Effective Vaginal Microbicide Remains Elusive

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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 Disease 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, halted its own cellulose sulfate trial.

FHI's 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. 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.

Because of the disappointing results with microbicides, researchers are now focusing much more attention on vaginal antiretrovirals.

"The positive thing is that this study did get completed, and the gel might have a future use as a vehicle for another microbicide," Dr. Marrazzo said.

Only the HIV results were released at the February meeting, she said, but researchers aren't hopeful that the results for other STDs will be any better. "I think it will be a surprise if Carraguard does prevent these other infections."

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 at 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 study population has been fully enrolled since last summer, and we hope to have results by the end of this year or early 2009," Dr. Marrazzo said.

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, Dr. Marrazzo said. "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."

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.

Any trial that asks young, healthy, HIV-negative women to take an antiretroviral drug for an unknown benefit raises concern, Dr. Marrazzo noted. "But if you are a 16-year-old girl in South Africa, your chances of getting HIV are extraordinarily high. The annual seroconversion rate there is 6%. When you look at the risk of becoming infected, balanced against a potentially toxic prophylactic regimen, it becomes a very complex decision."

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

Prediction Rule Estimates Likelihood of STIs in Men

CHICAGO — A prediction rule that takes into account penile discharge, sexual contact history, age, and insurance status can help emergency physicians rule out potential chlamydia or gonorrhea infections.

"While the ability to predict the presence of infection was modest, the rule did better at predicting the absence of infection," Dr. Roland Merchant said at a conference on STD prevention sponsored by the Centers for Disease Control and Prevention.

Dr. Merchant, an emergency physician at Rhode Island Hospital, Providence, created the rule using hospital records for 822 men who were tested for chlamydia and/or gonorrhea at the ED from 1998 to 2004. The patients' mean age was 28 years; 48% of patients were black, 15% were Hispanic, 26% were white, and 11% were from other ethnic groups. About half of the patients (53%) had no health insurance.

Of the 822 patients, 14% had chlamydia, 12% had gonorrhea, and 3% had both infections, for a total STD prevalence of 29%. However, because bacterial culture is the only certain method of diagnosis and cultures take time to return results, most patients received antibiotic therapy presumptively. Almost all of those patients with infections did receive antibiotics (96%)—but so did 89% of those patients without infections.

"We need methods of limiting antibiotic usage to when it is indicated to avoid antibiotic overusage, reduce antibiotic resistance and costs, and avoid adverse reactions," Dr. Merchant said.

To create the prediction rule, Dr. Merchant examined patient characteristics most strongly associated with infection. Most of the men (76%) had symptoms of a sexually transmitted infection that brought them to the ED. The most common was a combination of penile discharge and dysuria (45%). A total of 22% had dysuria alone, 17% had discharge alone, 2% had pain, 2% had lesions, and 11% had no symptoms at all. The rest had other symptoms.

Dr. Merchant concluded that penile discharge, sexual contact with a person with a known STD, age, and no insurance most strongly correlated with infection. Having at least three of these risk factors increased the odds of having chlamydia and/or gonorrhea by five times over having no risk factors.

The risk factors were much more accurate in predicting the absence of infection. Patients with no risk factors were 17 times less likely than were patients with at least two risk factors to have a chlamydia/gonorrhea infection. Those whose only risk factors were age younger than 24 years and/or no insurance were seven times less likely to be infected. Patients with only penile discharge or contact with someone with an STD were two times less likely, said Dr. Merchant, who made no financial disclosures.

Self-Collected Swabs Okay for Chlamydia Testing in Men

CHICAGO — Patient-collected rectal swabs are just as accurate as provider-collected swabs for diagnosing chlamydia and gonorrhea infections in men, Dr. Christine Wigen reported at a conference on STD prevention sponsored by the Centers for Disease Control and Prevention.

Allowing men to collect their own specimens may help boost testing rates at STD clinics that lack appropriate staff, Dr. Wigen said.

"Some STD testing sites don't have doctors, physician assistants, or nurse practitioners to take samples from anatomical sites such as the rectum," she said in an interview. "[They] may only have a phlebotomist to draw blood for HIV or syphilis tests and can only take urine specimens for genitourinary testing of gonorrhea and chlamydia. In the past, the provider had to collect the rectal specimens [and as a result], the test wouldn't be done. With the self-collected method, the testing is possible even in the absence of a provider."

In addition, she said, if the patient is asymptomatic, the self-collected method fast-tracks him through the screening process, which would free up the provider to focus on symptomatic individuals and on those with positive tests.

Dr. Wigen examined the accuracy of 225 paired rectal swab samples collected from men who had experienced receptive anal sex in the previous year. Each man provided both a self-collected swab and a swab collected by a clinician during a visit to the Los Angeles Gay and Lesbian Center sexual health program, a community partner of the Los Angeles County Department of Public Health.

The patients' mean age was 34 years; 78% said they were gay, 11% said they were bisexual, 8% heterosexual, and 1% transgender. They were provided with a collection kit and oral and written instructions on how to collect the sample.

The overall prevalence of rectal chlamydia was 19%. Provider- and self-collected swabs had a diagnostic agreement of 97%. Rectal chlamydia was found in 39 self-collected specimens and 40 provider-collected specimens.

The overall prevalence of rectal gonorrhea was 16%. Provider- and self-collected swabs had a diagnostic agreement of 95%. Gonorrhea was found in 42 self-collected specimens and 37 provider-collected specimens.

The sensitivity of self-collected swabs for both infections was 93%, whereas the sensitivity of provider-collected swabs was 95% for chlamydia and 82% for gonorrhea.