



OUR CURRENT MICROBICIDE TRIALS: LESSONS LEARNED AND TO BE LEARNED

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The era of large trials of second-generation microbicide products is upon us. Several late-stage trials testing the efficacy of microbicides to prevent HIV infection have begun within the past two years. With their implementation, complex design and operational issues have emerged that exceed the traditional clinical trial challenges of recruiting participants and maintaining protocol adherence. They also extend beyond vaginal microbicides to relevance for other HIV prevention technologies.

Recent meetings have convened investigators from various organizations to examine these issues and share ideas about strategies for overcoming them.^{1,2,3,4} This paper is a first attempt to lay out the most difficult of these challenges, together with solutions either implemented or suggested to confront them so that study power and validity are not compromised. Our intent is to spur a dialogue that will lead to better approaches to testing the next generations of this highly innovative technology for which there is so much promise but only limited instructional precedent.

Lower Than Estimated HIV Incidence

The Family Health International (FHI) Phase 3 trial of Savvy™ (C31G) in Ghana was recently halted by the study's Data Safety Monitoring Board due to concerns that the unexpectedly low HIV incidence found in the enrolled population meant that the study would be unable to determine whether or not the product could prevent HIV infection. Lower-than-estimated HIV incidence has been an increasing problem, not just for microbicide trials but for evaluations of other approaches to HIV prevention such as HPTN 037, an evaluation of the efficacy of network-oriented peer education interventions among injection drug users. Discrepancies between actual and expected incidence are critical for prevention trials because it is expected

¹ Quick/Clinical Trials Working Group meeting. Chapel Hill, North Carolina, 16 November 2005.

² Family Health International Pregnancy meeting. Chapel Hill, North Carolina, 17 November 2005.

³ Alliance for Microbicide Development. Meeting #9. Washington, DC, 27-28 March 2006.

⁴ Bill and Melinda Gates Foundation. Meeting of Principal Investigators. Seattle, Washington, 6-7 December 2005.

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incidence that is used to determine sample size and that constitutes the baseline against which the success of a given prevention strategy is projected.

Changing disease patterns and a greater-than-expected effect from ethically necessary trial risk reduction procedures, can both contribute to a lower-than-presumed incidence. For example, analysis of FHI results from West Africa showed that prevalence-to-incidence ratios depended on the phase of the HIV epidemic.⁵ And while the HIV screening prevalence in a recent Cameroon oral tenofovir (TDF) study (2004) was slightly higher than that seen in a previous Cameroon N-9 film study (1996), the actual incidence had dropped to almost half in the interval between the two studies.

To address this issue, recruitment strategies are being modified to increase the likelihood of targeting high-risk populations where incidence is likely to be higher than it is in the general population. Since younger women are often at the highest risk for new HIV infection,⁶ current efficacy trials are focusing on recruiting younger participants. Trial groups and sponsors are also working together to explore the use of new assays and surveillance techniques to better estimate HIV incidence

during screening and/or through pilot studies, in order to arrive at estimates of HIV incidence that are as accurate as possible.

Measuring Product Use

Calculations performed by FHI statisticians demonstrate the importance of high product adherence relative to HIV incidence in a prevention study. Assuming a trial designed to have 85% power to detect 40% effectiveness, if the incidence rate observed in the study proves to be half of what was planned (e.g., 70 infections are observed rather than the 140 infections expected), the power of the study is still approximately 60%. In contrast, however, if the incidence rate is as expected (i.e., 140 events are observed), but product adherence is low (e.g., 50% instead of an expectation of 80% compliance), the study power drops from 85% to 45%.⁷

In most of the current microbicide studies, a trial participant's use of product can only be assessed by self-report, which is generally considered undependable. Behavioral data about product use and sexual activity that are generated in the context of face-to-face interviews, especially after extensive counseling on the importance of consistent product use, are also considered unreliable. However,

self-administered questionnaires are inappropriate in communities with low literacy and therefore cannot take the place of such interviews. Pharmacokinetic assessment of product adherence in vaginal microbicide trials is difficult because, typically, products are not absorbed and therefore not readily susceptible to such assessment.

By way of remedy for this particular set of challenges, novel technologies have been developed to improve estimates of product use and protocol adherence. Sensitive behavior can, for instance, be assessed using Audio Computer-Assisted Self-Interviewing (ACASI) approaches that allow even illiterate study participants to answer questions simply and privately, which enhances the likelihood of data validity.^{8,9}

Another approach has been undertaken in the context of the Population Council (PC) Phase 3 trial of Carraguard®, which is using a biological adherence marker to assess product use.¹⁰ Trial participants are asked to return all used and unused applicators at each study visit. Each opened applicator is then tested with a sensitive and specific spray assay which, through characteristic patterns, can reveal which applicators have been inserted vaginally. The advantages of this procedure are

⁵ Family Health International. Unpublished data, 23 March 2006.

⁶ UNAIDS. 2004 report on the global HIV/AIDS epidemic: 4th global report, 2004.

⁷ Taylor D. Personal communication, 2006.

⁸ Rogers SM, Willis G, Al-Tayyib A, et al. Audio computer assisted interviewing to measure HIV risk behaviors in a clinic population. *Sex Trans Infect* 81(6): 501-7, 2005.

⁹ Hewett PC, Mensch BS, Erulkar AS. Consistency in the reporting of sexual behavior by adolescent girls in Kenya: a comparison of interviewing methods. *Sex Trans Infect* 80 Suppl 2: ii43-8, 2004.

¹⁰ Wallace A, Thorn M, Maguire R, et al. Assay for establishing whether microbicide applicators have been exposed to the vagina. *Sex Transm Dis* (8): 465-8, 2004.

two-fold: tracking returned applicators can help identify gel-sharing so that counseling can be tailored to emphasize the importance of using one's own gel. The spray assay can also help identify women who are feigning use (those who return open applicators that have never been vaginally inserted), at the same time that it can identify women who are reliable users, thereby enabling a separate (per-protocol) analysis on a subset of adherent women. Further, the clinic flow has been modified at trial sites so that participants return their applicators to counselors rather than to intake staff, but this modification has not yet been assessed to determine whether it does, in fact, fulfill its objective, which is to enhance participant adherence to product use by increasing accountability.

High Pregnancy Rates Leading to Interruption of Product Use

The likelihood of pregnancy in reproductive-age women having multiple sexual encounters (e.g., 20 acts per month) is quite high even with relatively high condom use. Using Wilcox's estimates of the probability of pregnancy resulting after one or more unprotected acts for each day of the menstrual cycle (and assuming 12 x 30 day cycles per year), we expect that if women have two days with unprotected acts on average during each cycle (e.g., 90% condom use, 20 acts per cycle, and no other contraceptive method use), the 12-month cumulative pregnancy probability would be 51%.¹¹

The non-clinical studies—specifically, Segment 3 toxicology—that are required to allow pregnant women to use an Investigational New Drug have typically not been completed before Phase 3 begins. Thus, all current microbicide efficacy protocols—as well as the trial of acyclovir to determine if HSV treatment reduces HIV transmission—require product interruption once pregnancy is detected, at least until evidence of non-pregnancy is produced (e.g., a negative pregnancy test). While all trials include in their eligibility criteria a requirement that participants pledge their intention to not become pregnant during study participation, our current trials have found pregnancy rates as high as 70%, despite all vows and best intentions.

The implications of high pregnancy rates are major. Excessive product interruption can compromise study power, complicate risk assessment and, possibly, bias analysis. The ethical, statistical, and behavioral issues around pregnancy in microbicide studies have been discussed in depth and will be published² but there is, so far, no obvious consensus around how this dilemma is to be confronted in any systematic way. Some ongoing trials have begun offering contraceptives on site to reduce pregnancy rates, while others refer for these services because of operational limitations, concerns about coercion, and lack of sustainability in countries where contraception is not otherwise readily available. The issue of product interruption due to pregnancy could be moot if the

necessary and sufficient preclinical studies were to be completed prior to the launch of late-stage trials, so that women who become pregnant might continue product use until scheduled study completion. This possibility remains to be further explored and may not be applicable to all product classes.

Evolution in Prevention Standard of Care (SOC)

... for study participants

As part of any HIV prevention trial, all study participants are provided with the current standard of prevention care. Most prevention trials include safer sex counseling, provision of male condoms, and treatment for sexually transmitted infections (STIs) (although the frequency of STI testing may vary between studies), and female condoms have recently been added to the prevention SOC in some studies. However, the field is dynamic and other approaches such as male circumcision may soon become accepted as possible prevention practices. Researchers need to continue to stay abreast of the current literature to address both evolving scientific practices and ethical imperatives.

... for screen failures and trial seroconverters

During recruitment for a microbicide or other HIV prevention trial, hundreds of women may test HIV-positive at screening, be ineligible for the trial, and are consequently referred into the local system.

¹¹ Dominik R. Personal communication, 2005.

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The issue of what level of care to provide these women, as well as those who become infected during a prevention study, has been at the forefront of global discussions of research ethics and multiple local, regional, and global meetings over the past year. Since the launch of the current microbicide efficacy studies, resources for HIV care and treatment in countries with generalized HIV epidemics have increased greatly. In some places, the available SOC in the community may have even surpassed the IRB-determined ethical SOC described in a particular protocol. At the same time, it is still the case that many trial communities lack adequate services.

Despite funding limitations, current studies have managed to implement a range of strategies for helping women who test HIV-positive, at both the trial and community levels. For women who test HIV-positive at screening and those who seroconvert within the trial, services may include partner counseling and/or testing, referrals to private physicians for WHO staging, accompaniment of participants to the referral clinic for the first visit, and immediate referral into seroconverter studies, which often enable access to state-of-the-art care while advancing scientific knowledge. Referral clinics are often offered support in the form of financial and/or human resources, which may include full- and part-time positions;

some HPTN 035 sites even provide staff on rotation from the trial clinic itself. The Carraguard® trial is conducting formal evaluations to assess barriers to referral use and identify specific areas of need in referral clinics. Researchers across all the organizations presently sponsoring trials recommend that established arrangements with local clinics be supported by written documents.

More challenging is the matter of pledging funding for provision of anti-retrovirals (ARVs) for any set amount of time. This has a great deal to do with the feasibility and accountability difficulties associated with establishing an insurance fund for individuals who have recently seroconverted and may well not need ARVs for an unknown number of years. This does not mean that nothing can be done: women who seroconvert during a trial often need psychosocial support before they need medical care. At one Population Council site, a support group for HIV-positive women was established, with the goal of being sustainable beyond the conclusion of the trial. For the time being, until guidance is clearer and there is some kind of consensus around the range of what is feasible and ethical, researchers must persist in advocating for the availability of care and monitoring the quality of care that HIV-positive study participants receive.

Costs/Complexity of Focusing on “Multiple Communities”

The microbicide field has made substantial efforts to involve local communities in its work. As a rule, most trial sites have a community advisory group or other mechanism designed to facilitate communication between researchers and those living in the site catchment areas. For a variety of reasons, including the instantaneous and global reach of the Internet, the gravity of HIV, and the history of research abuses in developing countries, communication with civil society through the media has become an essential dimension of prevention science. The negative media attention surrounding the trials of pre-exposure prophylaxis (PREP) of oral tenofovir^{12,13,14} highlighted the urgency of soliciting input to trial design and implementation from a broader, more heterogeneous range of “communities” and stakeholders than previously contemplated. Such engagement must go beyond potential participants and the immediate trial site communities to academics, activists, advocates, policy-makers, politicians, providers, and the local, national, and global media that act so critically at the interface of science, practice, and ethics.¹⁵

Following on the tenofovir experience, current trials have deepened and enlarged their focus on media training and

¹² Page-Schafer K, Saphon V, Sun LP, et al. HIV prevention research in a resource-limited setting: the experience of planning a trial in Cambodia. *Lancet* 366(9495): 1499-503, 2005.

¹³ Grant RM, Buchbinder S, Cates W, et al. Promote HIV chemoprophylaxis research, don't prevent it. *Science* 309(5744): 2170-1, 2005.

¹⁴ Mills E, Rachlis B, Wu P, et al. Media reporting of tenofovir trials in Cambodia and Cameroon. *BMC Int Health Hum Rights* 5: 6, 2005.

¹⁵ UNAIDS. Creating effective partnerships for HIV prevention trials: report of a UNAIDS Consultation. *AIDS* 20(6): W1-11, 2006.

preparedness, ensuring that both central and local teams are equipped with standard and accurate messages, and a communication/crisis plan. Although the costs and time entailed in these efforts are not trivial, the investment appears to be well worthwhile, particularly given the costs of aborting or not implementing a trial of a promising technology. The examples of recent, successful communications in connection with closure of the Savvy™ trial in Ghana and the responses to a misleading newspaper article about the Carraguard® trial in South Africa, demonstrate what trained, diligent staff can achieve when communicating globally with multiple stakeholders. The Microbicide Media Initiative (MMI), spearheaded by the Global Campaign for Microbicides, is a group of microbicide stakeholders that includes researchers and communication specialists in active ongoing communication with one another, across the microbicide field, and between stakeholders and the media. The central notions are that researchers must continuously build their own “community literacy”—just as communities need greater “research literacy”—in order to improve support for trials, at their inception and once under way.

Variability in Political Support for Prevention Trials

Research within any country depends on the support of political leadership. In past years, research teams have been forced to abandon well-developed research

infrastructures because of political violence (i.e., Congo, Côte d'Ivoire, Dominican Republic, Haiti, Rwanda). Even democratic changes of government (i.e., Cambodia, Cameroon, Malawi) and shifts in national research priorities can result in study disruptions and even closure. Such challenges cannot always be anticipated and there are no categorical solutions for addressing them once they arise, so that researchers are left with the imperative for obtaining clear national and local governmental support for projects at the outset and a state of constant alert to changing political situations that could undermine their efforts.

Effort/Costs of Registration-level Compliance in Resource-poor Settings

Since the eventual goal of efficacy trials is regulatory approval, protocols must be implemented according to registration standards. Achieving this goal even at experienced sites requires extensive training, supervision, monitoring, and support to ensure that the key elements of voluntary informed consent, participant safety, and data integrity are intact. In developing countries, getting to this level of study quality with limited infrastructure can be extremely taxing.

Nonetheless, the Institute of Medicine's recent vote of confidence in HIVNET 012,¹⁶ reinforced by four external audits, shows that registration-level study conduct can be achieved in resource-poor settings.

That said, operational difficulties in such sites as Nigeria (oral tenofovir) and Malawi (HIVNET 024) have demonstrated that constant vigilance is needed to assure compliance with Good Clinical Practice (GCP) standards. This requires sizeable investment in research infrastructure but, fortunately, scaling up infrastructure and training staff to adhere to GCP standards help build a foundation of technical capacity at trial sites.

Assurance of Laboratory Quality

Accurate laboratory data are the *sine qua non* for microbicide studies since they do (or do not) determine both safety and efficacy endpoints. Difficulty in establishing laboratory quality has been among the most important factors contributing to delays in site initiation and difficulties during implementation. Even when independent or reference laboratories in university settings have supported trials, problems have been identified during monitoring or auditing visits—problems that have resulted in trial shutdown (Nigeria, oral tenofovir) or censorship of data (South Africa, HPTN 023). To prevent delays and interruptions of future trials, the solution is the establishment of guidelines for selecting and training the best laboratories and identifying measurement problems as they occur, buttressed with visits to labs by optimally qualified laboratory scientists to verify the raw data and assay results, monitor procedures, and inspect equipment to ensure continued proficiency.

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¹⁶ Institute of Medicine. Board on Population Health and Public Health Practice. Review of the HIVNET 012 perinatal HIV prevention study. Washington, DC. National Academies Press, 2005.

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Mediocre Retention and Poor Adherence to Follow-up Schedules

As a rule, the level of loss-to-follow-up in a trial should be lower than the rate of study endpoints. Unfortunately, loss-to-follow-up in many prevention studies has been 3- to 10-fold higher than the occurrence of study endpoints, thereby threatening study validity.¹⁷ Retention is especially challenging in developing country settings, where participants often lack phones, formal addresses, and reliable transport, and have considerable family obligations as well. Even when participants are retained throughout a trial, they often miss one or more scheduled visits. Missed visits complicate product adherence, since most protocols provide only enough supplies for the interval between visits, and as the interval between observation periods increases, the precision of per-protocol assessment, which is dependent on time of infection, decreases.

The programmatic implication here is that a balance has to be found between providing adequate amounts of product to cover intervals between missed visits

and not providing excessive amounts of product so that storage becomes problematic. This is already an area of considerable innovation. Creative approaches have been developed to optimize retention and maximize adherence to visit schedules, and Global Positioning Systems (GPS), enhanced outreach, and satellite clinics are being utilized with encouraging results. As the current trials conclude, an evaluation of visit schedules will be conducted to determine their impact on retention. Researchers need to build on what seem to be rewarding approaches and continue to engage trial participants and communities to determine the optimal protocols for various future study populations.

In Conclusion

As in all HIV prevention trials, microbicide trials and the issues they generate are constantly evolving under influences from the ever-changing worlds of science, ethics, and politics. Unlike the products now in efficacy trials, the next generations of candidate microbicides are likely to include

products containing anti-retroviral components that bring new concerns about their potential for development of drug resistance, about which there will be many lessons to be learned.

The present environment of open communication across different studies among trials, trialists and, it is hoped, trial populations, can only enhance, perhaps even accelerate further progress. Initiatives such as the MMI and Quick/Clinical Trials Working Group can do much to extract such learning and share it to a variety of constructive, collaborative ends. The variability among the products now in efficacy testing, the growth in the number of trial sites, and the diversity of the study designs have already enabled identification of challenges and possible solutions addressed, if only preliminarily, in this paper. A range of innovative research tools and guidelines will increase our ability to identify an efficacious microbicide, just as a range of different prevention options will increase a woman's power to protect herself from HIV infection.

TABLE 1. CURRENT MICROBICIDE TRIALS: CHALLENGES ENCOUNTERED AND ISSUES FOR CONSIDERATION

Lower than estimated HIV incidence	Variability in political support for prevention trials
Measurement of product use	Effort/costs of registration-level compliance in resource-poor settings
High pregnancy rates leading to interruption of product use	Assurance of laboratory quality
Evolution in prevention standard of care	Retention and adherence to follow-up schedules
Costs/complexity of focusing on multiple communities	

¹⁷ Schulz KF, Grimes DA. Sample size slippages in randomized trials: exclusions and the lost and wayward. *Lancet* 359(9308): 781-5, 2002.