EDITORIAL

Oral Preexposure Prophylaxis for HIV — Another Arrow in the Quiver?

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Despite the growing global access to life-extending antiretroviral drugs for the more than 33 million persons living with human immunodeficiency virus (HIV) infection, approximately 7000 new infections occur daily. This alarming number speaks to the critical need for effective approaches to HIV prevention.[1] Early approaches to prevention were limited to the consistent use of barrier methods during sex,[2] a reduction in the prevalence of HIV in the blood supply, behavior modification, postexposure prophylaxis, and awareness of HIV-infection status. Antiretroviral drugs that were provided to pregnant women with HIV infection were shown to dramatically reduce the risk of perinatal transmission,[3] with added protection to treated breast-fed infants of HIV-infected mothers.[4] A single study suggested that treatment of intercurrent sexually transmitted infections could decrease the susceptibility to HIV.[5]

However, continually impressive advances in the effectiveness of potent antiretroviral therapy to treat chronic HIV infection from 1995 to the present were not matched with concomitant improvements in methods for HIV prevention until relatively recently. For quite some time, the HIV-prevention quiver held precious few arrows. This began to change in the period from 2005 through 2007, when studies showed that adult male circumcision, vaccination, or the use of a vaginal microbicide could variably reduce the risk of HIV infection.[6-10] However, the need for more and better preventive treatments remains.

In this issue of the *Journal*, Grant and colleagues[11] report evidence that antiretroviral medications, specifically the combination of emtricitabine and tenofovir disoproxil fumarate (FTC–TDF), taken orally on a daily basis by men and transgender women (born male) who have sex with men, can provide partial protection from HIV infection. The trial, called the Preexposure Prophylaxis Initiative (iPrEx) study (ClinicalTrials.gov number, NCT00458393), was a placebo-controlled, double-blind, randomized trial involving 2499 subjects in the Americas, South Africa, and Thailand. Of the 100 incident infections, 64 occurred in the placebo group and 36 in the FTC–TDF group, for an estimated efficacy of 44% with a 95% confidence interval of 15 to 63. In the FTC–TDF group, the study drug was pharmacologically detected in 51% of subjects who remained free of HIV infection but in only 9% of those who became infected. Thus, exposure to FTC–TDF was associated with a reduction in HIV acquisition, which supports the biologic plausibility of the primary result.

The results of the iPrEX study also reveal real challenges. First, the association between self-reported drug adherence and pharmacologic detection of the study drug was very poor, which underscores the need for better reporting tools to predict drug adherence. Second, although renal insufficiency was seen in a relatively small fraction of subjects and was reversible on drug discontinuation, this finding raises both safety and monitoring concerns regarding possibly cumulative toxic effects associated with large-scale exposure of at-risk persons to daily FTC–TDF therapy for an extended period. The side-effect profile for FTC–TDF was probably diluted, given the reported medication-compliance issues, and thus would probably be more substantial with full compliance. Third, and most worrisome, viral resistance to FTC was documented in both of the subjects who were found to have had acute HIV infection at enrollment. Secondary FTC resistance after exposure to the drug clearly developed in one of these subjects, and the second

subject had indeterminate resistance on baseline testing but showed FTC resistance 4 weeks after enrollment. This raises very serious concern about the deployment of oral FTC–TDF in populations of men who have sex with men and who are at greatest risk for HIV acquisition and thus have an increased risk of undiagnosed acute HIV infection. In addition, persons who have other chronic viral infections, such as hepatitis B virus (HBV) infection, may have intermittent antiviral exposure as well, which could lead to the emergence of resistance or HBV rebound with the cessation of prophylactic FTC–TDF therapy. We await the follow-up data from subjects with chronic HBV infection in the iPrEX study to provide some insight here.

The results of the iPrEX study represent a significant advance in HIV-prevention research in providing the proof of concept that a combination antiretroviral drug in widespread clinical use in the treatment of chronic HIV infection reduces the risk of HIV acquisition in men who have sex with men. What will be the public health effect of these results? The overall reduction in HIV incidence in the FTC–TDF group was less than 50%. Although increased medication adherence would raise this degree of protection (along with the risk of potential side effects), what is the likelihood that such a regimen could be accomplished in an implementation program that lacks the intense reinforcement of adherence counseling provided in the context of a clinical trial? How can medication-use fatigue be mitigated over potentially many years of daily therapy? What are the potential long-term safety issues for healthy persons, as well as those with coexisting illnesses, such as diabetes or hypertension? What will the iPrEX results mean for other populations with a lower risk of HIV acquisition? What would be the effect of open-label FTC–TDF use on the prophylactic use of condoms, on knowledge of HIV-infection status (both for subjects and their partners), and on the frequency of casual sex?

The risks of daily FTC–TDF use include the troubling development of secondary antiretroviral resistance in treated persons with undiagnosed acute HIV infection and a low but measurable degree of renal toxicity. Adherence to a daily regimen was low, nondurable, and difficult to assess without pharmacologic testing, which has substantial implications for research that uses this measure of behavior for medication compliance. Thus, the potential implementation of preexposure prophylaxis with FTC–TDF will probably be considered for men who have sex with men and who are at very high risk for HIV infection. In such men, the benefits of preexposure prophylaxis would be maximized and the costs of screening for acute HIV infection and monitoring of renal function and antiretroviral-drug adherence would be best justified.

Because of these considerations, the implementation of FTC–TDF therapy will be especially challenging in resource-limited health care settings. New information on the use of intermittent antiretroviral prophylaxis before risk exposure in men who have sex with men and in other high-risk groups will be coming from ongoing clinical trials. Taken together with the results of the iPrEX study, these data are likely to place another arrow in the quiver for HIV prevention.

The views expressed in this editorial are those of the author and do not necessarily reflect the views of the U.S. Army or the Department of Defense.

Disclosure forms provided by the author are available with the full text of this article at NEJM.org.

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