Kiss & Gel

HIV infects 6,000 women every day because their men won't wear condoms. But a solution could be at and on their fingertips. It's odorless, kills HIV -- and, best of all, he doesn't have to know.

June 1, 2002 By Stacie Stukin

Sara and Paul are like countless married couples in the developing world. While she raises children and looks after livestock on a farm in rural Zimbabwe, he works a subsistence-wage job in a distant town. They see each other, at best, once a month. The last time Paul came home,Sara noticed a vaginal discharge just days after he left. A local clinic confirmed her suspicion -- Paul had given her a sexually transmitted infection. But when she tried to get him to wear a condom, she received a severe beating.

If 20 years of AIDS have taught us anything, it's that men, straight or gay, rich or poor, would sooner chuck a condom than slip it on. In sub-Saharan African countries, condom use falls as low as 7 percent. Nearly half of gay American men in their 20s report that they recently had unprotected anal sex. "I don't think it's hard to ask someone to wear a condom, but guys hate them," says Dyanne Stempel, a single white female living in Los Angeles. "They don't say anything and then they either can't perform or they get uncomfortable."

But what if Sara and Dyanne had a stealth method of protection? Something called, let's say, Coochie Cream or Booty Butter -- an odorless gel, lotion, foam or suppository that could help protect them from STDs, but that would also ensure the seamless intimacy cherished in those passionate moments? "It would be a dream," Stempel says.

For 15 years, certain scientists -- gravely underfunded and mostly dismissed by the AIDS research mainstream -- have toiled to make this dream a reality. Now the fruit of their labor is ripening, just as the cause of women enters the vanguard of AIDS consciousness. Their inventions are called microbicides -- and while the unfortunate name sounds like a fungus-eradication product, if all goes well, these woman-controlled "chemical condoms" could reach the over-the-counter market in five years and become the biggest reproductive-health innovation since the birth-control pill.

No longer the fantasy of womanist policy wonks and heated activists, microbicides have become a cause célèbre, splashed onto the pages of publications like *Vogue* and *The Wall Street Journal*. Their credibility comes not only from the most promising candidates' recent clinical trial advances but also from the stepped-up efforts of billionaire philanthropists Bill and Melinda Gates, who have donated a total of $50 million to microbicide research. In February, they made their most recent

contribution, $20 million to fund a Phase III trial-- the final, FDA-required test of efficacy in humans -- of a promising seaweed-based product called Carraguard.

The need for such a revolutionary product has become alarmingly clear: Worldwide, 17.6 million women have HIV. A single unprotected sex act is eight times more likely to infect a woman than a man. Across Africa and Asia, women in ostensibly monogamous marriages are at great risk of contracting HIV and STDs. In Thailand, a study in the *Journal of Acquired Immune Deficiency Syndromes* reported, 76 percent of HIV positive women said that their only sexual contact was with their husbands.

“The issue of women has come front and center in the AIDS epidemic,” says Helene Gayle, MD, who championed women’s prevention programs as atop official at the Centers for Disease Control and Prevention and now oversees the Gates Foundation’s AIDS giving. “The reality is, we’re still many years from having a vaccine, and that’s made people realize we need to diversify research and development. We can’t just focus on treatments and vaccines -- we need to find intermediary technologies.”

Carraguard is just one of nearly 60 microbicides in development in the United States, India, Brazil, Belgium and Britain. These products come in a wide variety of formulations. Some are contraceptive as well as antimicrobial; others would allow for conception while nixing HIV. Because of the prevalence of anal sex, many researchers insist that microbicides must work rectally as well as vaginally. This has the added bonus of making them valuable to gay men as well as straight women. But each prototype aspires to a common goal: skin-to-skin contact, the ideal of intimacy across all cultures.

David Phillips, PhD, a senior scientist at the Population Council,wishes that he could say he’s the genius who discovered that a simple red, seaweed-based product called carrageenan prevents viral infections such as HIV. But in fact, carrageenan, a food thickener used in Campbell’s soups, ice cream and baby food, has been known for its antiviral properties since the ’60s. In the ’80s, scientists began looking at carrageenan’s potential for herpes prevention. That was when Phillips began the research that led to the formulation of Carraguardin the late ’90s. “We’ve shown that Carraguard is effective against HIVin the test tube and against several sexually transmitted pathogens in animals,” he says. “But there’s still a lot we don’t know about how HIV gets into the body. [See ”Enemy at the Gate“]. Now it’s our job to prove it will work with people.”

Carraguard is one of five microbicides set to enter advanced-stage clinical trials this year. With so much riding on the results of the research, scientists such as Zeda Rosenberg, the interim executive director of the International Partnership on Microbicides at Family Health International, has a barrage of urgent questions to answer. Overseeing the Phase III tests of two other top contenders, PRO 2000and BufferGel, Rosenberg is helping to design studies with upward of 8,000 women. As far as the sheer scale and ambition go, Rosenberg maintains an upbeat attitude. “Every challenge can be overcome with creative design and lots of resources,” she says.

But the investigations are starting with a financial straitjacket. Carraguard, for instance, has only

about $20 million in its research coffer, although conservative estimates put the cost of a trial closer to $50 million. Beyond the money, there are logistical and ethical problems. Scientists can't be in bed with participants when they actually use the gel, so they must rely on self-reporting rather than the data-gathering methods used in laboratory-controlled settings. Then there's the moral dilemma that arises when Western scientists give,say, an African woman -- whose chances of contracting HIV are 20 to 30percent -- a placebo gel rather than the real thing. It's true that the researchers will give all volunteers condoms and encourage the use of both latex and microbicide (or placebo gel). But even the best intentions could result in women being -- or ultimately feeling -- exploited when their risk of infection is frighteningly high. Rosenberg acknowledges the ethical implications but still defends the proceedings, arguing that the women will receive prevention and care at standards comparable to those in the U.S. "That means condom promotion and counseling and treatment of STDs," she says.

Rosenberg and her colleagues believe that a microbicide will have demonstrated efficacy if, over three years, there are at least 30percent fewer infections among users than in the control group. That may sound far from ideal. But researchers at the London School of Hygiene and Tropical Medicine estimate that a microbicide with 60percent effectiveness could avert 2.5 million new HIV infections over three years worldwide. On top of the obvious human benefits, that translates into a $2.7 billion savings in health-care costs (not including HIV meds) and $1 billion in productivity for developing countries.

"This has been discussed by many experts in the field, and there is some consensus, at least for the first clinical study, that 30 percent could potentially lead to approval," says Debra Birnkrant, MD, director of the FDA's division of antiviral drugs, who has reviewed every microbicide that has entered trials. "This is being developed globally-- not just for the U.S. -- and if we could prevent 30 percent of infections in Africa, that would be tremendous." Still, she envisions the FDA recommending the products for use with condoms. "The trials are being conducted with them, and the labels have to reflect that," she says.

Even with all the drum-rolling about the promise of the "fab five" microbicides, researchers have great cause for caution. Two years ago,four microbicide finalists had made it to Phase III trials, but all ultimately failed because they contained Nonoxynol-9. In studies, the spermicide was found to cause vaginal abrasions, making women even more susceptible to HIV.

The current crop works differently. Carraguard's carrageenan belongs to a family of compounds called sulfated polymers, which are believed to coat HIV and keep it from entering host cells. BufferGel, made of a foaming agent already used in many vaginal products, mixes with the vagina's natural acidity to create a pH level hostile to HIV. Then there are antiretroviral products like PMPA gel, which work like current AIDS therapies by blocking HIV replication. Since the '80s,hundreds of compounds have been screened in test tubes for their ability to prevent pregnancy and kill pathogens, says Henry L. Gabelnick, PhD, the director of a microbicide research consortium called CONRAD that in 2000 received $25 million from the Gates Foundation. After the devastating failure of Nonoxynol-9, he says, "people began looking for formulations that were less irritating and compounds that would bind the virus."

The finalists -- most of which have passed the small Phase II tests for safety and initial indications of effectiveness -- all offer promising approaches. The big problem now is money. The Rockefeller Foundation Microbicide Initiative, a working group of consultants,researchers and pharmaceutical analysts, estimates that total product-development costs for the first generation of microbicides will run more than $750 million (by contrast, the average drug, including HIV medicines, costs $500 million to develop.) Sadly, the Initiative projects only $230 million in public funding for microbicide development through the year 2005.

One solution would be for deep-pocketed pharmaceutical giants to partner with the current loose network of academics, nonprofits and plucky, indie biotechs such as ReProtect, the Baltimore company that developed BufferGel. But prevention has never been Pharma's bread and butter. "As a society, we talk a lot more about therapy than prevention," says Kevin Whaley, PhD, who helped develop BufferGel. "With microbicides, we're introducing a whole new category, and that's just stunning to some people." To make matters worse, the female condom and the Today Sponge, two products seen as business-case precursors to microbicides, were thought to enjoy strong market potential but turned out to be unmitigated flops. Annual worldwide sales of the female condom peaked at a miserable $6 million (in comparison, "male" condom sales have reached $295 million in the U.S. alone), and the sponge raked in a paltry $20 million -- hardly the numbers to justify microbicides' not-insignificant development costs.

For the most part, pharmaceutical giants are watching microbicide testing from the sidelines and withholding their wallets. Janet Skidmore, a spokesperson for Merck, explains that her company's HIV prevention commitment lies, and will remain, firmly in vaccine territory. "Given our experience in the vaccine field, it's just the more effective approach for us," she says. She denies that this decision is based on economics or microbicides' early clinical stumbles. "We feel strongly that the best way to approach this pandemicis with a vaccine."

But if Merck and its brethren were in fact to consider the "return on investment" numbers compiled by the Rockefeller Foundation Microbicide Initiative, they'd likely flee in horror. While the group rates current microbicides as "promising" and predicts that their global market size could reach $900 million by 2011, it places each candidate's statistical chances of clinical approval and market entry at only 25 percent. Even worse, projections show that any corporate backer of a first-generation microbicide is likely to incur financial losses in the tens of millions of dollars. For a microbicide to be effective in the developing world, it has to be cheap -- as little as35 cents per dose -- obliterating profit margins.

Researchers and academics argue that as long as the clinical trials are publicly and philanthropically funded, a pharmaceutical company that owns or acquires a successful microbicide does stand a chance to make money. "It's not going to be a billion-dollar blockbuster, "Gabelnick says. "But the market for spermicides now is only $40 to $50million, and that hasn't kept personal-product companies from selling them." He also envisions a two-tier pricing system to balance out the cheapness of microbicides in poor countries. "People forget that a cycle of oral contraceptives sells for $30 in a pharmacy, but donor agencies probably get them for 30 cents or less," he says, adding that in many developing nations such as Brazil, India and China, there's a

sizable, growing middle class that can absorb a higher price point.

That a viable, potentially lucrative microbicide market exists in developed countries is something that UC/Berkeley epidemiologist Bethany Young Holt, PhD, is seeking to prove with a soon-to-be-published study of young American women. “Across the board,women are uncomfortable talking to their male partners about sex --whether they’re rich, poor, white or black,” she observes. Holt held focus groups to gauge women’s interest in microbicides. Their responses were encouraging and even produced sexy packaging ideas, like a sleek gel (strawberry flavored preferred) contained in a lipstick-like case-- the must-have purse item of the coming decade.

For now, all eyes are on the holy grail of FDA approval, which could take another five years. But the war chest for microbicide development remains disturbingly light, with money coming in piecemeal from the government, academic grants, private foundations and small biotech firms. According to the Washington, DC-based Global Campaign for Microbicides, an organization that raises public awareness and political and financial support, only 1 percent of the federal AIDS research budget -- $35 million -- is currently allocated to microbicide research.

For veteran activists such as Anna Forbes, the Global Campaign’s field organizer, this is a frustrating state-of-affairs. “When we treat microbicides like the ill-fated, red-haired stepchild, we’re just cutting off our nose to spite our face,” she says. “This could be revolutionary.”

If microbicides are going to take hold, there needs to be a major public education push. According to the Kaiser Family Foundation, only 2 percent of Americans have even heard of microbicides.

A stronger show of political force will also be necessary, which is why people like policy officer Lara Stemple are working on campaigns like the California Microbicides Initiative (CaMI) in Los Angeles. CaMI and other groups have secured the sponsorship of eight senators and 38 house representatives for the Microbicide Development Act, which would appropriate money for a new microbicide program at the National Institutes of Health. Given the unpredictable AIDS climate under the Bush administration -- with abstinence dominating the federal HIV education agenda and a paltry $200 million committed to the UN global AIDS fund -- even Forbes concedes that the chance of passage is slim. But just introducing the act will generate legislative awareness and serve as a starting point for creative funding strategies. “Global AIDS is a hot issue on Capitol Hill,” she says. “And if we can position microbicides as part of the issue, then it has a much better chance of making it.”

With the profit sector playing possum until the proof comes in,what’s urgently needed is funding from public and philanthropic sources. “We’re looking for our Mrs. McCormick,” Stemple says, invoking the wealthy widow who, with reproductive-rights activist Margaret Sanger, unsuccessfully lobbied the pharmaceutical industry to develop a safe, effective oral contraceptive. In 1951, Katherine Dexter McCormick put her International Harvester money where her mouth was, hiring the scientists to produce the research that ultimately led to the birth-control pill.

Before then, liberating women’s sexuality from pregnancy might have seemed like speaking over

wires, flying through the air or rocketing to the moon -- once quixotic, even foolish, then suddenly, perhaps accidentally, attainable. When a microbicide liberates women's -- and gay men's -- sexuality from HIV, it could finally put the brakes on history's worst-ever public-health catastrophe. But in the absence of sufficient dollars and awareness, the revolution in the sheets will require what is sometimes equally hard to come by: movement in the streets. "It's clear microbicides are needed, and that they're imperative," Forbes says. "Since we're not able to attract corporate support, we have to make it happen ourselves."

ENEMY AT THE GATE

Researchers have spent 20 years and hundreds of millions of dollars trying to figure out how to undo HIV once it's in the body. But as virology and reproductive biology expert David Phillips, PhD, and his peers labor to prove the anti-HIV power of microbicides, a key mystery persists: How does the virus get into the body in the first place?

Theories of infection abound. Phillips believes that most acts of unprotected sexual intercourse with an HIV-infected partner won't result in transmission without certain mechanisms to facilitate viral entry. "It's like if a bunch of people drink contaminated water," he says. "Some will get sick. Others won't." The ideas about transmission vary, but ultimately any could be true -- or not. "There's so much we still don't know," Phillips says bluntly.

Most experts assume that semen carries the virus into the cervix,vagina or rectum, allowing it to invade other cells, which then circulate it bodywide. One leading theory holds that the fatal carriers are dendritic cells -- the ones that signal the immune system to produce antibodies. According to this view, dendritic cells pick up the virus and take it back to the lymph nodes, contaminating them.

Another top hypothesis links HIV infiltration to epithelial cells,which line the vagina, intestines and interior of the lungs. Even though these cells are designed precisely to protect these sensitive organs from infection, for some reason they are vulnerable to viral violation, especially in the rectum.

With a number of theories in play, the ideal microbicide would cover as many bases as possible, making the virus unsavory to dendritic cells and preventing the virus from binding to epithelial cells. But even if a microbicide trial is successful, it will be very difficult, if not impossible, to isolate which infection mechanisms were blocked. "It's my job to worry about them all," Phillips says. Clearly, the mystery of infection is fertile ground for future research.

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