1. Introduction: Rethinking the Ethical Roadmap

The shifting frontier of the microbicide challenge

Scientific and political challenges have dominated the field of microbicide development for the past decade—unlocking the secrets of the virus, identifying promising microbicide candidates, and mobilizing financial resources and political will. Our task has been to bring to reality a novel approach to HIV prevention that most of the scientific community viewed as wishful thinking just a few short years ago.

Remarkable progress has been made on both scientific and political fronts in recent years. From a "field" lacking even a name—much less significant research funding or a political constituency—the notion of a women-controlled method for HIV prevention has evolved into a global movement uniting researchers, foundations, governments, and thousands of women's health and AIDS activists. From virtually *no* funded research as of 1992, global investment rose from roughly $28 million in 1998 to nearly $140 million in 2004.[1] Scores of research papers are now being published annually, with results reported upon instantly through scientific meetings, AIDS conferences, and web media of hundreds of activist organizations.

Although the pharmaceutical industry still remains largely a bystander, a growing number of foundations and government agencies have joined the race for a low-cost, universally accessible microbicide. The United States Congress has introduced the Microbicides Development Act of 2005 to authorize increased federal funding for microbicide research and development and to mandate a clearly defined organizational unit at the National Institutes of Health (NIH) to spearhead this effort. Influential political figures, such as UK Prime Minister Tony Blair, have urged the G8 nations to focus on microbicides while continuing the race to develop vaccines and better treatments. And an eminent group of world scientists have pronounced microbicides one of the "top 10 most promising biotechnologies for improving global health.[2] "

While scientific and political challenges have guided our efforts over the past decade, the challenges and cutting edge of the next decade may be considerably different. Partly as a result of the field's successes, the frontier of microbicide development is taking on a new character. The determinative challenges that we face today may well be

[1] HIV Vaccines and Microbicides Resource Tracking Working Group. Public and philanthropic investments in preventive HIV vaccines and microbicides: 2000 to 2004: Preliminary report. New York: IAVI, AVAC, UNAIDS and the AMD. Available at: http://www.iavi.org/file.cfm?fid=9862.

[2] Daar AS, Thorsteinsdottir H, Martin DK, Smith AC, Nast S, Singer PA. Top ten biotechnologies for improving health in developing countries. *Nature Genetics*. 2002. 32(2): 229–232.

ethical, not scientific or political. And how thoughtfully and how well we respond to them is likely to be as critical to the eventual success of microbicides as was our response to the scientific challenges and political challenges of the recent past.

This change in terrain has come about for three main reasons. First, the scientific research that mostly involved lab and animal research in the 1990s has now moved to human communities in the first decade of the 21st century. We are no longer discussing results on microscope slides, but effects on real human beings. Microbicide candidate products now need to be tested—not only by women in general, but the women who most urgently need them: primarily poor vulnerable women in developing countries.

Second, a dramatic drop in cost for antiretroviral drugs and a growing demand by developing-world citizens for access to treatment has redefined expectations and hopes with respect to access to HIV care. This in turn has kindled debate on access to HIV treatment in the context of prevention trials.

And finally, recent controversies over the design and conduct of clinical trials of oral tenofovir have highlighted how difficult prevention trials can be, and how essential transparency and ethics are to building community trust.[3] Two trials—one in Cambodia and the other in Cameroon—have already been halted in response to activist and community concerns regarding trial ethics. Unless dealt with proactively, ethical quandaries could delay or derail a generation of future trials.

The International Consultation on Ethical Issues in the Testing of Microbicides, October 2003

On October 23–24, 2003, the Global Campaign for Microbicides brought together 64 people from 12 countries to rethink the issues and ethical dilemmas facing the field of microbicide development. The Consultation comprised a broad range of stakeholders, including advocates, ethicists, clinical investigators, community members, drug regulatory authorities, and past participants in microbicide clinical trials. (See Appendix A: Participant List.)

The purpose of the Consultation was to provide a forum for deliberation, taking on some of the toughest ethical questions in the conduct of clinical research on microbicides. What is an appropriate balance of risks and benefits for those who participate in trials? What constitutes meaningful (versus nominal or legalistic) informed consent? Should trials enroll adolescents under 18 years old? To what extent should male partners be included in the research process? Should partner consent be required? What is the appropriate ethical line between fair compensation and undue inducement? Should sponsors be obligated to guarantee antiretroviral therapy (ART) to those who become HIV positive during the trial? And looking to the future, what does finding a

[3] Tenofovir is an existing drug used for HIV treatment that is currently being tested as a possible once-a-day prophylactic pill to prevent HIV transmission among healthy individuals. For more on the oral tenofovir trials see: The trials of tenofovir trials. *The Lancet*. 2005; 65(9465):1111.

AIDS Vaccine Advocacy Coalition. Will a Pill a day prevent HIV? Anticipating the results of the tenofovir "PREP" trials. New York: AVAC; 2005. Available at: http://avac.org.phtemp.com/pdf/tenofovir.pdf.

partially effective microbicide mean for the design of the next generation of microbicide trials?

The organizers of the Consultation hoped to shed light on the ethical and practical dilemmas faced by communities, investigators, donors, research institutions, and host governments as they proceed with large-scale clinical trials on microbicides. (See Appendix B: Consultation Agenda). The goal was not to render judgments but to offer insights and to expand the range of actors involved in the deliberation of these important issues. In keeping with this spirit, the consultation was preceded by a daylong training session in ethical reasoning to help prepare participants to participate fully in all discussions. The course—now being offered more widely by the Global Campaign for Microbicides—includes background information on prevention trials, an introduction to ethical principles and reasoning, and several applied case studies. (See Appendix B for more details).

Roots of the Consultation

The decision to organize the 2003 Consultation was rooted in a history of earlier deliberations and motivated by developments in the HIV prevention research field. In April 1997, the Women's Health Advocates on Microbicides (WHAM)[4] and the Population Council jointly sponsored a symposium, "Practical and Ethical Dilemmas in the Clinical Testing of Microbicides." That symposium anticipated—and began to concretely address—some of the thorniest dilemmas in the clinical testing of HIV-prevention products, particularly microbicides. As shown in Box 1, the symposium report offered a number of important ethical recommendations, based on the points of greatest concern and consensus during that meeting.[5] (See Box 1, Recommendations from the 1997 Ethics Consultation on Microbicide Trials).

Since 1997, several microbicide and HIV vaccine trials have gone into the field, providing first-hand experience to inform the ongoing ethical discussion. Moreover, a number of controversies around the ethics of HIV-prevention trials have helped to stimulate wide-ranging, often heated debates.[6] UNAIDS has convened a series of meetings on ethical challenges in the clinical testing of HIV vaccines—many of which parallel those in the microbicides field. And the HIV Prevention Trial Network (HPTN) has formed an International Ethics Working Group and issued it own ethics guidance document.[7]

These discussions have drawn in many new actors and helped to broaden and deepen the debate on these issues. At the same time, the dramatic decrease in the cost of antiretroviral therapy (ART) has altered the

[4] The Women's Health Advocates on Microbicides (WHAM) was a group of 12 women's health networks that collaborated between 1993 and 1997 to influence and guide the microbicide development program of the Population Council. In 1998, WHAM officially disbanded and reorganized into today's Global Campaign for Microbicides.

[5] Heise L, McGrory CE, Wood S. *Practical and Ethical Dilemmas in the Clinical Testing of Microbicides: A Report on a Symposium*. New York: International Women's Health Coalition; 1998.

[6] For an introduction to on-going ethical debates see: Weijer C, Anderson JA. The ethics wars: disputes over international research. *Hastings Center Report*. 2001; 31:18–20.

[7] HPTN Ethics Working Group. HIV Prevention Trials Networks Ethical Guidance for Research. Arlington, VA: HPTN; 2003. Available at: http://www.hptn.org/ResearchEthics/HPTN_Ethics_Guidance.htm.

BOX 1. Recommendations from the 1997 Ethics Consultation on Microbicide Trials

General Recommendations on Clinical Testing of Microbicides

- Microbicide research and development should be embedded in a larger commitment to address the full range of factors that place individuals at risk of sexually transmitted infections.
- Social science research is critical to informing the design of trials, interpreting results, and answering key questions related to formulation and product introduction.
- Clear and transparent mechanisms should determine which products get access to publicly funded trial infrastructure.
- Issues of access must be addressed now, so that any future microbicides are available to and affordable for those who need them most.

Site Selection, Participant Enrollment, and Host-Country Relations

- Trials should be multisite in both the North and the South, in order to share the burdens and benefits of research and to increase the applicability of the results to different populations.
- Ideally, the selection of trial sites should reflect a careful weighing of scientific, ethical, and political imperatives, following full consultation with host-country governments, research sponsors, and local communities and advocates.
- The principle of distributive justice demands that all reasonable efforts should be made to include sites from the United States and Europe in any global effort to evaluate the efficacy of topical microbicides.
- Investigators and trial sponsors should place more emphasis on enrolling non-sex-worker populations in microbicide efficacy trials.
- Researchers and product developers should investigate a product's safety and effect on women who are infected with HIV.
- Microbicide clinical trials, particularly their exclusion criteria, must be designed by researchers and understood by the community to protect the confidentiality of participants' HIV status.
- Research collaborations should be cognizant of the historical imbalance in power that derives from the inequalities in resources and infrastructure between individuals and institutions in the North and South.
- International investigators should respect and seek to enhance host-country regulatory mechanisms for research.

Appropriate Standards of Care

- Investigators have an ethical responsibility to actively and conscientiously encourage all trial participants to use condoms in addition to the test product (or placebo) during each act of intercourse.
- To minimize real or perceived conflicts of interest, investigators should consider partnering with other entities to conduct a trial's risk reduction intervention.

- Investigators should either provide services to treat sexually transmitted infections discovered during the trial or arrange to refer participants for treatment.
- Community consultation and social science research can and should help to determine what services and interventions are appropriate as part of a trial within each local context.
- Investigators should establish and maintain formal relationships with NGOs and other sources of AIDS–related health care in the community.
- Studies should be prepared to provide HIV counseling and referral for HIV positive individuals.
- Wherever possible, trial sponsors and investigators should strengthen local health and laboratory resources rather than establish services that will "disappear" once the trial is complete.
- Investigators must develop clear policies for handling women who become pregnant during the trial.

Informed Consent

- International guidelines for the ethical conduct of research require a thorough and meaningful informed consent process to ensure that each individual's participation is voluntary. Informed consent is a process, not simply the act of signing a form.
- Study organizers must present the information in a language and manner that potential participants can fully understand.
- Researchers must provide potential trial participants with all relevant information necessary for making a decision.
- Each individual's decision must be fully voluntary, without undue influence or implicitly coercive incentives.
- Trial protocols should include formal mechanisms to remind participants that they can withdraw at any time.
- Ideally, each trial should have an independent community advocate to receive complaints, resolve concerns, and answer questions.
- Investigators should not substitute community or household consent for explicit consent by the woman who will participate in the trial.
- Investigators should think carefully before requiring the consent of the male partners of women participating in Phase 1 and 2 safety trials. Partner consent should not be sought in Phase 3 efficacy trials.

Maximizing Community Involvement

- Genuine community involvement is essential for ethical, scientifically sound research.
- Research agencies involved in developing clinical trial infrastructure should be committed to community consultation at all sites. They should look to social scientists and advocates to help carry this out appropriately and effectively.
- Trial sponsors should hold public forums—at both local and national levels—to discuss the ethical, scientific, and social issues accompanying trials.
- Consultation on trial implementation and ethics should include input from individuals who share the characteristics—class, race, gender—of the study participants.

(The full report is available from: *http://www.global-campaign.org/researchethics.htm)*

discourse on provision of ART to trial participants and to their communities. When WHAM held its first ethics consultation the issue of access to ART was not even on the agenda. Finally, with the possibility of a second generation of microbicides on the horizon, a completely new range of ethical problems will need to be addressed. As one of the Consultation participants observed, "The ground has been moving under our feet for the last five years."

The Global Campaign for Microbicides organized this meeting in hope of creating a "roadmap for deliberation" over the roughest spots of the present and future ethical terrain. This report summarizes some of the most significant presentations and discussions. It is intended not only to capture the richness of ideas but also to bring new tools and insights to those who will grapple with the ethical as well as scientific challenge of bringing microbicides to life.