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Use of HIV Medications Reduces Risk of HIV Infection in Uninfected People, Study Suggests

In a finding with the potential to fundamentally change strategies to slow the global HIV epidemic, a new study called "iPrEx" shows that individuals at high risk for HIV infection who took a single daily tablet containing two widely used HIV medications, emtricitabine and tenofovir (FTC/TDF), experienced an average of 43.8% fewer HIV infections than those who received a placebo pill (95% CI 15.4 to 62.6%; P=0.005). The study, reported in the New England Journal of Medicine, is the first evidence that this new HIV prevention method, called pre-exposure prophylaxis or PrEP, reduces HIV infection risk in people.

A total of 2,499 individuals at high risk of HIV infection participated in the six-country iPrEx study. All study participants received a comprehensive package of prevention services designed to reduce their risk of HIV infection throughout the trial, including HIV testing, intensive safer sex counseling, condoms and treatment and care for sexually transmitted infections. Half of study participants also received the PrEP pill, while the other half received a placebo.

In all, 64 HIV infections were recorded among the 1,248 study participants who received a placebo pill, while 36 HIV infections were recorded among the 1,251 participants who received the study drug. The average reduction in HIV infection risk of 43.8% includes all study participants -- even those who did not take the daily pill consistently.

The iPrEx study found that PrEP was more protective among those, who reported taking the pill more regularly. Among participants, who used the tablet on 50% or more of days, as measured by pill counts, bottle counts and self-reports, risk of HIV infection fell by 50.2% (95% CI 17.9-69.7%; P=0.006); among those who used the pill on 90% or more of days, as determined by the same measures, the PrEP pill reduced infection risk by 72.8% (95% CI 40.7-87.5%; P=0.001).

While pill-taking measures that rely on self-reports are not objective, testing to measure levels of the PrEP drug in the blood of study participants -- a more reliable measure of pill-taking -- also indicated that those participants, who were protected against HIV infection were likely taking the study drug more regularly. Among a subset of study participants who received the active drug, detectable levels of the PrEP drug combination were found in the blood of 51% (22 of 43) of a group that remained HIV-negative, but in only 9% (3 of 34) of participants who became HIV infected. Low or absent drug levels underlay all of the infections that occurred among those who received active PrEP, while those who used the drug more regularly had higher levels of protection against HIV infection.

"The iPrEx study proves that PrEP provides important additional protection against HIV when offered with other prevention methods such as HIV testing, counseling, condom use and management of sexually transmitted infections," said iPrEx Protocol Chair Robert Grant, MD, MPH of the Gladstone Institutes and the University of California at San Francisco. "As with other prevention methods, the greatest protection comes with consistent use. I hope this finding inspires a renewed commitment from communities, industry and government to stop the spread of HIV."

"iPrEx is a significant advance in HIV prevention," said Javier R. Lama, MD, MPH, the co-chair of the study protocol who is based in Lima, Peru. "Thanks to the extraordinary efforts of our study participants, their families and communities,

iPrEx shows that a preventive drug can significantly reduce HIV infection risk. Further research is now needed to optimize the efficacy of oral PrEP based on iPrEx results."

About iPrEx and PrEP

The iPrEx study (Iniciativa Profilaxis Preexposicion or Prexposure Prophylaxis Initiative) is a double-blind, placebo controlled Phase III clinical trial that began in 2007, following three years of community consultation. iPrEx is the first human efficacy study of PrEP to report data. The iPrEx study was sponsored by the U.S. National Institutes of Health (NIH) through a grant to the Gladstone Institutes, a non-profit independent research organization affiliated with the University of California at San Francisco. Additional support for iPrEx was provided by the Bill & Melinda Gates Foundation.

"The devastating impact of HIV continues to spread around the world," said R. Sanders Williams, M.D., president of the Gladstone Institutes, which coordinated the iPrEx study. "Gladstone will continue its research into new ways to prevent HIV infection, and we urge community organizations and governments to make available effective scientific advances to stop HIV such as PrEP."

In all, 2,499 men and transgender women who have sex with men (MSM) at high risk for HIV infection participated in the iPrEx study at 11 sites in Brazil, Ecuador, Peru, South Africa, Thailand and the United States. Other studies of PrEP are currently underway among heterosexual men and women, serodiscordant couples and injection drug users. iPrEx researchers are careful to point out that those trials should continue, as results from the iPrEx study cannot be extrapolated to predict the impact of PrEP on other populations. Approximately 20,000 participants are currently or expected to be enrolled in PrEP trials worldwide. PrEP was previously demonstrated to be highly effective in animal studies.

In July, 2010, a study known as CAPRISA 004 found evidence that a topical gel containing 1% tenofovir helped reduce HIV negative women's risk of HIV infection via vaginal sex. The topical gel is another form of HIV prevention using antiretroviral drugs currently being explored, in addition to oral PrEP.

The drug used in the iPrEx study, a single-tablet combination of emtricitabine (FTC 200 mg) and tenofovir (TDF 300 mg), is marketed by Gilead Sciences, Inc. under the brand name "Truvada®", and is available generically in many countries at prices as low as approximately 40 cents (U.S.) per tablet in the poorest countries of the world. Gilead Sciences provided study drug for, but did not participate in any other way in the design, implementation or analysis of the iPrEx study.

National and international health authorities and regulatory bodies must now meet to review the iPrEx study data and to determine whether and how to recommend use of PrEP for people at increased risk of HIV infection. Much remains to be learned about how to maximize the impact of PrEP and use this new tool most effectively. An 18-month "open label" study of FTC/TDF PrEP, which will provide the drug to HIV uninfected participants in the original study who wish to join, will begin next year and should provide additional information on efficacy, safety, behavior and pill taking. HIV-positive iPrEx participants will also be invited to enroll in this phase of the study for ongoing monitoring.

The impact of HIV on MSM

iPrEx studied the impact of PrEP on one of the populations hardest hit by the global HIV epidemic, men and transgender women who have sex with men (MSM). Globally, even in regions with generalized HIV epidemics such as Africa and Asia, MSM often have much higher rates of HIV infection than the population at large. HIV prevention tools that reduce infection in MSM not only have the potential to save thousands or millions of lives directly, but could also greatly reduce the impact of HIV on all communities at risk by reducing overall prevalence of the disease and thus the global risk of HIV infection.

iPrEx is one of the largest HIV prevention clinical trials to focus on men who have sex with men, the first HIV prevention study to focus on MSM to be conducted in either Africa or Asia, and the first demonstration of a biomedical intervention to prevent HIV infection in MSM.

Side effects, resistance and behavioral issues in iPrEx

Side effects from use of the PrEP pill were mild and infrequent in the iPrEx study. These included a small

number of reports of low-grade transient nausea, which dissipated after several weeks. Such symptoms are relatively common after initiation antiretroviral therapy, and reassurance from peers and providers in the first few weeks is important to promote long term adherence. In addition, isolated mild elevations of creatinine, a naturally occurring molecule filtered by the kidneys, occurred in a small number of individuals receiving the active drug and resolved spontaneously or with discontinuation of the pill. Slight increases were also detected in headache and unintentional weight loss among participants in the study arm that received FTC/TDF.

The iPrEx study carefully monitored for any indications of HIV drug resistance among individuals who became HIV infected during the study. No iPrEx study participant developed detectable resistance to tenofovir (TDF), one of the component drugs of the PrEP pill used in this study. Two participants who received the active PrEP drug developed resistance to the its other component drug, emtricitabine (FTC), and one participant who received placebo appears to have been infected with a strain of HIV that was already resistant to FTC. All three participants with FTC resistance were HIV-infected at the time of enrollment in iPrEx, but their infection was too new to be detected by standard HIV antibody testing. Investigators emphasize the need for additional testing and clinical screening to ensure that anyone starting PrEP is not already HIV infected.

A concern that the use of the PrEP pill could cause study participants to relax their use of safer sex practices was not demonstrated in the iPrEx study. In fact, self-reported HIV risk behavior decreased among participants in both arms of the study, and condom use increased. More research is needed to see how risk behavior may change now that information is available about PrEP safety and efficacy.

Additional data from the iPrEx study will be collected, analyzed and released in the coming year. This will include analyses designed to detect any low level side effects related to bone mineral density or kidney function, which have been associated with some HIV therapies. Other analyses will search for any additional evidence of drug resistance, look for evidence of use of the PrEP tablet through measures of drug exposure and will examine HIV risk behavior through the occurrence of sexually transmitted infections.

"Every year 2.7 million people are infected with HIV, and PrEP has the potential to help bring those numbers down. We have a moral obligation and a public health imperative to quickly act on these results. The HIV prevention field and national HIV policymaking bodies, along with WHO and UNAIDS, must promptly review the iPrEx data, consult with both experts and affected communities and develop clear plans and recommendations for next steps in research and possible access to PrEP," said Mitchell Warren, executive director of AVAC, a global HIV prevention advocacy organization.

Editor's Note: This article is not intended to provide medical advice, diagnosis or treatment.