The Jelly Revolution

If a new crew of activists has its way, a slew of topical goops and jams just may be the solution to stop the spread of HIV. Deb Schwartz goes inside the movement for microbicides.

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Imagine if you could design the perfect method for blocking HIV transmission. What would it look like?

It would be easy to use -- something that wouldn't interrupt the moment or require a big, serious talk about serostatus or what's too risky. It would be cheap. And it would let you have sex without a barrier.

In fact, some of these dream substances are now in the works: colorless, odorless HIV-blocking gels and suppositories called microbicides. If this new field of research gets the support it needs, five to 10 years from now women and gay men worldwide will reach into their medicine cabinets and pull out a tube of goop that they can apply -- vaginally or rectally -- hours before having sex. Suddenly, people will be able to protect themselves without their partner's knowledge.

You may have never heard of any of them, but there are more than 50 microbicides now in development in small labs around the world. In the last few years, several new advocacy campaigns have cropped up to spread the word on the miracle goos and challenge the institutional apathy keeping them off drugstore shelves. These microbicides employ a variety of strategies to protect people from HIV in semen -- killing or blocking HIV, inhibiting HIV fusion or, in women, making the vaginal environment hostile to the virus. Many will likely be tested for rectal use as well, making them attractive for gay men. While most microbicides would double as contraceptives, a few products in development are thought to be sperm-friendly, which could, for the first time, allow a woman to protect herself from disease but still conceive -- critical for the millions of women worldwide facing cultural pressure to bear children. In theory, some microbicides should be "bidirectional," allowing HIVers to self-apply and reduce a partner's risk of infection.

And they may cost as little as a dollar per use.

"This is what women in villages and towns are asking for, pleading for," says Geeta Rao Gupta, president of the Washington, DC-based International Center for Research on Women (ICRW). The ICRW conducted a seven-year research project in 13 developing countries that investigated the factors that increase women's risk of contracting HIV. "They know their men have multiple

partners, and they are pragmatic about it, but they are trapped. We give them no way to improve those circumstances and no options, and then we wonder why there are more women infected in Africa than men."

Now, where female-controlled contraception and HIV prevention meet, a new advocacy movement has emerged. Its leaders are the two-year-old Alliance for Microbicide Development (AMD), the undisputed hub of the nascent microbicide world, and the five-year-old Center for Health and Gender Equity (CHANGE), both in Baltimore; as well as a number of older reproductive health and population groups, such as the ICRW. Though no major pharmaceutical has thrown its hat into the ring, these advocates are supporting a cottage industry of small biotech firms and university labs whose microbicide research is beginning to bear fruit.

On Capitol Hill, microbicide advocates are working with Reps. Connie Morella (R-MD) and Nancy Pelosi (D-CA) to introduce a bill early in 2000 that would secure a steady commitment ($100 million spread over several years) to microbicide development at the National Institutes of Health (NIH). August 1999 witnessed the first meeting of the Trans-NIH Microbicide Working Group, a stab at coordinating microbicide work within the agency. In March, hundreds of advocates and researchers from around the globe will convene for Microbicides 2000, a groundbreaking conference in Washington, DC. "This is the first high-visibility, microbicides-only meeting," says Kenneth Mayer, chief of infectious diseases at Memorial Hospital in Pawtucket, Rhode Island, and a microbicide researcher. "It will be very important, allowing us to formalize links between basic and clinical researchers and advocates, and to tighten up the agenda and make research more efficient."

Yet the obstacles are substantial: Microbicide development is dogged by a lack of funding and leadership, as well as by the scientific hurdles to testing faced by all new prevention technologies. The most innovative products -- the ones that combine a variety of compounds that boost the vagina's natural defenses and block or disable HIV -- are still mostly in the early stages, with only a few standout candidates. But researchers and advocates feel confident that the arrival of some new products is imminent, as a number of first-generation microbicides are already in Phase III trials.

The push for microbicides comes at a time when prevention advocates are casting about for new approaches. Years of safer-sex education and the distribution of countless condoms have failed to achieve consistent condom usage: Studies show that even after directed intervention, condom use in primary relationships hovers at a low 20 to 30 percent. "In the land of family planning, it was generally understood that condoms weren't going to work for everyone, and neither was monogamy," says Anna Forbes, a political consultant on women's health and AMD's field organizer. "But somehow in the land of AIDS we managed to forget all that. All we could think of to say was 'Condoms, condoms, condoms -- you have to use condoms!'"

In fact, the first generation of microbicides may be less effective against HIV than condoms (which, when used correctly, are 98 percent effective), but that doesn't mean they'll have a lesser impact on prevention. Microbicide advocates point to a mathematical prevention model developed by

CHANGE Codirector Lori Heise. She says the success of any method is a function of not only how well it prevents transmission but how often it is used. In other words, condoms used inconsistently would offer the same level of protection as a less effective microbicide used very consistently. “Prevention strategies must increasingly rely on novel combinations of interventions rather than on one ’silver bullet,’” Heise says. A holistic prevention strategy, advocates say, means promoting condom use, vaccine research and microbicide development.

Polly Harrison, who left a prestigious job at the Institute of Medicine to pursue microbicides full-time as president of AMD, is decidedly upbeat. “There’s loads of work to do,” she says, “but we’ve never had this much money, momentum or potential interest.” Forged in March 1998, AMD is a consortium of companies, scientists and advocates that includes just about everyone involved in making microbicides a reality. AMD’s mission is to accelerate the science and build a funding base that will make it all possible. CHANGE is the legislative and organizing arm of the movement. Its Global Campaign for STI/HIV Prevention Alternatives for Women -- sponsored by more than 30 AIDS and women’s organizations around the world -- includes a massive international petition drive calling for increased access to prevention technologies other than condoms.

But it may be easier to generate public support than scientific progress. “Think about it,” says Harrison, a medical anthropologist. “The first thing you look for with a new disease is a vaccine, and a cure. But it’s not a logical jump to think about goops, jams and jellies. Microbicides are revolutionary.”

Zeda Rosenberg agrees. The scientific director of the HIV Prevention Trials Network at Family Health International, headquartered in Durham, North Carolina, Rosenberg says that the long history of successful vaccines, from polio to smallpox, gives scientists the confidence to pursue one for HIV, but “nothing has ever been shown to prevent an STD vaginally.”

Showing that a product can prevent transmission isn’t easy, as vaccine researchers know. Because researchers for prevention studies are ethically obligated to counsel participants extensively about safer sex, there are usually a very small percentage of new infections in both the control and the treated groups. Efficacy trials must therefore track thousands of people over a long period of time; per-study costs routinely run into the tens of millions of dollars. But microbicides face another hurdle. While a vaccine is injected by the researcher, microbicides must be applied at home by the study participant. So researchers can’t know with certainty whether their product is being used correctly.

Few microbicides have good in-vitro or early clinical data yet, which makes it difficult to sort the wheat from the chaff. “We have a lot of products in development,” Rosenberg says, “but we don’t know how to choose which ones to move into Phase III first. Since these studies are very large and very expensive, that is a difficult decision to make.”

Only four microbicides have made it to Phase III trials. One, a vaginal film, has failed; all four either contain nonoxynol-9, the one microbicide that’s already FDA approved, or work in the same way. N-9, which is readily available in over-the-counter foams and lubed condoms as a spermicide, has

also been shown to kill many STD pathogens in a test tube. Its results in humans are conflicting: Some studies show up to 50 percent efficacy, while others show that N-9 can cause vaginal abrasions that leave women even more vulnerable to infection. So this round of N-9 copycats has hardly excited the scientific community.

“The science is seen as too kitchen sink,” Heise says, “not cutting edge.” But in addition to the many low-tech detergents being developed -- which work by killing or disabling a wide array of pathogens and viruses -- researchers are exploring products that would prevent infection by other means. The lactobacillus pill being developed by Sharon Hillier at Magee Women’s Hospital in Pittsburgh, and BufferGel, being developed by Kevin Whaley at Reprotect in Baltimore, both work to maintain the vagina’s natural pH, which, in the absence of the neutralizing effects of semen, is acidic and therefore fairly hostile to HIV and other microbes. Anne-Marie Corner, president of BioSyn in Philadelphia, is developing Savvy, a gel with broad antimicrobial properties. She’s also working with Penn State, Duke and the University of North Carolina to combine C31G, Savvy’s active ingredient, with sodium dodecyl sulfate to create a powerful compound with action against HIV, herpes and HPV.

A handful of researchers, including Deborah Anderson at Harvard and Julie McGrath at the University of Washington, are crossing into edgier territory, trying to produce a sort of localized vaccine that could contain the virus in the vagina. “Mucosal immunity” to HIV is still highly theoretical, but researchers are intrigued by findings that some women exposed to HIV seem to contain the virus in their vaginas, where the local immune system apparently manages the infection and prevents it from spreading. Researchers hope to design a vaccine, possibly administered as a spray, that could work within the mucosal linings of the gastrointestinal and genital-urinary tracts. It would keep HIV contained in a small reservoir that may never emerge.

Despite these developments, microbicides remain isolated from the larger HIV research world. As International AIDS Society president Mark Wainberg wrote last April in *AIDS Research and Human Retroviruses*, “Some individuals are working in areas of HIV research that have direct relevance to microbicide strategies . . . but may conceive of their projects as having relevance only to treatment and not prevention.”

Until very recently, microbicides have been an orphan cause as well, stranded in the gap between AIDS activism and the women’s health movement. “We get positive responses from both women’s health and AIDS organizations,” Forbes says, “but we’ve had a lot of difficulty getting action. We can’t figure out whether it’s because there’s already so much on the agenda, or because they’re just hesitant to get involved in something that they know so little about.” Also, she says, some gay male leaders of AIDS organizations seem to view microbicides as a women’s issue -- it’s mostly treatment activists who’ve pushed for rectal microbicides for gay men -- while the middle-class leaders of women’s groups don’t think of AIDS as their issue at all. Meanwhile, the research heavyweights -- the feds and the pharmaceuticals -- have yet to pick up the slack.

One of the main reasons Harrison launched the AMD was that, she says, “The feds needed a fire lit under them.” According to Victoria Cargill, who is director of clinical studies at the Office of AIDS

Research (OAR) and who oversees the NIH's work on microbicides, combined spending across the NIH for microbicides in 1998 came to $5.8 million for basic research and $15 million for product development and evaluation -- just 1 percent of the federal HIV budget. "When you consider how many lives could be saved, that's just ridiculous," Forbes says.

"It's easy to bash the feds," Harrison says, "but because there has been almost no private sector investment -- little from foundations and nothing to speak of from big pharmaceuticals -- federal support becomes critical." If Harrison had her way, the feds would bump up yearly spending on microbicide research to $75 million. "We know where putting some money would get us answers to some significant questions," she says. "If you put public sector money into R&D you could make a quantum leap."

Though Anthony Fauci, director of the National Institute of Allergy and Infectious Diseases, recently voiced support for microbicides, and Cargill says OAR director Neil Nathanson is "a staunch supporter," advocates generally agree that a coherent federal strategy for microbicide research is sorely lacking. "It's the same dialogue AIDS advocates had back before the Levine report," Harrison says, referring to a 1996 NIH panel that criticized the feds for poor coordination of AIDS research. "The U.S. government and the NIH do not have a strategy, and they're not spending enough to make a critical difference."

Advocates say that without federal leadership, disinterest in microbicides at major drug companies is likely to continue. Heather Boonstra, a public policy analyst at the Alan Guttmacher Institute in New York, says that despite the institute's research indicating that American women across a range of races and classes would be interested in using microbicides, companies aren't biting. "They think that if we developed something, we couldn't sell it here," Boonstra says, "that it could only be sold to poor women in developing countries."

Drug companies tend to judge microbicide marketability by the same criteria they use for contraceptives. Most women aren't all that keen on intravaginal birth-control methods such as diaphragms, cervical caps or spermicidal creams, and pharmaceuticals presume that women will feel the same aversion to microbicides. "The biggest single problem with the drug companies is their idea that there's no money to be made," Forbes says. "When they don't think there's money to be made, they're not interested in pursuing research. We have to get people jumping up and down, saying, 'Where are my microbicides? I want my microbicides!'"

Kirsten Moore, program manager for the Reproductive Health Technologies Project, has met with several pharmaceuticals, including Organon and Wyeth-Ayerst (a vaccine researcher), to discuss the possibilities. She reports that companies are as concerned about the liability issues associated with a product claiming to prevent HIV infection as they are with profit potential.

To date, most microbicide research has taken place at universities, small start-up biotechs and nonprofits such as the Population Council, all of which rely on government grants. More creative funding strategies are only in the early stages. The Lifesaving Vaccine Technology Act, introduced in the House and Senate last year, would provide tax credits to businesses that research

interventions, such as vaccines and microbicides, against HIV, malaria and tuberculosis. CHANGE has kicked off an ambitious fundraising drive -- “Looking for Mrs. McCormick,” named for the New York heiress who bankrolled Margaret Sanger’s drive for oral contraceptives -- to recruit private backers for AMD’s advocacy efforts and to provide venture capital for their consortium of researchers and small biotechs.

Until they find their Mrs. McCormick, advocates are working to generate enough grass-roots support to set off a chain reaction: building political will to spur federal funding to excite the interest of researchers and large pharmaceuticals. “We believe that popular will, sooner or later, is reflected in political will,” Harrison says. “And we believe that when there is greater public awareness of these products, people will press for them and the public sector will respond with money.”

WORKING OUT THE BUGS

The big drug companies are conspicuously absent from the list of microbicide researchers. Still, 57 microbicides are in development at universities and small biotechs. Here are some that look promising—though only a few are likely to make it into your medicine cabinet. (Labs are noted in parentheses.)

Prevent conception and HIV infection

Detergents: Five of thesegels and creams are in Phase I or III clinical trials, including Advantage-S (Columbia Labs), Conceptrol gel (ACP) and Savvy/C31G (Biosyn). Like nonoxynol-9, they disrupt or destroy the lipid membranes of bacteria and the outer shells of viruses. B-195,cellulose acetate phthalate (New York Blood Center), is one to watch, even though only in animal trials so far. It’s probably safe, since it’s the substance that coats over-the-counter pills, and researchers say it seems extremely active against HIV.

Natural products: Praneem suppository (M/S Reproductive Technologies, India), in Phase I trials, and gossypol acetic acid (Hebron, Brazil),in Phase II, use plant extracts that function like detergents. Praneem uses neem tree oil; developers say it may also be an immune regulator.

HIV fusion blockers: PRO-2000 (Procept) and PC-515 (Population Council), in Phase I and II trials, coat and incapacitate viruses and other microbes, keeping them from invading mucosal cells. PC-515 uses carageenan—the seaweed extract that thickens ice cream. PRO-2000 proponents say it’s more vagina-friendly than detergents.

Acid buffers: Acidform (TOPCAD/Cemicemp, Brazil) and BufferGel (ReProtect), both in Phase I, keep vaginal pH hostile to HIV. The vagina is normally acidic, due to friendly lactobacillus. Semen makes it more alkaline, so microorganisms flourish. Buffers counteract that, reducing risk of infection.

Fight HIV but allow conception

HIV blockers: Britain’s Medical Research Council and M-L Laboratories are using dextran sulfate—tested early on as an HIV treatment—to keep HIV from entering mucosal cells in the vagina or rectum; now in Phase II.

Acid buffers: Lactobacillus suppositories (University of Pittsburgh), in Phase I, infuse lactobacilli into the vagina, raising its acidity enough to harm HIV but let sperm survive.

Nucleotide analogs: PMPA/ tenofovir, a reverse transcriptase inhibitor, stops viral replication once HIV has fused with cells. Gilead Science has a topical tenofovir gel in Phase I trials.

—Laura Whitehorn
