women--particularly women of color--and intravenous drug users. Each population comes with its own challenges. What's more, the levels of drug in the body needed to protect against HIV may differ according to type of exposure. In other words, drug concentrations needed to defend against vaginal exposure to the virus may be very different from those needed to defend against anal exposure.

Fortunately, a number of other studies--involving more than 20,000 people--are being conducted around the world to explore the safety and efficacy of PrEP in these other at-risk populations.

Third, it's important to take "subset analyses" with a grain of salt. Many accounts of the study are quick to point out that the rate of PrEP efficacy was higher than average among a segment of iPrEx participants dubbed to be at high-risk for infection--a 58 percent reduction in the number of infections among subjects who reported at screening that they had previously had unprotected receptive anal intercourse. This is not insignificant, given that many public health experts have argued that PrEP may only be recommended for those at the highest risk of infection in specific populations.

The efficacy rate was higher still among those who strictly adhered to their daily Truvada dosing (73 percent fewer HIV infections).

Both findings are encouraging, but consider the fact that only 60 percent of the 2,500 study volunteers reporting having unprotected receptive anal intercourse. In turn, it is difficult to draw strong conclusions from an analysis involving a select group of volunteers in an already limited population of people at risk for HIV. While this finding should definitely help shape future studies to determine the likely effectiveness of PrEP amongst those at greatest risk of infection--in fact, the iPrEx study authors calculated that if all subjects had strictly adhered to Truvada, the number of new infections would have been reduced by at least 92 percent--it shouldn't overshadow the much more conservative efficacy rate seen in the overall study population, which speaks to the fact that adherence is a significant problem.

Third, side effect data remain limited. Nausea and unintentional weight loss were the only two side effects that were statistically more likely to occur amongst those receiving Truvada compared with placebo, and at very low rates (approximately 2 percent vs. 1 percent). Good news, but it's important to keep in mind that this study was short--volunteers were followed for an average of 14 months. Data regarding the possible long-term side effects of Truvada when used as PrEP, such as kidney disease and bone loss, are needed.

Fourth is the issue of drug resistance. Encouragingly, no tenofovir or emtricitabine drug resistance was documented in the 36 people participating in iPrEx who became infected with HIV while taking Truvada. One reasons for this is that tenofovir and emtricitabine levels were detectable in only 9 percent of those who became infected, hence they didn't likely have enough of the drugs in their bodies to prompt the emergence of drug-resistance mutations. It is also important to note, however, that study volunteers were tested for HIV every month while participating in iPrEx and instructed to discontinue their assigned study drug if found to be positive. This important safeguard also likely contributed to the absence drug resistance among those who seroconverted.

Are we prepared to offer monthly HIV testing to all those using PrEP in the real world?

It is also worth pointing out that ten people entered the study with acute HIV--infection that couldn't be documented using rapid HIV antibody testing. Unfortunately, two of the ten were assigned to the Truvada arm and were inadvertently treated with sub-standard therapy (people living with HIV should be treated with at least three drugs, not just Truvada). As a result, they acquired a key mutation (M184V) associated with resistance to the emtricitabine in Truvada.

How can we safeguard against providing PrEP to those who are in the initial, difficult-to-detect throes of HIV infection in the real world?

What isn't addressed at all in the study is the issue of cost. Truvada isn't cheap, nor is the adherence counseling, regular HIV testing and monitoring of side effects that will be needed. Who will pick up the tab for such a costly approach in a world of shrinking HIV prevention and treatment resources?

In short, as encouraged as I am--and many are--by these results, they bring to the surface many more pertinent questions than they do solid conclusions. We've established that PrEP works, *and has the potential to work very well*, in humans. November 23 was truly a good day for HIV science, not to mention newspapers.

Where do we, as a community, go from here? Consider the following warning included in a public statement by San Francisco's Project Inform:

As promising as the iPrEx results are, Project Inform strongly urges gay and bisexual men and trans

females not to attempt PrEP on their own. We strongly discourage HIV-negative people from acquiring Truvada from HIV-positive people for PrEP, thus threatening the health of both individuals. We stress that iPrEx data are based on taking TDF/FTC daily along with participation in behavioral counseling, condom use, medication adherence counseling and clinical monitoring. There are no data whatsoever to suggest that using PrEP episodically or around the time of sex is at all effective.

We continue onward and upward, but cautiously.
