

Progress Lacking in Vaginal Microbicide Research

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CHICAGO — Safety concerns and lack of efficacy continue to dash researchers' hopes of a vaginal microbicide that would protect women from sexually transmitted diseases and HIV.

"In the last year, we have had some major, huge disappointments," Dr. Jeanne Marrazzo said at a conference on STD prevention sponsored by the Centers for Dis-

ease Control and Prevention. "It has proven very, very difficult to deliver a broad-spectrum microbicide while preserving safety and protecting the integrity of the vaginal mucosa as well as the vaginal flora."

The last 24 months have seen the closure of four highly anticipated studies—one of them when the data safety and monitoring committee actually found an increased risk of HIV among women taking the active product.

Two phase III studies involved cellulose

sulfate, a topical microbicide gel, said Dr. Marrazzo, an infectious disease specialist at the University of Washington, Seattle. The trials, which comprised 2,600 women, were being conducted in Africa and India.

The first study, sponsored by CONRAD—an organization established jointly by the U.S. Agency for International Development and Eastern Virginia Medical School, Norfolk—was halted in January 2007 because of a higher number of HIV infections in the active group, compared

with the placebo group. In light of those findings, Family Health International, a nonprofit international public health agency in North Carolina, halted its own cellulose sulfate trial.

Family Health research had suffered a previous setback in 2006, when it closed its trial of Savvy gel, a vaginal microbicide tested in a phase II randomized, controlled trial of 2,150 women in Nigeria. After slightly fewer than half the expected number of HIV infections was observed, the investigators saw no evidence that the product was effective in preventing infections.

A similar disappointment occurred at a microbicide research meeting in New Delhi in February, when the Population Council, an international nonprofit research institution, released negative data on its phase III, randomized controlled trial of Carraguard. The seaweed-based vaginal gel was being tested as an HIV and STD preventative.

That trial enrolled 6,200 women in South Africa, and investigators found that although the product was safe, it was not effective for preventing HIV infections; 134 new infections occurred in the experimental arm, compared with 151 new infections in the placebo arm.

Three studies are ongoing, she noted. The National Institute of Allergy and Infectious Diseases is studying BufferGel, a gel designed to maintain vaginal acidity at a level that deactivates HIV particles, and PRO 2000/5, a gel that inhibits viral entry into susceptible cells. Both of these agents will be tested in seven sites (one in the United States and six in Africa). The patient cohort of 3,100 will be followed for up to 30 months.

The U.K. Microbicide Development Program is also looking at PRO 2000/5 in a larger study of 9,600 women. Results are expected in 2009 or 2010.

Because of the disappointing results with microbicides and increased pressure to find a prophylactic approach to HIV infection, researchers are now focusing much more attention on vaginal antiretrovirals, especially tenofovir, Dr. Marrazzo said. "This is exciting, but also scary because some women who use these drugs prophylactically will contract HIV, and there is a possibility that they will then show early treatment resistance to tenofovir, which is the backbone of antiretroviral therapy."

A gel containing 1% tenofovir is getting the most attention. "Some data presented at the New Delhi meeting showed that it was very safe, had no local inflammatory response, and doesn't change the vaginal microflora. It is absorbed, however, and so there are questions about later resistance," she said.

The National Institutes of Health are now launching the VOICE (Vaginal and Oral Interventions to Control the Epidemic) study. VOICE will enroll 4,200 women at 10 African sites. The women will be randomized to active compounds or placebo in one of three arms: once-daily oral tenofovir, a daily two-drug oral antiretroviral regimen, or once-daily 1% tenofovir vaginal gel.

Dr. Marrazzo did not report any financial conflicts of interest. ■



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