EDITORIAL

Preexposure Prophylaxis for HIV — Where Do We Go from Here?

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Transmission of the human immunodeficiency virus (HIV) continues at a staggering rate in many areas of the world. The rate of HIV acquisition in young, healthy adults (mostly women) was 3 to 5 per 100 person-years in two trials studying heterosexual transmission of HIV in sub-Saharan Africa, now reported in the *Journal* (the Preexposure Prophylaxis Trial for HIV Prevention among African Women [FEM-PrEP][1] and the TDF2 study[2]). This rate of HIV transmission demands the urgent development of new prevention strategies as well as the deployment of all existing strategies, including the use of condoms, male circumcision, and the treatment of HIV-infected partners.[3]

The use of antiretroviral agents by HIV-uninfected persons before potential sexual exposure to HIV-infected partners, known as preexposure prophylaxis, is a new approach to HIV prevention. A trilogy of field trials from Africa — the two mentioned above and the Partners Preexposure Prophylaxis (PrEP) study[4] — explored the ability of oral daily tenofovir disoproxil fumarate (TDF) or tenofovir–emtricitabine (TDF-FTC) to prevent HIV acquisition in several high-risk populations of sexually active women[1,2] and men,[2] including HIV-discordant couples.[4] These results, now reported in the *Journal,* are especially timely because, on the basis of these and earlier findings,[5,6] a Food and Drug Administration panel recently recommended approval of the TDF-FTC antiretroviral combination for preexposure prophylaxis.[7]

These trials have complex and disparate results. In the TDF2 and Partners PrEP studies, an efficacy rate of about 62 to 75% for HIV prevention was found, yet the FEM-PrEP study was discontinued early because of a lack of protection. Inconsistency in this area of study is not unique. Tenofovir gel used during intercourse by women in the Centre for the AIDS Programme of Research in South Africa (CAPRISA) 004 study[8] showed efficacy, but the results were not confirmed in the ongoing Vaginal and Oral Interventions to Control the Epidemic (VOICE) trial, in which the use of a daily tenofovir gel was stopped early because of futility.[9] The Partners PrEP study showed efficacy with oral TDF alone, but in the VOICE trial, the use of TDF alone was also stopped early because of futility.[10]

The striking differences in these findings highlight the importance of conducting additional studies to allow a proper understanding of the potential efficacy of and adverse events associated with preexposure prophylaxis and to identify other factors that might influence efficacy. The differing results also emphasize the central role of the data safety and monitoring boards (DSMBs) charged with overseeing study conduct and results in real time, reviewing the progress of a trial, and ensuring the safety of the study participants. The various DSMBs for the three trials reported here were confronted with tough and critical decisions.

Why the results differ across the various studies reported to date is unclear. However, important considerations include the populations studied; the likely routes of HIV transmission (vaginal vs. anal mucosa); the inclusion of established discordant couples in the Partners PrEP study, whose sexual behaviors and susceptibility to HIV may be

different from those of couples in which both partners are HIV-negative; and most important, medication adherence by study participants. All three studies used some measurement of antiretroviral concentration in blood plasma as a biomarker of adherence. The results showed that self-reported pill usage and pill counts can be unreliable measures of adherence[1] and that decreased efficacy for prevention was associated with the absence of the antiretroviral drug or drugs in the blood plasma. These data highlight the importance of objective measures of adherence and the substantive challenge, even in a research setting, of daily medication for the prevention of HIV in a healthy population.

Because TDF and TDF-FTC are readily available for clinical use, questions emerge as to how to consider these data in practice. How should preexposure prophylaxis be managed? Most anti-infective prophylactic agents are used as a bridge through an exposure window, much as antimicrobials are used at the time of surgery to prevent wound infection. If preexposure prophylaxis is started, how and when will it be stopped? What messages should the health care worker provide to the patient? And how should preexposure prophylaxis be monitored for adherence and safety? Providing a daily medication to healthy, HIV-uninfected persons demands an extraordinarily high degree of safety. There is substantial clinical experience with the TDF-FTC combination in the treatment of people with HIV infection, and no major safety concerns have been identified. However, the drugs have the potential to affect kidney[1,5] and liver[1] function and to reduce bone density.[2] The current studies were time-limited (about 1 to 2 years), so the long-term safety of TDF-FTC in healthy persons must be monitored, because the implied use may be for many years.

Although no evidence of increased risky sexual behavior or decreased condom usage was reported in these studies, we must ensure that preexposure prophylaxis does not indirectly encourage such behavior. The high rate of pregnancies reported actually demonstrates the occurrence of unprotected intercourse and the need for increased family planning, and it raises a concern about the inadvertent use of these medications in the first trimester of pregnancy.

HIV acquired during preexposure prophylaxis has the potential to develop resistance to the antiviral agents used (TDF-FTC), jeopardizing the therapeutic use of these drugs both for the patient in his or her subsequent treatment and for the community at large if resistance to the agents spreads more broadly.[11] This risk is highest if preexposure prophylaxis is started during unrecognized acute HIV infection (as seen in the current studies), but there can also be risk with subsequent HIV acquisition.[11] Because these antiretroviral agents have activity against the hepatitis B virus (HBV), this latter infection must also be considered; withdrawal of anti-HBV antiviral agents has been associated with severe HBV flares.[12]

Concern about the management of preexposure prophylaxis of HIV infection should not detract from the potential importance of the intervention. Further research is needed to identify the highest-risk populations and time periods and the preferred dosing strategy (daily or less frequent). We also need to better define the medical risks of the long-term use of these agents in a healthy population, to determine the costs, and to understand the effect on the induction and amplification of antiretroviral resistance in the patient and the community. The use of preexposure prophylaxis to obtain a population-level benefit is already receiving attention.[13] We must ensure that those with HIV infection who would benefit from HIV therapy receive it, because it has preventive effects as well.[14] As shown in the Partners PrEP study,[4] additional preexposure prophylaxis can be considered for uninfected partners of HIV-infected persons under some circumstances.

The prevention of HIV infection is a critical global public health priority. Preexposure prophylaxis is emerging as part of an integrated HIV prevention strategy. The health care provider who recommends preexposure prophylaxis needs a management plan that recognizes the effects of this intervention on the patient's sexual behavior, safety, and well-being as well as the ramifications of the intervention for the health of the public.

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