HIV/AIDS: VAGINAL MICROBICIDE CLINICAL TRIALS
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Abstract
HIV/AIDS in increasing in women and the continent with the largest rate of new infections is Africa. Condoms during sexual intercourse are the only documented protection against HIV infection; their use is limited by men who do not want to use them and because their female partners are not always able to negotiate. A method of preventing HIV transmission that could be controlled and used by women without their sex partner's knowledge and consent could have a large effect on HIV infection rates in many parts of the world. Vaginal microbicides have been proposed as such a method, and organizations, drug developers and advocacy groups have formed to develop and publicize them. Several microbicides are in different stages of development and clinical trials phases (www.clinicaltrials.gov; the Alliance for Microbicide Development, www.microbicide.org) and have different mechanisms of action that affect HIV and other sexually transmitted infections in different ways. An ideal vaginal microbicide differs from country to country (whether to include a contraceptive effect, how much or little lubrication is desired, efficacy against other STIs), and different types of clinical trials address these issues. Efficacy is demonstrated both in vitro and in human trials, but even an agent that is 100% effective may not be used by the target population if it does not address all requirements of the local culture (in some countries, dry sex is preferred to lubricated, while in others, the opposite is true; in some countries, women who use vaginal microbicides may be considered sex workers, while their use is acceptable in other countries). Finally, the logistics of carrying out these trials raise ethical questions - how much condom counseling to provide, whether the comparator gel is placebo or current standard of care, how much ancillary medical care to provide, the standard of care for trial subjects who become HIV-infected during the trial and whether to continue providing the same standard of care once the trial is complete.

Methods
A PubMed search through the Univ Sciences in Philadelphia portal on search terms “vaginal microbicides and Africa” on 19 Oct 2007 yielded 52 articles, of which 20 were related to efficacy in preventing HIV transmission, cultural issues in the use and adoption of vaginal microbicides, and the ethics of vaginal microbicide clinical trials.

Candidate microbicides
The first generation of products include membrane disrupting compounds, non-specific fusion inhibitors and acid buffering agents. Newer compounds target attachment, fusion and reverse transcription in the viral life cycle, but gain greater specificity at the loss of the broad-spectrum action of earlier candidates. A combination product, containing the specificity and potency of an antiretroviral with other elements with activity against non-HIV sexually transmitted infections, would likely be a third generation target.

Introduction
In sub-Saharan Africa, women represent nearly 60% of new HIV infections.(1) While condoms have been proven to protect against new HIV infection, their use cannot always be negotiated by women. Alternatively or in addition, microbicides can be used within the vagina to prevent HIV, other sexually transmitted infections and potentially pregnancy. One of their benefits is that they can be used by women without men's knowledge or consent, thus allowing women to protect themselves from sexually transmitted infections in situations where they otherwise do not have much personal power. However, how effective they are depends not only on their performance in preventing HIV transmission but also on whether men and women are willing and able to use them consistently, and whether they are able to used correctly every time.
Lime juice has been touted as a possible microbicide, as in vitro anti-HIV action has been demonstrated. However, a safety study in 25 women demonstrated a number of side effects when used at 10% and 20% concentrations, and in vitro studies show that greater than 50% concentration is required to prevent HIV transmission. This concentration has been demonstrated to be toxic.\(^2\)

Nonoxynol-9 was a first-generation microbicide, a broad spectrum agent that acted against sperm, STIs, bacteria and viruses. Nonoxynol-9 demonstrated in vitro activity against HIV, as well as some in vivo activity. However, both in early safety studies and later in phase 3 efficacy trials, vaginal toxicity caused by nonoxynol-9 led to nominally increased potential for HIV infection (World Health Organization press release, http://www.who.int).

Agents that block HIV binding include PRO 2000, carrageenan and cellulose sulphate. Cellulose sulphate had been a promising candidate that had moved into phase 3 trials, but they were recently canceled because the gel appeared to be increasing the risk of HIV infection in trials in India, Uganda, Benin and South Africa.\(^3\) Dextrin sulphate is another candidate with in vitro activity against HIV that has undergone safety testing in HIV-negative and HIV-positive women in London and Antwerp. Dextrin sulphate has also been tested for both safety and acceptability in a partially blinded, placebo and observation arm study in 2005.\(^4,5\) Vaginal bleeding was reported for all study treatments, and 2 subjects showed abnormal colposcopy findings, both of whom were in the Dextrin sulphate arm of the study. Though there was also some evidence of spotting, it was otherwise well-tolerated and has gone on to further study.

Tenofovir is a third-generation microbicide, a nucleotide analog reverse transcriptase inhibitor with a long half life. The Centre for the AIDS Programme of Research in South Africa (CAPRISA) is running a trial in KwaZulu-Natal (HIV prevalence of 39.1%). In this trial, women can use the gel up to 12 hours before or after vaginal intercourse. This trial is intended to enroll 1,000 women.\(^3\) Enrolled women will be given counseling and free condoms. Thus far, this antiretroviral demonstrates few side effects.

The Trials Watch site, by the Alliance for Microbicide Ongoing Clinical Trials, has been a resource for tracking vaginal microbicides in later stages of clinical development. These include BufferGel, which is in phase 2/2B and is being tested alongside PRO 2000. BufferGel works by keeping the vagina acidic, which directly inactivates HIV. The Carraguard trial, run by the Population Council, completed enrollment in June 2006. Carraguard works by creating a physical barrier between pathogens and the vaginal or rectal cell wall. PRO 2000, a naphthalene sulphonate polymer, is in a trial with BufferGel. PRO 2000 binds to viruses and bacteria, preventing them from binding to cells.

SAVVY, a surfactant microbicide that disrupts lipid bilayers, was thought to be less cytotoxic than nonoxynol-9 and had been in phase 3 trials in Africa.\(^6\) The HIV incidence in Ghana was too low to show a difference in trial treatments, and though the incidence in Nigeria was also low, that trial demonstrated no protective effect from SAVVY for HIV protection.\(^7,8\)

Praneem, an herbal vaginal microbicide, was shown to be safe when used by 100 HIV-negative, monogamous women, and recommendations have been made to conduct phase 3 efficacy trials. Acidform was compared to KY Jelly in a 14-day randomized trial examining safety and acceptability, and demonstrated significantly more genital irritation than KY (OR 2.6, \(p=0.009\)) and more peeling on colposcopy. However, it also demonstrated a decrease in pro-inflammatory cytokines, thus maintaining an acidic vaginal environment. This candidate has since progressed to phase 3 trials (www.microbicide.org/publications/digest/html).

**Cultural Issues with Testing Vaginal Microbicides**

**Acceptability studies**

As many researchers have discovered, testing microbicides is not as simple as planning a trial, carrying it out, then analyzing the data. Community outcry due to the closing of trials (for example, cellulose sulphate in 2006), misunderstanding that participation in a trial can lead to increased risk of HIV, and cultural concerns that if women have access to birth control and anti-infection measures that they might become ‘promiscuous’ all confound the ability to carry out trials in developing nations.

Because of these ethical and practical concerns, more than 60 acceptability trials have been performed, to find out ways to conduct effective trials that the community accepts, as well as uncover the most critical attributes of a microbicide that will make it adoptable (learning from the backlash that accompanied the introduction of the female condom).\(^1\)

ProGel is a water-based antiviral buffered to pH 4.5 and is about twice as viscous as K-Y® Jelly. Its acceptability was evaluated in a safety trial in 63 United States and South African Women.\(^10\) Fifty women were sexually active, monogamous, and HIV-negative, and 13 were sexually abstinent and HIV-positive. Subjects were restricted to penile-vaginal sex (no oral-vaginal or penile-anal sex was allowed with the use of the gel). The dosing regimen was once or twice daily, and subjects were either interviewed or participated in a focus group within 1 month of the final clinic visit. Results: When discussion centered around the use of the product and...
heightened HIV risk, all subjects (100%, 60/60) found the product use acceptable. Most women (77%) wanted a product that both protected against HIV and STIs and prevented pregnancy, while over half (55%) wanted a product that would allow pregnancy while protecting against HIV and STIs (because multiple answers were possible, responses do not add up to 100%). It was ‘extremely important’ to 79% that the product could be used without a condom and still be protective against HIV and STIs. Most women (50% to 65%) liked the color and odor of the product and found the consistency acceptable. Most did not find it too sticky, too wet or too dry. Preference was expressed for a clear product over a white or creamy product, for hygienic and detection reasons. Nearly all subjects found the product and its single-use applicator easy to use (82%). Most did not find the gel too ‘wet, drippy, or sticky’, though a number reported some product leakage. Clear leakage was associated with no sex, whereas a more cottage cheese-like leakage was associated with sex. Leakage associated with sex was reported by 27%, but nearly all these women considered this ‘unacceptable.’ About half the women stated that the gel improved sex, but one-third thought it adversely affected the sexual experience. Most women thought that this product could be used covertly, though women who experienced the cottage cheese-like leakage were more concerned. Women were divided as to whether the product should be used covertly, with many women with HIV/AIDS against it. Some women were concerned about hygiene and the need to remove product from the vagina after use or before the next insertion, especially women who were using the product twice a day. Some concern was expressed by women with HIV/AIDS about reusable applicators and infection.

BufferGel is a clear, odorless gel buffered to 3.9, and works by buffering semen to a pH of about 5.0. A safety and acceptability trial was completed in 1998-1999 and reported in 2004.(11) Subjects were 98 women who were not infected with HIV in Malawi, Zimbabwe, India and Thailand, and focus groups were conducted with women and their partners after completion of the study. Subjects used a reusable applicator to apply BufferGel morning and evening for 14 days. Sexually abstinent subjects (n=30) were asked not to have sex during the study, while sexually active subjects (n=68) were to have sex at least twice a week, using study-provided condoms. Results: All women in African sites, most in Thailand (57% abstinent, 65% sexually active) and fewer in India (17% abstinent, 60% sexually active) stated they would use the product if approved, whereas women in India would. This difference was based on perceived risk for HIV infection. While African women were happy to have a potential method to protect them if their husbands were unfaithful and infected with HIV; some men expressed concern that use of a microbicide would make their wives promiscuous and said that it should not be sold to women. Women and men felt undisclosed use could risk violence or demonstrate lack of trust, but some African women felt that they could use it to protect themselves silently without impugning their partners’ fidelity. Some women also suggested calling microbicides a vaginal health product for discussion with their partners. Though nearly all (92%) found the applicator easy to use, 1/3 did not like cleaning it (some had no access to running water). Nearly all women liked the odorlessness and colorlessness of BufferGel (81% to 94%), and some thought the gel could be used to prevent odor or enhance hygiene. Fewer Africans were concerned about the gel’s wetness, but Indians and Thais were more concerned with too much wetness. Staining of clothing due to leakage was reported by 31% of women. Increased sexual pleasure was reported by 51% of women and 43% of their partners.

Dextrin sulphate was examined in a randomized phase 2 safety and acceptability trial in Uganda versus placebo gel.(5) Recruitment took place in 2001 and 2002. One hundred nine healthy, sexually active women were recruited who agreed to HIV testing, sexually transmitted infection screens and exams, and use of condoms throughout the study. Study patients either had use of Dextrin sulphate gel (women infected with HIV, n=27; uninfected women, n=38) or placebo gel (women infected with HIV, n=6; uninfected women, n=9) twice a day (blinded), no gel (women infected with HIV, n=5; uninfected women, n=15), and use of Dextrin sulphate gel before sex only (uninfected women, n=9). Results: Some side effects were observed, including abnormal colposcopic findings, spotting, itching and burning, but most of these were observed across all study arms (the 2 abnormal colposcopies were both in the Dextrin sulphate twice-daily arm). Of the subjects using active or placebo gel, 89% (70/79) were compliant with the study protocol. In the twice-daily gel arm, 11 women thought the gel was too wet, but 63 of 65 women in the active gel arm said they would recommend the gel to others and would continue to use it if it were available for free. In this study, there was no apparent drop-off in condom use; however, it is likely that women who could not negotiate condom use with partners would not participate in this study, as it was an exclusion criterion.

Finally, Carraguard was evaluated for acceptability in South African women living with HIV/AIDS in 2002 and 2003 and reported in 2007.(12) The study subjects were healthy, sexually abstinent men and women, and sexually active women (n=20 per group) living around Durban. Subjects were randomized to Carraguard gel, placebo gel or observation for 14 days. All were counseled about condom use and safe sex. All subjects were issued questionnaires at the end of the study, and all subjects in the
sexually active group, as well as their partners, were asked to participate in an in-depth interview. 

Results: Ninety-three percent of women indicated liking the study gel (Carraguard or placebo), while 15% of men and women disliked some aspect of the gel. Every woman and all but 1 man reported compliance with product use requirements. Little pain or irritation were reported due to gel application (2 women reported pain or irritation during use, and 1 reported pain or irritation after use). A few women reported that the gel was "too wet." However, 71% of sexually active women reported that the gel enhanced sexual pleasure, and many of the male partners preferred the gel to condoms. One fifth of the women and two-fifths of the men said that covert use of a microbicide would be okay, but a strong majority (74% of women and 79% of men) said that both the man and the woman should agree to microbicide use. More than two-thirds of both sexes would rather replace condom use with a microbicide. The investigators stated that condom migration of a partially effective microbicide could be a concern in the future.

ISSUES, CHALLENGES AND OPINIONS

In order to have feasible samples sizes in phase 3 trials, the HIV prevalence must be 2% or greater. However, in areas with this high incidence rate, counseling and treatment for STIs becomes critical, and since adherence to usage will likely decline over time, as has been seen with condoms, the trials should be as short as possible, to avoid dilution of the antiviral effect of the microbicide. Even a microbicide with only 50% efficacy used in only 50% of sex acts could demonstrate a reduction in HIV prevalence in sub-Saharan Africa from 10.8% to 8.1% after 20 years. (13)

In addition, several failed trials have tried the patience and trust of the populations in which they were run. Nonoxynol-9 trials in the late 1990s in several countries in Africa showed an increase in HIV infection rate, due to inflammation and damage to the cervical mucosa. Last year, the 2 SAVVY trials were stopped because of lower than expected HIV incidence rates. In 2007, cellulose sulphate, already through safety trials, was being tested for efficacy in 5 sites (South Africa, Uganda, Benin, and 2 sites in India) and safety data review demonstrated higher rates of infection with HIV in patients who were treated with the microbicide than placebo, leading to a premature closing of the trial.

The closing of these trials affects not just the pharmaceutical companies and organizations sponsoring the trials, but the local communities that house the infrastructure the trials use and the trial subjects and their spouses and boyfriends.

Partly based on study closures and failures harming trust, and in response to ethical questions raised in these and non-microbicide trials, investigators and healthcare workers decided to ask the affected communities how trials should be run and what services should be provided during and after trials. The responses provide not only the benefit of different perspectives, but allow for bridge- and trust-building between researchers and the local communities.

In 2002, researchers from the Virginia Commonwealth University, WHO, UCSF, and the University of Zimbabwe reported on interviews with key informants in Harare, Zimbabwe in 1996 and 1997. (13) Zimbabwe has a high rate of HIV infection, as well as low adoption of the condom, though it has been made widely available. This investigation intended to assess the feasibility of initiating vaginal microbicides or other female-initiated measures. Key informants included government officials from the Ministry of Health, the Department of Health, nongovernmental organizations, advocacy organizations, academics, healthcare providers, and religious leaders. Results: Respondents mentioned the gender imbalance in the local culture, where women find it difficult to negotiate condom use and are expected to remain monogamous while their husbands may visit prostitutes. In this culture, procreation is important and spermicidal products would likely conflict with this. Informants also raised the issue that men must be included in these trials and in the consent process for their wives. Some subjects noted that microbicides would give women power, but others thought that covert use by wives was threatening. Female subjects were excited by the opportunities presented by female-initiated protection. Both sexes stressed that men should be consulted during studies and might provide a unique and important perspective. Concern was expressed over the cost of various potential products, as well as how long before a sexual encounter they would need to be inserted, as well as storage requirements of different products.

In late 2004, researchers from the Population Council in New York and the International Antiviral Therapy Evaluation Center in the Netherlands conducted key informant interviews in 9 countries (Brazil, Burkina Faso, Senegal, India, Kenya, South Africa, Thailand, United States, and Zimbabwe). (14) All informants were highly educated and worked in women's healthcare and HIV prevention as researchers, professors, HIV/AIDS counselors, nurses or therapists. Results: Opinions on the optimum amount of vaginal lubrication varied from country to country, but in general, informants thought that some amount of lubrication was expected. In South Africa and Zimbabwe, 'dry sex' was reported as common, though in Kenya, vaginal lubrication was more prized. However, the more highly educated, the less dry sex was practiced. Thai women generally do not add lubrication. In India, the subject was considered taboo. In Brazil and the United States, added lubrication is more common. In some South African settings, vaginal wetness indicates promiscuity and sex
workers are known to use products to dry their vagina. Regarding vaginal hygiene practices, in South Africa and Zimbabwe, women may use household cleaners, sometimes containing bleach, to clean the vagina. In India, cleansing may include hot water, carbonated drinks, lime juice, vinegar and antiseptic soap. American women tend to be conscious of odor and use products to eliminate or mask them. The use of added lubrication is common practice in Thailand, the United States, India, and Burkina Faso, although the types of products use vary widely. Indian women are expected not to have prepared for sex, whereas in most of the other countries represented, women engage in daily vaginal hygiene. An informant from Burkina Faso was quoted stating that women's preferences are not necessarily why lubrication might be used:

"I don't even know if tradition mentions women's preferences because her preference is determined by what can give the man pleasure."

In some countries, violence ensues if a sex worker is overly-lubricated or does not remove vaginal secretions before sex. Women in South Africa have been beaten or abandoned for being lubricated (a husband may check by inserting a finger into the vagina). With regard to spermicides and lubricants, many informants stated that one of the main reasons for not using these is the messiness (leakage, too much lubrication). In the United States, spermicides are rarely used because they interfere with oral-genital contact. However, the key informants stated that lubricated condoms were generally preferred over non-lubricated ones. Finally, the key informants expressed strong support for vaginal microbicides, even if it provides added lubrication, and they thought both men and women would accept some added lubrication in order to protect against HIV.

Research in Rwanda in 2006 aimed to to understand local sexual and genital hygiene practices, and gather information on preferences regarding added lubrication during sex.(15) The focus group subjects were 18 to 55 years old and were female students, unmarried women, married women, rural women, female sex workers, and men.

**Condom use:** Participating women thought condoms were used 20% to 50% of the time, but men thought they were used 1% to 2% of the time and only with sex workers. All stated that condoms were not used within stable relationships. Sex workers stated that condoms were too drying, so they did not use them all of the time. No one had heard of or used the female condom. Most agreed that condom use had increased in the last 10 years.

**Contraception:** Most participating women thought that most women would be interested in family planning and contraception, possibly excepting women in rural areas. All agreed that women were more interested in family planning than men, and that many men refused to participate in contraceptive practices. Older women mentioned traditional methods of family planning, such as burying the first menstruation after giving birth.

**Couple communication:** Most thought that men initiate discussions of sex, and women initiate discussions of contraception and family planning. All agreed that women cannot refuse to have sex with their husbands, and all agreed that male infidelity is very common, while female infidelity is uncommon.

**Vaginal hygiene:** Women agreed that women would recognize abnormal discharge, but might self-treat or use traditional methods rather than seek medical help and be seen naked by a doctor. A common hygiene practice was washing with water, though some women reported using soap. Washing may be as frequent as twice a day, or every time a woman urinates. Washing was felt to be important to smell nice for one's husband. All women and men except for the sex workers felt that sex during menstruation was unacceptable.

**Vaginal lubrication:** All subjects reported that vaginal lubrication was important for sex. Traditional methods for stimulating natural lubrication were mentioned. Herbs, petroleum-based gels and alcohol were mentioned as methods of enhancing lubrication. If women were inadequately lubricated, consequences could include painful sex and infidelity.

**Microbicide acceptability:** After the concept of a microbicide was explained to the subjects and a lubricating jelly shown as a model, the subjects were generally supportive. The lubricating effects were considered an advantage in Rwanda, as well as the possibility that it could be used in place of a condom. A microbicide that is also a contraceptive was supported. Most subjects disagreed with the idea of covert use, with the exception of sex workers.

Researchers report in AIDS Care on a large-scale interview trial (130 interviews and 20 focus groups) in 7 countries.(16) The interviews and focus groups were conducted in South Africa, Malawi, Zimbabwe, Tanzania, Zambia, India and the United States, sites chosen for planned participation in a phase 2 microbicide trial (www.hptn.org). Subjects included research and non-research healthcare providers, village elders, community advocates, study subjects, and other users of HIV/AIDS prevention services. Interviews included hypothetical HIV/AIDS prevention trial designs followed by questions as to whether the interviewees felt the treatment of trial subjects was fair or not. Results: Nearly all subjects associated fairness with access to counseling, healthcare and HIV/AIDS drugs. Many subjects expressed concerns that care might be stopped when the trial was over. The perception was that 'referral' (where trial researchers refer subjects to local health resources) meant 'assured access to continuous and effective care' provided by the researchers. Nearly all subjects felt it was unfair to
withdraw therapy when a trial was over. Subjects had perceptions of the researchers' responsibilities to women participating in the trials, as well as the perception that trial participation increased exposure to HIV/AIDS. Subjects also did not feel the use of placebo arms was fair, even with condom and safe sex counseling. Something else that was elicited was the interdependence of spouses and families, to the effect that if the researchers treated the wife, they must also treat the husband. It was widely assumed by potential subjects that the women would share any treatments with their husbands.

Another interview study in South Africa in 2002 and 2003 was reported in 2006. It examined perceptions of microbicides and attempted to unearth challenges in the use of them.(17) Researchers conducted focus groups with community members and in-depth interviews with key informants in and around Cape Town. A total of 23 focus groups and 38 in-depth interviews were conducted with 213 humans, including community members (men and women 18 to 45 years), influential community members including traditional healers, outreach and non-governmental organization workers, public and private sector healthcare providers, and national and provincial policy makers. All discussions began with an explanation of what microbicides are and how they may work, that they are not 100% effective, and all subjects were shown a model of what a filled applicator might look like. Results: Community members communicated a sense of desperation brought about by HIV infection and illness, and a willingness to try anything that might alleviate the deaths. However, when confronted with partial effectiveness, subjects expressed concern for how this would be communicated. A partially effective microbicide was not rejected out of hand, however, due to the desperation caused by the HIV/AIDS epidemic. Respondents felt that the microbicide should be able to be applied well before any encounter and should have long-lasting protection. Concerns about protection against HIV/AIDS in cases of rape were mentioned. When questioned about who should use the microbicides, responses varied. Some felt unmarried young adults were the target audience and married adults would not use the product. Others thought married women would want to be able to use microbicides as protection from the consequences of infidelity. Some policymakers were concerned that young humans would be tempted to stop using condoms if microbicides were widely available. Regarding covert use, while subjects agreed that male involvement was ideal, they also agreed that covert use might be appropriate in some circumstances. Healthcare service providers thought it gave women power they were otherwise lacking, but some policy makers were concerned women might face violence or abandonment if covert use were discovered. Interviewees felt that wetness before intercourse might be equated with promiscuity. Some community members raised the concern that microbicides might affect fetal health. Key informants thought that microbicides would provide an alternative to condoms, and this was considered both a good and a dangerous thing. Overall, this study did not suggest there was any stigma associated with microbicide use.

Some of the concerns raised in the previous study also were echoed in a focus group study conducted with female sex workers who participated in a phase 3 microbicide trial in South Africa in 2001.(18) The focus groups were conducted 12 to 15 months after the subjects (94 South African female sex workers) learned that the microbicide in the trial they participated in was ineffective against HIV and STIs (nonoxynol-9). Results: Though the women were informed of the inefficacy of the microbicide, they still believed that the gel was protective against HIV, and that it helped 'cleanse' them. Women reported feeling protected because they were using the gel, and that when men refused to use condoms, they were comforted by the use of the gel. Most women felt the gel also alleviated vaginal symptoms (menstrual pain, rashes, discharge), and some even reported that symptoms returned after they stopped using the gel. Despite repeated explanations of a placebo trial, subjects expressed the wish that they had 'active' gel and they wanted the microbicide available though it had not been demonstrated to be effective. Part of this trial involved treatment of sexually transmitted infections with drugs, but it appears that the subjects associated the cure with the microbicide. Because of this, more recent trials have redoubled education efforts with subjects, using flipcharts, videos, study booklets, and scripts in local languages.

In 2007, a study was published on the perception of vaginal microbicides from healthcare providers in South Africa.(19) Data were collected in 2004 from semi-structured interviews with 149 healthcare providers in South Africa, all largely serving the public sector. Altogether 57% (8/14) of hospital managers, 40% (4/10) of pharmacists and 35% (44/125) of nurses had heard of vaginal microbicides before, most within the last year. They understood that it was extra protection, though they also realized microbicides could also be used in the absence of condoms. One of the nurses expressed the view that microbicide researchers wanted women to have sex with HIV-infected men to know whether or not the microbicide works. All responders recognized and embraced the empowerment microbicides could provide women, though a few of the nurses had negative opinions of microbicides (cultural restrictions, messy gels, HIV not being preventable). Regarding who should have access, most felt that microbicides should be available to all sexually active humans. However, 23% felt that microbicides should not be given to everyone (humans already infected might feel free to have multiple partners with no other protection), and a few thought teenagers
might not be responsible. Researchers queried whether healthcare providers would be able to recommend use of a product that is less effective at preventing HIV transmission than condoms, and nearly 80% replied in the affirmative. The feeling was that 'safer sex' was better than unprotected sex, though there was not 100% agreement. A few of the nurses would not recommend a partially effective product, though the researchers felt that this was due to a misunderstanding that 'partially effective' meant 'not effective at all,' despite repeated clarification. When the researchers asked about a microbicide that would be as effective as condoms, nearly 100% were enthusiastic, largely because of nearly universal dislike of condoms. Subjects foresaw a number of barriers to introduction, due to political, religious, cultural, literacy, and misunderstanding of the concept of clinical trials. Some also noted that microbicides would be problematic for those who prefer dry sex, and African men would not condone women having sexual power.

Finally, a study published in 2007 discussed how microbicides may change sexual practices, based on behaviors noted during a study on ACIDFORM gel and diaphragm. This randomized, placebo-controlled safety and feasibility trial was carried out with the participation of 120 sexually active, non HIV-infected women in mutually monogamous relationships in the Johannesburg, South Africa area in 2004 and 2005. Half the women were assigned to ACIDFORM gel and diaphragm group, and the other half to placebo gel and diaphragm, and all subjects were also instructed to use male condoms every time they had vaginal sex. Condoms and safe sex counseling were provided at every visit. Results: The frequency of sex increased from baseline to month 3 and had not returned to baseline levels by month 6, and all increases were statistically significant. Women in the trial perceived that the gel and diaphragm was protectant against HIV/AIDS, even though the experimental nature of the gel and the placebo were repeatedly explained. Women also reported enjoying sex more, largely due to the extra lubrication. In fact, many of the subjects stated the experience less discomfort and enjoyed sex more when the gel was used. In addition, the sense of safety from using the diaphragm and the gel also helped to increase enjoyment, by making the women feel safe and protected from HIV infection, as embodied in this quote from one subject: "I don’t know what he is doing in my absence, and he doesn’t know what I am doing in his absence so we are safe when we are using the diaphragm."

Condom use during the trial was high in general, increased from enrollment to month 3, then showed a slight decrease to month 6. The researchers surmised that the increase was due to a number of factors; increased partner cooperation, lubrication from the gel, and perceived quality of the study condoms. Before the study, not everyone used condoms and male resistance to condoms was mentioned by subjects. Subjects noted that the study condoms seemed to be stronger, less uncomfortable (generated less heat and friction) and smelled better than condoms available locally. Researchers noted that safe sex behavior was facilitated by study counseling, but that condom use was likely only study related; several subjects mentioned they planned to go back to non-condom use ("normal sex") when the study completed.

Discussion

HIV researchers agree that more solutions are needed in the fight against new HIV infections. Abstinence and monogamy, while highly effective preventers of HIV transmission, are not a reasonable expectation, and condoms, while effective when used correctly and diligently, are not widely accepted. The female condom also has not been widely accepted. A hypothetical vaginal microbicide with 100% efficacy in halting HIV infection, if accepted and used by many women, would greatly decrease new HIV infections. As shown by a number of mathematical models, even a microbicide with something closer to 50% efficacy would have a great effect in HIV infection rates.

Issues with product acceptance: Though the importance of ‘dry sex’ has often been raised as important to some cultures, in actual studies, most of the subjects, male and female, prefer some lubrication. However, in some cultures, excessive vaginal wetness is a sign of promiscuity and could lead to violence. Some women want a spermicidal effect, while some cultures would likely avoid products with spermicide properties. Some men believed that use of a microbicide might allow women to become more promiscuous, and some men did not think women should be given access. Most men felt that the participation and consent of men was important in these trials.

Factors that could lead to higher HIV transmission rates: Microbicides increased sexual pleasure for many trial subjects, which could lead to more sex than without the use of microbicides, and many male partners expressed the opinion that microbicides were more enjoyable to use than condoms, which could lead to replacing condom use with a potentially less-effective microbicide. In fact, nearly every trial subject wanted a microbicide that could be used in place of a condom, and research has shown that great trust will be placed even in experimental and unproven products.

In some of the seminal nonoxynol-9 studies where its inefficacy was statistically demonstrated, many of the subjects still believed over a year after the trial that the gel was protective and ‘cleansing.’ This was also found in the ACIDFORM gel/diaphragm trial; women felt protected using it, though the experimental nature of the gel and the fact that the trial
also contained a placebo arm was carefully explained.

Difficulties in planning and running ethical clinical trials: When asked, potential trial subjects expect access to high-quality healthcare and believe placebo arms are unfair. Even when healthcare is given during a trial, it can lead to the expectation that the care will be continued when the trial has completed.

Misperceptions to overcome: Many had the perception that participation in these trials inherently increases exposure of the subjects to HIV infection, and that researchers in fact deliberately expose subjects to it. Most subjects and key informants believe that a vaginal microbicide will replace condoms.

The Global Campaign for Microbicides (www.global-campaign.org) tries to dispel some misperceptions by putting out “fact sheets” on how clinical trials are run, how products are tested prior to initiation of trials in humans, and how the subjects are protected before and during the trial, as well as trying to dispel some of the popular myths surrounding clinical trials. Some of the organization’s main goals are to ensure that participating communities have a say in trial design, helping to negotiate ethical debates, and maintaining high ethical standards while still allowing research to progress.

However, the very populations that most need an effective alternative to condoms are also vulnerable populations with the potential to be exploited by their own great need for effective HIV protection.

References


