I started my infectious diseases fellowship at the University of California, Los Angeles, in June 1982—one year after the first reports of a new and terrifying syndrome among men who have sex with men (MSM). The syndrome was characterized by unusual opportunistic infections, wasting, dementia, and blindness. Everyone died. By the end of that year, I had cared for the first woman in Los Angeles who had what would later be called AIDS. Eventually it became clear that AIDS was transmitted by sex and blood, was caused by a retrovirus, and was global in scope.

Initial advances in treating and preventing specific opportunistic infections, followed by the development of astonishingly effective antiretroviral drugs, have transformed HIV into a manageable chronic disease. Recently, treatment of the infected person in a serodiscordant relationship has been shown to prevent transmission to the uninfected partner. Now, the next chapter in the control of the HIV pandemic is unfolding: preexposure prophylaxis (PrEP)—the use of drugs to prevent HIV infection among persons who are HIV-negative but at high risk.

On 10 May 2012, a meeting of the U.S. Food and Drug Administration (FDA) Antiviral Drugs Advisory Committee, which I chaired, considered the use of 2 antiretroviral drugs, tenofovir and emtricitabine (coformulated in a single tablet as Truvada [Gilead Sciences, Foster City, California]), for PrEP against HIV infection. Overall, tolerance was good, adverse effects were mild, and no resistance was seen during a limited period of observation. The potential importance of chemoprevention is underscored by recent demographic trends showing increased infection rates among U.S. MSM, particularly among black and Latino MSM aged 13 to 34 years.

The rationale for PrEP has its roots in a 1990s clinical trial (ACTG [AIDS Clinical Trials Group] 076) that showed that the first licensed antiretroviral drug (zidovudine [AZT]) reduced vertical (mother-to-child) transmission by two thirds to 6.7% (1). Subsequent studies showed that triple antiretroviral therapy during pregnancy could reduce vertical transmission to considerably less than 1%. Even when maternal viral load remains detectable, the lower it is, the less likely that the newborn will be infected.

The observational Rakai cohort study in Uganda concluded that the likelihood of heterosexual transmission was directly related to the infected partner’s viral load (2), and a randomized clinical trial (HPTN [HIV Prevention Trials Network] 052) definitively demonstrated that antiretroviral therapy of the infected person in a heterosexual serodiscordant relationship was 96% effective in preventing infection of the seronegative partner (3). Thus, the stage was set for studies aiming to prevent sexually acquired HIV among high-risk seronegative individuals.

Two key studies among populations at high risk for HIV formed the basis of the 10 May FDA advisory committee review: iPrEx (Preexposure Prophylaxis Initiative) (4), a multinational study among 2499 MSM, and Partners PrEP (5), a study among 4758 heterosexual couples in Africa. Participants in iPrEx were young—50% were younger than 25 years—and had a mean of 18 sex partners in the 12 weeks before study entry. Compared with placebo, daily Truvada reduced HIV acquisition by 42% (P = 0.002). Efficacy was associated with adherence; protection ranged from 16% for those with less than 50% adherence to 68% for those with more than 90% adherence.

Partners PrEP evaluated daily tenofovir, tenofovir plus emtricitabine (Truvada), and placebo among serodiscordant heterosexual couples. Both active treatments were protective, reducing transmission rates by 67% to 75%, with similar effects among men and women. Efficacy was also tied to adherence in this study, as measured by drug levels.

As striking as these results are, inconsistent results were seen for PrEP among women in Africa in 2 other randomized, controlled trials: the VOICE (Vaginal and Oral Interventions to Control the Epidemic) and FEM-PrEP (Pre-exposure Prophylaxis Trial for HIV Prevention among African Women) studies (6). Participants were at high risk for HIV by virtue of living in areas with high HIV prevalence and the difficulty of negotiating consistent condom use. However, it has been suggested that the negative results from these 2 studies may reflect low medication adherence (6).

The FDA advisory committee members had to weigh both the risks and benefits of PrEP. Because all PrEP studies have been relatively short, long-term adverse effects in HIV-uninfected individuals are not yet known. In both positive studies, gastrointestinal symptoms, primarily nausea, occurred in participants in the active groups during the first 1 to 3 months. In iPrEx, there was a trend toward renal toxicity. Although it did not reach statistical significance, it still raised concern in committee discussions, especially with probable long-term use. Evaluation of bone mineral density in iPrEx at 72 weeks showed that partici-
pants in the treatment group had a statistically significant decrease in bone mineral density in both the hip and lumbar spine.

Although antiviral resistance was not seen, the possibility that it could occur with long-term use cannot be eliminated because of the limited period over which the studies were conducted. Because tenofovir and emtricitabine are key components of the regimens for initial treatment of HIV infection recommended in the U.S. Department of Health and Human Services guidelines (7), development of resistance with prophylactic use could have a distinct negative effect on future treatment options for those in whom PrEP fails, and such individuals could transmit resistant virus to others.

The FDA advisory committee discussed other issues, such as the use of PrEP as a “party drug,” general behavioral disinhibition, monitoring to avoid or limit drug toxicity, testing for HIV acquisition despite PrEP in order to prevent resistance development with continued use of only 2 active drugs in an infected person, and recognition of acute retroviral syndrome in such individuals. Sexual behaviors reported in iPrEx gave no evidence of increased risk-taking by participants in either study group. All of the participants had received condoms, reiterative safe sex counseling, and evaluations for sexually transmitted diseases as part of the study.

The FDA’s Risk Evaluation and Management Strategy (REMS) policy monitors approved drugs that have risks that may outweigh benefits; isotretinoin is a classic example of a drug with a REMS. The manufacturer of Truvada was required to propose a REMS, largely because of concern about the development of resistance to drugs that are part of first-line treatment for HIV. The advisory committee found the REMS proposal to be incomplete, critical issues being how and how often to monitor PrEP recipients. After a revised REMS was submitted, the FDA approved Truvada for PrEP on 16 July 2012.

Although not part of committee deliberations, concerns have been raised about providing antiretroviral drugs to uninfected individuals when there are still so many infected people, globally and in the United States, who are not receiving treatment because of the cost of and limited access to medical care. Others see prevention and treatment as different points along a continuum of care that together will stem the pandemic (8).

Who will pay for this expensive approach to prevention, and who will provide it? Will PrEP be limited to persons who are well-informed and have good insurance, rather than reaching those at highest risk? How will primary care providers become comfortable enough with counseling about sexual practices, adverse drug effects, clinical recognition of acute HIV infection, and evaluating for resistance to be good resources for persons seeking HIV prophylaxis?

In the end, each committee member came to his or her own conclusion about the wisdom of approving PrEP based on available evidence. The backdrop to my decision was the incontrovertible fact that over the 30 years of the HIV pandemic, 60 million persons have been infected and 30 million have died. Hundreds of millions are at high risk. There is no effective vaccine available or even on the horizon. After careful study and deliberation, I concluded that PrEP is a strategy that, when appropriately used and monitored, can help turn the tide. I voted “yes.”

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