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**Postcard From Delhi: The View From the Microbicide 2008 Conference**

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The scientific troupes were restless at the biannual Microbicides 2008 Conference, held earlier this month in Delhi, India. Prevention experts from around the world had gathered there to discuss the latest developments in this important arena of HIV/AIDS prevention. Despite the international AIDS community's high hopes for these gels or creams—possibly to be paired with a device such as a diaphragm or vaginal ring—incorporating an HIV-neutralizing substance to block sexual transmission of the virus, the development of a safe and efficacious microbicide continues to elude researchers.

Indeed, just prior to the conference, one massive study conducted among South African women concluded that the microbicide being studied—in that case, Carraguard—made no difference in HIV infection rates. And another recent study indicated that the microbicide in question may have actually increased the participants' risk of infection rather than protecting them. Still, despite the frustrating news of late, indeed perhaps in response to it, there was little indication of any waning commitment to develop an effective microbicide.

HIV prevention advocates have been urging the development of such compounds since the early 1990s, when they started noting how much more vulnerable young women were to HIV, both for biological reasons and because men are the ones who generally make the ultimate decisions regarding condom use. Giving women, including those in marriages that may not be monogamous, a tool to protect themselves against HIV without having to have complicit agreement from their male partner, could drastically impact the rate of HIV infection around the world. Research has also begun into microbicides that could be used rectally, an option that could benefit both straight and gay people.

However, though it has seemed that progress is being made in the development of microbicides, just over a year ago big efficacy trials of two candidates, Savvy (C31G) and Ushercell (cellulose sulphate), were stopped when it was found that, far from protecting the women who used them, they may have actually increased their vulnerability to the virus. In the Savvy trial, 21 women on microbicide and 12 on placebo contracted HIV. In the Ushercell trial, the figures were more dramatic: 60 women using the microbicide and 27 on placebo were infected, though in neither trial were the differences between the groups statistically significant (they could have been due to chance).

The Ushercell trial results were the bigger shock. Because Savvy was a nonoxynol-9-type surfactant, many suspected it would be a vaginal irritant and potentially increase the risk of infection. Cellulose sulphate, however, the active ingredient in Ushercell, seemed to have a clean safety record, and scientists were surprised to discover that the microbicide did not prevent infection.

Then, just before the conference, another trial—the biggest trial so far—in which the seaweed-derived gel Carraguard was pitted against placebo in more than 6,000

South African women, concluded with the announcement that Carraguard was not effective. At 3.4 percent on Carraguard and 3.8 percent on placebo, HIV infection rates were the same in both arms of the trial. Researchers breathed a sigh of relief that at least Carraguard appeared safe. But the results were nonetheless a disappointment.

However, I found no sense in Delhi that researchers were demoralized. Rather, there was a new understanding of the sheer difficulty of putting on trials of an anti-HIV “lube,” and a calm determination that with the next generation of trials they’d try to fix the two biggest problems this research faces: toxicity and adherence.

Researchers now know why Ushercell didn’t work—it damages the protective cellular meshwork of vaginal tissue—and hope that new-generation microbicides, which incorporate antiretroviral drugs, will be less toxic. And the knowledge gained from the Carraguard study about the complexity of putting on trials and the difficulty participants had in adhering to the microbicide is helping scientists look at ways of improving adherence and data collection. This time, researchers told me unanimously, we will get a result.

Why put so much effort into the hunt? After all, we already have condoms.

“Yes, I still get people digging in their heels and saying ‘Why can’t people use condoms; microbicides will just encourage misbehavior,’” says Jim Pickett of the International Rectal Microbicides Advocates (IRMA). “But that’s like saying seat belts are the only safety feature you should have in cars, and air bags will encourage bad driving.”

### **Sticking to it: the problem of adherence**

Imagine getting a group of largely poor women in a developing country, whose role is still largely to marry, submit uncomplainingly to sex and support their family, to agree to squeeze goo every day for a year (or every time they think hubby is going to want sex) into their vaginas, do it despite the disapproval of conservative moms and suspicious spouses, report regularly to a clinic for checkups, and answer impertinent questionnaires about their sex lives to researchers, when they’ve been told that half of them are getting a placebo anyway.

Such was the task given to Dr. Elof Johansson, who has just retired as vice president in charge of biomedical research at the Population Council, the group that conducted the Carraguard trial. A veteran of trials of contraceptives, especially in the developing world, Dr. Johansson said, “We old guys from the contraceptive world have been humbled by the complexity of microbicide trials. In contraceptives, you have clinical endpoints: You can measure blood hormone levels. In microbicides, everything is just testing for safety until you put on a large efficacy trial.”

Human beings’ tendency to lie about sex and associated matters to researchers was what really complicated the Carraguard trial. If you rely on self-reporting, the women in the trial told the researchers that they used the gel 94 percent of the time. Splendid. However, halfway through the trial, a dye was found that reacted to vaginal secretions and could be used to see if the applicator tubes of microbicide had actually been inserted. When the women took the “dye-detector” test—just 61 percent tested positive, proving that many claimed to use the substance when they did not. The eventual estimate for microbicide adherence was just 44 percent.

Even in a high prevalence area, HIV infection is a relatively uncommon event. This means that if participants in a trial use your microbicide far less often than expected, the ability of a trial, even one involving thousands of women, to detect a difference dwindles to zero: Any effect observed could just be random “noise.” If Carraguard may have had a small protective effect, we’ll never know.

There are still results to come from two more trials of the first-generation microbicide PRO 2000 (polynaphthalene sulfonate). One, being conducted by the U.S. National Institutes of Health, has enrolled 3,100 women, and the biggest of all, a U.K. Medical Research Council (MRC) study involves nearly 10,000 women. Results from both studies are expected in 2009.

But signs are not promising. Last month, women receiving the higher of two doses in the MRC study were pulled from the trial due to “futility”—a term statisticians use when they’ve determined that there’s unlikely to be a meaningful benefit.

They still hope that the lower dose may prove efficacious, but in monkey studies the dose (0.5 percent) was less than 30 percent efficacious, and the fact that it was the stronger dose that was pulled may indicate that the chemical’s ability to trap HIV in its sticky molecules may have been canceled out by an irritant effect that made infection more likely.

### **Irritation versus protection: the problem of toxicity**

This is exactly what happened with Ushercell. In a series of elegant microphotographs of the vaginal wall, researcher Pedro Mesquita of Albert Einstein College of Medicine at Yeshiva University in the Bronx, New York, found that the gel loosened the connection between cells so that tissue weakened and HIV could seep through. There was tentative evidence that PRO 2000 might have a similar, though much less serious, effect.

Safety studies so far indicate that the new generation of microbicides, which will contain antiretroviral drugs, have far less toxicity and tendency to irritate. Not absolutely none, though. One study of tenofovir gel—reported widely in the Indian press because half of the 200 women involved lived in the southern Indian city of Pune—found signs of vaginal inflammation in six out of 50 women who used the gel compared with none on placebo when it was used only immediately before sex, and eight versus six when it was used daily. Any foreign substance introduced into these sensitive areas may produce some degree of irritation and resultant vulnerability to HIV, in the same way that oral drugs produce side effects. Researchers are hoping that the next generation will be potent enough to outweigh any toxicity.

### **The second generation trials**

The next generation will involve gels containing HIV drugs. The trials already starting involve one licensed HIV drug, Gilead Science’s tenofovir (Viread), and the non-nucleoside reverse transcriptase inhibitor (NNRTI) drugs dapivirine, from Tibotec, and Cellegy Pharmaceuticals’ UC-781, both of which failed as oral HIV treatments but may work as microbicides. Further into the future lie plans to try two CCR5 inhibitors—the recently licensed Pfizer’s maraviroc (Selzentry) and Merck’s MRK 167 and L’644.

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Indications that they may be more potent come from studies involving monkeys. We can't use humans in preliminary efficacy tests because it's not ethical to try and infect them with HIV. In animal studies, monkeys are given a dose of microbicide either vaginally or rectally. They are then "challenged" with what should be a 100 percent infectious dose of SIV—the monkey HIV equivalent—either by direct injection or by introducing the virus vaginally or rectally. Studies of tenofovir, for instance, indicate an efficacy of about 66 percent in stopping rectal infection compared with 30 percent for PRO 2000, and almost complete protection using tenofovir plus Gilead's emtricitabine (Emtriva).

Determining the efficacy of these microbicides in humans may take a while. One efficacy trial of tenofovir gel has already started in South Africa. The CAPRISA 004 Study asks 980 women to use 1 percent tenofovir gel when they think they're likely to have sex, and if they do, use it again afterward. Results from this trial are due in 2010.

This, however, is just a prequel to two much bigger studies. Late this year, the Microbicides Trials Network will start a trial called VOICE, involving 4,200 women in five African countries. VOICE stands for Vaginal and Oral Interventions to Control the Epidemic and, as its name suggests, incorporates a study arm that involves oral pre-exposure prophylaxis (PrEP)—taking tenofovir pills to prevent HIV infection—as well as one using the microbicide. This will be the first study to compare two of the most promising biomedical HIV prevention approaches, with results expected in 2011.

The biggest program thus far, coordinated by the International Partnership for Microbicides (IPM), will use dapivirine. IPM will not just put the drug in a gel. The IPM is also perfecting the technology that enables researchers to infuse the drug into a silicone rubber ring. This will sit on the cervix like a cap and will be able to supply enough microbicidal drug for a month, thus circumventing adherence problems.

A vaginal ring would also be a lot easier to keep secret from a sex partner than a gel. A study by Jennifer Ann Smit, MD, of the University of Witwatersrand in South Africa found that young women who were most shy about talking of sex and condom use with their partners were the ones who expressed most interest in a vaginal ring.

A large trial of the gel, IPM 009, may yield reports by 2012 or 2013. Safety and drug-release studies of the latest model of the vaginal ring will start this summer, and IPM hopes that efficacy results from the vaginal ring will arrive soon after those for the gel itself. IPM is also actively looking at ways of closely monitoring adherence to gel use without compromising the women's confidentiality and safety, such as creating "drop-off" locations for used applicators in safe locations.

Did IPM's Chief Executive Officer Zeda Rosenberg, ScD, think the first-generation trials had been premature? "No. There had to be a test of the concept of the class of polyanions" [the sticky virus trappers that include Ushercell and PRO 2000].. If I'd been running the world," she said, "we might have picked the best out of them and only trialled that. But, though we may have stumbled, we have also made progress."

She's passionate about getting a result. "The IPM wants to take the obsessiveness of the pharmaceutical industry into the world of publicly funded prevention."

But she won't give a date when she expects to see a microbicide. "If the antiretroviral-containing generation works, then you have to add on five years to

that to perfect marketing, packaging, find funds for rollout programs and so on.” That means that if the front-runner, tenofovir, looks good, we may have a microbicide in 2016 or so.

### **Could resistance be a problem?**

A new problem may arise with the second generation of microbicides. Because these are HIV drug-based, the possibility exists that if enough drug gets into the body, a woman using the microbicide who was already HIV positive, or who contracted HIV despite using the microbicide, might develop drug resistance. To cause resistance, an HIV-positive person needs to have an amount of drug in her body that is too small to completely suppress HIV replication, but large enough to suppress some of it.

Two studies of tenofovir and dapivirine found that small amounts of the drug—100 times lower than oral dosing, in the case of tenofovir—did get into the bloodstream. Whether this amount is large enough to cause resistance in someone with HIV, no one yet knows.

Dr. Rosenberg says, “I don’t think resistance is going to be a big problem,” but we do need to be cautious about it.

Sally Blower, PhD, of the University of California, Los Angeles has introduced a mathematical model designed to predict possible outcomes of an effective microbicide that would cause HIV drug resistance. The model found that, paradoxically, because more women than men would develop HIV drug resistance if they used such a microbicide, men would benefit more in terms of reduced HIV infections.

### **Rectal microbicides**

What about UC-781? We haven’t talked about this drug yet because it’s the one for men (and some women): It is so far the only antiretroviral being used in the first human studies of a rectal microbicide. (There is no reason in terms of its properties why UC-781 was chosen over, say, dapivirine; it’s simply to do with which drug company licenses its product for development to which research organization.)

So far only 28 HIV-negative male and female subjects have tried the rectal microbicide in a small safety study, and results are still blinded—we don’t know who got drug and who got placebo.

I spoke to top rectal researcher Ian McGowan, MD, PhD, of the University of Pittsburgh, the city that will host the next microbicides conference in 2010. Dr. McGowan and his team are using a clever trick that may one day allow them to predict whether their microbicide might be efficacious. They got their trial subjects to use the microbicide and then removed small snippets of rectal tissue, cultivated them in laboratory dishes, and tried to infect them with HIV. After the first microbicide dose, a third of the samples refused infection and a third were infected with lower viral loads.

Dr. McGowan’s group also plans to study the microbicide in HIV-positive subjects. He reckons that gay men are likely to use a microbicide, regardless of their HIV status, and safety and resistance may both be even thornier issues for people with HIV.

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Again, the rectal researchers are ahead of the vaginal researchers. In Delhi, Wafaa al-Sadr, MD, of Columbia University in New York urged a “paradigm shift” so that HIV-positive women were included in trials, as they too would likely use a microbicide. Zeda Rosenberg, on the other hand, told me that she didn’t want to see HIV-positive women in trials “until a product is shown to be effective. Why risk adverse events?”

Dr. McGowan is bullish about the eventual chance of success of rectal microbicides, a concept that until recently was regarded as a long shot that might not even be technically possible. “Coming from the field of sexually transmitted infections as we do,” he explains, “we’ve always been conscious that any product you put in the bowel has the potential to cause damage, so we’re looking at a huge range of makers of inflammation. We’ve moved the field from ‘You must be joking’ to almost embarrassing respectability. These new drug-containing microbicides are so potent, there’s a real sense we’re moving forward.”

However, Dr. Johansson and Dr. McGowan know that the final proof of safety will come from a large efficacy study, which, in the case of rectal microbicides, we’ll have to find the funding for first.

### Advocacy and fun

Drumming up enthusiasm and money for microbicides is a job for advocates like Jim Pickett of IRMA. He also feels no sense of discouragement.

“There’s a real buzz around advocacy here. People are realizing microbicides research has all kinds of spin-offs in terms of helping cultures be more honest and accepting about human behavior.”

He also brings up something that may turn out to be microbicides’ biggest asset: People like them. There had been fears that men and women in traditional cultures would not like something that made sex more slippery and squishy. On the contrary, a third of participants of both sexes in several different studies of acceptability found that microbicidal sex was better sex, and hardly anyone found it was worse. The Pune tenofovir study found that both women and their partners liked the gel. In the Carraguard trial, users told researchers that “it improved sex” and they “liked the feel.” And Dr. Lut van Damme of CONRAD, who put on the Ushercell trial, told the conference that in Benin, West Africa, some women refused to give their gel back when the trial was stopped and had to be given supplies of placebo.

“The reason we need a microbicide so badly,” says Pickett, “is that for all sorts of good reasons both men and women like sex and aren’t going to stop having it. [They] dislike barrier methods—chiefly condoms—that make it seem less spontaneous, symbolize distrust and prevent conception. An HIV prevention method that was associated with fun and passion would be a lot easier to sell.

“Having said that,” he continues, “we can’t oversell—we have to prepare for success but it took 40 years to get a polio vaccine, and we have to manage our expectations.”

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He finishes by reiterating something that virtually every other person I met at Delhi said: There is no sense of failure around microbicides. What there is, instead, is the sense of having walked the first mile in an exciting journey.

“We’re going through the discovery process. Products have failed. But the trials didn’t. Twenty thousand women have already used a microbicide. This is a vast undertaking and there’s a long way to go yet, but we’ll get there.”

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