Commentary

Thinking About Vaginal Microbicide Testing

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A B S T R A C T

A vaginal microbicide could slow the spread of HIV. To date, volunteers in placebo-controlled trials of candidate microbicides have been counseled to use condoms. This does not reduce the number of volunteers exposed to possible risk, but it shifts the allotment of risk from those conducting the trial to those women who may be least able to make autonomous decisions. Alternative ways of meeting the obligation to offer volunteers active benefits are explored. Counseling the use of condoms prolongs clinical trials and could cause tens of thousands of otherwise avoidable deaths. (*Am J Public Health*. 2000;90:188–190)

The Joint United Nations Program on HIV/AIDS (UNAIDS) estimates that 16 000 new HIV infections occur daily throughout the world. HIV is a fragile virus, and a great many chemical entities destroy it in vitro. Several have been approved by the Food and Drug Administration (FDA) for other purposes, and all the others are relatively nontoxic. While success cannot be proved before testing takes place, it is likely that a microbicide can be developed that can be applied by a woman before a sexual encounter. Such a product would be especially valuable for women who suspect their sexual partners are putting them at risk of HIV infection but who cannot compel them to use condoms.[1] The most time-consuming step in bringing such a product to market would be clinical trials of efficacy. When the number of possible products is combined with possible variations in formulation, 10 or 20 individual clinical trials—maybe even more—might be needed to discover the optimum product.

Developing Guidelines for Microbicide Trials

How would such trials be conducted? The level of heterosexual HIV transmission in the west is such that a clinical trial would require thousands of volunteers and take several years. For this reason, microbicide studies to date have engaged commercial sex workers in developing countries. The high incidence of HIV infection among sex workers means that statistically significant studies involving small numbers of volunteers can be conducted relatively rapidly. Sex workers in Africa and India have a high incidence of HIV because they often have untreated sexually transmitted diseases (STDs) and are commonly unable to negotiate condom use with their clients. On the one hand, commercial sex workers are a group that would benefit directly from access to a microbicide, but on the other hand the very lack of empowerment that creates the high incidence of HIV transmission also makes the ethics of a study problematic.

A widespread consensus on an empirical set of guidelines governing research on human subjects already exists; these guidelines include a scientifically sound research design, respect for the autonomy of the volunteer subject, nonmaleficence (or "do no harm"), beneficence, and justice. A microbicide trial would require a consent form approved by independent review boards in both the local community and the sponsoring institution. To further protect the volunteer's autonomy, careful research could be conducted on the sex workers' understanding of any written and verbal material used.

Regarding the "do no harm" guideline, the most serious adverse consequence of an existing microbicide would not be failure to destroy HIV but acceleration of the acquisition of HIV through vaginal damage. Any test of a new drug or device carries an irreducible risk of harming volunteers. Fortunately, in the case of a microbicide, this risk can be minimized if animal studies are followed by human tests on informed volunteers not exposed to HIV or STDs. Careful clinical evaluation of vaginal health could be conducted before and after exposure to the product. Sexual activity would not be a prerequisite for such a test, and, if necessary, sex worker volunteers from a study community could be paid not to receive clients for an interval while the product was being tested for vaginal irritation.

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This commentary was accepted July 12, 1999.

Beneficence and Justice

If we assume that a trial has been devised in which guarantees of safety are satisfactory, the design is scientifically sound, and potential volunteers are able to give informed consent, then 3 out of the 5 principles generally accepted as the foundation of an ethically acceptable trial will have been met. But how are the generally accepted obligations for the equitable treatment of volunteers and for doing as much active good to volunteers as possible (beneficence) to be met?

It is commonly considered unacceptable to recruit volunteers for a placebo-control study without first treating their STDs and counseling them to use condoms as the optimal protection against HIV infection.[2,3] At first sight, this interpretation of ethics appears compelling and necessary; when followed through, however, it raises some complex issues, and the protocol can even be seen to be counterproductive.

In a 1998 microbicide study, Roddy et al.[4] found that 90% of women in both the user and control groups used condoms when they were counseled to do so. From a prevention perspective, this was an unexpectedly satisfactory result, but such an interpretation of beneficence demands recruiting more volunteers and conducting longer and inevitably more expensive trials. It would be difficult, for example, to test a new antibiotic if those with infection were treated with an already existing antibiotic before they enter the trial of a new product. Given the limited human and fiscal resources available for microbicide development, this interpretation of beneficence will significantly prolong—and perhaps even totally inhibit—otherwise achievable trials designed to bring a potentially lifesaving product to the market place. From an ethical perspective, the condom counseling model increases the number of volunteers without offering any active benefit to those volunteers who, for a variety of reasons, do not use condoms and who are the real focus of the trial.

Considering the Implications

HIV now infects 20% or more of pregnant women tested in some parts of Africa, and in many places the epidemic continues to grow exponentially. Given that an effective microbicide can eventually be developed, how many otherwise preventable deaths might result from the delay caused by a strict interpretation of beneficence and justice during the trial period? Having had senior executive responsibility for the design of some of the early microbicide trials (which used condom counseling), I estimate that counseling volunteers can increase the time taken to implement a trial from perhaps 15 months to 30 months.

It is estimated that 6000 of the 16 000 new HIV infections that occur each day are among women. If we assume that 2% of these women might use a low-cost microbicide after it reaches the marketplace, and if we further assume that such a microbicide would prevent HIV transmission in 7 out of 10 of the 2% of exposed women using the product, then the delay resulting from this particular application of beneficence and justice before the product could be put to widespread use would be associated with 37 800 or more preventable deaths (6000 infections $\times$ 0.02 adoption of method $\times$ 0.7 effectiveness $\times$ 15 months $\times$ 30 days per month). Clearly, other plausible estimates—some higher and some lower—could be made, but there is no doubt that the number is large. If "downstream" infections characteristic of a growing epidemic are factored in, the burden of possible deaths would be even greater.

Consideration of the deaths that might occur as a result of the additional time taken to bring the product to market is philosophically the same as consideration of the deaths that might be associated with the possibility of vaginal damage and acceleration of the acquisition of HIV. Both are possibilities that need to be taken seriously, but they cannot be proven in advance of an actual trial. I suggest that there is an obligation to explore alternative scenarios, even if some are eventually dismissed as clinically or ethically unacceptable.

What Happens if Volunteers Are Not Counseled to Use Condoms?

Any placebo-control trial of an agent designed to prevent or cure an infectious disease must track a statistically significant number of volunteers who acquire the infection. If the product does work, then those who are allotted the placebo fail to become exposed to a benefit that would have occurred had the coin fallen differently. In the case of a trial designed to prevent HIV, those running a placebo-control study cannot avoid watching volunteers acquire a lethal, incurable disease. Whether the social ecology in which the trials are conducted is left unchanged or, conversely, volunteers are counseled to use condoms and STDs are treated, the number of volunteers who are going to be infected will be the same. Those coital episodes protected by condoms are irrelevant to the actual trial, although they "dilute" the data, making the final end point more difficult to determine. In addition, the inevitable loss to follow-up associated with a large trial means some subjects will be exposed to possible risk without contributing to the final result. For both these reasons, it is possible that a condom counseling model could increase the number of volunteers exposed to HIV infection and subsequent death.

What condom counseling really does is shift the locus of risk taking. In a non–condom counseling design, those running the trial accept the reality that they are randomly allotting the risks (if any) across the population of volunteers, as well as perpetuating the absence of a potentially lifesaving intervention among placebo users. In the counseling design, it is the individual woman who by not using condoms exposes herself to whatever element of risk may exist. But by not using condoms she is demonstrating that either she lacks an average level of health-seeking behavior or she finds herself in such an exploited and disadvantaged position that she is unable to follow the advice she knows is lifesaving. Is it more ethical to shift the lottery of a placebo-control trial to the volunteer?

Must Beneficence Be Chronologically and Geographically Linked to the Individuals in the Trial?

Consider a group of 5000 sex workers with a high incidence of HIV. Suppose that 500 are recruited as volunteers and asked if they want to take part in a placebo-control trial of the new microbicide. Many of the locations where this type of trial might be conducted lack condoms, people with diagnostic skills, and adequate supplies of antibiotics to treat STDs. While a trial is under way, volunteers exposed to HIV will receive STD treatment and condom supplies, but when the study ends, services are likely to degrade rapidly. Would it not be more ethical to conduct the trial without counseling on condom use, but once it is complete guarantee all the volunteers—or perhaps better still, every one in the local community—a long-term supply of condoms and/or any product that the conducting of the trial might produce, along with continuing opportunities for treatment of STDs? Is it preferable to apply the principle of beneficence for perhaps 1 year during the study or for 10 or more years after the study is completed?

Or consider the same group of 5000 sex workers, of whom 500 are recruited as volunteers in the trial and offered the candidate microbicide but without any other intervention. Then take 1000 different women from among the same 5000 and counsel them to use condoms in addition to

the microbicide. This would add little additional cost to the trial, and it would be logistically straightforward. The trial would be conducted more rapidly, and the results would be less ambiguous. A vital product might reach the marketplace sooner; in addition, twice as many women would have the opportunity to benefit from using condoms. Can the principle of beneficence be applied to a group contiguous with, but not identical to, those involved in a clinical trial? If the community of sex workers taking part in the study were asked their opinion on this scenario and endorsed it as a commonsense step, would this alter the ethical analysis?

The core of the problem is the heartrending inequality that exists with respect to the status of women, condom use, and STD control between developed and developing countries. Are those who are planning trials of a microbicide obligated to try and solve the enormous inequalities and injustices that exist in access to health care around the world, or should they focus on making a potentially lifesaving choice available—particularly if, as in this case, it is a method that might be most readily accepted by the very group of women who are most disadvantaged by poverty and social injustice? What level of beneficence and justice should be adopted? If there were no limit, resources would simply be spent to remove women from prostitution, and the study would never take place. If, on the other hand, the desire to do good is necessarily tempered by practical realities, then where is the boundary to be placed? For example, to date, no commentator has suggested offering lifelong treatment, with the full complement of antiviral therapies now available in the west, to volunteers who acquire HIV during a clinical trial of a microbicide. Such treatment would meet the test of beneficence, but presumably it has been rejected because it is too expensive.

Are There Alternatives to Placebo-Control Trials for Establishing the Efficacy of a Microbicide?

While we are used to the idea that therapies for AIDS should be "fast-tracked," we have not applied this thinking to prevention. Most formulations of possible microbicides will also act as vaginal lubricants, or might be treatments for common vaginal infections. Would it be responsible to market a product where in vitro data demonstrate effectiveness and in vivo human data ensure safety? Or could animal models that use simian immunodeficiency virus be developed as surrogate tests? This is not the place to answer such a new set of questions, but perhaps they need to be explored. Once a product were used on a large scale, case–control studies could be conducted with high-risk groups to determine whether users of the product are acquiring HIV less rapidly than nonusers. If the formulation were then shown to be efficacious, it could be actively promoted on a large scale for HIV prevention. If unsuccessful, it could be withdrawn or left on the market for the original indication.

Conclusions

The aim of this discussion is not to advocate a particular solution but to marshal reasons to question the prevailing assumption that "no one disagrees that condoms must be provided to all research participants."[2] Alternative scenarios for implementing beneficence and justice can be envisaged. When condoms are provided, the same number of women are exposed to possible risk, although they are self-selected largely as a result of being disempowered rather than of being randomly allotted by an outside investigator. It is harrowing for the researchers to be caught in a situation where they cannot avoid watching volunteers acquire an incurable disease, but the real world is exceedingly painful, and the possibility of tens of thousands of otherwise preventable deaths is also tormenting to contemplate.

In the last analysis, every ethical assertion—like every scientific conclusion, however strongly held—must be open to review and possible reappraisal. A truly ethical solution will require input from people with a variety of skills and a great deal of wisdom and, whenever possible, the full involvement of the community from which the volunteers in any trial will be drawn. Consultations on these ethical issues have been initiated with elite social groups from developing countries, but they need to be widened to include sex workers themselves.

It is hoped that in the coming years, opportunities for testing HIV vaccines will increase; if they do, similar ethical considerations will arise. Delay in testing a microbicide with relatively limited use could result in tens of thousands of avoidable deaths; delay in testing a vaccine that could be given to virtually everyone might result in millions. □

Acknowledgments

I am grateful for insightful comments from Megan Dunbar, Bethany Holt Young, and Martha Campbell.

References

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