GMHC treatment ISSUES
NEWSLETTER OF CURRENT ISSUES IN HIV/AIDS
SEPTEMBER 2003 VOLUME 17, NUMBER 9

Women, Men and Microbicides

By Bob Huff

Mucosa Nostra
Understanding sexual transmission of HIV 1

Guided by Epidemiology
A talk with microbicide pioneer Zena Stein 6

More than Protection
Deenen Robinson looks at what women have to gain 8

Pushing the Point
The Global Campaign coordinates international advocacy 9

Neighbor to Neighbor
Profiles of microbicide advocacy in the U.S. 10

Drug News
Kaletra solo startles ICAAC 11

FDA: Global Citizen
Jen Curry on choices the agency must make 12

We've heard a lot about HIV entry inhibitors in 2003. The new injectable fusion blocker Fuzeon (T-20, enfuvirtide) is the first member of this new class of HIV drugs to hit the market, and several oral drugs intended to block HIV entry into cells at other steps are just starting clinical trials. As a class, the entry inhibitors are designed to keep HIV from merging with a new cell in someone who is already infected. But before HIV can put down roots and start infecting those billions of immune cells, at least one viral particle must make its way past the body's skin or mucosa—barriers that are supposed to keep the outside out, and the inside in. This premiere moment is called transmission, and new understanding about how the virus first enters the body is stimulating progress in the fields of therapies, vaccines, and topical microbicides.

Like all miracle cures, education, abstinence and condom use have proved too good to be true.

Direct blood-to-blood transmission of HIV seems straightforward. People infected through a transfusion, blood products or shared injection equipment probably received a significant dose of the virus in multiple forms that efficiently found its way into their immune system. Immediate post-exposure prophylaxis with antiretroviral (ARV) drugs has a good record for preventing blood-borne infections from needle-stick accidents and may prevent some sexually transmitted infections as well. Another main route of exposure is through mother-to-child transmission during pregnancy or birth. It was eventually discovered that most newborns could be spared from infection by reducing the viral load of the mother with antiretroviral drugs before labor, or in some cases, by choosing C-section over vaginal delivery.

But sexual transmission of HIV is the leading source of infection, and although infections between men having sex were most common at the beginning of the epidemic, nowadays infections passed between men and women are pushing the scale of the world AIDS crisis into uncharted territory. With an estimated 14,000 new infections occurring every day, and as many as 42 million infected worldwide, preventing new infections between men and women is an unmet emergency. The most available lines of defense are education, behavior change and condom use. Simply not having sex or assiduously using a condom every time can do wonders for reducing the infection rate. But like all miracle cures, education and condom use has proved too good to be true. Most new infections occur among young people—a group powerfully motivated to have sex—and among people with little control over the material conditions of their lives, such as men and women in resource poor areas who lack the power, education and opportunities to protect themselves.

Beyond education and condoms, public health policy has pushed for development of a vaccine. In a few historical cases, vaccines have been able to effectively protect mass populations from communicable pathogens at a rock bottom, one-shot and on-with-your-life cost that sounds like salvation. As HIV spreads unrestrained in some regions; when as many as 40 percent of a nation's citizens are in danger of becoming infected, even a partially effective vaccine that can't reliably protect any particular individual would have a huge impact on the social catastrophe of AIDS.

But a vaccine for HIV has proved difficult to solve. In every year since the mid-1980s, someone has estimated that a vaccine will appear in the next 5 to 10 years; wise scientists now refuse to guess when one will come. Because HIV infects and influences the very immune system called upon to fight it, vaccine research remains vexed by unanswered questions of basic science. Meanwhile others have been looking for simpler solutions. Over a dozen years ago, seeing the rising worldwide death toll prefigured in epidemiology and social reality, some public health thinkers (such as Zena Stein) began to propose novel ways to augment conventional, barrier-based prevention methods. They first recognized that male condoms would never be a viable option for every woman because, among many reasons, the technology depended upon male participation to be effective. In too many cases and cultures, men simply refuse to accept condoms, and women become infected, powerless to object. With the chances of infection during one episode of heterosexual sex put at 1 in 200 or less, even a partially protective method could lower that risk and start saving lives.

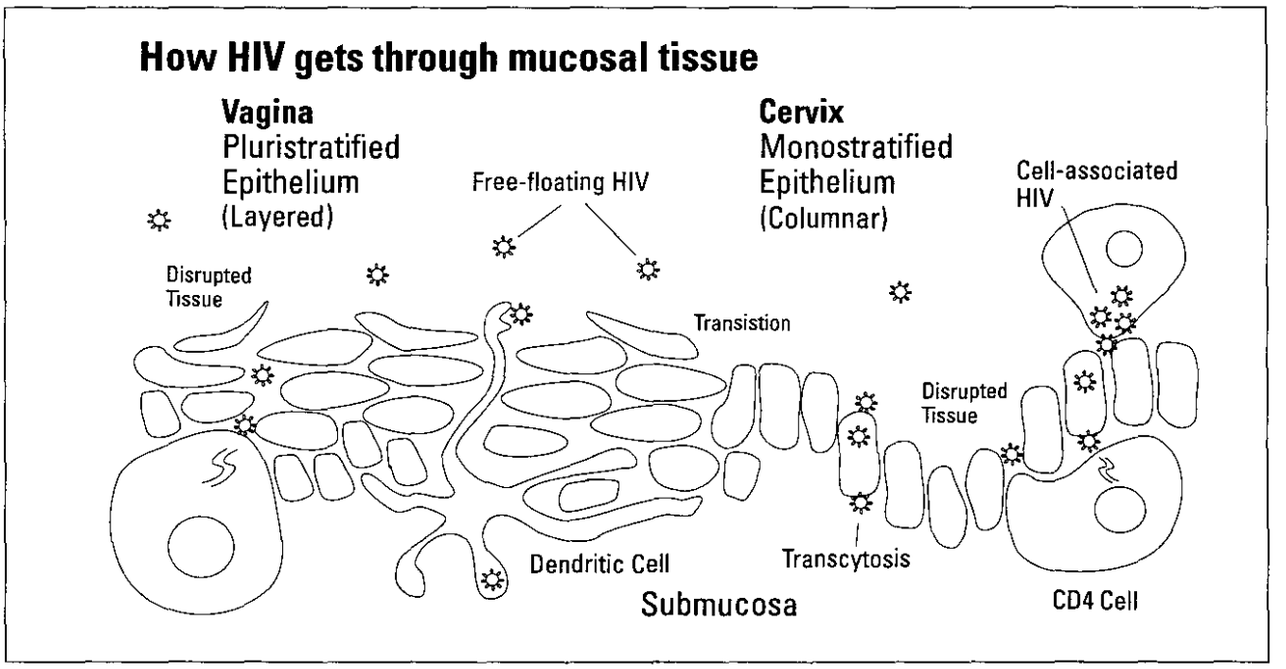
A highly effective microbicide would likely protect against HIV transmission in multiple ways and might even act against several other kinds of microbial invaders.

Enter the Microbicide

One clever proposal for keeping HIV out of the body is to apply a liquid or gel substance before sex that could block infection by physical, chemical or medicinal means. Known generically as a microbicide, the idea was derived from products to prevent pregnancy that were already on the market. (One contraceptive product, N-9 or nonoxynol-9, was initially thought to have anti-HIV properties until it was discovered that N-9 actually increased susceptibility to HIV infection by breaking down the body's natural cellular barriers to microbes.) Despite the exciting potential for an inexpensive method that can be used without the participation of a partner, microbicide research has met with some of the same problems slowing vaccine development. And microbicides have posed a new set of challenges altogether, ranging from applicator design to placebo validation. Simply coming up with a gel to stop viruses from sticking to their targets has not proved as elementary as many thought.

A highly effective microbicide would likely protect against HIV transmission in multiple ways and might even act against several other kinds of microbial invaders. Begin with the gels and foams. These are based on a medium that would be inserted, squirted or secreted into a vagina or rectum and may or may not carry other active ingredients. But before a product can be found effective, it must first be found safe, tolerable and acceptable. For example, if the product is a gel, the physical properties must be right—not too sticky, too runny, or prone to dry out. These are qualities that matter to the user, and different users are likely to have different needs and preferences. Then there are the chemical properties to consider. Some forms of gel might be designed to simply keep HIV from ever coming into contact with the mucus membranes that line our vulnerable body cavities. Or it may contain chemicals to help maintain the naturally protective acidic environment of the vagina. Another gel might be optimized to carry an active ingredient that disrupts HIV's lipid membrane. Still another type might be best for delivering an antibody, a vaccine or a drug to the mucosal tissue so it can penetrate into the submucosal layers and become active. A good gel must avoid harming the mucosal barrier cells or any submucosal cells that become exposed through tiny breaks and tears in the vagina, cervix or rectum. It must not cause irritation if it is left on overnight, especially to unsuspecting penises. Furthermore, the gel must not set off any local or general immune response in the vast majority of people who use it; the last thing you want to do is attract immune cells—the primary target of HIV—to the scene. All of these stringent requirements mean that any gel expected to perform in a mass-produced microbicide—not to mention the active ingredients it carries—must be thoroughly tested to prove it is safe.

Although there is a long list of potential microbicide candidates, only a handful of products have advanced far enough through the clinical trials process for them to realistically become available within the next five years. And lack of investment by industry and government is holding back more rapid development. The cadidates furthest along the pipeline work in non-specific ways; most by impeding viral access to vulnerable mucosal tissues.

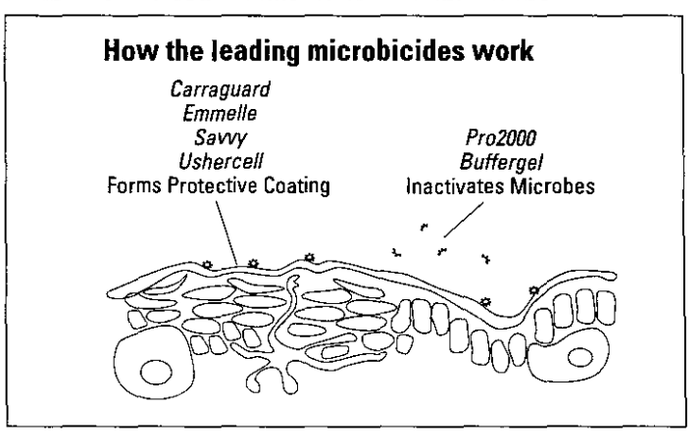


Our Mucosa—Basic Biology

The biology of the mucosal tissues that line our body parts susceptible to infection determines how likely and how preventable sexual transmission of HIV will be. These tissues are composed of various types of *epithelial cells* arranged in either layers or in columns. The vagina, outer cervix, anus and foreskin (of an uncircumcised penis) are covered by overlapping layers of epithelium in a fish scale-like structure called *pluristratified mucosa*. The upper cervix and rectum are lined with a single layer of columnar shaped epithelium called *monostratified mucosa* (see illustration). There is also a brief transition zone that bridges these tissue types in both the vagina and the rectum. Another theoretically infectable region of mucosa is in the mouth and throat, although saliva seems to provide a natural microbicidal action and infection of these tissues, while it does occur, is relatively rare.

In healthy, intact pluristratified mucosa, as in the vagina, one mechanism for infection is thought to use a type of immune cell called a *dendritic cell*, which moves through the submucosal layers of tissue and sends its dendrites (octopus-like arms) into the stratified epithelium to scan for foreign pathogens. Dendritic cells (DC) carry a cell-surface receptor called DC-SIGN that is capable of binding to HIV's gp-120 spike. In CD4 T-cells, the predominant target for HIV, attachment of one of the viral envelope spikes to a CD4 receptor begins the process of fusion and infection. But in dendritic cells (mature cells at least; immature DCs may be infectable), attachment to HIV causes the virus particle to be taken inside a bubble-like vesicle within the cell where it stays while the DC continues its immune patrol of the mucosa. After the dendritic cell finally leaves the mucosa and makes its way back to the immune system's regional headquarters in a nearby lymph node (a process that may take several days), it puts the HIV virion on display for other immune cells to inspect. When a CD4 T-cell comes along that recognizes the virus as an outsider, contact is made. Unfortunately, HIV uses this very act of self-defense to enter the CD4 cell and hijack it into making new viral copies. As new HIV virions start to bud off from the infected cell, they quickly board other CD4 cells in the lymphatic neighborhood and the primary infection is launched. Within days, millions of immune cells are infected and distributing the virus throughout the body.

In healthy, intact monstratified mucosa, the process is thought to be a little different. Although it's not exactly clear how, it seems that a receptor on the columnar cells with properties similar to DC-SIGN attaches to HIV and causes



it to be internalized into the cell where it is passed through to the other side in a process called transcytosis. Once deposited on the submucosal underside of the epithelial barrier, the virus may come into contact with a patrolling CD4 cell or other immune sentry cell and infect it directly. As with dendritic cells, the CD4 cell likely carries the virus back to a lymph node where the infection is amplified.

But mucosal tissue is rarely completely healthy and intact, and variations on these paths to infection may be common. Microscopic nicks and tears in the mucosal barrier due to physical abrasion may allow direct contact between the outer environment and the submucosal immune cells to occur. The monostratified cells of the rectum are particularly vulnerable to physical damage during sex. Vaginal infections such as chlamydia or herpes may disrupt the protective mucosa and enhance HIV transmission by attracting target immune cells to the inflamed region. There are other wrinkles and exceptions to these basic modes of sexual transmission. For instance, not all virus is free floating; HIV may also be transmitted via a virus-laden cell in the semen that crosses the epithelial barrier like a Trojan Horse. But once HIV has made it into the mucosa, the barrier-based methods have failed. The next challenge for microbicide research is to find ways to stop an infection in its earliest stages.

Products at the Head of the Pipeline

Product name	Pipeline status	Sponsor	How it works
Carraguard	Phase II safety studies in progress. Phase III to begin in 2004.	Population Council	Forms protective coating
PRO2000	Phase IIB planned.	Indevus Pharmaceuticals	Forms protective coating
Buffergel	Phase IIB planned.	ReProtect LLC	Maintains normal vaginal pH
Savvy (C-21G)	Phase I/II completed.	Biosyn, Inc.	Disrupts viral membranes
Emmelle (dextrin-2-sulfate)	Phase II safety studies in progress.	Multiple sponsors	Forms protective coating
Ushercell (cellulose sulfate)	Phase II in progress.	Multiple sponsors	Forms protective coating

The Bottleneck in Microbicides Development

In the absence of major pharmaceutical industry participation, a number of universities and small, independent biopharmaceutical firms have taken the lead on microbicide research. But in order to fund their research, these entities require public grants and—to the extent they can raise it—venture capital. The result: chronic underfunding and a clogged research pipeline.

In 2002, a major economic analysis of the field concluded that if a single pharmaceutical company were managing all microbicide research leads, that company would have to invest $775 million over five years to ensure the production of at least one safe, effective product. The Rockefeller analysis was a "bare bones" scenario that only considered the costs directly related to product development, omitting other necessities like basic research, discovery of new leads and work to assure that the products will be acceptable and accessible to users.

The report also showed that if current funding levels continue, the amount spent on microbicide research and development (R&D) worldwide between 2001 and 2005 would total about $230 million. This leaves a $545 million shortfall at minimum between current funding levels and the expected cost of getting one successful microbicide on the market. Even the recent generosity of the Bill & Melinda Gates Foundation doesn't cover that gap.

Over 60 potential microbicides have been identified to date, yet most are stuck in the preclinical phase because funding to move them into human trials isn't available. The few candidate products of proven safety have not moved forward in 2003 as planned because their sponsors are unable to support the cost of large Phase III effectiveness trials.

Microbicide R&D cannot advance efficiently without substantially increased governmental and foundation funding. At present, the U.S. National Institutes of Health (NIH) invests only about 2% of its AIDS-related research budget in microbicide R&D.

Anna Forbes -Global Campaign for Microbicides Advocacy

New Research

Certain areas of advanced microbicide research overlap with work going on in the HIV vaccine field seeking to target the virus with exquisite selectivity. In the early pipeline are proposals ranging from small molecule inhibitors to mucosally-directed vaccines. At the AIDS Vaccine Conference held in New York City in September 2003, some new ideas emerged about how HIV enters the body that may help focus the development of a topical (applied to the skin) method for preventing sexual transmission using antibodies to neutralize infectious HIV.

One new observation has to do with the specific kind and quality of HIV that can be transmitted sexually. It's long been recognized that only viruses that use the CD4 cell's CCR5 receptor during entry seem to be present in newly infected people. It was thought that the barrier epithelium or dendritic cells filtered out the CXCR4-using HIV at the point of transmission. This less-common form of HIV sometimes appears later in the disease and is associated with rapidly progressing AIDS.

New work by Eric Hunter and colleagues from the University of Alabama, Birmingham (UAB) now suggest that the kind of virus most likely to be transmitted may also be especially vulnerable to immune attack—that is if the immune system has been prepared to recognize it. Their work drew upon a highly productive research project conducted by UAB in collaboration with researchers in Zambia. The study has followed a cohort of sero-discordant (one positive, one negative) couples in Lusaka for over eight years. Couples in the study are counseled about safe sex and provided with condoms. About 8 percent of the partners become infected each year; yet because counseling and condoms are effective, this is a reduction from an expected infection rate of 20 percent per year.

The researchers obtain blood samples from participants throughout the study. If a partner becomes HIV-positive, the pair's samples are analyzed to determine the genetic sequence of the gp120 viral envelope protein responsible for attachment and entry. Hunter presented 8 cases of transmission, with 4 from male to female and 4 from female to male. In every case, the received virus was of the CCR5-using type. Unexpectedly, the genetic analysis showed that a particular envelope region on the received virus was unusually compact, lacking several features characteristic of a typical virus as found in established infections. Furthermore, this envelope region of the received virus did not resemble that on the virus obtained from the donor's blood. What was particularly exciting about this finding was that the received virus was unusually susceptible to neutralization by several specific antibodies, while the virus obtained from the donor's blood was protected against these antibodies. This may mean that a virus that is especially suited for sexual transmission may also be especially vulnerable to antibody neutralization. If so, then there is a possibility that, one day, these antibodies might be elicited in the mucosa by a vaccine or perhaps delivered by a microbicide to attack newly transmitted virus.

While the UAB study did not find a virus in the blood of the donor that matched the virus that was transmitted, they were not able to look at virus that may have been contained within the genital tracts. It is possible that a protected compartment allows the transmission-specialized virus to exist without competition from the more accessible viral strain coursing through the blood.

Although some vaccines under investigation seek to benefit chronically infected individuals by stimulating cellular immunity, the findings about a vulnerability in transmitted virus mainly applies to the uninfected, since HIV seems to begin mutating a protective carbohydrate (glycan) cover for its vulnerable spots soon after a primary infection has taken hold. However, there has been some evidence that these vulnerable epitopes may eventually reappear on gp120 as an infection matures; once the evolving shield of protective glycans begins to let down its guard against those early, presumably long gone, antibodies.

With so much still to be learned about the basic science of HIV infection, and so much intractable about the social reality that allows HIV to flourish, the impact of either an effective vaccine or microbicide remains many years away. Yet workers in the field remain hopeful—and with good reason. The energy and commitment evidenced by microbicide and vaccine advocates, and the increasing elucidation of the underlying science, argues that an eventual breakthrough is inevitable.

References:

Shattock RJ, Moore JP. Inhibiting sexual transmission of HIV-1 infection. Nat Rev Microb. Vol 1, Oct 2003.

Pope M, Haase AT. Transmission, acute HIV-1 infection and the quest for strategies to prevent infection. Nat Med. 2003 Jul;9(7)

Derdeyn C, Decker J, Hunter E, et al. Hetersexual transmission of HIV-1 involves envelope-constrained, neutralization-sensitive variants. AIDS Vaccine 2003. Abstract 123.

The International Epidemiologist
A Talk with Zena Stein

By Jen Curry

For many years in the early part of the U.S. epidemic, there was a general denial that women were at risk for getting AIDS from sex. Even when it was clear that women were being infected, the risk was not taken seriously. Now, half of new HIV infections occur in women. How did you, as an epidemiologist, go about understanding what you were seeing when this new disease first appeared?

When I began my very first work with AIDS it was still called "Gay-Related Immune Deficiency." The cases were mostly in gay men, but we knew it was blood borne because hemophiliacs got it from blood transfusions, and some patients who got it were injection drug users. And we began to ask, well, if gay men are getting it through sex, then why wouldn't women get it too? For a long time people just kept saying, "Women don't get it." I started talking with a colleague—and this is before we knew it was a virus causing the disease—and we said, "Women must be getting it. And there must be some reason why women get it." We did some very exciting work going around to different scenes where people were having sex, to see if the women knew anything about these men they were having sex with. Some of these were men who usually had sex with other men. And it made sense. Think of the social circumstances: gay men cross over into women's society. But people didn't really believe us. It took time and effort and continually saying "Well, women do get it this way." My proposal to the NIH for further study was turned down because "it wasn't a woman's disease."

If we find that women aren't really using the microbicide during sex, then this problem of improving the method of delivery has got to be taken seriously.

How did looking at the epidemiology given your previous work on pregnancy help you understand what was happening with infants born to HIV-positive women?

The transmission of disease from women to children has always been central to family health and reproduction. I think what especially intrigued me was when I realized that transmission only occurred in one of three children. So, why doesn't it always occur? My colleague and I tried to think of ways we could come closer to understanding in which babies does transmission occur, and why? And we thought of looking at planned C-sections, to see if the baby wouldn't get infected through the canal and if we could reduce transmission to babies. Another study about twins came out around the same time, where the first twin didn't get infected very often, but the second twin down the birth canal was more often infected. So we realized that the environment of the birth canal must be a place where the transmission takes place. Which indeed was true, and is why most of our mother to child prevention protocols say, as long as you get to the woman before she goes into labor, transmission rates go down. And now we also know, nevirapine given before labor lowers the viral load and reduces transmission by quite a lot. Knowing the circumstances of the birth was the key.

When was it that you really began to see the need for a microbicide that women could have some control over?

When I began to think about AIDS in Africa, people kept talking about male condoms. I talked a lot with a friend and colleague who is a sexologist about how, before we had the hormones to prevent pregnancy, we had condoms – the male condom, or a woman could use a diaphragm. Neither of these were 100 percent effective, but they were reasonably effective. The male condom goes back in history much farther than the diaphragm, but once the diaphragm started emerging in the 1920s, the responsibility started shifting from men and their condoms to the woman to use the diaphragm. Then in the 1960s it moved completely to the woman with "the pill," which was very effective for contraception, so that if something happened the man could say, "Well, the girl didn't take the pill." The threat of pregnancy was largely eliminated by the pill but now the onus was on the woman. And now we have emergency contraception, which enables you to mess up occasionally and we have legalized abortion too, if you want it. These are big advances for women, to have this control over pregnancy. But they don't protect against HIV.

When I first started writing about microbicides, I used to say we needed a "woman-controlled" method and argued that it could or should be a secret from the man—clandestine. It's been a long time since then and I've come to understand that that's really not quite right. First of all it depends on the relationship. In

many relationships, women don't want to hide anything from their partner because if they do, they upset the relationship. It's better to discuss it. If you can discuss it, you could argue, then he can use a condom. True. If you can discuss it, he might be quite relieved to know he doesn't have to worry about a pregnancy. But if he discovers that you're doing something and not telling him, or if he expects children and won't accept contraception, that's very tricky. If he wants her to get pregnant, he may start to wonder if there's something wrong with her when she doesn't get pregnant. And different groups of women use and need different strategies for getting around this.

Another problem is that the microbicide must be clandestine at the time of sex or before, because the maximum period of time it can be applied before sex is very important for efficacy. Even so, microbicides are not going to be as good as condoms—everybody knows that—still they can go mostly unnoticed. But I don't think you can or should betray your relationship with these clever, funny devices.

What specific problems do you think activists should be focusing on?

Women in certain parts of Africa who already have two or three children—they're not always the ones getting infected. But if a woman is 17 or 18, she may go in to the clinic for a few years of contraception and use a barrier. But at some stage, she will want to get pregnant, and I think nobody's dealing with that.

And then, there's the sweeping problems no one wants to address: the economic and political realities that are driving transmission. For example, we see it quite plainly in South Africa among men—migrant gold miners from the rural areas—who consort with sex workers and are a source of STIs (sexually transmitted infections). And before HIV, it was syphilis. They'd go away for work and then they'd go back home and their wives often got infections of the cervix. There have always been jokes about commercial travelers—in Sub-Saharan Africa it's truck drivers all along the regular routes they travel—and these things are true: when men are separated from their families, they get more STIs. The trucks come down and the sex workers are around where the drivers stop. So, the workers in occupations involving migrant laborers or work far from home need special education, because the breaking up of families is an integral part of such industies and economies. And it's less the sex workers than the truck drivers who should be the subject of special education. All the studies suggest that sex workers won't push for condom use by their driver or miner clients because that reduces what the client is willing to pay.

What do you see as some of the main stumbling blocks for microbicides becoming responsive to the needs of different women?

Well, one thing is the way they're planning to deliver it—by squeezing it in. We've got to get new technology there. There's a ring you can put against your cervix that's currently being used for contraception. Now, if the ring can be made to carry a microbicide, and if women choose to use the ring, then you won't have this bother of putting the stuff in—it will already be there. If the microbicide just sits in this little container by the bed, then you won't have proof of concept from your clinical trial. If we find that women aren't really using the microbicide during sex, then this problem of improving the method of delivery has got to be taken seriously.

We've a long way to go before we have a microbicide that women who want at least one or two children are going to use.

Another important thing to many women is whether they can become pregnant. For example, Carraguard may not be contraceptive; but some of the others will likely be. For some women, and for some societies, it's extremely important to be fertile. That will be the next problem, assuming we observe some efficacy in the trials: after the ten years it takes to get a microbicide, at the end we won't know whether it's contraceptive or not. We've a long way to go before we have a microbicide that women who want at least one or two children are going to use.

I don't think the microbicides delivered as we are doing it now in the trials are going to be terribly effective. They are possibly only about forty or fifty percent effective, but nobody knows because we haven't got anything to compare them with. The only comparison we have is with 95 percent consistency from the direct use of a condom. So I am in favor of not only of having a microbicide approved but of also having the female condom, and one of these cervical devices. We need an array of options for a woman.

There is no simple path to achieving more effective methods for woman-initiated STD/HIV risk reduction. Women who desire both pregnancy and protection from HIV/STDs may not have a safe and effective microbicide available in the foreseeable future.

—Zena Stein, *Treatment Issues*, July 1997

Women, Power and Microbicides

By Deneen Robinson

Do women in the U.S. really need a microbicide? Good question. It seems to me that most of us—whether in Vietnam or in Texas—could use some form of protection that would allow us to control our risk for HIV and other STIs without depending upon a partner. This being the case, an ideal microbicide—one a woman could use ahead of time; that provided near 100 percent protection and was not apparent to her partner—would be welcomed. As one woman said to me, "I want something I do not have to ask him if we can use. I am always scared that he is going to say no and then what am I going to do?" Many women are afraid that their partner will refuse to wear a condom. Others are afraid that they will be harmed either physically or emotionally if they insist on using condoms. In some relationships, simply suggesting the use of a condom can cause suspicion, rejection and even violence. A good microbicide would help alleviate some of these women's fears and hopefully reduce their risk of getting HIV.

We need to begin reaching out to women who will eventually be using microbicides, even while we are trying to get a product past Phase II trials. We must begin to advocate for ourselves.

Condoms offer excellent protection, but too often they are not used and women cannot control their use. Studies have shown very low use of male condoms even in favorable circumstances. The lack of enthusiasm for male condoms makes microbicides a potential option for men as well, including gay men. Ideally, microbicides should be capable of protecting the insertive and the receptive sexual partner, making them attractive for men who have sex with men as well as for any man who does not want to use condoms because of the loss of sensitivity and intimacy.

But any microbicide now on the horizon probably won't offer perfect protection. Most likely, when the first microbicide does become available, it will still have to be used in combination with another form of prophylaxis to provide an individual with a high degree of reliable protection from HIV. The Global Campaign for Microbicides says, "Even when microbicides reach the market, it is unlikely that they will match the efficacy of male and female condoms for HIV prevention. Logically, it is safer to keep a virus from coming into contact with one's body than it is to try to disable it once is there."

There are also concerns that women will not use or will stop using other prophylactics when they start using the microbicide and will therefore increase their risk of getting or spreading disease. The other side of that argument is that for the women who most need a microbicide, condoms were never a good option to begin with. At least with a microbicide, women who cannot use condoms will have some opportunity for protecting themselves from sexually transmitted infections, including HIV. It is better to have some type of protection than none at all, which is the situation now faced by too many women.

Advocating for Ourselves

Despite the need for an effective microbicide, it will be several years before we get one, and there will be little chance for getting a microbicide without continued advocacy from scientists, governments, and especially the men and women who will be using them.

In the United States, the word microbicide still does not resonate with some of the very women who are perceived to most need options for protecting themselves from HIV. In discussions with a number of women age 20 to 55 in my town, the majority of them could not even define the term microbicide, let alone explain how they would be used. It is disturbing that scientists and advocates are struggling to get a microbicide to market for consumers who do not yet understand its relevance to their lives. In a group in Dallas, Texas, an activist gave a talk to help a group of HIV-positive women understand the use of microbicides. After the presentation, one of the participants said to me, "What was that about? I am not going to use that while having sex—no way." Obviously this means that we need to begin reaching out to women who will eventually be using microbicides, even while we are trying to get a product past Phase II trials. We must begin to advocate for ourselves. The advocacy of women legitimizes the need for more research to produce an effective microbicide.

How do we get more women involved in the campaign for a microbicide? How can we get more women empowered to protect themselves from disease? Education is a start. We must find a way to get information to women in communities where microbicides will be most beneficial—communities where the risk is greatest. This includes HIV-positive women, teenage girls at Planned Parenthood clinics, transgendered women, college students, sex workers, homeless

women, and married women showing up in domestic violence shelters. In addition to providing people with information, we must teach the importance of advocacy. Historically, the women who could benefit the most from a microbicide (or female condom, or needle exchange, or responsive medical care, and so on) have been the least active in advocacy. The reasons are the same as why women need a microbicide in the first place. Getting women involved will be difficult if we do not talk about microbicides in a way that resonates with their experience. This means it is our job to pay attention to the realities of sexuality, economic, geographic, and family differences regardless of whether we're talking with rural women, poor women, sex workers, married women or lesbians about this issue.

The power in relationships between men and women is too often unequal. Women tend to have less power in relationships than men—and not only in India and Africa, which is what people usually talk about when discussing microbicides—but here in Texas as well. As a result, many women learn that speaking up on the job, in school, at home, or in a relationship, can have negative consequences. The inability to control the method of prophylaxis used during sex and the resulting risk of disease is a symptom of this lack of power.

Of course, none of these problems will end with the creation of a microbicide, however we may see the tide begin to turn. Another participant from a local Dallas support group said, "I want a relationship where I do not have to worry about the fight over condoms. I get tired of always having to ask him to put one on. I really hope someone will create something that I can use for my own protection." As women begin to have more control over their sexual health, the balance of power in their relationships might begin to change. This shift could have consequences for how women operate in relationships and society. Hopefully, the most dramatic change will be a reduction in the growing number of women who test positive each year for HIV and other sexually transmitted infections.

Eventually, a microbicide will appear that benefits women. Having additional protection against HIV and STIs would be a great breakthrough, but another important benefit will be if it helps women gain more control in their relationships and their lives.

Building a Microbicides Advocacy Campaign

By Anna Forbes and Megan Gottemoeller

The Global Campaign for Microbicides is a broad-based, international coalition initiated in 1998 to build support among policy makers, opinion leaders, and the general public for increased investment into microbicides and other user-controlled HIV prevention methods. The Campaign uses advocacy, policy analysis, and social science research to accelerate product development, facilitate widespread access and use, and protect the needs and interests of users, especially women worldwide.

People cannot demand what they have yet to envision, so one of chief functions of the Global Campaign is to make microbicides a visible possibility, thus catalyzing public demand for new options.

In the U.S., the Campaign's legislative advocacy strategy targets the U.S. Congress and microbicide research funding at the NIH, the CDC and the U.S, Agency for International Development (USAID). The strategy was designed and implemented in collaboration with the Alliance for Microbicide Development and the International Partnership for Microbicides. To date, it has resulted in an increase of tens of millions of dollars at NIH and CDC, and the USAID appropriation for microbicide R&D may rise to $22 million in 2004. The Microbicide Development Act, authorizing federal spending and creating a designated program at the NIH, was introduced with bipartisan support in the Senate in April 2003.

In Canada, women's health and AIDS advocates have been similarly successful in generating increased attention to microbicide research by the Canadian Parliament. The UK/Ireland Campaign for Microbicides, established in 2002, is working on raising awareness in the British Parliament, and has participated in briefing the European Parliament on microbicides.

Because of the vast differences in resources between U.S. and Europe and regions in south Asia, Africa, and Central America, microbicides advocacy in the global South is less focused on mobilizing resources and more on demonstrating demand. This includes creating opportunities for people who will be using microbicides in clinical trials over the next few years to actively participate in the research and development process.

Advocacy organizations in countries like India, Nigeria, and Uganda are forming local networks to articulate policy needs relevant to their national situations. For example, advocates in Kampala recently organized a forum for national parliamentarians and policy makers to discuss the position Uganda should take toward microbicide clinical trials in that country. A community stakeholders meeting in Delhi in October 2002 resulted in a statement of principles on prevention options for women in India.

Because much of the clinical research, particularly the Phase III efficacy trials of microbicides, will take place in highly affected countries, the Global Campaign is working with community organizations, national networks and research institutions to support meaningful community involvement in the design and implementation of these trials. Community involvement is widely recognized as a key component of both scientifically rigorous and ethically sound clinical trials. However, U.S. and European activist models of community involvement may not translate directly into global south settings. To that end, the Global Campaign works with NGO, community-based, and research entities to develop, implement, and document innovative approaches that have worked to get local communities meaningfully involved in the research process.

With nearly 200 worldwide NGO partners to date, the Global Campaign serves as a conduit through which this global demand can be harmonized and collectively articulated at an inescapable volume. Through unified advocacy strategies and a growing body of resources and materials made freely and publicly available to anyone who wants to use them, the Campaign links and amplifies participants' voices. The work of the Campaign is coordinated by its secretariats, housed at NGOs in Washington DC, London and (soon) South Africa. But, in essence, the Campaign is nothing more than a shared idea: that receptive sex partners must have a way to protect themselves that they can control, and that advocates must take responsibility for determining when, how and in what fashion this technology becomes available to all who need it.

For more information: www.global-campaign.org or phone: (202) 454-5048.

Profiles of Grassroots Advocacy

The Global Campaign for Microbicides in North America is involved with groups in several U.S. and Canadian cities. Primarily these are collaborations with family planning, women's health, and AIDS organizations, with the local groups undertaking to serve the dual purpose of local community education and legislative advocacy. The work of these independent groups is extremely varied, and reflects both the geographic diversity and the specific backgrounds and interests of the individuals pushing the efforts forward. Here are some snapshots of microbicide advocacy in the U.S.

New York's group, housed by GMHC and the Harm Reduction Coalition, is a loose collection of individual members who have done HIV treatment activism, needle exchange work, and community education. As one member put it, "We're about as grassroots as you can get. We tend to be people who understand the need for more options, and the relationship between global poverty, and women's health." Contact: Talata Reeves at GMHC, (212) 367-1360.

In Connecticut, a group has focused on developing a campus organizing project, involving young women and (some men) from four schools in the state, including a Catholic university. The group employs two student interns who organize dorm workshops on microbicides, letter writing campaigns and speaker's training for other women. The group works with Connecticut Planned Parenthood and the AIDS Education and Training Center (AETC). They have produced a video on microbicides and have partnered with a community ethnography institute that received a grant from the National Institute for Mental Health (NIMH) to perform an acceptability study of microbicides among high-risk injection drug using women in New Haven. See www.global-campaign.org/localsites.htm for contact information.

Microbicides as an Alternative Solution (MAS) is a northern California group that is involved with grassroots education. They have been organizing community forums for over six years and are one of the oldest groups in the country. Recently, they produced a comic and brochure series for San Francisco teenagers about microbicides and sexual choices. Contact: www.microbicidesnow.org

The California Microbicides Advocacy Coalition (CAMI) is a spin-off of MAS organized to advance microbicide research by coordinating policy among a coalition of California biotech companies, community advocates, and research partners.Contact: Alison Regan, (213) 736-4806.

One of the newer and most energetic groups is based in Georgia, whose zealous members visit Southern colleges, radio stations, and HIV-positive support groups, talking about microbicides to anyone who'll listen. The group has an active speaker's bureau of women, men, and PWAs, who have addressed many diverse audiences such as the gay men's chorus, students at a women's college, radio talk shows, and Atlanta's AIDS Survival Project. Contact: Terri Wilder, (404) 502-4710.

Kaletra Goes it Alone

By Bob Huff

At the 43rd Annual ICAAC Conference in Chicago, Joseph Gathe, a clinical investigator and HIV clinician at a large inner city clinic in Houston, Texas, presented a poster reporting 24-week results from a controversial pilot study that employed only one antiretroviral to treat HIV-infected patients starting their first regimen. The 30 patients in the study were treated with the twice-a-day protease inhibitor Kaletra, a co-formulation of lopinavir with low-dose ritonavir added for pharmacokinetic enhancement. At week 24 of the 48-week study, the one-drug strategy had produced virologic efficacy comparable to that seen with standard triple-drug HAART.

The study group contained a large proportion of individuals with advanced HIV disease, with 54% having both a CD4 count below 50 and viral load above 100,000. Overall the group had a mean viral load of 260,000 copies/mL and a mean CD4 cell count of 170. Persons with active, life-threatening AIDS were excluded. Nearly all of the subjects were male; 60% were white, 20% black and 20% Hispanic. Kaletra dosing was adjusted by weight, with patients weighing less than 70kg receiving 3 capsules twice-a-day and those over 70kg receiving 4 capsules. Viral load and CD4 cell counts were monitored during usual patient visits to the Ryan White funded free clinic. No pharmaceutical support or other outside funding was available to the study.

By week 24 of the 48-week study, 8 of the 30 participants had left, with 2 lost to follow-up, 2 withdrawing due to GI intolerance, 1 due to active hepatitis B infection and 1 because of non-adherence. One patient was deported. Another patient was excluded because of virologic failure, although the details of this case were not reported.

Of the 22 patients who remained on treatment, 21 (95%) achieved virologic response defined as viral load less than 400 copies at week 24. Using an intent-to-treat analysis, with 21 of 30 patients achieving viral load below 400 copies, the 24-week response rate was 70%. The mean reduction in viral load for those remaining on the study to week 24 was –2.57 log copies/mL. The average CD4 count had increased by 219 cells at week 24. No significant toxicity was seen and no genotypic or phenotypic resistance mutations were detected.

A single patient remaining on the study failed to achieve viral suppression below 400 copies and added saquinavir to his regimen at week 32. The failing individual's baseline viral load was 500,000 and had declined to about 1500 at week 24 then rose to just under 5,000 at the time of treatment intensification.

Dr. Gathe pointed to results from a dose-finding trial that administered lopinavir/ritonavir alone to 32 patients for 3 weeks before adding NRTIs. By week 3, the mean viral load decrease was -1.85 log copies/mL. At week 2, the mean decline in viral load in patients receiving monotherapy was similar to that of those on a 3-drug combination (-1.73 vs. -1.68 log copies/mL). (Murphy RL, et al. AIDS 2001;15:F1–F9)

He also cited a 48-week trial of Kaletra that reported finding no genotypic or phenotypic resistance in subjects experiencing virological failure. This suggested that, in the event viral suppression could not be maintained with single drug Kaletra, subsequent susceptibility to intensification would likely not be in jeopardy. (Walmsley S, et al. NEJM Volume 346:2039–2046)

Triple combination therapy produced welcome and dramatic benefits for patients when it was widely introduced in 1995. Since then, the idea of "monotherapy" has become synonymous with an era of inadequate treatment options and a high death rate from AIDS. Increasingly, however, economic pressures are stimulating research into strategies that may possibly conserve scarce resources without compromising outcomes. Dr. Gathe will continue this study to 48 weeks and is preparing a follow-up study of single-drug HAART that will begin enrolling later this year.

Gathe JC, et al. Pilot study of the safety and efficacy of Kaletra (LPV/r) as single drug HAART in HIV+ ARV naive patients. Interim analysis of subjects completing at least 24 weeks of a 48 week study. 43rd ICAAC, Chicago, 2003. Poster 845.

GMHC treatment ISSUES

Editor
Bob Huff

Guest Editor
Jen Curry

Art Director
Adam Fredericks

Volunteer Support Staff
Edward Friedel

Proofreaders
Edward Friedel
Gregg Gonsalves
Richard Teller

GMHC Treatment Issues is published twelve times yearly by GMHC, Inc.

GMHC Treatment Issues
The Tisch Building
119 West 24 Street, New York, NY 10011
Fax: 212/367-1235
e-mail: ti@gmhc.org
www.gmhc.org

FDA: Global Citizen

By Jen Curry

In August 2003, the U.S. Food and Drug Administration's (FDA) Antiviral Drugs Advisory Committee met to discuss clinical trial designs for topical microbicides. The FDA has received several sponsor applications to conduct trials of candidate microbicides with an eye to approval. From the agency's standpoint, two anxieties hung over the discussion. The first was the sobering lesson of the COL1492 study of nonoxynol-9, which turned out to actually increase HIV risk. The second was agency skepticism, and palpable fear, about releasing a product that might be less effective than what is considered the U.S. gold standard: condoms.

The microbicide advocacy and research community brought its own anxieties, over cost (that sponsors can not afford, or do not want to fund these trials, or that funding will dry up if one of the first trials fail) and a pervading dread that if the field does not move forward soon, an incalculable number of lives will be lost.

Earlier this year, two products (Buffer Gel and Pro 2000) were slated to go head-to-head in HPTN 035, an 8,000 woman, placebo-gel controlled trial. But the FDA asked for changes, arguing that the trial should aim to produce data that could support product licensure. They proposed a dramatically more stringent statistical test and added a fourth arm that offered no treatment, only the condoms and counseling that every arm received. These changes would have boosted the number of participants by several thousand and added millions to the cost. When the NIH said it wouldn't fund such a costly trial, the design was amended to a Phase IIB, 3,100 woman trial that will include the fourth, no-treatment arm.

At the FDA meeting, the committee was asked to consider the no-treatment arm. They also discussed if one trial could serve as well as two without difficult to meet statistical tests and how long a Phase III trial must last. Each of these questions involves complications that could set back microbicide clinical research by years. And on each issue, the FDA seemed to take a hard line.

One thing this meeting did was force the microbicide community to come together and think hard about the strategic plan for microbicide R&D. The testimony that day reflected an overwhelming consensus that FDA must not heap requirements onto these trials that would spike their cost, cause delay, produce uninterpretable data, or otherwise drain a resource-scarce field. In particular we heard that a no treatment, condom only arm could introduce confounding behaviorial variables, which may result in uninterpretable data or a false declaration of product failure.

What we need to know from the FDA is whether any of these candidates are safe and moderatly effective. That's the strict regulatory question before them, it's the question that matters to countries that desperately need these products, and it's the question the agency should stick to. The FDA should not concern itself with hypothetical questions about what might happen to condom use if a microbicide were available.

While the FDA only has jurisdiction within the U.S., it's influence extends much further. It must recognize this and think creatively and flexibly to consider strategies that allow for moderately effective products to be detected and moved forward—not weeded out. A product demonstrating moderate effectiveness (50–60 percent) would not likely be approved for U.S. licensure. But in another country, that same product might be considered essential. As committee member Lynn Paxton put it, "If I'm a regulator in a country where 1 out of 3 women is infected, I might be willing to take a risk."

So, what does this mean for the FDA? Does it have an ethical obligation not to set policy that would harm people outside of the U.S.?

The European regulatory agency (EMEA) and the World Health Organization (WHO) has initiated an entirely new process to approve and review drugs for safety and effectiveness in a developing country context. The Alliance for Microbicide Development, representing consensus from the research community, asked the FDA to "recognize contextual realities" of global AIDS and urged the Agency to "actively engage in the new WHO/EMEA process." Seeking to balance speed, flexibility and good science, this process may offer a way to accommodate the differing risk/benefit demands that we will continue to see globally.