CLINICAL DECISIONS
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Preexposure Prophylaxis for HIV Prevention

This interactive feature addresses the diagnosis or management of a clinical case. A case vignette is followed by specific clinical options, none of which can be considered either correct or incorrect. In short essays, experts in the field then argue for each of the options. In the online version of this feature, available at NEJM.org, *readers can participate in forming community opinion by choosing one of the options and, if they like, providing their reasons.*

CASE VIGNETTES

The first patient, a 46-year-old sexually active man who has sex with men, presents for routine primary care. He lives in New York City and reports that he is in a long-term, stable, open relationship with a male partner and that he has had multiple recent sexual encounters with acquaintances. A recent HIV test was negative. He has seasonal allergies, for which he occasionally takes antihistamines, and chronic lower back pain, for which he takes nonsteroidal antiinflammatory drugs on a regular basis. Otherwise he takes no medications and has no known allergies to medications. He had syphilis 10 years earlier for which he was successfully treated. His physical examination is notable only for the fact that he is uncircumcised. You review HIV prevention strategies in detail with him, including the potential benefits of circumcision and of the use of condoms. He has been reading information on the Internet, including information about preexposure prophylaxis (PrEP), and asks whether he should be receiving this therapy.

Choose an option and comment on your choice at NEJM.org

The second patient, an 18-year-old heterosexual woman in South Africa who has recently become sexually active, presents for voluntary HIV testing. She does not know the HIV status of her male partners. She reports no medical problems, is taking no medications, and has no known allergies to medications. She reports that her older sister recently received a diagnosis of HIV infection. Her physical examination is unremarkable. Testing for sexually transmitted infections is performed. A pregnancy test is negative. She would like to initiate birth control and elects to start taking oral contraceptive pills. She returns to the clinic the following week and is informed that all the tests for sexually transmitted infections, including the HIV test, were negative. She thinks that she had received the hepatitis B vaccination series. She is negative for hepatitis B surface antigen. She is given extensive HIV counseling, and the various HIV prevention strategies are reviewed in detail.

Which one of the following approaches would you find appropriate for these patients? Base your choice on the published literature, your own experience, recent guidelines, and other sources of information, as appropriate.

1. Recommend initiating PrEP.

2. Do not recommend initiating PrEP.

To aid in your decision making, each of these approaches is defended in the following short essays by experts in the prevention of HIV infection. Given your knowledge of the patients and the points made by the experts, which approach would you choose? Make your choice and make individual recommendations for the two patients at NEJM.org.

TREATMENT OPTION 1

Recommend Initiating PrEP

Salim S. Abdool Karim, M.B., Ch.B., Ph.D.

The decision-making process for recommending PrEP begins with an assessment of the risk of HIV, followed by a determination of the combination of HIV-prevention strategies that provides the maximum protection. In the United States, men who have sex with men comprise approximately 2% of the population but account for more than 60% of new HIV infections. A history of sexually transmitted diseases and multiple partners places the man in the first vignette at

high risk. Despite education and condom-promotion programs, young women are the highest-risk group in Africa, where the prevalence of HIV among women 20 years of age is as high as 26.7%.[1] The fact that the young woman in the second vignette has had multiple partners places her at high risk in the generalized HIV epidemic in South Africa, where 12% of the population (approximately 5.6 million people) are HIV-infected. Her risk is higher if any partner is 5 or more years older than she is.

The effective options for HIV prevention that are available for the persons in both vignettes include the use of condoms, "sero-sorting" (choosing only partners who are HIV-negative), treatment for prevention (ensuring that all HIV-positive partners are taking antiretroviral treatment), and, finally, PrEP. Although medical circumcision of men is an established HIV-prevention option for heterosexual men, it has not yet been proven to be effective in protecting women[2] or men who have sex with men.[3] Although an HIV-prevention strategy that is based on knowing every partner's HIV status is desirable, this is rarely possible. Even partners who recently tested HIV-negative have a tangible risk, in high-incidence groups, of having an undiagnosed "window-period" infection or of having acquired HIV after the test was performed. Among HIV-positive partners who say they are receiving treatment, the risk of their transmitting the virus to others depends on their having actually initiated treatment, their adherence to treatment, and consequent viral suppression. In the case of young African women, who are seldom able to insist on the use of condoms or to establish the HIV status or treatment status of their partners, placing their risk of infection totally in the hands of their male partners is risky and fundamentally undermines efforts to empower women to control their own risk.

Hence, PrEP, which empowers receptive partners to control their HIV risk, is an essential component of an effective combination prevention strategy for the persons in both vignettes. In the absence of renal disease, daily treatment with tenofovir disoproxil fumarate (TDF) coformulated with emtricitabine (FTC), a therapy for which there are extensive safety data, should be prescribed, since it was shown to be effective in reducing HIV acquisition among men who have sex with men in the Preexposure Prophylaxis Initiative (iPrEX) trial[4] and among heterosexual partners in the Partners PrEP[5] and TDF2[6] trials. In these studies, drug resistance, which is a concern with the use of any antiretroviral agent, was an uncommon occurrence and was largely restricted to persons who initiated PrEP during an undiagnosed window-period infection. Nucleic acid testing (which tests for the presence of virus before antibodies can be detected) at the time of the initiation of PrEP, a costly option, could reduce the risk of resistance. For resistance that may still be present at the initiation of future treatment, effective therapeutic options other than TDF–FTC are available. It is important that PrEP be accompanied by counseling on the continued and increased use of condoms and on adherence to therapy, in order to avoid the lack of effectiveness that was observed in the Preexposure Prophylaxis Trial for HIV Prevention among African Women (FEM-PrEP).[7]

Widespread implementation of PrEP is, however, not without challenges that will require additional financial resources and health services capacity. Nevertheless, PrEP is an essential new HIV-prevention strategy that can and should be implemented in combination with the use of condoms, HIV testing, and promotion of treatments for HIV infection. PrEP prevents HIV infection, thereby reducing the need for treatment of AIDS in the future, is cost-effective,[8] and empowers vulnerable populations to directly control their risk of HIV infection.

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

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TREATMENT OPTION 2

Do Not Recommend Initiating PrEP

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There are an estimated 5.6 million HIV-infected people in South Africa, and countrywide surveillance of pregnant women shows that 14.0% of pregnant girls and women 15 to 19 years of age and 26.7% of pregnant women 20 to 24 years of age were HIV-infected in 2010[9] — statistics that suggest that the woman in the second vignette is at high risk for HIV infection.

PrEP with daily TDF–FTC[4] has been shown to reduce the risk of HIV acquisition in two specific populations — men who have sex with men and serodiscordant couples in Africa. However, the data are inconclusive, since other trials have shown no effect in women. PrEP was not shown to be effective in the FEM-PrEP study,[7] in which daily TDF–FTC was administered in women, nor in the TDF group of the Vaginal and Oral Interventions to Control the Epidemic (VOICE) study,[10] which was discontinued early for futility. Although adherence to daily medication has been shown to influence the effectiveness of PrEP, the inconsistent results among similar PrEP studies suggest that additional factors influence the effectiveness of PrEP in preventing the acquisition of HIV.

The efficacy data reported from the Partners PrEP study are difficult to extrapolate to the general population, since there may be unique features associated with HIV transmission in the context of a long-term, stable, serodiscordant partnership. The data on the efficacy of PrEP in the TDF2 study, which was conducted in Botswana,[6] are tantalizing, but there are substantial challenges to understanding these data, especially the effect of the low rate of retention of participants (which resulted in early termination of the study), the poor adherence to the study medication, and an apparent benefit only early after the initiation of PrEP. At first glance, the reported 62.2% reduction in HIV acquisition is compelling; however, of nine participants who were HIV-infected despite the receipt of TDF–FTC, seven were women, and in a subanalysis that was restricted to women, there was no significant protection with TDF–FTC as compared with placebo. Moreover, this and other studies raise concerns about the interaction of TDF–FTC with oral contraceptives, the selection of viral resistance in persons with undetected HIV-infection at baseline and in those who undergo seroconversion while receiving PrEP, and the proper monitoring over time of the safety of PrEP, including the effect on renal function and bone mineral density. Given the high risk of inducing HIV resistance at the initiation of PrEP, HIV nucleic acid testing (not just HIV antibody testing) should be considered as part of the assessment before the initiation of PrEP. This testing is costly and not widely available. The implications of all these issues in the context of the increased clinical use of PrEP are substantial and have yet to be pragmatically sorted out.

Our management of the cases described in both vignettes would therefore include HIV testing and counseling, including encouragement that the partners be tested for HIV. We would encourage the woman in the second vignette to approach her partners (who are assumed to be heterosexual, HIV-negative, and uncircumcised) to be circumcised.[11] We would provide an adequate supply of male and female condoms and highlight the importance of adherence to oral contraceptives.

Given the available data, recommending initiation of PrEP is premature in either circumstance. For example, in South Africa, approximately 1.8 million people have initiated antiretroviral therapy, representing 55% of the people who require this therapy. First-line therapy now includes TDF, at a cost of $11 billion (in U.S. dollars). The implementation of antiretroviral therapy in South Africa has been further stressed by the increase in the threshold for initiating treatment to a CD4 count of 350 cells per cubic millimeter.[12] In addition, the frequent lack of availability of antiretroviral drugs suggests that existing antiretroviral treatment programs are already overwhelmed.[13] Until robust concordant trial data are available to guide the complexity of practice here, we should not grasp at straws. Giving effective antiretroviral treatment to HIV-infected persons earlier and enhancing the use of proven strategies should be the current mainstays for preventing HIV transmission.

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

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