The Urgent Need for a Vaginal Microbicide in the Prevention of HIV Transmission

It takes two people to have sex, but only one to slow the spread of sexually transmitted diseases and acquired immunodeficiency syndrome (AIDS). A man can use condoms, but a woman's choices are limited. The most glaring gap in AIDS prevention is the lack of a method a woman can use when she suspects her partner may have a sexually transmitted disease or human immunodeficiency virus (HIV) infection and she cannot compel him to use a condom.

The paper by Weir et al.[1] on a reduction in cervical gonorrhea among sex workers (prostitutes) in Cameroon using nonoxynol-9 and the letter by Feldblum and Weir[2] reporting a protective effect of nonoxynol-9 against HIV infection are important steps forward. It is to be hoped that such publications will lead to more aggressive research strategies.

Nothing is being done in this field today that was not clearly understood and advocated by some people in the mid-1980s.[3,4] The primary question has always been, Can an acceptable, effective, and potentially cheap microbicidal agent be developed for vaginal use that will kill HIV but not damage the epithelium of the reproductive tract of either partner?

The risks of sexually transmitted diseases and AIDS are cruelly stacked against women. Sexually transmitted diseases present fewer symptoms but carry more long-term sequelae in women than in men; sexually transmitted diseases and HIV pass more easily from men to women than vice versa,[5] so even though the average man has more sexual partners than most women, women acquire HIV at an earlier mean age than men; and women can pass sexually acquired infections and HIV to the next generation during pregnancy, delivery, or breast feeding. Sexual injustice and violence against women are common, and sexually transmitted diseases and AIDS spread most rapidly where women are most disadvantaged: among prostitutes it is those who charge least who are most likely to get infected. The female condom is a welcome new choice for women that should slow HIV transmission, but it cannot be used without the man's knowledge.[6]

Chemical methods that can be controlled by women are likely to have a powerful effect on the spread of HIV for several reasons. They could be distributed rapidly and cheaply by well understood social marketing techniques. They have the potential to slow HIV transmission directly and to reduce other sexually transmitted diseases that are cofactors in transmission.[7] Women make a heavier investment in reproduction than men and therefore are often more cautious in their reproductive behavior: in Rwanda, three quarters of women with whom AIDS prevention was discussed chose a method they could control alone.

It has been suggested that a vaginal microbicide might be less effective than condoms but so simple to use that some couples would stop using condoms and consequently expose themselves to a greater risk of HIV infection. One US study, however, found that women who used spermicides or a diaphragm had a lower sexually transmitted disease reinfection rate than those whose partners used a condom, suggesting that compliance may be more important than effectiveness in slowing transmission.[8] Simple analysis demonstrates that unless very implausible variables are put into models of HIV transmission, the addition of a woman-controlled method will have a welcome positive impact on slowing the spread of infection.[9] The consistent experience of family planning is that contraceptive prevalence is most likely to reach useful levels when many methods are available through a variety of channels, and the same generalization seems likely to apply to sexually transmitted diseases and HIV prevention.

Sadly, the global AIDS pandemic has often been associated with poor decision making and political cowardice, and the scientific community has stumbled several times on the path toward vaginal microbicidal agents. Rosenberg and colleagues provided clinical evidence in 1987 that nonoxynol-9 in a vaginal sponge slowed the transmission of gonorrhea and chlamydia among Thai sex workers.[10] When a similar study was conducted among women sex workers exposed to HIV in Kenya, however, an increased risk of genital ulcers and possibly of HIV transmission was observed.[11] Although it was a small study with a limited design (only case subjects used the intravaginal sponge, the vehicle for treatment), the study was convincing enough to stop policymakers from recommending the sponge as a prophylactic[12]; however, it also seems to have slowed research in this field when in fact it should have accelerated it. Most drugs are toxic in high doses, and the sponge used in Kenya contained 10 times as much nonoxynol-9 as the suppository used in Cameroon. Frequent repeated use of high doses of nonoxynol-9 is associated with signs of damage to the vaginal epithelium.[13]

In the Cameroonian study, 303 sex workers were counseled to use suppositories containing 100 mg of nonoxynol-9 and to ask their partners to use condoms every time they had sex. The results were analyzed according to self-reported use of both methods, condoms or spermicides alone, or nothing at all. Few gonoccocal infections occurred in the group that used both methods consistently, and for every 1% increase in the use of condoms or spermicides alone the risk of gonorrhea was reduced.[1] The effectiveness of nonoxynol-9 in low doses is encouraging. Feldblum and Weir's reanalysis of previous data from Cameroon is the strongest evidence to date that nonoxynol-9 can deter HIV transmission; it suggests that the Kenyan study was misleading because the high doses used damaged the genital epithelium, increasing the risk of HIV acquisition.

Many chemical entities kill HIV in vitro.[14] A recent paper draws attention to a new entity, gramicidin, that is 1000 times as effective as nonoxynol-9 against HIV.[15] The vaginal pH and the buffering capacity of the product are important variables that must be taken into account in determining the survival of the virus.[16] In addition to nonoxynol-9, chlorhexidine, benzylkonium chloride gossypol, and even dextran sulfate are effective in vitro and have regulatory approval for use in humans. It would be prudent to conduct a coordinated program of international research on more than one product and formulation. Focus groups could be used to test the acceptability of delivery vehicles (pessaries, films, foams, etc.) among both sex workers and women in domestic sexual partnerships. Acceptable formula-

Editor's Note. See related article by Weir et al. (p 910) and letter by Feldblum and Weir (p 1032) in this issue.

tions should then be tested at a number of concentrations, initially in female volunteers *not* exposed to the risk of sexually transmitted diseases or HIV, to screen for evidence of damage to the vaginal epithelium in the way pioneered by Roddy et al.[13]

Short-term policymaking and careful analysis of the next steps in research must be set in the framework of the continued exponential growth of HIV infection in many parts of the world. Even in the United States, HIV-infected women are among the most rapidly growing groups affected by the disease.[17] Globally, the largest number of cases are the result of heterosexual transmission. By the turn of the century, it is projected that HIV will infect more people than died as combatants and civilians in World War II. From a public health perspective, a modest reduction in HIV transmission brought about by a vaginal microbicide made available today might save as many lives as a more effective method (e.g., a vaccine) made available in 10 years' time, when there might be 5 or 10 times as many infected people.

Should a vaginal microbicide be marketed on the basis of in vitro effectiveness against HIV and evidence that it does not damage the epithelium, or should new and existing compounds be withheld until convincing clinical trial data on their effectiveness are available? Specifically, should 100-mg nonoxynol-9 suppositories (which are approved by the Food and Drug Administration [FDA] and commercially available) now be recommended on the basis of Feldblum and Weir's reanalysis? If not, what data are needed and how will they be obtained?

At the least, just as the FDA has developed an accelerated route for testing AIDS therapies, it should accelerate the review process that will allow the labeling of a vaginal microbicide as protection against HIV. Weir et al.'s study is important because it presents an ethically acceptable model for testing the effectiveness of a microbicide: either everyone in a population at high risk of HIV infection is counseled to use both condoms and the microbicide and then groups are separated and analyzed by self-reported use or everyone is counseled to use condoms and then the microbicide and a placebo are allotted randomly. Elias and Heise calculate that a study of a new product that was 70% effective in slowing HIV transmission, when used in a population with a 2% to 3% annual seroincidence of HIV infection, would require a sample of approximately 1000 women.[14] In the interests of US women and the global community, it would also be prudent to explore other entities and formulations. It might cost $2 million and take 12 to 24 months to select and develop new entities and perhaps another $2 million and as long again to complete clinical trials.

The National Institutes of Health, the US Agency for International Development, the World Health Organization (WHO), and the Medical Research Council in the United Kingdom have all discussed vaginal microbicides. The WHO Global Program on AIDS has acknowledged the need for research, and the Population Council is giving the topic priority. Nevertheless, an appropriately financed and coordinated research program is not yet in place. Those who control resources should either change their policies to recommend low-dose vaginal preparations on the basis of available data or immediately put in place the money and personnel needed to gather more data so a policy decision could be reached by early 1995.

Many lives might have been saved if such work had been initiated earlier, and the lack of decisive action is unacceptable when for every year we wait there may be twice as many HIV-positive individuals in vulnerable groups. □

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