100% Efficacy for Gays Who Adhered in PrEP Study; Most Didn't

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Men and transgender women who have sex with men who took Truvada (tenofovir/emtricitabine) as pre-exposure prophylaxis (PrEP) four or more days a week were 100 percent protected against HIV in a recent study. However, participants actually took Truvada that frequently just 33 percent of the time during the 72-week trial, and overall adherence declined throughout the study. Daily adherence to Truvada was detected just 12 percent of the time. When considering all participants who received Truvada, regardless of their adherence, the study showed that PrEP lowered the risk of acquiring HIV by about half.

The trial showed no evidence of risk compensation, which is when someone taking PrEP increases sexual risk taking. Actually, study participants, who were given risk-reduction counseling, trended toward less risky behaviors during the trial.

Uptake of Truvada was high at 76 percent, and those at higher risk of HIV were more likely to take the drug. However, in an accompanying editorial in The Lancet, Raphael J. Landovitz, MD, MSc, of the UCLA Center for Clinical AIDS Research and Education at the David Geffen School of Medicine at the University of California, Los Angeles, asked if such uptake was high enough, considering all the participants had come from previous clinical trials of PrEP, making them more likely to take the drug than the average person at risk or HIV.

One study participant who took Truvada and contracted HIV developed resitance to the drug.

Publishing their findings in The Lancet Infectious Diseases, researchers from the open-label extension phase of the iPrEx study (iPrEx OLE) enrolled 1,603 participants from three previous PrEP studies—ATN 082, iPrEx and US Safety Study—and offered them the chance to take daily Truvada if they were HIV negative. Participants were enrolled between June 2011 and June 2012. The study results were also presented at the 20th International AIDS Conference (AIDS 2014) in Melbourne, Australia.

The study is the first to show results from what is known as a demonstration project, which examines medication use outside the rigid confines of a placebo-controled randomized controlled trial, making its findings a somewhat better prediction of PrEP's effects in a real-world setting.

"Findings from iPrEx OLE are particularly important in relation to emerging guidelines

recommending expanded use of PrEP," iPrEx lead researcher Robert Grant, MD, MPH, of the Gladstone Institutes and the University of California, San Francisco, said in a release. "The project provides critical insight into what happens as PrEP transitions from clinical trials to clinical practice. It is particularly compelling to see such strong interest in PrEP among young gay and bisexual men, who are increasingly impacted by HIV."

A total of 1,225 (76 percent) of the participants chose to receive PrEP; the remainder, who did not take the drug, were also followed for the duration of the study. There were study sites in the United States, Brazil, Peru, Ecuador, South Africa and Thailand. A total of 287 of the participants (18 percent) were enrolled in the United States, with 224 of them (78 percent) opting to take PrEP.

The participants made visits to the study sites at weeks 4, 8, 12, 24, 36, 48, 60 and 72. During these visits they received sexual health and PrEP adherence counseling. They received HIV tests at each visit and were screened for syphilis, herpes and urethritis every 24 weeks or if they had symptoms. The investigators also took blood plasma and then, for one of the visits during the first 12 weeks (participants did not know which) prepared dried blood spots to analyze for drug levels. The researchers tested a random sample of 27 percent of participants' drug levels at every visit. Those who tested positive for HIV had drug levels tested at that time and all previous visits' samples were retroactively tested for drug levels.

A total of 373 participants opted not to take PrEP. Their reasons for this decision included concerns about side effects (50 percent), not wanting to take a daily pill (16 percent), not liking taking pills (13 percent), a preference for other HIV prevention methods (14 percent), fear that they will be perceived as HIV positive (7 percent) and fear that people will know they have sex with men or transgender people (3 percent).

Those at higher risk of HIV appeared more likely to opt for PrEP. Eighty-one percent of the enrolled participants who chose to take Truvada reported intercourse without a condom, compared with 75 percent of those who opted not to take PrEP.

A total of 41 people contracted HIV during the study, including 13 of the 373 who did not receive PrEP, for an infection rate of 2.6 per 100 person-years, and 28 of the 1,225 who did receive PrEP, for an infection rate of 1.8 per 100 person years. Seven of the cases in the PrEP group had chosen to discontinue Truvada more than two months before seroconverting, five of whom stopped because of side effects.

Thus, the PrEP group had a 49 percent lower HIV incidence when compared with the non-PrEP group after adjusting for higher risk sexual practices reported at the beginning of the study. The estimate range of PrEP's overall efficacy, also known as a confidence interval, was between a 1 percent increase in HIV incidence and a 74 percent decrease. Because the estimate range included the possibility that PrEP increased the likelihood of infection, the difference in HIV incidence between the two groups was not statistically significant, meaning it could have occurred by chance. However, when comparing just those PrEP-taking participants who were in the original iPrEx trial with the placebo group from that study, Truvada yielded a 53 percent risk reduction

rate. The confidence interval for that comparison was between a 26 percent and 70 percent decrease in the likelihood of infection, making the risk reduction statistically signficant and giving greater weight to the finding that in this study PrEP reduced the rate of HIV by about half across the board.

PrEP's overall efficacy in this study, as with all previous trials, was dragged down by poor adherence to Truvada. None of those whose blood tests showed they were taking Truvada four or more days a week tested positive for HIV during those particular clinic visits. However, just 33 percent of the clinic visits showed that the PrEP users were taking Truvada that frequently.

The study stratified PrEP's risk reduction rates based upon how frequently participants were actually taking the drug according to blood tests taken at the various clinic visits. Participants showed no evidence of the drug in their systems in 25 percent of visits. There were 18 HIV infections detected during these particular visits, for an incidence rate of 4.7 per 100 person-years and a 25 percent increased risk of HIV infection when compared with the non-PrEP group. This increased risk was not statistically significant, however, meaning it could have occurred by chance, so one cannot presume that PrEP increased the risk of acquiring HIV in this circumstance.

Participants showed evidence of taking the drug less than two times per week at 26 percent of the visits. Nine infections detected during these visits meant an incidence rate of 2.25 per 100 person-years and a 44 percent reduction in risk when compared with the non-PrEP group.

Participants were taking Truvada two to three times a week at 12 percent of visits. There was one HIV infection detected at these visits, for an incidence rate of 0.56 per 100 person-years and an 84 percent reduction in risk when compared with the non-PrEP users.

Participants took Truvada four to six times a week at 21 percent of visits and seven times a week at 12 percent of visits. There were no infections in either category, for an incidence rate of zero for both, with an estimated range of HIV incidence of zero to 0.61 per 100 person-years for those adhering four to six days a week and zero to 1.06 in those adhering perfectly. (That means that if 10,000 people matching the demographics of the group receiving PrEP took PrEP every day for one year, an estimated zero to 106 of them would contract HIV.)

Based on the findings in this study, the researchers estimate that taking Truvada four or more days a week is 100 percent effective at preventing HIV. The combined estimate range of four to six days a week dosing and daily dosing is 86 percent to 100 percent efficacy. That means that, according to this trial, four or more days a week of PrEP reduces the risk of contracting HIV by at least 86 percent, but that figure may indeed be as high as 100 percent.

By comparison, the original iPrEx study showed a 92 percent risk reduction among those who had any Truvada in their systems, with an estimate range of 40 to 99 percent efficacy. A subsequent study of the iPrEx data used statistical modeling to estimate that four doses a week reduced the risk of HIV by 95 percent, with a 90 percent to more than 99 percent estimate range, and that daily dosing reduced the risk by 99 percent, with an estimate range of 96 to more than 99 percent.

The study authors are still working to determine details about the infection of the one participant in the PrEP group who contracted HIV and developed drug resistance. The iPrEx trial only saw drug resistance develop in those who turned out to be acutely infected with HIV at the beginning of the trial (which meant they tested false negative and were admitted into the trial when they should have been rejected for being HIV-positive already). A major difference in this trial is that participants were eventually tested for HIV every 12 weeks, possibly giving a new case of HIV more time to mutate and develop resistance, while those in the iPrEx trial were tested every four weeks throughout. U.S. guidelines recommend testing for HIV every three months when taking PrEP.

The study suggests that those at greater risk of HIV were more likely to adhere to PrEP. Higher drug concentrations were correlated with receptive anal intercourse without a condom, greater numbers of sexual partners, a history of syphilis or herpes and having sex with any HIV-positive partners. Higher drug concentrations were also linked to more advanced education. Drug levels were 69 percent higher in those who reported condomless receptive anal intercourse, 57 percent higher in those who reported having sex with more than five partners in the three months prior and 40 percent higher in those reporting sex with a partner they knew was HIV postiive.

Better adherence was most strongly associated with older age. Participants who were in their 30s had double the likelihood and those over 40 were three times as likely to have detectable drug at study visits when compared with those under 25

Those participants who opted to receive PrEP and who contracted HIV were likely to do so during gaps in use as opposed to during periods of using the drug only a few days a week. The researchers found that such intermittent use of Truvada was not common and that a more typical pattern was taking the drug at least two to three days a week followed by completely stopping. People tended to stop taking Truvada earlier in the trial.

Sixty-seven percent of the participants eligible to take PrEP were good candidates for Truvada based on their risk profiles, reporting receptive anal intercourse without a condom, multiple anal sex partners or a recent sexually transmitted infection. Three quarters of this group opted to take PrEP, 93 percent of whom were retained in the study by week 12.

There was no evidence of risk compensation in the study. On the contrary, the number of reported sexual partners and the proportion of those reporting receptive or insertive anal intercourse without a condom all decreased at similar rates among both those receiving PrEP and those who did not. The proportion of those taking PrEP reporting receptive anal intercourse without a condom dropped from 34 percent to 25 percent during the study while the proportion reporting condomless receptive anal intercourse among those not taking Truvada dropped from 27 percent to 20 percent. The syphilis rates were similar between the two groups.

“This study provides still more evidence that gay and bisexual men and transgender women want access to this safe and highly effective form of HIV prevention,” Jim Pickett, director of prevention advocacy and gay men’s health at AIDS Foundation of Chicago, said in a release. “Moving forward,

we must increase awareness of PrEP among all who could benefit from it, and overcome critical barriers to PrEP access including misinformation, lack of provider training, and insufficient coverage via health insurance and other payor programs."

UCLA's Raphael Landovitz, however, was more equivocal in his assessment of the study, writing in The Lancet that "it raises nearly as many questions as it answers." Among his questions are: the reasons for steady drop-offs in adherence; why HIV incidence is not "vanishingly low" despite comprehensive prevention counseling in PrEP trials; the likelihood that those on PrEP will develop drug resistance; whether those most at risk for HIV will use the drug in real-world settings; and whether risk compensation will be a significant problem in real-world settings.

Landovitz concludes his essay by writing, "The future is rich with possibility, but we have far to go to realize the full potential of PrEP."

To read the Lancet paper, click here.

To read the Lancet editorial, click here.

To read the press release, click here.
