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Oral antiretroviral pre-exposure prophylaxis reduce the risk of HIV acquisition among men-who-have sex with men

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Context

Additional interventions to combat the HIV/AIDS epidemic are needed urgently. Prevention interventions using antiretroviral agents to prevent sexually acquired HIV are being studied in humans. Current evidence suggests that, by reducing viral load to undetectable level, combination antiretroviral therapy used to treat and extend the life of HIV-infected individuals may also reduce their infectivity thereby reducing the risk of transmission to their uninfected partners.[1] In 2010, a topical antiretroviral-based vaginal microbicide, Tenofovir 1% gel, was shown to reduce HIV acquisition among South African women.[2] The iPrEX study is the first multicentre double-blinded randomised trial evaluating the efficacy and safety of antiretroviral drugs used as oral pre-exposure prophylaxis (PrEP) to prevent HIV infections.

Methods

The study enrolled HIV-seronegative men and transgender who have sex with men (MTSM) from 11 sites worldwide. The study drug, Emtricitabine (FTC) and Tenofovir Disoproxil Fumarate (TDF) combined in a single daily tablet (Truvada), was chosen because of its favourable characteristics and good safety profile. A total of 2499 MTSM (mean age of 25 years) were randomly assigned to the FTC/TDF PrEP or the placebo arm and followed for a median of 1.2 years between 2007 and 2009. At each quarterly visit, participants received a standard package of prevention and sexually transmitted infection treatment services. Adherence to the daily regimen was measured using pill count and self-report. In addition, a nested case-control study within the trial measured intracellular and plasma drug-level concentrations.

Findings

FTC/TDF PrEP reduced HIV incidence by 44% (95% CI 15% to 63%). Although self-reported adherence was high (around 90%), study drug measured in subsamples from the FTC/TDF arm was detected in only 51% of seronegatives (indicating low adherence) and 9% of seropositives. Thus, individuals with detectable study drug had a 92% (95% CI 40% to 99%) lower risk of HIV infection than those without detectable drug. PrEP effectiveness was larger among participants reporting more than 90% pill use (73%, 95% CI 41% to 88%) and participants reporting unprotected receptive anal intercourse (URAI) at enrolment (58%, 95% CI 32% to 74%). Plasma HIV RNA levels and T cell counts of HIV-infected individuals did not differ between arms during follow-up. Overall, adverse events were reported to be mild and infrequent, and rates were similar between trial arms. Although three patients already infected at study entry had FTC-resistant infections (2/1 in the PrEP/placebo arm), no TDF or FTC resistance was reported among participants who became HIV infected during follow-up.

Commentary

It was recently announced that the iPrEX trial results were sufficient for the Food and Drug Administration to consider changing the indication for Truvada to include an efficacy claim on preventing HIV acquisition among high-risk Men who have sex with men.[3] Despite this important step, uncertainties remain regarding the potential wide-scale use of FTC/TDF PrEP to help control the HIV epidemic. First, IPrEX results cannot be generalised to females and other risk populations. Second, the level of protection conferred by the drug is partial and imprecise, with estimates ranging between 15% and 63%. Results from ongoing trials will hopefully narrow this range and provide evidence of effectiveness in other risk populations. Third, the effectiveness measured in the trial is a mixture of true reduction in HIV risk under optimal adherence and actual adherence. On the basis of the drug concentration data, the adherence in the trial was quite low. Thus, FTC/TDF effectiveness may perhaps be higher among highly adherent users. New results showed that the drug was detectable in 76% of MTSM who reported URAI in the previous 12 weeks and in 97% of US participants, suggesting that high compliance may achievable in some risk populations.[3] Nevertheless, it is premature to tell whether such high-adherence levels obtained in a clinical trial setting can be achieved and maintained in the real world over many years. Clearly explaining the importance of adherence and the notion of partial protection to potential PrEP users will be challenging, yet crucial. Finally, although the safety profile reported over the short trial duration was good, additional studies are needed (some are ongoing) to document the longer term risks of PrEP use, which may worsen or develop over time (eg, bone mineral loss, increase in risk behaviour, poor adherence). Because drug use was rapidly discontinued following HIV infection, the risk of developing resistance may also have been underestimated. Answering these questions is important to provide appropriate counselling to individuals and to assess the potential public health benefits and risks impact of large-scale oral PrEP intervention programme to combat HIV.

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