

# Commentary

## Challenges in Microbicide Trial Design and Implementation

by Janneke van de Wijgert and Heidi Jones

Microbicide development began more than fifteen years ago, when optimism about the swift development of an HIV vaccine began to wane, and researchers recognized that significant progress in HIV transmission prevention could not be expected with the currently available HIV-prevention tools (van de Wijgert and Coggins 2002).

Sexual abstinence and limiting the number of sexual partners may not be feasible for those women who, because of their constrained educational and employment opportunities, are financially dependent on men. After two decades of male condom promotion, the absolute number of male condoms used worldwide has increased dramatically, but consistent condom use in primary partnerships remains rare. Women are often unable to convince their male partners to use a condom, or to remain with one partner, because of social, cultural, and economic gender inequalities. Microbicides are being developed as products to apply topically inside the vagina or rectum to prevent infection with HIV and, potentially, with other sexually transmitted infections (STIs). They could be formulated as gels, creams, suppositories, or vaginal rings; they could be contraceptive or not; and they could be used alone or in combination with a physical barrier. For many women and couples, the importance of having children is a major obstacle to condom use, and noncontraceptive microbicides would offer them a means of protecting themselves from HIV while trying to conceive. By reducing the risk of HIV infection among women, microbicides could contribute to a

reduction in mother-to-child transmission. They could prevent transmission from women to their male partners, and reinfection among women who are HIV-positive. Researchers are also investigating ways that microbicides can be formulated for use in the rectum during anal sex.

Remarkable progress has been made in the microbicides field in recent years. According to the Alliance for Microbicide Development, 29 candidate products are in the pipeline (AMD 2006). The majority of these are in pre-clinical stages of development, approximately ten are in Phase I and II safety trials, and five are in Phase IIb/III effectiveness trials. Funding for microbicide development increased significantly (Harrison et al. 2005), and the global movement for microbicides continues to grow, uniting women's health and AIDS advocates, researchers, governments, and institutions. A biennial international microbicides conference was established in 2000, and attendance has grown steadily with each subsequent meeting.

As candidate products are moving from the laboratory to human communities, many challenges in microbicide trial design and implementation have surfaced. Some of these challenges are scientific in nature, but others are ethical, political, or logistical. In this Commentary, we highlight some of the challenges that we have encountered while establishing microbicide trial sites and in designing and implementing microbicide trials in Africa and Asia.

### Trial Populations

No validated surrogate endpoints for the biological activity of microbicides currently exist. Therefore, the primary endpoint of microbicide effectiveness trials must be HIV incidence (Mauck et al. 2001). Testing of a vaginal microbicide thus requires the participation of thousands of women at risk of HIV infection through heterosexual sex. The higher the HIV incidence in a trial com-

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munity, the smaller the required sample size. For feasibility reasons, trials are, therefore, typically conducted in communities with an HIV incidence of at least 2.5 percent per year. Because of the strong links among poverty, gender inequity, and HIV prevalence in the heterosexual population, such communities are mostly found in developing countries, with the exception of some communities of sex workers in the industrialized world (Hallman 2004). Even in communities with an HIV incidence of at least 2.5 percent per year, researchers can never be sure which women are exposed to HIV through vaginal sex, through another transmission route, or not at all, without knowing the HIV status of their sex partner(s). Although randomization minimizes systematic exposure differences between study groups, effectiveness trials of vaginal microbicides should not be conducted in communities with high levels of HIV transmission through injections, blood transfusions, or anal sex (these communities may, however, be suitable for vaccine trials). Unfortunately, anal sex is often highly stigmatized and therefore difficult to measure; the proportion of new HIV infections transmitted during anal sex versus during vaginal sex in heterosexual populations is usually not known. Finally, microbicide trials should not be conducted in communities where clinical trials of other experimental HIV prevention methods (such as other candidate microbicides, barrier methods, or vaccines) are already under way. In such communities, women and their sexual partners may be exposed to multiple interventions simultaneously, which may result in unpredictable changes in HIV incidence and cross-contamination of trials through sharing or selling of experimental products.

## **Trial Sites**

Candidate microbicides are experimental products that could save many lives if proven safe and effective. The international community is committed to making successful products available to those women who need them (Zewdie 2004). This access can only be achieved if successful products are registered with as many drug regulatory agencies worldwide as possible. Microbicide trials must, therefore, be conducted according to the regulatory standards set by the International Conference on Harmonization of Technical Requirements for Registration of Pharmaceuticals for Human Use (ICH) in the Good Clinical and Laboratory Practice (ICH-GCLP) guidelines and according to national drug regulatory and ethical review guidelines (ICH 1996). Few potential trial communities in developing countries have the required infrastructure or experience to conduct rigorous clinical

trials according to such guidelines. Fortunately, this situation is improving through capacity-building within international partnerships such as the HIV Prevention Trials Network (HPTN), the UK Microbicides Development Programme (MDP), the International Partnership on Microbicides (IPM), and the European Developing Countries Clinical Trials Partnership (EDCTP) program. Furthermore, the World Health Organization and other agencies have initiated programs to strengthen and streamline drug regulatory and ethical review processes in developing countries (WHO 2002; Coplan et al. 2004).

More trial sites that are ICH-GCLP compliant are needed to test efficiently as many candidate microbicides (and vaccines) as possible as they move through the pipeline. Setting up a microbicide trial site takes from two to five years, depending on the availability of qualified human resources and infrastructure in the host country, the availability of funds and experts to build the required capacity, and the chosen organizational structure (for example, embedding the trial within an existing institution or establishing an independent research clinic). Once established, trial sites should be given the opportunity to implement trials continuously so that skills are maintained, qualified staff are retained, and costs are minimized (the present-day cost of maintaining a trial site that is not currently implementing trials has been estimated at about US\$750,000 per year [Harrison et al. 2005]). In our experience, keeping trial sites continuously fully occupied has been more difficult than one might expect.

## **Microbicide Trial-design Issues**

Phase III microbicide trials are difficult to conduct and interpret because of a variety of methodological and ethical challenges. First, for ethical reasons, effectiveness trials must measure the incremental effect of the potential microbicide over and above a package of already proven HIV-prevention interventions that include HIV counseling and testing, condom promotion, and treatment of curable STIs and vaginal infections (World Medical Association 2000). Measuring such an incremental effect may be particularly problematic for microbicides that have a lower expected method efficacy than condoms, which is likely to be true for most first-generation microbicides. Second, in contrast with vaccines but like condoms, most (but not all) microbicides would have to be used whenever intercourse takes place, or at regular intervals over time, in order to be protective. Perfect adherence has not been achieved in any long-term microbicide trial to date (Roddy et al. 1998; van Damme et al. 2002; Kilmarx et al. 2005). Third, extensive research has

shown that, currently, no reliable way exists to measure sexual behavior, including microbicide and condom use (Bloom 1998). Research is ongoing to improve collection of sensitive data and to measure product-use adherence, but completely reliable data will probably remain elusive (Hewett et al. 2004; Wallace et al. 2004). Unreliable data complicate the monitoring of adherence with product use and sexual activity during trials, and complicate subsequent interpretation of trial results. Lastly, no proven placebo currently exists, as discussed below. Many of these challenges are likely to result in underestimates of microbicide effectiveness, even within the context of randomized controlled trials (Trussell and Dominik 2005). To take this possibility into account, the majority of planned Phase III microbicide trials are designed to demonstrate modest effects of between 30 and 50 percent.

Scientists are still debating the most appropriate control arm for microbicide effectiveness trials: a matching placebo arm, a no-product/condoms-only arm, or both in parallel (Jones et al. 2003; Kilmarx and Paxton 2003; Padian 2003; Stein et al. 2003; Fleming and Richardson 2004; Gross 2004; Padian 2004; Stein and Susser 2005). A matching placebo arm allows for a double-blind trial, which, in turn, yields the least biased estimate of product efficacy. However, even though a placebo typically does not contain the active ingredient of the candidate microbicide, it could, nonetheless, decrease HIV transmission (for example, as a result of its lubricating or physical barrier properties) or could increase transmission through local toxicity from long-term use (although placebos are chosen carefully in terms of their previous safety records). In a condoms-only arm, women do not receive a vaginal product, but they receive the currently available HIV-prevention package in a clinical trial setting. Using a condoms-only arm allows for comparisons between “best-case scenario HIV-prevention with microbicide” and “best-case scenario HIV-prevention without microbicide.” The disadvantage of a condoms-only arm, however, is that it cannot be blinded, which may result in differential behavior changes (for example, more condom use in the condoms-only arm), lower enrollment and retention rates in the condoms-only arm, and increased product-sharing among participants receiving a test product and those not receiving a test product. Having both types of control arms in parallel would allow for blinding between the microbicide and matching placebo arms; it may also allow the researchers to measure the effect of the matching placebo on HIV acquisition and local toxicity and would allow for comparisons between the microbicide arm and each control arm. However, the disadvantage of having two control arms is that the sample size of the trial increases, which raises

concerns about feasibility and cost. Furthermore, scientists disagree whether the ability to make multiple comparisons allows researchers to better understand results or makes interpreting results more difficult (for example, no consensus has yet been reached on how success would be defined in a trial with two parallel control arms).

Future microbicide trial designs may have to be modified significantly if the ongoing trials of first-generation microbicides show positive results or other new HIV-prevention strategies (such as vaccines or pre-exposure prophylaxis with antiretroviral drugs) are proven effective. Whether such new prevention tools become part of the standard package that is offered to all trial participants or become the comparator product in equivalence or superiority trials most likely will depend on (a) the robustness of the new prevention-method trial results, (b) whether the results can be extrapolated to other populations and settings, (c) whether providing the new prevention method in addition to currently available methods would increase overall protection, and (d) whether experts agree about all of the above conditions. Extensive debates on this topic are to be expected in the future.

## **Microbicide Trial Implementation: Ethical Issues**

An in-depth discussion of microbicide trial ethics is beyond the scope of this commentary. An excellent report on this topic has been published recently by the Global Campaign for Microbicides (Heise and Wood 2005). Here, we would like to share some ethical dilemmas that we have encountered at a variety of trial sites in Africa and Asia.

### *Informed Consent*

Researchers in the microbicides field generally agree that informed consent is a process, not a single action or moment, and that the emphasis should be on participants' comprehension and voluntary choice, not only disclosure of information. Many research groups have developed supplementary materials—such as booklets, flipcharts, videos, and interactive computer programs—in local languages, based on extensive input from local social scientists, study counselors, trial participants and/or representatives from trial communities (Friedland et al. 2004; Population Council 2005). Formal or informal comprehension tests often are used to assess comprehension of important trial concepts over time. Unfortunately, hard data on the effect of these various approaches on comprehension and other aspects of informed consent

are scarce and are urgently needed. One aspect of comprehension is of particular concern: a woman's belief that the product assigned to her will protect her from HIV infection even after she has been told repeatedly that the effectiveness of the experimental product is unknown and that she may be receiving an ineffective placebo. Research suggests that this "therapeutic misconception" does not appear to be a problem at the trial population level (results of most studies to date indicate that condom use increases when women are given a candidate microbicide plus condoms and that HIV incidence decreases in all groups), but it may be a problem at the individual level (Ramjee et al. 2000; Foss et al. 2003). Innovative approaches and more research are needed to address this concern.

### *Involvement of Men*

Microbicides are being developed to give women greater autonomy in protecting their own health. However, in many of the microbicide trial communities, men are the principal decisionmakers. Requiring male partners' consent may be appropriate for Phase I or II safety trials because male partners may be exposed to a product for which penile safety has not yet been assessed or because they may be required to abstain from sex or use a condom. Such a requirement is questionable in Phase III effectiveness trials, however, both logistically and from the perspective of enhancing women's autonomy.

Many researchers believe that product sponsors should ensure that penile safety studies are conducted prior to the initiation of Phase III effectiveness trials (Mauck et al. 2001). When adequate penile safety data are available, the woman should decide if and how she wants to involve her male partner(s). Experience has taught us that many women (especially those who are in a committed relationship with one partner) will want to involve their partner. His involvement may improve the relationship, reduce HIV risk, increase product-use adherence, and maximize retention of participants (Braunstein and van de Wijgert 2005; Mantell et al. 2005). When women choose to involve men, researchers should support their decision, but without requiring formal male consent. Long-term penile safety could be assessed by using a passive surveillance system during Phase III effectiveness trials and in the postmarketing phase.

## **Medical Care in Microbicide Trials**

Medical and psychological care issues are among the most difficult and stressful to handle for microbicide trial in-

vestigators and their teams because the need they encounter is distressingly high. Demands placed on them can be overwhelming, and the limits of their responsibilities are often unclear. Health-care systems in resource-poor communities cannot cope with existing problems, let alone "new" problems uncovered by research. Most trial planners agree that researchers should, at a minimum, provide participants with the local standard of care; the provision of slightly better care than what is available in the community seems to be the norm. For example, many microbicide research clinics provide the best available HIV- and pregnancy-prevention programs; state-of-the-art laboratory diagnosis of reproductive tract infections (as opposed to syndromic management); Pap smears and colposcopy (which are either not at all or not routinely available); expanded counseling services (such as couple/marriage counseling and domestic violence counseling; often as a result of high participant demand); and active and effective referrals (often the clinics help referral sites cope with increased demands).

Although deviations from local public health policy may be resisted initially, eventually they are well accepted and may lead to sustainable improvements in reproductive health services in the entire community. Care should be taken to prevent trial participants from becoming dependent on trial services, and study teams should make an effort to reduce the impact of services ceasing at the end of a trial (Pistorius et al. 2004). Clearly, ensuring universal access to an adequate national health-care system and resolving national or regional conflicts regarding major health-care issues cannot be the responsibility of one research team. Many research teams are willing to contribute to the broader health-care agenda in trial communities, however, and actively engage in national and regional debates. How much they can contribute often depends on the availability of trial funds (which, in turn, depends on donors and product sponsors), staff time, and support received from others, such as national and regional governments, nongovernmental organizations, care providers, and advocates. Unfortunately, tension exists between the urgent need for a microbicide and the time and funds required to contribute to the broader health-care agenda in trial communities.

### *Identifying HIV-positive Women*

Access to antiretroviral treatment (ART) is still limited in developing countries but is improving rapidly. Access to alternative ART regimens in case of first-line treatment failure may remain limited for many years to come, however, because most developing countries can afford to make only a few drugs available through their national

programs, and second-line drugs are often more costly than first-line drugs. Large numbers of HIV-positive women are identified through screening for or participation in microbicide trials, and these women may have children and other relatives who are also HIV-positive. Are trial sponsors responsible for providing ART treatment to these women when they need it (even if they need it many years after their participation in the trial has ended), and if they are, for how long should they provide it? Many debates have addressed these questions in the HIV microbicides and vaccines fields, and these debates are constantly shifting as a result of the ever-changing access to ART in developing countries (Bass 2003; Berkley 2003). Most microbicide and vaccine trial networks intend to provide ART to those who become HIV-positive during a trial (using national guidelines to determine when to start ART and linking with national ART roll-out programs when possible). Treatment may include second- and third-line regimens if the candidate microbicide introduces resistance mutations that rule out first-line regimens. Generally, the networks intend to provide ART neither to women who test positive at screening nor to their family members. However, several trial teams are also trying to help the latter two groups by referring the women and their families to existing ART roll-out programs, by offering CD4-positive lymphocyte counts to HIV-positive women (paid for by the trial) to facilitate referrals to existing programs, and by conducting studies (or referring to studies) that are enrolling HIV-positive women. Because many seroconverters will need ART long after the trial has ended, trial sponsors and research teams must set up sustainable mechanisms to track these women and treat and monitor them over long periods of time. Most researchers agree that a plan should be developed for these mechanisms prior to the initiation of studies designed to identify seroconverters.

### *Community Involvement*

Most microbicide trial sites have established community advisory groups to obtain input from the community regarding many of the topics discussed here. Yet, who represents and speaks for “the community”? Although finding out which local community groups are actively advocating for issues that are relevant for microbicides research and who the formal community leaders are is a simple process, how “the end-user” should be represented is not always clear. Furthermore, some advocates argue that community involvement should move beyond advisory groups into much broader outreach programs, preferably developed by the community advisory group or other stakeholders themselves, and im-

plemented by trusted community-based organizations (Global Campaign for Microbicides 2003). Most advisory group members and other stakeholders have had no prior training or experience in public health, medical ethics, or research methodology. To enable them to become efficient intermediaries between the community and the research team, and to provide meaningful input for research procedures, they should receive training in these areas. Some advocates argue that the trainers should not be members of the research team, in order to minimize conflicts of interest (Global Campaign for Microbicides 2003). Community involvement should be an ongoing, transparent, two-way communication between research teams and community members. The researchers should take care, however, not to raise community members’ expectations about the imminent availability of a successful product.

### *Continued Access to Study Product*

Although many investigators, product sponsors, and host governments agree that, ideally, effective products should be made available to study participants and communities at the end of the trial, several obstacles can impede such access. A time lag always occurs between the conclusion of a trial and regulatory approval of the product. During this time lag, products can be made available only through clinical trials (usually Phase IV studies). Such studies are costly and would occupy study sites and trial teams that could otherwise conduct trials of new products. Once regulatory approval has been obtained, the introduction of a new product to the market poses new challenges. Given these many obstacles, ensuring that the participants’ and the community’s expectations are realistic regarding continued access to the study product is important. Microbicide advocates (often including members of research teams and former trial participants) can play an important role in maintaining pressure on regulatory agencies to review registration applications in a timely fashion and on product sponsors and donors of social marketing programs to distribute registered products to the women who need them.

### **Microbicide Trial Implementation: Logistical Issues**

As noted above, testing of a vaginal microbicide requires the participation of thousands of women at risk of HIV infection through heterosexual sex. This type of trial is expensive and logistically challenging. Usually it requires the collaboration of multiple trial sites in multiple

communities and/or countries. The greater the number of trial sites, the smaller the required sample size at each site, but the more challenging overall coordination and standardization of data collection will be. A difficulty related to large sample sizes is the inherent tension between voluntary participation and the need to retain participants. This problem can be minimized by allowing each volunteer to participate for no longer than one year, by providing fun incentives when certain milestones are reached (for example, t-shirts or towels), and by allowing some trial services to evolve over time to keep volunteers engaged (for example, providing counseling on issues other than HIV and safer sex). Care must be taken, however, not to overburden trial counselors, who have to cope with highly emotional issues such as the identification of HIV-positive women and domestic violence. Counselors often need ongoing training and emotional support to prevent high burn-out rates.

## Conclusions

From a scientific point of view, what the microbicides field needs most is proof of concept, validated safety and surrogate effectiveness endpoints, and true placebos. Therefore, testing candidate products with different mechanisms of action is crucial in the near future; multiple products could be tested simultaneously to maximize efficiency and minimize costs (Gross 2004). Research on ways to improve the collection of sensitive data, including adherence to product use, should continue. More trial sites should be established, but existing sites should be used to the fullest extent possible. The microbicides field has made a strong effort to date in addressing the issues of informed consent, the involvement of men, provision of medical care to trial participants and communities, community involvement, and long-term access to study product. However, these ethical issues should continue to be debated, and responses should be adjusted as the field develops.

Recently, several trials of the product Tenofovir for pre-exposure prophylaxis of HIV in Africa and Asia were stopped prematurely as a result of ethical concerns (Grant et al. 2005). A microbicide effectiveness trial in Ghana was halted because HIV incidence in the trial population was lower than expected. The negative consequences of these aborted trials included a delay in the development of new HIV-prevention interventions, a waste of scarce resources, and decreased trust between research teams and trial communities. These consequences highlight the importance of ensuring that microbicide trials are carefully designed and ethically sound from the outset.

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