

## As Research Accelerates, Focus Intensifies on Options for ‘First-Generation’ Microbicide

By Heather Boonstra

As the AIDS pandemic continues to burn its way across the developing world, microbicides are generating increasing interest for their potential to strengthen HIV prevention efforts. The Bush administration and Congress are poised to increase funding for global HIV/AIDS efforts next year, and microbicide advocates are seeking to ensure that the development of technologies that women can use to protect themselves from infection are part of the government’s strategy. The Microbicide Development Act of 2001, introduced in the House in June, will soon be introduced in the Senate as well, with the hope that it will be passed next year as part of a larger global AIDS bill. The microbicide legislation would formally establish research programs at the National Institutes of Health and the Centers for Disease Control and Prevention.

This increased energy and focus on vaginal microbicides, which women would apply topically to prevent HIV and other sexually transmitted diseases (STDs), comes at an important time in the development of such products. More than 55 different compounds are being investigated, and large-scale clinical trials—Phase III studies required by the Food and Drug Administration—have begun or will begin soon on six of the products considered most promising (see table, page 2). Still, most experts agree that a product effective against HIV will not be available until at least 2007, largely because of the inherent difficulties in conducting HIV-related clinical trials. These challenges are so significant, in fact, that some developers are working to

advance a first-generation microbicide that would be tested and marketed for the prevention of pregnancy and at least one other STD—but not HIV—as a way of demonstrating “proof of concept” and establishing an initial market niche.

### Examining the Options

As various compounds have made their way through the research and development pipeline, researchers have come to understand that making microbicides a reality is infinitely more challenging than once thought. Questions in basic research center on understanding how HIV and other STDs are transmitted and, specifically, what role the physiology

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of the vagina plays in infection. Researchers also must deal with such issues as knowing when there is adequate safety data to advance to the next stage of development, which in the case of microbicides means ensuring that a product does not change the environment of the vagina in such a way as to put women at greater risk of harm.

Ironically, however, these basic questions of science may not be as daunting as the practical aspects of testing potential products. This is especially true of studies designed to assess the

safety and effectiveness of a product against HIV. One major reason is the large number of women required for efficacy trials. In any given community in which a clinical trial is being mounted to determine whether a compound has any effect over a placebo, the incidence of HIV determines the number of people needed to be enrolled in the trial; the lower the incidence, the more enrollees needed. Because the incidence of HIV among women is, relatively speaking, so low in the United States, it simply would be impractical to conduct trials in this country because the number of participants required would be so high. Experts agree that HIV efficacy trials inevitably must be conducted in the developing world, specifically in areas where the incidence of new HIV infections is at least 5% among the general population. Even at that level, researchers estimate that Phase III clinical trials—which typically involve 1,000 to 4,000 participants—will require over 11,000 women and 120,000 clinic visits. Efforts are underway to streamline trials as much as possible. Nevertheless, researchers are up against a difficult task. Sharon Hillier of the University of Pittsburgh/Magee Women’s Hospital, who is principal investigator in the trial of a microbicide compound, explains, “With the exception of cancer studies, clinical trials of this scale have never been done before—anywhere, let alone in settings that are resource-poor and without a strong research infrastructure. The challenges are simply mind-boggling.”

Many researchers share Hillier’s view that the challenges are enormous but remain committed to the development of a first-generation product that protects against HIV. Zeda Rosenberg, scientific director for the HIV Prevention Trials Network at Family Health International, supports this approach: “We need a microbicide for the developing country context. Developing, testing and bringing a product to market will be

## MICROBICIDES IN OR NEARING LARGE-SCALE TESTING

| <i>MICROBICIDE</i>                        | <i>DEVELOPER</i>   | <i>MECHANISM OF ACTION</i>       | <i>MAY PROTECT AGAINST</i>                               |
|---|--|----------------------------------|--|
| BUFFERGEL™                                | ReProtect; Baltimore, MD   | Enhances normal vaginal defenses | Chlamydia, herpes, HIV, human papillomavirus, pregnancy. |
| CARRAGUARD™ (PC-515)                      | Population Council; New York, NY   | Inhibits viral binding/fusion    | Chancroid, herpes, HIV                                   |
| EMMELE™ (DEXTRIN SULFATE)                 | ML Laboratories, UK  | Inhibits viral binding/fusion    | HIV  |
| LACTIN VAGINAL CAPSULES (LACTOBACILLUS)   | University of Pittsburgh/Magee Women's Hospital; Pittsburgh, PA                            | Enhances normal vaginal defenses | Bacterial vaginosis, gonorrhea, HIV                      |
| PRO 2000™ (NAPHTHALENE SULFONATE POLYMER) | Interneuron; Lexington, MA   | Inhibits viral binding/fusion    | Gonorrhea, herpes, HIV                                   |
| USHERCELL™ (CELLULOSE SULFATE)            | Polydex; Toronto, Ontario; and Contraceptive Research & Development Program; Arlington, VA | Inhibits viral binding/fusion    | Chlamydia, herpes, pregnancy                             |

Source: "Products Database," Alliance for Microbicide Development, September 2001.

costly and difficult, and it will take longer than we had once hoped. But I feel strongly that the microbicide we need to bring to market first is one that is anti-HIV."

Other developers are working to bring a first-generation microbicide to market without an HIV indication, that is, one for which FDA approval would not be sought on the grounds that it has been demonstrated to be effective in preventing HIV. These developers plan instead to seek approval for a vaginal contraceptive product that also protects against one or more STDs. Anne-Marie Corner, president and CEO of Biosyn, a commercial entity pursuing this strategy, explains that while the focus on HIV is important in the global context, it is not the focus of companies hopeful of capturing U.S. consumer interest

in microbicides. "Women in the United States do not perceive themselves at risk of HIV," she says. "They worry about infertility, cervical cancer, genital warts—those conditions that are the result of STDs. American women need a product for the prevention of STDs, not HIV."

Kevin Whaley, director of antibody discovery at EPIcyte Pharmaceutical, a biotechnology firm also pursuing the development of a vaginal contraceptive and STD microbicide, agrees and adds that pregnancy prevention may be one key to consumer interest in microbicides: "We believe that for U.S. and European women, their interest in a microbicide will be enhanced by the addition of nonsystemic contraceptive activity," giving women the option of a nonhormonal contraceptive method.

Remove HIV as an indication, says Corner, and development is free of a whole host of issues having to do with the conduct of trials. "Testing a product for the prevention of pregnancy and STDs is a much more straightforward path. As a result, these kinds of microbicides will be approved faster. And that's important to my company, my investors and the U.S. market, all of which cannot wait the years required to conduct HIV efficacy trials."

### Impacts on Future Development

Not surprisingly, experts have strong opinions about the merits of various development strategies and their impact on future microbicide research and development.

"Marketing a product for the prevention of pregnancy and chlamydia, let's say, is a way of establishing a market niche," Corner says, "while at the same time trials continue for other STDs. It's a way of 'seeding the world.'" In addition to building a market niche, this first-generation product would demonstrate that microbicides as a new technology are effective in reducing the risk of contracting an STD.

Deborah Arrindel, an STD-prevention advocate and director of public policy at the American Social Health Association, agrees that the availability of an STD microbicide—even without an HIV indication—would be an important milestone. "Often people overlook the impact of STDs. Chlamydia, for example, is the most frequently reported infection in this country. A microbicide that helps prevent STDs would be a significant accomplishment."

Whaley contends that the question of which comes first, HIV trials or contraception/STD trials, should not be an "either/or decision" for the field. "All of the studies—for HIV, STDs and contraception—should be done in parallel," he says. Rosenberg, however, views the question of priorities as essential. "If we had unlimited research funds, these studies

should be done concurrently, but until that time, we must keep our focus on HIV.” Rosenberg argues that many people in the United States and Europe have a viable way of protecting themselves against infection—the male condom—and that behavioral interventions encouraging condom use in this country have largely turned the HIV epidemic around. But the main strategies for HIV prevention are “woefully inadequate” in the context of the developing world, she contends. “Women, as compared to men, still lack the power to negotiate condom use in sexual interactions. The need for a female-controlled method of HIV prevention is the number one public health objective for most parts of the developing world—it hasn’t gone away.”

Rosenberg says she fears that if the field were focused on the prevention of STDs other than HIV in the early stages of development, the effort to develop a vaginal microbicide for the prevention of HIV would suffer. “There is a tremendous amount that goes into these studies, and there is a good chance that a product being tested for STD prevention won’t work. But it could work against HIV.” The reason for this, she says, is that other STDs are harder to prevent than HIV. “For example, gonorrhea has a high chance of infection for every sexual encounter. This means that the microbicide has to protect more often, killing more bugs, each and every time.” Rosenberg worries that by putting off HIV efficacy trials in favor of STD trials now, a number of products that show promise for preventing HIV will be shelved. “We will have to do HIV studies, no matter what. There is no reason to lengthen this process by delaying those studies.”

### Implications for Funding

These discussions about the various options for a first-generation microbicide are being echoed in the advo-

cacy world, where a central issue is the pursuit of federal funds for research and development efforts. Some advocates have expressed the concern that if a first-generation product is marketed as a vaginal contraceptive and STD microbicide, rather than for HIV prevention, it

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may be the “kiss of death” for the field by embroiling microbicides in the politics of family planning. ASHA’s Arrindel, on the other hand, argues that her experience indicates that advocating for disease prevention is not necessarily less controversial than advocating for contraception: “STDs are acquired sexually, still a taboo subject on Capitol Hill. While the sequelae of STDs—infertility, cervical cancer, infant mortality, and AIDS—are major concerns, policymakers have been unwilling to acknowledge the link between these concerns and STDs.”

Meanwhile, the fact remains that federal funding for microbicides is overwhelmingly the result of Congress’ concern about HIV. This year, the House and Senate already are in agreement that at least \$15 million should be spent in FY 2002 on microbicide research and development as part of the U.S. Agency for International Development’s HIV/AIDS prevention efforts. And while federal agencies have developed ways of ensuring that contraceptive research and development activities are not counted as funding for microbicides, Pam Norick, legislative advocate for the Campaign for Microbicide Development, contends, “If Congress sees that the first product out of the gate is not effective against HIV, they may think we sold them a bill of goods.” Anything

less than a microbicide for preventing HIV, she says, could be perceived as a “broken promise” to Congress.

### The Calculator Analogy

Lori Heise, long-time microbicide advocate and national coordinator of the Global Campaign for Microbicides, envisions that one day a variety of products will be available to couples providing protection not only against HIV but against a broad spectrum of STDs as well. The potential exists, she says, for microbicides to exceed even this expectation by meeting broader needs, including pregnancy prevention as well as hygiene, vaginal health and general protection against infection. Under this scenario, contraception is more of a by-product of microbicide development rather than its primary focus.

Until that day, however, promoting microbicide development requires a nuanced message. “I wish we could tell people as soon as the first microbicide is available, ‘Throw away your condom!’ But we need to keep in mind what’s realistic. We may not have a product that is as effective as the condom for another 15 to 20 years.” Heise says she tries to “spark people’s imagination” while also “qualifying” the vision. “I speak in terms of generations. It’s like the early calculator. At first, calculators were big and clunky and had limited functions. But we were thrilled that they could divide! Today, calculators fit on the end of your pen. Likewise, microbicides will greatly improve over time. We should applaud the development of a first-generation microbicide; despite its limitations, it will still do something that hasn’t been done before.” ☪