FDA Panel Recommends Anti-HIV Drug for Prevention

SILVER SPRING, MARYLAND—On 10 May, the Antiviral Drugs Advisory Committee of the U.S. Food and Drug Administration (FDA) held a marathon debate about whether an anti-HIV drug on the market as a treatment should receive approval as a preventive for uninfected people. For more than 12 hours, the committee heard scientific evidence and impassioned arguments for and against, ultimately recommending that FDA approve the use of the drug Truvada for what’s called pre-exposure prophylaxis (PrEP). The decision was not unanimous, and there was a protracted back and forth about how to reduce the possibility that PrEP might cause more harm than good. By the time the committee chair asked whether the 22 members were ready to vote—which took place after the scheduled 6:30 p.m. adjournment—one person in the audience said, “Amen!”

There’s little question that Truvada, made by Gilead Sciences Inc. in Foster City, California, can prevent sexual transmission of HIV. Large, controlled studies in both uninfected men who have sex with men (MSM) and uninfected heterosexuals who have long-term partners known to be infected have proved that the drug reduces risk by more than 90% when taken daily. But adherence is the rub. Many of the participants in clinical trials had difficulty taking the pill each day, dramatically reducing the overall efficacy in the two pivotal studies with positive results—and leading to outright failure in two large trials in heterosexual women (Science, 16 March, p. 1291). This intermittent use raises a host of troubling questions, including whether PrEP will encourage risky behavior or fuel drug resistance to Truvada, outcomes that could seriously undermine its benefits.

There’s widespread agreement that current prevention efforts fall short. For the past 2 decades, new HIV infections in the United States have remained steady at roughly 50,000 people a year. Susan Buchbinder, an epidemiologist at the San Francisco Department of Public Health, explained to the committee that the majority of these infections have occurred in MSM; incidence in this group rose from 2006 to 2009, despite intensive efforts to counsel people about reducing their risks.

PrEP studies found increases in risky behavior, she said, noting that other fields assess risk compensation differently. “We’re not asking whether people who are on statins are eating more ice cream,” said Buchbinder, who supports Gilead’s request for a label change to indicate that Truvada can be prescribed either to treat or prevent infections.

During the public comment period, two dozen staff members from the AIDS Healthcare Foundation—which bills itself as the largest AIDS organization in the world—waged a coordinated attack against the label change, with several insisting that risk compensation will occur. Michael Weinstein, head of the foundation, argued that people who took the pill would assume they didn’t need to use condoms. “If you want to do no harm, do not reduce the use of condoms,” he said.

The advisory committee spent much of the day wrestling with the possibility that PrEP could create massive drug resistance to Truvada, a mainstay of antiretroviral treatment. “The potential harm here is stupendous,” said the committee’s acting chair, Judith Feinberg of the University of Cincinnati College of Medicine in Ohio.

Although Truvada, a combination of the antiretrovirals tenofovir and FTC, works well by itself to prevent an HIV infection, as a treatment, it must be used with other drugs to avoid the emergence of resistant strains. The challenge with PrEP, then, is making sure that people use Truvada as a solo drug only if they are not infected—otherwise, resistant strains could run rampant and render the drug useless as both a treatment and a preventive.

If FDA approves the label change, Gilead explained in a “risk mitigation” plan how it would educate providers about the importance of prescribing PrEP only to patients who test HIV negative. But making sure only uninfected people use PrEP is easier said than done.

In clinical trials of PrEP, few cases of drug resistance were seen in the thousands of study participants. But researchers checked for infection each month and also ran sensitive PCR assays that can detect HIV in the first few weeks after infection, which is missed on standard antibody tests. In the real world, who would oversee repeated tests of people prescribed PrEP? Would retesting be required for refills? It is possible to restrict access to drugs—women receiving the acne medication Accutane must receive pregnancy tests before each prescription is filled—but as several committee members stressed, it would create a huge burden to do something similar with PrEP.

The final vote recommended that FDA approve Gilead’s request without a testing requirement. The decision outraged Weinstein. “It’s a very, very sad day in the battle against AIDS in America,” he complained. If FDA accepts the committee’s recommendation—which is expected—Weinstein said it would be a “reckless act” and a “new Tuskegee experiment.”

But Weinstein and his group clearly were the minority voice. “The meeting and vote represent a tremendous milestone for HIV prevention,” said Jared Baeten, an epidemiologist at the University of Washington, Seattle. And Baeten, along with the committee, said many of the questions surrounding PrEP can best be answered by carefully studying what happens after approval.

—JON COHEN