THE
MICROBICIDE QUARTERLY

ALLIANCE FOR MICROBICIDE DEVELOPMENT

APRIL — JUNE 2008 *v.*6 *no.*2 WWW.MICROBICIDE.ORG

CONTENTS

CHANGING NEEDS AND EXPECTATIONS IN MICROBICIDE DEVELOPMENT: A SUMMARY REPORT FROM THE 11TH ANNUAL MEETING OF THE ALLIANCE FOR MICROBICIDE DEVELOPMENT

23-24 April 2008 • Arlington, Virginia, USA

Sam Avrett and Polly F. Harrison

Background

With a number of large clinical studies recently failing to show product effectiveness, the microbicide research and development effort finds itself at a crossroads. The extent of scientific unknowns is sobering, the challenges plentiful and profound.

Not all is doom and gloom: microbicide development continues to offer promise with new lines of inquiry, a preclinical pipeline that is thin but not empty, and 14 products in clinical testing. The potential of microbicides for reducing HIV transmission has been increasingly accepted over the last 10 years, policy and financial support have grown accordingly, and the pool of engaged scientists has broadened and deepened. It is also the case that unexpected results and studies showing no effect are an integral part of drug development. A 20% success rate is regularly cited by the pharmaceutical industry and while this proportion varies by drug class and analytical approach, there is solid consensus that drug development is inherently risky, complex, unpredictable, time-consuming, and costly.

While a pharmaceutical failure rate of 20 to 1 is what reality looks like, there are other realities in the host countries where most HIV prevention trials are taking place and there is also a constellation of ever-changing realities around the entire topic of HIV/AIDS. The optimism of the early days of microbicide development, while motivated by the pressures of the pandemic and mounting evidence for its impact on women, also generated expectations that were simply unrealizable.

For the relatively new science of microbicides, the lack of rapidly-gained positive results has been an occasion for reflection. Researchers, companies, and community advocates are recalibrating previous hopes and optimism, with some calling for dramatic paradigm shifts and others calling for adjusted perspectives in light of the longer-term nature of the research and development effort. It had become clear that

Continued on p.02

CHANGING NEEDS AND EXPECTATIONS IN MICROBICIDE DEVELOPMENT *(Continued from p.01)*

the microbicide field was primed for a re-thinking of strategies and systems. The forthcoming meeting of the Alliance for Microbicide Development[1] seemed a timely opportunity for taking that on and discussing what a departure from "business as usual" might look like.

Among the implications of the events of these past months, those that had surfaced as of greatest concern and urgency as the Alliance meeting was being planned were the following:

- The possibility that trial disappointments might dampen funder interest, scientific engagement, advocates' enthusiasm, and host-country support, thereby becoming a substantial impediment to progress;
- The fact that the HIV vaccine field is returning to basic research to solve questions emerging from its trial failures, so raising the question as to whether, and to what extent, the microbicide field might need to do similarly;
- Questions about the adequacy of pre- and early-clinical testing underpinning investments in first-generation trials as possibly compromising confidence and the proper advancement of new microbicide candidates; and
- Decision-making about which candidates to advance through the pipeline persistently hampered by lack of adequate information, common systems, agreed-on criteria, and challenges to peer review.

These implications and concerns provided the background that shaped the meeting reported upon here.

Meeting Summary

In April 2008, the Alliance marked the anniversary of its founding a decade earlier with its 11th Annual Meeting. More than 160 participants gathered for a retrospective look at the implications of recent research results, and a prospective look at what would be needed to recalibrate the field. The meeting comprised 16 presentations on data from current research, progress, efforts to learn from recent events, and evolving issues, including a review of both the recent Institute of Medicine (IOM) report[2] on clinical research and the February *Microbicides 2008* conference in Delhi, India.

The themes that emerged across virtually all presentations and discussions showed that scientists are already reassessing and recalibrating strategies for microbicide research and development. Expectations are changing, in some cases substantially. The following six themes reflect a shift in the field toward more intensive preclinical research; increasingly subtle evaluations of safety; longer and larger clinical studies and product development timelines; and a concerted effort to tackle cross-cutting policy and program constraints to more innovative science, especially in the zone of translational science.

1. Intensifying basic research, including harmonized use of biosafety indicators

The biological dynamics and factors in HIV infection across the genital epithelium are increasingly defined and understood. New preclinical models—including mouse, non-human primate, and *ex vivo* human tissue epithelial barriers—are now available for researchers to examine the processes of HIV infection and the ways that candidate microbicides might interrupt or augment those processes. Yet more is needed to expand basic scientific knowledge and capacity, including such basic questions as those around the roles of cell-free and cell-associated virus in HIV transmission. A major objective of this work is the establishment of a harmonized minimum set of safety-related assays, models, and endpoints.

2. Designing animal studies and Phase 1 studies to better measure safety and product potential

Now entering into animal testing and Phase 1 clinical trials is a "new generation" of microbicides, dominated by ARV-derived candidates, importantly including reverse transcriptase inhibitor (RTI) compounds in several formulations and delivery systems. The animal and early clinical studies of this candidate class must be larger, longer, and more consistent and comparable. There may also need to be more of them, so that decisions about late-stage trials, including not only Phase

[1] The annual Alliance meeting has regularly convened all major constituencies in the microbicide field to exchange information, discuss critical and emerging issues, explore collaborations, and ultimately accelerate common research, development, and advocacy goals.

[2] Institute of Medicine. 2008. *Methodological Challenges in Biomedical HIV Prevention Trials.* Washington, DC: The National Academies Press.

3 effectiveness but Phase 2 "run-in" trials, can be made efficiently and rationally. For animal studies to better detect potential safety issues, researchers are recommending greater numbers, increased duration of exposure, and systematic measurement and comparison of safety-related endpoints. For Phase 1 studies, researchers are suggesting longer product exposures, larger numbers of participants, and possible recruitment of participants whose sexual activity (yet not exposure) is similar to the eventual at-risk population. With respect to procedures both for animal model testing and Phase 1 studies, researchers are recommending consistent routine collection and analysis of samples to monitor epithelial integrity, bioflora, pH, innate immunity, and other possible indicators of immunological or physical vulnerability. Ultimately, all of these recommendations reflect a concern throughout the field for adequate comparable data and agreed-upon criteria for advancing microbicide concepts through the development pipeline.

3. Incorporating data from current effectiveness trials into design of future clinical studies

Many in the microbicide field—and those monitoring its progress and prospects—are awaiting with keen interest the results from retrospective analyses of data and samples from the completed Phase 3 trials. The hope is that these analyses will provide additional insights about the safety of the tested products, including possible epithelial alteration or disruption, microflora disturbance, and/or effects on HIV binding to antigen-presenting cells. Researchers are also reporting innovative use of clinical trial samples for *ex vivo* safety and challenge experiments, recent rectal safety research that demonstrates the feasibility of routine Phase 1 rectal safety studies for all candidate microbicides, and new toxicity tables for both rectal and vaginal research.

4. Sustaining capacity for large-scale clinical trials of increasing complexity

There is strong recognition across the field that ongoing large-scale clinical research requires not just major investment but major *sustained* investment. All recently-completed Phase 3 trials encountered both successes and challenges in trial design, site preparation, population selection, and participant adherence to protocols. More than 45 clinical research sites now engaged in HIV prevention research have gained valuable experience in securing and retaining human capacity and physical infrastructure, managing regulatory oversight, recruiting and retaining participants, implementing behavioral risk-reduction interventions, anticipating HIV incidence, and engaging with community stakeholders. In the long term, microbicide development will have to draw on this clinical research capacity. And more will be needed, since researchers are beginning to conclude that future clinical trials should have greater power to detect modest and nuanced effects related to safety and effectiveness. This, in turn, may imply larger trial populations and more sophisticated, exacting procedures for assuring trial quality. Researchers are also exploring alternatives to traditional superiority trial designs in order to increase trial power to detect safety and efficacy and simultaneously incorporate evaluation of participant behaviors and product use. As the new generation of candidate microbicides moves toward effectiveness trials, site capacity for global clinical research must be ready. Yet, at the same time, for a range of reasons, that capacity cannot languish unused in the interim; this is a challenge for the HIV prevention field as a whole.

5. Modifying designs of large-scale clinical trials to accommodate high rates of pregnancy and incorporate key aspects of behavior, product use, and adherence

There is growing consensus among those working in the wider HIV prevention field that "alternative" approaches to large-scale clinical trial designs need to be explored. High rates of pregnancy have led researchers to discontinue ("censor") female participants becoming pregnant in clinical trials, which can result in decreased study power and increased bias. However, the seemingly obvious solution, contraception, remains a challenging option from several perspectives: current contraceptive methods and their

Continued on p.04

CHANGING NEEDS AND EXPECTATIONS IN MICROBICIDE DEVELOPMENT *(Continued from p.03)*

availability, protocols for counseling about their use, and actual use. Investigators can take several steps to address this sizeable issue. Information about women's fertility intentions, likely contraceptive use, and putative pregnancy rates can be factored into trial designs, importantly sample size. Based on what is known about benefits and risks of individual products (tenofovir, for example), it is possible that there are cases when it is safe for women who become pregnant during a trial to continue using the test product. Behavioral considerations such as problems with adherence to study product have also contributed to the search for alternative study designs. Accurate assessment of microbicide effectiveness will ultimately depend not only on the degree to which the product is used, but also understanding the reasons for variation in use and frequency of risk behavior. There is accumulating consensus that reliance on self-reports, unless confirmed through other qualitative or quantitative approaches, may weaken study power and validity to the point of futility; thus, use of multiple methods to measure adherence is encouraged and recommended.

6. Communicating and coordinating across (and outside) the microbicide field

The meeting as a whole reflected a good level of common substantive understanding across the microbicide field around a number of critical issues. Perhaps most important among those were approaches to analysis of Phase 3 data, urgency and challenges in the search for surrogate markers, rectal microbicide research, clinical site capacity and maintenance, and civil society engagement.

Yet, while many are ready for continued integration and communication across microbicide and HIV prevention technologies more broadly, there is significant divergence in the ways the microbicide effort is perceived by civil society, basic scientists, clinical researchers, product developers, policy-makers, and donors. The growth of the microbicide effort has also generated sub-specialties at the same time that some technologies—for example, oral and topical HIV prevention—present significant overlaps; thus, there are dilemmas around the extent to which "silos" of knowledge and expertise should be bridged without sacrificing productive autonomy and focus. Participants recommended new approaches to coordinating and communicating across constituencies to ensure common information, understanding, and engagement, and to better reflect the gradual and interlinked nature of HIV prevention research to come. Some approaches suggested were more agile and open publishing and data-sharing, new consultative committees to advise on optimal allocation of resources and scientific effort, and organization of the *Microbicides 2010* conference to encourage more integrated discussion. The foundation for these themes was laid by the meeting panels and presentations. Those are summarized below and are available at: *http://www.microbicide.org/cs/alliance_meeting_11.*

Analysis of the Institute of Medicine Report *Methodological Challenges in Biomedical HIV Prevention Trials*

Introduction and overview – Alicia Gable, Report Study Director and Co-editor

Developed under the leadership of the corresponding committee of the IOM Board on Global Health, this 270-page report reviews and analyzes methodological challenges to late-stage non-vaccine biomedical HIV prevention trials, focusing specifically on microbicide and pre-exposure prophylaxis (PrEP) trials, and makes a series of recommendations for addressing them. *[NOTE: A free, downloadable Executive Summary of this report is accessible at http://www.nap.edu/catalog/12056.html, or on the Alliance website at http://www.microbicide.org/cs/directors_corner.]*

Basic design issues – Steve Lagakos, Committee Chair and Report Co-editor

Clinical studies to determine the potential effectiveness of candidate microbicides must be designed to detect and elucidate modest intervention effects, their links with participant behaviors, and a range of data related to safety. Studies can be

designed, funded, and implemented with enough power to anticipate partial product effectiveness combined with realistic rates of participant accrual and retention; HIV incidence; and product use, adherence, and discontinuation. Research designs can also incorporate randomized comparisons of behavioral risk-reduction interventions. *[See* Report *Chapters 2, 3, 10.]*

Site preparation – Laura Guay, Committee Member

The field of HIV prevention research has accumulated valuable experience in establishing clinical research sites, and much is known about how to secure and retain human capacity, physical infrastructure, and capacity for regulatory oversight, and about ways to conduct pre-trial research and enhance community engagement. The quality and timeliness of future clinical research depends on sustained investment in all these elements and collaboration in site maintenance and support. *[See* Report *Chapters 6, 7, 8.]*

Pregnancy – Sally Hodder, Committee Member

The history of exclusion of pregnant women in clinical trials dates to the 1970s when the US FDA specified conditions against participation of premenopausal women in clinical trials. Conventionally, "product" use in pregnant women is not permitted. Further exploration of several aspects of this issue are needed, including: 1) impact on the study and degree of necessity of discontinuation of the product by pregnant women, and 2) whether or not contraception should always be required for participation in a clinical trial. Preclinical testing for reproductive toxicity, pharmacokinetics, and carcinogenesis is needed to generate safety data in pregnancy. The creation of registries of women becoming pregnant during trials is encouraged as is 1) the accurate estimation of pregnancy rates, 2) incorporation of those rates into sample size calculations, and 3) consistent monitoring of rates along with adjustments to trial size and duration where appropriate. *[See* Report *Chapter 4.]*

Adherence – Els Goetghebeur, Committee Member

Effectiveness evaluation of coitally-dependent microbicides will require either high rates of adherence or controls for variability in adherence and risk behaviors. Ultimate effectiveness of coitally-dependent microbicides will also be heavily determined by patterns of product use and sexual risk. (This is not as much the case for non-coitally dependent products, where the evaluation of the prevention intervention becomes similar to PrEP.) Unfortunately, self-reports do not accurately capture true patterns and rates of sexual risk, product use, or protocol persistence and adherence. The implication of this may be weaker study power and validity of both safety and effectiveness. Adherence can be defined as the percent of sexual contacts covered by microbicide (against baseline of number of all contacts); the percent of microbicide doses used; correct product timing, quantity, and use; and the timing of non-adherence events (e.g., holiday, intermittent or scattered adherence, or adherent-then-discontinued). Researchers should use multiple methods to measure adherence. Methods and indicators for predicting the patterns, variability, and influence of sexual risk behaviors, behavioral interventions, and product use and adherence should be deliberately compared and validated, and this should be used in the design of study sizes and protocols, in site preparation and study enrollment criteria, and also in analysis of Phase 3 data. A "tool kit" is needed to help researchers address adherence, including individualized, multi-component, dynamic, and adaptive adherence regimens and strategies. To retrospectively analyze adherence, approaches include stratified analysis, causal models and randomized-based analysis, and matched case-control analysis. *[See* Report *Chapter 5.]*

Preclinical and Early Clinical Studies

Overview: What have we learned? – John Kaldor

A systematic review of 42 Phase 1 microbicide studies concluded that, for a number of reasons, both clinical and animal studies as now conceptualized and implemented cannot detect significant differences in characteristics known to influence HIV risk, e.g., mucosal disruption, pH levels, and presence of

Continued on p.06

CHANGING NEEDS AND EXPECTATIONS IN MICROBICIDE DEVELOPMENT *(Continued from p.05)*

bacterial vaginosis. Future studies would be most productively designed and powered were they to incorporate longer participant exposure to product, larger numbers of participants, and a consistent array of agreed-upon safety endpoints. Additional review of 26 animal studies came to similar conclusions, i.e., larger numbers of animal subjects and increased duration of exposure, in order to systematically measure and compare safety-related endpoints. A concluding recommendation was that there should be agreed-upon ways of reporting the results of safety trials and a requirement to publish, regardless of outcome.

The perfect Phase 1 trial – Betsy Herold

Phase 1 safety studies of microbicides can be improved in a number of ways to provide clearer insights into safety, efficacy, and adherence. Critical attributes of improved studies would be longer product exposures and recruitment of participants with sexual activity/exposure similar to that of the intended target population. Other recommended improvements would be routine collection and analysis of biopsies and either cytobrush or lavage (CVL) samples to monitor epithelial integrity, bioflora, pH, innate immunity, and other possible indicators of immunological or physical vulnerability. Early rectal and post-coital studies should also be added, since they are critical to assessing the impact of semen on product anti-viral activity.

The *Microbicides 2008* Conference: Themes, Messages, and Directions[3]

Basic Science (Track A) – Gustavo Doncel

More is now understood about biological dynamics and factors in HIV infection across the genital epithelium. New preclinical models—including mouse, non-human primate, and *ex vivo* human tissue epithelial barriers—are now available for microbicide evaluation. These tools and new data are allowing steady and incremental advances in product development, including a new generation of reverse transcriptase inhibitor (RTI) compounds in a range of formulations and delivery systems. More research is especially needed around formulations and delivery systems with respect to various aspects of feasibility. New understanding of the interstitial movement of HIV through the cervico-vaginal epithelium raises new questions and challenges about transmission and the role of mucus and inflammation in HIV transmission processes that are of high potential relevance.

Clinical Science (Track B) – Anne Coletti

Recent rectal safety research has demonstrated the feasibility of routine Phase 1 rectal safety studies for all candidate microbicides, and produced compelling blinded safety data for UC-781. New toxicity tables are now available for both rectal and vaginal research, and recent work has demonstrated the stability of cytokine assays and innovative use of clinical trial samples for *ex vivo* challenge. In Phase 2 studies, tenofovir gel has generated no safety signals or concerns, and high reported adherence and high levels of drug detection confirm and correlate with self-reports of product use. Experience has demonstrated that Phase 3 studies can satisfy high-quality standards and that participant retention and reported product adherence can both be high. Attention is now being focused on mining data from completed Phase 3 studies to derive as much information and understanding as possible on safety-related biomarkers, product adherence, contraception and pregnancy, and risk behaviors and other predictors of HIV infection.

Social Science (Track C) – Betsy Tolley

Phase 3 microbicide studies also continue to generate data and opportunities related to behavioral and social science research. Every individual's sexual risk behaviors, response to behavioral interventions, and product use and adherence are influenced by his or her partner(s) and by social networks, communities, and cultures. As part of Phase 3 trial design, clinical researchers can develop validated quantified measures of these dyadic and social influences, and can correlate these data against other key indicators of seroincidence, product use and adherence, behavioral risk-reduction, and study retention.

Policy, Advocacy, and Community (Track D) – Kelly Blanchard

The microbicide field has become much more sophisticated in engaging with

[3] An analytical summary of this conference appears in *The Microbicide Quarterly* 6(1): 1-36, 2008.

communities, both through clinical research sites (for example, engaging communities in protocol design and participant recruitment, retention, and risk-reduction), and through broader communications and advocacy. The community of microbicide advocates has expanded and is producing analyses and recommendations to both critique and advance the microbicide effort. Increasingly, advocacy is one venue where all constituents in the microbicide effort are able to "cross tracks" to integrate findings and observations.

Plans Going Forward

The Microbicide Research Working Group (MRWG) – Robert Eisinger

The MRWG was conceived as an inter-disciplinary committee that could provide the microbicide field with sound scientific opinions and recommendations. Convened by the Office of AIDS Research (OAR) as an advisory group to the NIH, the MRWG has met twice. At its February 2008 meeting in Delhi, the Group agreed on several areas of emphasis, including the need for non-human primate research, development of standards for preclinical assays and data, new microbicide formulations and delivery methods, rectal microbicide research, and research on participant adherence. Planned activities include providing input on the *FY2010 Trans-NIH Plan for HIV-Related Research*, and participating in an annual assessment process to re-program NIH funds into high-priority research.

Profiting from Experience: Presentations by Product Developers

CONRAD – Gustavo Doncel, Henry Gabelnick

In assessing the data from the Phase 3 study of cellulose sulfate (CS), CONRAD is exploring three hypotheses to explain the results: 1) there was increased HIV binding to antigen-presenting cells, 2) there was epithelial alteration, and/or 3) there was microflora disturbance. To pursue these hypotheses, blinded samples have been sent to multiple labs for analysis. The CS study experience suggests that while preclinical and Phase 1 studies can and, in some cases, should be designed differently as new analytical tools become available, any long-term clinical effort will necessarily expect a certain number of Phase 3 studies showing no benefit. CONRAD is pursuing work on UC-781, tenofovir, other CONRAD proprietary compounds, and new delivery systems. The intention is to develop product combinations and dual-protection technologies, since combination strategies are expected to be more effective as prevention technologies. The goal is to have a new combination product ready for clinical evaluation at the end of five years. CONRAD also expects to produce validated animal models, assays, and biomarkers over that same time period, all agreed to be essential to the evolution not just of microbicides but all HIV prevention technologies.

IPM – Zeda Rosenberg, Joe Romano

IPM continues to develop a range of RTI compounds, including TMC120, dapivirine, the gp120 inhibitor DS003 (BMS 793), and maraviroc, in combination with alternative dosing regimens, formulations, and delivery methods, including gels and vaginal films, rings, and tablets. IPM has invested heavily in comparative assessments and portfolio management. Like the rest of the microbicide field, IPM has been learning from the Phase 3 results and overall experience, and has updated its thinking about preclinical and Phase 1 study designs. IPM anticipates initiating Phase 1 studies of TMC120/dapivirine gel in southern Africa by end-2008 and is planning production of a vaginal ring for Phase 3 study.

Microbicide Trials Network (MTN) – Sharon Hillier, Ian McGowan

Evolution of the MTN portfolio has been tracking learning from all the later-stage trials and has taken into explicit account lessons learned about community engagement, involvement of adolescents, the impact of pregnancy and its management, rectal safety, antiretroviral resistance and side effects, and the value and importance of collaboration with other research entities. With these lessons as background, the Network is proceeding with development and implementation of a number of studies: a safety study of VivaGel®/SPL7013, three studies related to pregnancy and microbicides, and two rectal safety studies.

Population Council – Robin Maguire

The Population Council is analyzing data from its Phase 3 study of Carraguard®

Continued on p.08

CHANGING NEEDS AND EXPECTATIONS IN MICROBICIDE DEVELOPMENT *(Continued from p.07)*

and concludes that women aged 16-17 are an absolutely critical population for microbicide effectiveness studies. It encountered high HIV incidence in this population (N=250) and found that they could be appropriately recruited and enrolled. The study also yielded somewhat discrepant data on product use and adherence, and the Council is following up to assess the correlation (or lack of correlation) among computer-mediated interviewing (ACASI), self-report of protocol compliance, applicator staining, and a PSA assay. This study and analysis should be completed by late 2008.

Coda

The Alliance meeting was a first attempt to begin digesting some of the news and events of the past year that have had—or should have—implications for microbicide research and development. We view it as a useful start. The next step is to breathe new life into the *Microbicide Development Strategy* and the subsequent *Mapping the Microbicide Effort* by carrying out a task the Alliance has been asked to undertake: production of a *"Scorecard"* that will systematically review and tally the Priority Gaps presented in the *Strategy* and the *Mapping Exercise* to evaluate progress to date and the Priority Actions implemented. This is scheduled for the first quarter of 2009 and is intended to inform the work of the Microbicide Donors Committee, the Microbicide Research Working Group, the microbicide and HIV prevention fields, and their independent and mutual directions forward.

DIALOGUES

EDITOR'S NOTE: ***We are pleased to announce the addition of a new* TMQ *feature, "Dialogues." Its goal is to foster conversation around unresolved issues in the microbicide field and other relevant disciplines. If you would like to comment, please contact Betsy Finley at bfinley@microbicide.org.***

Dry Sex and Implications for Topical Microbicide Development

Stephanie N. Tillman, Alliance for Microbicide Development

The issue

Cultural practices employed in pre-coital preparation vary widely both geographically and individually. What is generally termed "dry sex" is one such practice, researched and reported on for its possible contributions to HIV and STI infection. Through the use of diverse products or methods, women in many cultures and countries worldwide alter natural vaginal secretions prior to sex, with potential implications for the acceptability, use, and efficacy of a topical, lubricating microbicide formulated for insertion prior to sex.

This review of the purposes and prevalence of dry sex, together with trial participant feedback from clinical trials, is meant to encourage attention to this topic and discussion of its importance. Seven topical candidates with indications against HIV and STIs are now in the clinical pipeline, and most of them are being tested in countries where dry sex practices have been reported *(see Table 1)*. The implications of these practices are not limited to clinical trials; they may well prove important in the use of topical microbicides when they become available.

Current knowledge

Location and utilization

Dry sex is "more common than acknowledged"[2] and is found in a broad array of countries, including Cameroon,[3] Costa Rica,[3] Haiti,[3] Kenya,[3,4] Malawi,[3,5,6] Nigeria,[7] Saudi Arabia,[3] Senegal,[3] South Africa,[3,5,8] Zaire,[3,5,9] Zambia,[3,5,10] and Zimbabwe.[3,4,11-16] Women in these settings report using various approaches to altering what is typically a naturally lubricated cervicovaginal environment.

[1] Alliance for Microbicide Development. *Microbicide Research and Development Database (MRDD).* Silver Spring, MD, USA: 2008.
[2] World Health Organization (WHO). Preliminary reports and findings: Multi-country study on gender, sexuality, and vaginal practices, 2007.
[3] Kun KE. Vaginal drying agents and HIV transmission. *Int Fam Plan Perspect* 24(2): 93-4, 1998.
[4] Schoofs M. Part 5: Death and the second sex. *The Village Voice*, 1999.

TABLE 1. TOPICAL MICROBICIDE CANDIDATES IN ONGOING AND RECENT CLINICAL TRIALS[1]
Summary as of June 2008 (Bolded countries are those in which dry sex practices are reported to occur.)

Phase	Candidate Name	Sites by Country
3	Carraguard®*	**South Africa**
	PRO 2000	**South Africa**, Tanzania, Uganda, **Zambia**
2B	Tenofovir	**South Africa**
2/2B	PRO 2000 and BufferGel®	**Malawi**, **South Africa**, United States, **Zambia**, **Zimbabwe**
2	Tenofovir	**South Africa**, Uganda, United States
1/2	Dapivirine (TMC120) gel*	Rwanda, **South Africa**, Tanzania
	Invisible Condom®	**Cameroon**
1	Ethanol in Emollient Gel	**Kenya**
	UC-781	Thailand, United States
	VivaGel®*	**Kenya**, Puerto Rico, United States

For a full list of ongoing clinical trials, please visit the Alliance website (www.microbicide.org).
**These trials have completed clinical studies, but data analyses are ongoing.*

Each approach is typically dependent on resources available in both rural and more urbanized settings. These include alum,[7] antiseptics,[3,5] cloth,[3,14,15] cotton,[4] cotton wool,[14,15] cream,[7] gel,[7] herbal aphrodisiacs,[5] herbs,[3,4,6,7,14-16] household detergents,[4,5] leaves,[3,5,10] paper,[15] pharmaceutical products,[3] powders,[3,5,9] salt,[4] shredded newspaper,[4] soap,[7,8,14] soil with baboon urine,[4] stones,[3,6] tissues,[3] toilet paper,[3] traditional substances,[5,12,16] Vaseline®,[7] water,[3,7,8,13,14] and wet towels.[8]

The methods employed to apply these products include cleaning with fingers,[8,12] drinking "porridge,"[10] either ingesting herbs or tying them around the waist,[12,14] and wiping with cloth.[10,14]

Attitudes and beliefs: Women

Women's use of what are essentially desiccating products and methods is directly aimed at achieving a state of vaginal contraction,[16] closure,[2] dryness,[4,8-11,15,16] heat,[2-4,16] friction,[3,5] and tightness[2,5-11,15] before initiating intercourse. Other, less direct physical and psychological outcomes may also be desired.[11] For example, sex workers in South Africa are reported to dry the vagina to remove vestiges of a previous client, for themselves and future clients.[5] For other women, the aim is to dry the vagina to create a smaller opening, thus making men feel that their penises are larger;[4] increasing friction and heightening sexual drive, preference, or pleasure for one or both partners;[3,5,7-10,16] or invoking magical properties or preventing curses.[3,11] The purpose in most cases is to ensure a male partner's fidelity.[2,4,11]

Continued on p.10

[5] Baleta A. Concern voiced over "dry sex" practices in South Africa. *Lancet* 352(9136): 1292, 1998.
[6] Dallabetta GA, Miotti PG, Chiphangwi JD, et al. Traditional vaginal agents: Use and association with HIV infection in Malawian women. *AIDS* 9(3): 293-7, 1995.
[7] Otuonye NM. The use of intravaginal products and vaginal hygiene practices among women in Lagos State Nigeria. The 3rd IAS Conference on HIV Pathogenesis and Treatment. Rio de Janeiro, Brazil, 24-27 July 2005. Poster Abstract WEPE6.3C01.
[8] Jones H, van de Wijgert JH, Sebola M, et al. Vaginal product use by Phase 2 microbicide trial participants in South Africa. 14th International AIDS Conference. Barcelona, Spain, 7-12 July 2002. Abstract MOPED3653.
[9] Brown JE, Ayowa OB, Brown RC. Dry and tight: Sexual practices and potential AIDS risk in Zaire. *Soc Sci Med* 37(8): 989-94, 1993.
[10] Sandala L, Lurie P, Sunkuta MR. "Dry sex" and HIV infection among women attending a sexually transmitted diseases clinic in Lusaka, Zambia. *AIDS* Suppl: S61-8, 1995.
[11] Civic D, Wilson D. Dry sex in Zimbabwe and implications for condom use. *Soc Sci Med* 42(1): 91-8, 1996.
[12] Van de Wijgert JH, Mason PR, Gwanzura L, et al. Intravaginal practices, vaginal flora disturbances, and acquisition of sexually transmitted diseases in Zimbabwean women. *J Infect Dis* 181(2): 587-94, 2000.
[13] Coggins C, Blanchard K, Friedland B. Men's attitudes towards a potential vaginal microbicide in Mexico, Zimbabwe, and the USA. *AIDS* 15(Suppl 1): S29, 2001.
[14] Ray S, Gumbo M, Mbizvo M. Local voices: What some Harare men say about preparation for sex. *Reprod Health Matters* 4(7): 34-45, 1996.
[15] Van de Wijgert JH, Khumalo-Sakutukwa GN, Coggins C, et al. Men's attitudes toward vaginal microbicides and microbicide trials in Zimbabwe. *Int Fam Plan Perspect* 25(1): 15-20, 1999.
[16] Runganga AO, Kasule J. The vaginal use of herbs/substances: An HIV transmission facilitatory factor? *AIDS Care* 7(5): 639-45, 1995.

DIALOGUES *(Continued from p.09)*

Overwhelmingly, research on dry sex practices underscores the desires of women to please men sexually, beyond their own sexual desires, despite negative side effects before and after coitus, which may include increased discharge,[16] lacerations,[16] pain,[4,14,16] peeling,[10] and swelling.[10]

Attitudes and beliefs: Men

Men in countries where dry sex practices have been reported believe existing or excessive vaginal lubrication to be indicative of infection,[3,14] infidelity,[3,4] uncleanliness,[14] and/or a woman's use of contraception.[3] Men in Zimbabwe report that "'wet sex' is actually undesirable because it reduces friction and sensation during intercourse, prevents the vagina from 'heating up,' and causes an annoying sound."[4] These men added that normal vaginal fluids "smell bad and carry germs," adding that, without dryness, semen could accumulate in the woman, an unintended outcome.[15] Though some men in these countries indicated a preference for dry sex despite reports of pain or rashes, some also viewed the practice of pre-coital vaginal drying as a female tradition, passed down through generations of women rather than something imposed by men.[15] Men in Zimbabwe also reported use of "aphrodisiacs to increase their own sexual performance without telling the women,"[15] but men in both Mexico and Zimbabwe equated their wives' use of such products with loss of control over their sexuality and consequent infidelity.[13]

Attitudes and beliefs: Researchers

Sexual health researchers maintain that "the rectal and vaginal environments represent natural barriers for the incoming [HIV] virus,"[17] and "innate defences against pathogens."[18] They warn that any disruption can cause epithelial abrasions[3,9] and ulcerations[3] that can lead to deterioration of the critical structure of cell layers. Microtrauma is of special concern in the rectal environment whose "monolayered epithelium is more prone to lesions, which might make it even more susceptible for HIV" acquisition.[17] Additional lubrication in both environments is believed to reduce friction and consequent damage to both the vaginal and rectal walls, which may in turn decrease risk of infection. However, research to date on increased susceptibility to infection resulting from dry sex practices remains inconclusive,[3,6,10,12] although research has shown a positive association between vaginal practices and bacterial vaginosis,[7,18] which may "be an intermediary factor between vaginal practices and HIV infection" and possible HSV-2 infection.[18]

The World Health Organization (WHO) recently completed a Multi-Country Study on Gender, Sexuality, and Vaginal Practices (GSVP), in which six different categories of vaginal practices were defined. Preliminary findings suggest that of these six, cleansing and inserting substances into the vagina are believed to be the most injurious and thus most likely linked to increased risk of HIV acquisition.[18] These categories will aid in classifying harmful vaginal practices, but further understanding of their biologic and epidemiologic impact remains a research imperative.

Alternative views

User perspectives

The success of a topical microbicide for vaginal use appears to be at least somewhat dependent on its lubricating properties and the acceptability of those properties in user populations; however, the extent of that dependence remains imprecise. Still, information about the relevance of lubrication for microbicide acceptability has been increasing, most recently thanks to three ongoing and completed clinical trials that have yielded preliminary data on participant comments about the lubricating properties of the gels tested.

- Thai couples reported that the lubricating properties of *Carraguard*® topical gel not only heightened sexual pleasure for both partners, but also increased the frequency of sexual interactions. In fact, "when asked about desired characteristics of a microbicide product, a large majority of women and men viewed extra lubrication as very important."[22] Anecdotal feedback from Phase 3 trial participants revealed disappointment in returning study gel at the end of the trial, because the gel's lubricating properties improved sex.[20]
- *Cellulose sulfate* researchers found women in Benin reluctant to return trial product due to high preference

[17] Trapp S, Turville SG, and Robbiani M. Slamming the door on unwanted guests: Why preemptive strikes at the mucosa may be the best strategy against HIV. *J Leukoc Biol* 80: 1076-83, 2006.
[18] Hilber AM, Chersich MF, van de Wijgert JH, et al. Vaginal practices, microbicides, and HIV: What do we need to know? *Sex Transm Infect* 83: 505-8, 2007.
[19] Whitehead SJ, Kilmarx PH, Blanchard K, et al. Acceptability of Carraguard vaginal gel use among Thai couples. *AIDS* 20(17): 2141-8, 2006.
[20] Friedland B. Personal communication, 17 September 2007.

for additional lubrication during sex, among other factors. Because the trial closure protocol required collection of study product, after consulting with an ethicist, researchers exchanged additional lubricant gels for the study microbicide.[21] One trial participant was quoted as saying, "Now you get us used to the gel, how to help us find an alternative [at least as lubricant]?"[22]

- The Microbicides Development Programme Phase 3 study of *PRO 2000* (MDP 301) is encountering similar responses from many South African participants, one of whom responded that "the gel makes it easier, it is slippery and comfortable, and… I am enjoying sex more than before." Another focus group participant commented that while she used to refuse sex because she was apprehensive about pain, she now approaches her partner for sex as the gel brings enjoyment to them both.[23]

Health care providers

When an effective microbicide completes clinical testing and has received the necessary regulatory approvals, health care providers, including hospital managers, doctors, nurses, and pharmacists, will play critical roles in supporting its distribution, access, and use. However, providers in South Africa have expressed uncertainties about the future acceptance of microbicides in South African populations. They cite as possible impediments local cultural beliefs such as the "preference for dry sex and the importance of preserving a woman's virginity," along with men's control over sexual decisions;[24] they encourage researchers to further address these potential barriers.

Implications

The fact that in a number of countries and cultures, women have used a range of traditional methods vaginally suggests that they may be comfortable using a vaginally-applied microbicide.[15] Nevertheless, there are a number of variables to be taken into account in considering and developing microbicide formulations. The interests of women who prefer products that create a drier or only slightly lubricated environment, and the perceptions and preferences of male partners may be significant.[3,7,8,25-27] For example, a woman whose male partner prefers dry sex may find covert use of a lubricating microbicide and even negotiation about such use impossible or at best difficult.[13,15,18,19,25-28] The same male focus group that disapproved of "wet sex" expressed the belief that while girlfriends or prostitutes might use microbicides, their wives would not.[15] While some men thought that covert use of a lubricant might be feasible, they also said that they would be angry if they found out their wife had engaged in such use; they also expressed concern that a topical microbicide with lubricating properties could cause permanent infertility.[15] All that said, research in Mexico and Zimbabwe found that men's enthusiasm about microbicide use was correlated with their perceptions about their own personal risk of infection and their knowledge about area-specific HIV prevalence rates; this may explain why men in Zimbabwe were more interested in microbicides than men in Mexico.[15]

Studies of the prevalence of anal intercourse among women in heterosexual relationships and men who have sex with men (MSM)[29] raise additional questions about formulation preferences, including products and practices employed in preparing the rectum for anal sex. Research on current use of lubricants or douches among MSM could inform the design of topical microbicides or use

Continued on p.12

[21] Van Damme L. Personal communication, 7 September 2007.
[22] Guédou F. Personal communication, 6 September 2007.
[23] Gafos M. Personal communication, 26 September 2007.
[24] Ramjee G, Morar NS, Mtimkulu J, et al. Perceptions of vaginal microbicides as an HIV prevention method among health care providers in KwaZulu-Natal, South Africa. *AIDS Res and Therapy* 4(7), 2007.
[25] Jones DL, Weiss SM, Chitalu N, et al. Acceptability of microbicide surrogates among Zambian women. *Sex Trans Dis* 35(2): 147-53, 2008.
[26] Mason TH, Foster SE, Finlinson HA, et al. Perspectives related to the potential use of vaginal microbicides among drug-involved women: Focus groups in three cities in the United States and Puerto Rico. *AIDS Behav* 7(4): 339-51, 2003.
[27] Hammett TM, Mason TH, Joanis CL. Acceptability of formulations and application methods for vaginal microbicides among drug-involved women: Results of product trials in three cities. *Sex Trans Dis* 27(2): 119-26, 2000.
[28] Woodsong C. Covert use of topical microbicides: Implications for acceptability and use. *Int Fam Plan Perspect* 30(2): 94-8, 2004.
[29] Gorbach PM. Emerging epidemiology of anal intercourse. IRMA teleconference. 9 June 2006.

DIALOGUES *(Continued from p.11)*

of douches for product delivery.[30-32] This area of inquiry should be illuminated by the International Rectal Microbicide Advocates' (IRMA) Lube Survey, the largest ever conducted on this topic. This survey was intended to identify the lubricants most frequently used for anal intercourse, encourage further safety and efficacy testing, and outline future decisions for rectal microbicide testing and formulation. Its results revealed that "little more than a quarter of people who indicated they had engaged in anal sex in the past six months provided reasons for why they did not use lube;" 18.7% of these respondents indicated a preference for dry sex.[32] The wealth of knowledge that can be derived from its 8,945 responses from 107 countries will be valuable for rectal microbicide research and development in general and preferences around douches, lubricants, and drying products in particular. It should also inform upcoming Phase 1 safety and acceptability studies of vaginal microbicides used rectally and candidate microbicides formulated specifically for rectal use.

Conclusions and emerging needs

Topical microbicides offer potential for reducing sexual susceptibility to HIV and enhancing sexual pleasure, and there is evidence of acceptance of topical microbicides even in countries where dry sex practices and preferences have been studied and reported. Behavioral studies and qualitative data emerging from current clinical trials will continue to provide real-time information on use and acceptance of the topical microbicides being tested and their lubricating properties.

This review scrutinized the published literature on dry sex and preliminary information from current clinical trials and concurs with the WHO survey finding that dry sex is more common than acknowledged and is found in a broad array of countries. It seems reasonable to conclude that further, well-tailored research would be justified to answer the following questions:

- Is risk of HIV and non-HIV STI infection enhanced by dry sex practices, which ones, and how?
- Can the assumption that lubricating the vaginal or rectal environments provides protection against those infections be tested and, if so, how?
- To what extent are dry sex practices a factor in current or future clinical trials of topical microbicides?
- Might the combination of dry sex practices and microbicide use result in either harm or a substantial decrease in the efficacy of the microbicide in question?
- Could other practices used for perceived cleansing, contraceptive, hygienic, preventive, or therapeutic properties affect microbicide efficacy, and how?
- Have the lubricating properties of the microbicides tested in current trials enhanced product use and adherence to trial protocol, and can that be quantified?
- Have the physiologic effects of dry sex practices combined with the use of the topical microbicides tested in trials to date been monitored? If there were any effects of significance, have they varied by type of practice, and how?
- If dry sex practices, or a specific type of dry sex practice, are dominant preferences in certain cultural settings, what does this mean for the design and siting of forthcoming clinical trials?
- If it is still deemed feasible for women to use topical microbicides covertly without partner knowledge or approval, and if there are significant numbers of women who wish to do so, what modifications should be made in formulating future topical microbicides to respond to these needs and desires?
- Similarly, if dry sex practices, or a specific type of dry sex practice, are dominant preferences in certain cultural settings, what does this imply for the design of formulations and delivery systems? Should further consideration be given to development of non-lubricating topical applications, such as vaginal rings?

Such research could lead to more solid understanding of the physiological effects of different dry sex practices, the protective value of lubrication, implications for product design and testing, possible behavioral interventions, and successful utilization of topical microbicides in trial and post-trial settings.

[30] Carballo-Diéguez A, Bauermeister JA, Ventuneac A, et al. The use of rectal douches among HIV-uninfected and infected men who have unprotected anal intercourse: Implications for rectal microbicides. *AIDS Behav*, 12(6): 860-6, 2007.

[31] Carballo-Diéguez A, Stein Z, Sáez H, et al. Frequent use of lubricants for anal sex among men who have sex with men: The HIV prevention potential of a microbicidal gel. *Am J Public Health* 90(7): 1117-21, 2000.

[32] International Rectal Microbicide Advocates (IRMA). *Less Silence, More Science: Advocacy to Make Rectal Microbicides a Reality*, 2008.

MEETING ON NON-HUMAN PRIMATE MODELS FOR MICROBICIDE R&D

USAID and Partners

Summary of Discussion and Conclusions

Christopher Mauney and Lee Claypool, USAID

Overview

On January 9th, 2008, staff from the USAID Global Health Bureau hosted a meeting to discuss the use of non-human primate (NHP) models as a tool for the development of microbicides. These models are one of several approaches being reevaluated as increased emphasis is placed on more predictive preclinical testing. Investigators from USAID cooperating agencies (CAs) specializing in NHP work and a number of other local experts attended the meeting and discussed an agenda that covered ongoing studies and planned future work. Specifically, USAID was interested in fostering discussion on the following topics in relation to NHP work:

- Priorities and gaps
- Players: who is working with or for whom
- Current status of various products and models
- Pros and cons of the current models
- Limitations of non-human primate models
- Standardization and validation
- Duplications
- Efficacy vs. safety and pharmacokinetics models
- Future directions

The following is a brief summary of some major discussion points and conclusions.

Discussion Points

Preclinical characterization of test products

An adequately extensive characterization of the biochemical and physical properties of experimental microbicides is necessary to allow for a comprehensive and accurate evaluation of any NHP model results. As it stands now, results obtained with these models may or may not show a degree of efficacy, but without sufficient characterization of the active agents and prototype formulations used, researchers may not be able to correctly explain why a particular product did or did not work. This is especially relevant in cases where *in vitro* and *in vivo* data may not agree, or whenever the results appear to be inconsistent. Preclinical characterization of formulations might usefully include release kinetics in *in vitro*, rabbit vaginal irritation, and PK studies, among others, that could play a critical role in improving a test product and interpreting the results in NHP models. This might ultimately contribute to greater success of products in human trials.

NHP model gaps

A number of important questions remain inadequately answered by current NHP testing regimens. The development of models tailored to specifically address these questions will provide a more complete picture of an experimental microbicide, thus allowing researchers to make more informed decisions about which products have the greatest potential for success in humans. As discussed by the meeting participants, the following list comprises some key models that are not currently available or that need further refinement:

1) Cell-free infection model: While there are a number of cell-free models currently in use or under evaluation, there are significant inconsistencies between them. Cross-analysis between models is difficult, since there is no standardized protocol and it is unclear which model most accurately tests product efficacy or approximates HIV infection in humans. Therefore, a need exists for standardized and well-characterized cell-free infection models (e.g., multiple low-dose models or single high-dose models) that can reasonably approximate microbicide efficacy in humans and be useful as screens for further NHP testing.
2) SHIV, RT-SHIV, RT/envelope-SHIV: In NHP models, hybrid viruses that more closely approximate infection and pathogenesis with HIV are useful to predict the potential efficacy of products in humans. The continued development and refinement of suitably engineered hybrid viruses is also essential to appropriately test products with different mechanisms of action.
3) Coital effects model: The development of a model that more accurately simulates the actual conditions of sexual transmission, including changes in vaginal pH, the

Continued on p.14

MEETING ON NON-HUMAN PRIMATE MODELS FOR MICROBICIDE R&D *(Continued from p.13)*

presence of seminal fluid, the effects of trauma, and variations in microflora, would be a useful tool in evaluating potential product efficacy in real-world scenarios. Models incorporating potential transmission by cell-associated virus could also be included in this category.
4) Viral resistance model: Due to the nature of daily-use gels and products that will persist for long periods in the body, a safety model that determines the potential for development or selection of drug-resistant virus would be a useful addition to the suite of NHP tests.
5) Enhancement model: Given the unexpected results of the clinical trial with cellulose sulfate in which product use appeared to increase infection rather than decrease it, there is a need to develop a standard NHP model to test for potential enhancement effects. This model might also help explain discrepancies between *in vitro* and *in vivo* results or between different concentrations of the same drug.
6) Co-infection model: Like the coital effects model above, or as another category within it, a co-infection model could also represent real-life transmission scenarios in which previous or simultaneous infection with an STI may be a significant risk factor for HIV infection.

Protocol gaps

Protocol differences between trials and investigators also make cross-analysis and comparison of results difficult and can lead to contradictory data that make accurate conclusions about product efficacy impossible. The following are suggestions from the meeting participants of ways to address the protocol gaps:

1) Standardization: Although it was recognized that there will not be one specific model and protocol to fit all situations, and that different experimental microbicides may require different testing, it was agreed that a greater degree of standardization between models is possible and would improve the interpretation and usefulness of the results. Three suggested focus areas include:

a. Methodologies: Finding a consensus, where possible, on issues such as viral concentration, viral strain, monkey species, dosing regimen, inoculum, etc.
b. Endpoints: Endpoints that best measure the results of interest (e.g., CD4+, CD8+, proviral DNA, viral RNA, etc.) need to be defined and incorporated into the appropriate protocols.
c. Definitions: Each measured result parameter needs to be defined, vetted, and then strictly applied. For example, at present, researchers may not define "infected animal" in the same way.

2) Virus characterization: Experimental virus strains need to be rigorously characterized since they affect the test results and are a critical variable when comparing trials.

3) DMPA pre-treatment: DMPA or other progestin treatment may enhance infection but the variety of potential effects and mechanisms involved are not completely understood. Whether pre-treatment is useful and, if so, how to standardize it, needs further discussion.

Limitations of NHP models

The interpretation and analysis of studies with NHP models can be severely limited by gaps in the characterization of the test product, the virus strain, and the particular protocols used, as well as by the still very incomplete understanding of SIV and HIV transmission biology. These are areas that may benefit from future research, although a complete understanding of all variables may not be possible. In the context of the pandemic, the most critical gaps around understanding experimental results should be identified and addressed. Ideally, the most important criteria, safety and efficacy, would be demonstrated in well-defined NHP models, but given the present lack of validation for these models, conclusions may sometimes be uncertain. These and other existing limitations have significant implications and suggest caution about using protective results in NHP models as an absolute prerequisite or "gatekeeper" for studies in humans. In some cases, time and other resources may be better used to study products in humans when it is technically and ethically appropriate.

It is the mandate of this field to make acceptable microbicides for HIV prevention available to those women who desperately need them, and all efforts should be made to expedite the process without compromising safety and effectiveness.

Major Conclusions

Best practices

With the realization that there will be several concurrent models tailored to different endpoints and mechanisms of action, the recommendation of the participants of the meeting was not for a single standardized NHP model but, instead, the development of a suite of best practices for NHP models used to test microbicides. This suite of best practices would include standardization of definitions and endpoints, characterization of prototype products and viral strains used, and adoption of standardized or well-characterized methods and protocols whenever possible. In this way, studies would be more consistent, data comparison and analysis normalized, and results more conclusive and useful for product R&D. These best practices could be developed as an "expectation" or "norm" that certain product and model characteristics, and certain endpoints or other parameters, need to be assessed to make NHP studies as useful as possible to the whole field—in terms of their interpretation for a given test product and their relationship to other data in the field.

Priority models

While a number of models were identified as gaps in the field, participants at the meeting concluded that three of these were the highest priority for development:

1) Cell-free infection model: Several variations of this model are currently in existence, but the field would benefit from a more extensively proven and agreed-upon model.

2) SHIV, RT-SHIV, RT/envelope-SHIV models: Continued refinement of these models, which more closely resemble human HIV infection and pathology in NHPs, is needed to better determine the efficacy of products with different mechanisms of action, and will be vital for testing future generations of microbicides.

3) Enhancement model: This could be an important new screening tool for safety before taking next-generation microbicides into large clinical trials, especially given recent unexpected results in this field.

The discussion largely endorsed the perspective that further model development in this field needs to focus on problem solving to make microbicide testing in monkeys as useful as possible.

NHP studies as gatekeepers

This diverse group of participants generally agreed that NHP results should *not* be used as an absolute "gatekeeper" in deciding what products should advance to testing in humans. While it would be extremely useful to have an animal model that would reliably predict whether a product will work in humans or not, the common point of view was that current NHP models are not yet adequate for this purpose, for a variety of reasons. At this time, there is not enough evidence or confidence that positive or negative results in NHP studies predict activity in humans. It was agreed that the results of NHP studies are worthwhile and may be very useful for testing concepts such as combination microbicides and for evaluating various microbicide delivery systems, such as new formulations and vaginal rings. NHP results, however, should only be considered along with those from all the other preclinical testing done *in vitro* or in other animal models; they should also, at least in some cases, take into consideration what may already be known about the therapeutic properties of the active or related agents in humans, e.g., for ARVs. There was concern that using current NHP testing as a "gatekeeper" could lead to major mistakes in the selection of active agents, doses, formulations, etc., and in the associated use of time, funds, and other resources.

THIS QUARTER IN MICROBICIDES

1 APRIL *PUBLICATION:* Rosen RK, Morrow KM, Carballo-Diéguez A, et al. Acceptability of tenofovir gel as a vaginal microbicide among women in a Phase I trial: A mixed-methods study. *J Womens Health (Larchmt)* 17(3): 383-92, 2008. "Quantitative results indicate that tenofovir vaginal gel was acceptable to almost all users, while qualitative findings indicate that acceptability is complex, varies among users, and is likely shaped by a variety of contextual factors that manufacturers will need to consider to optimize use-effectiveness. Because of the differences in the qualitative and quantitative responses, the authors argue that future trials of candidate microbicides should include strategic collection of mixed-methods microbicide acceptability data."

1 APRIL *PUBLICATION:* Woodsong C, Alleman P. Sexual pleasure, gender power and microbicide acceptability in Zimbabwe and Malawi. *AIDS Educ Prev* 20(2): 171-87, 2008. "Even though acceptability of microbicides was found to be high, sexual intercourse is accompanied by issues of power and gender norms that place women, particularly those in stable union, at a disadvantage for enactment of risk reduction strategies. Although woman-initiated use is an important goal in development of microbicides, the need for men's cooperation or agreement must be addressed in strategies for future product introduction."

1 APRIL *PUBLICATION:* Exner TM, Correale J, Carballo-Diéguez A, et al. Women's anal sex practices: Implications for formulation and promotion of a rectal microbicide. *AIDS Educ Prev* 20(2): 148-59, 2008. "Women were uncertain about the amount of lubricant used during sex, with typical estimates of 1 to 2 teaspoons. This may prove challenging to the formulation and promotion of rectal microbicides, as substantially higher amounts may be required. Additional challenges include infrequent use of packaged lubricants, and typical male lubricant application, which may make women's control of rectal microbicides more difficult. Women overwhelmingly expressed interest in rectal microbicides."

14 APRIL The Population Council appointed Louise Pedneault, MD, Clinical Director of Microbicides for the organization's HIV and AIDS Program. In addition to managing clinical trials, Pedneault will work on strategic planning for next-generation microbicide candidates as part of the Council's continued commitment to develop products that provide women with the means for protecting themselves from HIV infection.

14 APRIL *PUBLICATION:* Sater AA, Ojcius DM, Meyer MP. Susceptibility of *Chlamydia trachomatis* to the excipient hydroxyethyl cellulose: pH and concentration dependence of antimicrobial activity. *Antimicrob Agents Chemother* 52(7): 2660-2, 2008. "Hydroxyethyl cellulose (HEC) is used as a neutral excipient in microbicides against sexually-transmitted pathogens. However, HEC inhibits infection of cervical epithelial cells by *Chlamydia trachomatis* at pH 5 in a concentration-dependent manner. At pH 7, infection is inversely dependent on the concentration of HEC, possibly due to pH-dependent calcium sequestration."

5 MAY Alliance for Microbicide Development launches new website! New features include intelligent navigation, improved search technology, user-friendly appearance, and future expandability. Visit us at *www.microbicide.org*.

6 MAY Clinical trial researchers announce discovery of participant co-enrollment in microbicide trials HPTN 035, a Phase 2/2B study of BufferGel® and PRO 2000/5, and CAPRISA 004, a Phase 2B study of tenofovir gel. Researchers are working to ensure the safety of the co-enrolled participants and secure future enrollment systems to avoid the possibility of future co-enrollments.

15 MAY Dr. Roberta Black is appointed Chief of the Microbicide Research Branch in the Division of AIDS, National Institute of Allergy and Infectious Diseases, at -the National Institutes of Health (NIH). Her experience at the National Cancer Institute, Uniformed Services University of the Health Sciences, and DAIDS, as well as her pioneering role in the field of microbicides, are the great assets she brings to this new role.

30 MAY NIH launches the Office of AIDS Research (OAR) website, which contains information about the OAR and its Advisory Council, the *FY2009 Trans-NIH Plan for HIV-Related Research*, the NIH AIDS Research Budget, details on upcoming meetings, and a wealth of HIV/AIDS statistics and resources. *http://www.oar.nih.gov/*

1 JUNE *PUBLICATION:* Omar RF, Trottier S, Brousseau G, et al. Distribution of a vaginal gel (Invisible Condom®) before, during and after simulated sexual intercourse and its persistence when delivered by two different vaginal applicators: A magnetic resonance imaging study. *Contraception* 77(6): 447-55, 2008. "Using the new PVA, the Invisible Condom® covered the vaginal/cervical mucosae before and during simulated intercourse, offering immediate protection, whereas only the cervical mucosa was covered using the CA. Forty percent of the gel persisted mostly in the upper vaginal/cervical area at 24 h following its administration with the CA, while only 5% of the gel was left using the PVA. The new applicator, with its unique design, ensures an even and immediate coating lasting throughout the first 6 h and could prevent potential microbicide vaginal toxicity at 24 h."

1 JUNE *PUBLICATION:* van der Straten A, Moore J, Napierala S, et al. Consistent use of a combination product versus a single product in a safety trial of the diaphragm and microbicide in Harare, Zimbabwe. *Contraception* 77(6): 435-43, 2008. "Despite high reported acceptability and few problems with the products, the participants reported only moderate product adherence levels. Consistent use of condoms and consistent use of products were strongly associated. If observed in other studies, this may bias the estimation of product effectiveness in future trials of female-controlled methods."

1 JUNE *PUBLICATION:* Auslander BA, Rupp RE, Short MB, et al. Male partners of young women: Assessing their attitudes toward topical microbicides. *J Adolesc Health* 42(6): 626-8, 2008. "Male partners' attitudes toward microbicide use are important to understand; however, there are challenges in conducting research with adolescent couples. We describe the experience of recruiting male partners of adolescent females enrolled in a microbicide acceptability study. Creative solutions to enrolling partners of young women in studies need to be explored."

9 JUNE NIH Director Dr. Elias Zerhouni announces the beginning of critical changes to enhance and improve the NIH's peer review process. For more information about enhancing peer review at NIH and to learn about the implementation plan, please visit *http://enhancing-peer-review.nih.gov*.

11 JUNE *PUBLICATION:* Bouschbacher M, Bomsel M, Verronese E, et al. Early events in HIV transmission through a human reconstructed vaginal mucosa. *AIDS* 22(11): 1257-66, 2008. "For the first time, we documented that, within 4 h following contact with HIV-infected cells, translocation of free HIV particles across a pluristratified mucosa is not detectable and that, in this context, it seemed that Langerhans cells do not increase HIV transmission. Moreover, we provided a useful model for the development of strategies preventing HIV entry into the female genital tract, especially for testing the efficiency of various microbicides."

12 JUNE Microbicide Trials Network (MTN) announces launch of the first trial of a microbicide in pregnant women. The trial, known as MTN-002, will enroll 16 healthy HIV-negative women who are scheduled for caesarean delivery at Magee-Womens Hospital of the University of Pittsburgh Medical Center. The women will have a single dose of tenofovir topical gel applied inside the vagina about two hours before giving birth. For more information on this trial and the MTN, visit *www.mtnstopshiv.org*.

21 JUNE *PUBLICATION:* Celum C, Wald A, Hughes J, et al. Effect of aciclovir on HIV-1 acquisition in herpes simplex virus 2 seropositive women and men who have sex with men: A randomised, double-blind, placebo-controlled trial. *Lancet* 371(9630): 2109-19, 2008. "Our results show that suppressive therapy with standard doses of aciclovir is not effective in reduction of HIV-1 acquisition in HSV-2 seropositive women and MSM. Novel strategies are needed to interrupt interactions between HSV-2 and HIV-1."

MICROBICIDE CANDIDATES IN ONGOING CLINICAL TRIALS *Summary as of June 2008*

Phase	Candidate Name	MoA	Title of Study	Sponsor*	Sites by Country
3	PRO 2000/5 gel	EFI	Efficacy and safety of 0.5% PRO 2000/5 gel for the prevention of vaginally acquired HIV infection	Indevus, MRC, DFID (Funder)	South Africa, Tanzania, Uganda, Zambia
2B	Tenofovir gel	RI	Safety and effectiveness of the vaginal microbicide 1% tenofovir gel to prevent HIV infection in women in South Africa (CAPRISA 004)	CAPRISA, USAID, LIFElab, Gilead, FHI, CONRAD	South Africa
2/2B	PRO 2000/5 gel (P) and BufferGel®	EFI, VDE	Safety and effectiveness study of the vaginal microbicides BufferGel® and 0.5% PRO 2000/5 Gel (P) for the prevention of HIV infection in women (HPTN 035)	NIAID, Indevus, ReProtect	Malawi, South Africa, United States, Zambia, Zimbabwe
1	Dapivirine (TMC120) gel	RI	Safety and pharmacokinetics of two intravaginal dapivirine gel formulations in healthy, HIV-negative women (IPM 012)	IPM	Belgium
	Ethanol in Emollient Gel	S	Safety and acceptance of 62% ethanol in emollient gel as a topical male microbicide	NIAID	Kenya
	HEC/CS/N-9†	N/A	Assessment of markers of inflammation after vaginal product use	CONRAD/USAID	USA
	Tenofovir/PMPA gel	RI	Pharmacokinetic study of the vaginal microbicide agent 1% tenofovir gel (A04-095)	CONRAD, IPM/USAID	Dominican Republic, United States
	Tenofovir gel	RI	Interventional study of mucosal and antimicrobial responses to repeated vaginal applications of tenofovir gel in HIV-uninfected women	NIAID	United States
	UC-781 gel	RI	Safety and persistence of 0.1% UC-781 vaginal gel in HIV-1 seronegative women	NIAID, CONRAD	United States
	UC-781 gel	RI	Safety and acceptability study of the UC-781 vaginal microbicide gel formulation applied rectally in HIV-1 seronegative adults	UCLA, NIAID, CONRAD	United States
	UC-781 gel	RI	Safety and acceptability of 0.1% and 0.25% UC-781 topical vaginal microbicide in women and acceptability in their male partners	CDC, Thailand Ministry of Health, CONRAD	Thailand
	UC-781 gel	RI	Male tolerance study (A06-104)	CONRAD	United States
	UC-781 gel	RI	Safety and acceptability of UC-781 topical vaginal microbicide in heterosexual women and male partners (HC 101)	CONRAD, CDC, Emory University	United States
	VivaGel® (SPL7013 gel)‡	EFI	Safety and acceptability of 3% w/w SPL7013 Gel (VivaGel™) applied vaginally in sexually active young women (MTN-004)**	DAIDS/NIAID, NICHD, Starpharma	Puerto Rico, United States
N/A	Placebo ring±	Placebo	Safety and acceptability of a placebo vaginal ring microbicide delivery method for the prevention of HIV infection in women (IPM 011)	IPM	Kenya, South Africa, Tanzania

For modifications, please contact Stephanie Tillman, email stillman@microbicide.org, tel. 301-587-3302.

Definition of acronyms used in this table: Mechanism of Action (MoA), Entry/Fusion Inhibitor (EFI), Replication Inhibitor (RI), Vaginal Defense Enhancer (VDE), Surfactant (S), and Combination (C).

**The Alliance uses the term "sponsor" as defined by the International Conference on Harmonisation (Guideline for Good Clinical Practice, 1996) as follows: "An individual, company, institution, or organization which takes responsibility for the initiation, management, and/or financing of a clinical trial."*

†HEC, CS, and N-9 are not in development as microbicides. Rather, this trial's objective is to characterize inflammation and genital epithelial changes in healthy, sexually abstinent women before, during, and after 13 ½ days of twice-daily applications of one of three products: a hydroxyethylcellulose (HEC)-based "universal" placebo, 6% cellulose sulfate, or 4% nonoxynol-9 (Conceptrol®) gel; to determine the degree of correlation between different methods of clinical assessment; and to determine the degree of correlation between the results of this clinical study and the results of the preclinical assessment of the same compounds.

‡ This trial has been paused pending a protocol amendment.

***ATN 062, "Tell Juliana," is an observational study taking place in parallel to MTN-004. Please visit the* MRDD *for further information on this ancillary study.*

± This device is intended for use with a microbicide.

MICROBICIDE CANDIDATES AND ANCILLARY DEVICES IN PLANNED AND FUNDED CLINICAL TRIALS ***Summary as of June 2008***

Phase	Candidate Name	MoA	Title of Study	Sponsor*	Sites by Country
3†	ACIDFORM™/ Amphora™	VDE	Trial of the diaphragm with a candidate microbicide to prevent sexually transmitted infections	CDC, CONRAD, NIH	Madagascar
3	Dapivirine (TMC120)	RI	Dapivirine efficacy study (IPM 009)	IPM	N.D.
2/3	Invisible Condom™	EFI	Effectiveness of Invisible Condom™ in high-risk women	N.D.	N.D.
2/2B	Tenofovir/PMPA gel	RI	Safety and effectiveness of tenofovir 1% gel (PMPA) with two oral HIV prevention approaches – tenofovir and Truvada™, a tenofovir-FTC drug combination (MTN-003 – VOICE)	MTN	Malawi, South Africa, Uganda, Zambia, Zimbabwe
2	Tenofovir/PMPA gel	RI	Adherence and pharmacokinetics study of oral and vaginal preparations of tenofovir (MTN-001)	MTN	South Africa, Uganda, United States
1/2	Dapivirine (TMC120)	RI	Safety and acceptability of dapivirine gel, conducted using daily monitored adherence in healthy HIV-negative women (IPM 014)	IPM	Malawi, South Africa, Tanzania
	Dapivirine (TMC120)	RI	Safety of an intravaginal matrix ring with dapivirine for the prevention of HIV infection in healthy HIV-negative women (IPM 015)	IPM	South Africa, Tanzania
	Dapivirine (TMC120)	RI	Dapivirine gel expanded safety study (IPM 020)	IPM	United States
	Dapivirine (TMC120)	RI	Dapivirine intravaginal ring expanded safety study (IPM 021)	IPM	Europe
1	Dapivirine (TMC120)	RI	Quantitative assessment of the effects of a vaginal ring containing 25mg dapivirine on the vaginal flora of healthy women (IPM 017)	IPM, EMPRO	Belgium
	Dapivirine (TMC120)	RI	Dapivirine gel male tolerance study (IPM 010)	IPM	Belgium
	Dapivirine (TMC120)	RI	PK study in healthy HIV-negative women to assess delivery of dapivirine from both matrix and reservoir intravaginal rings (IPM 013)	IPM	Belgium
	Duet®	C	Duet® acceptability and safety study	IPM, ReProtect, Inc., RTI International	Zimbabwe
	PC-815	C	Randomized, double blind, crossover safety study of two microbicide formulations: PC-815 and Carraguard®	Population Council	Dominican Republic, South Africa
	PC-815	C	Probing study of infectivity of vaginal lavages from HIV-positive women after vaginal administration of PC-815	Population Council	N.D.
	PRO 2000	EFI	Postcoital antiviral activity of cervicovaginal secretions following intravaginal application of 0.5% PRO 2000/5 Gel (P)	AECOM, Indevus, NIH	United States
	Tenofovir/PMPA gel	RI	Device for Vaginal Drug Delivery (DVD2) with tenofovir gel vs. plain tenofovir gel	FHI	N.D.
	Tenofovir/PMPA gel	RI	Maternal pharmacokinetics and placental perfusion of tenofovir/PMPA gel (MTN-002)	MTN	United States
N/A	Placebo ring	Placebo	Expanded safety and acceptability study of a non-medicated intravaginal ring (MTN-005)	MTN, IPM	India, United States
N/A	No product	RI	Seroconverter protocol (IPM 007)	IPM	N.D.

For modifications, please contact Stephanie Tillman, email stillman@microbicide.org, tel. 301-587-3302.

Definition of acronyms used in this table: Mechanism of Action (MoA), Entry/Fusion Inhibitor (EFI), Replication Inhibitor (RI), Vaginal Defense Enhancer (VDE), Surfactant (S), and Combination (C).

**The Alliance uses the term "sponsor" as defined by the International Conference on Harmonisation (Guideline for Good Clinical Practice, 1996) as follows: "An individual, company, institution, or organization which takes responsibility for the initiation, management, and/or financing of a clinical trial."*

†This study concept is under review.

THE MICROBICIDE QUARTERLY

EDITOR: Polly F. Harrison

PRODUCTION MANAGER: Betsy M. Finley

DESIGN AND LAYOUT: Lomangino Studio Inc.

The Microbicide Quarterly ("TMQ") is published at the end of every calendar trimester by the Alliance for Microbicide Development.

The Microbicide Quarterly
8484 Georgia Avenue, Suite 940
Silver Spring, MD 20910, USA
Tel: 301-587-9690; Fax: 301-588-8390
www.microbicide.org; alliance@microbicide.org
www.hivresourcetracking.org

Founded in 1998, the Alliance for Microbicide Development is a nonprofit, multidisciplinary, multisectoral organization that employs monitoring, research, communication, convening, and evidence-based advocacy to speed development of microbicides to prevent HIV and other sexually transmitted infections.

The work of the Alliance has been made possible by the dedication of its participants and contributions from the Bill and Melinda Gates Foundation, CONRAD, the William and Flora Hewlett Foundation, International Partnership for Microbicides, John M. Lloyd Foundation, Moriah Fund, Rockefeller Foundation, and the generosity of private and anonymous contributors.

TMQ welcomes your support!

Your tax-deductible financial contribution will help the Alliance continue to publish *TMQ*. Please make your check payable to the Alliance for Microbicide Development and mail to:

Alliance for Microbicide Development
8484 Georgia Avenue, Suite 940
Silver Spring, MD 20910, USA
ATTN: TMQ

Please visit *www.microbicide.org/cs/donate* for additional ways to donate to support the work of the Alliance.

QUOTABLE QUOTES

"WHAT IS IMPORTANT IS TO KEEP REMEMBERING THAT THE DECISIONS [THAT] WE TAKE AS INDIVIDUALS WILL ULTIMATELY DETERMINE WHETHER WE ACHIEVE THE GOAL OF AN HIV-FREE GENERATION. WHEN ALL THE INFORMATION HAS BEEN PROVIDED, IT IS AN INDIVIDUAL'S DECISION NOT TO HAVE SEX, TO BE LOYAL TO ONE PARTNER, OR TO USE A CONDOM. THESE ARE DECISIONS THAT EACH AND EVERY ONE OF US HAS TO TAKE."
—Mbhazima Shilowa, Premier of Gauteng Province, South Africa

"IT IS VERY IMPORTANT TO SEE HIV DEVELOPMENT IN THE BROADER CONTEXT OF VACCINE DEVELOPMENT...IT TOOK 47 YEARS FROM THE TIME OF IDENTIFYING POLIO TO ACTUALLY FINDING A VACCINE...AND ALONG THE WAY THERE WERE ALSO THESE STUMBLING BLOCKS LIKE WE ARE FACING NOW WITH HIV. IN FACT, THERE WERE TWO TRIALS WHERE PEOPLE BECAME INFECTED WITH POLIO. THEY [SCIENTISTS] WERE CALLED TO STOP THE POLIO VACCINE PROGRAM. OF COURSE IT DIDN'T [STOP]. THANK GOODNESS IT DIDN'T, BECAUSE IF IT DID, WE WOULDN'T HAVE A POLIO VACCINE TODAY."
—Glenda Gray, Associate Professor, Department of Paediatrics, University of the Witwatersrand

"CONCURRENT OR SIMULTANEOUS SEXUAL PARTNERSHIPS ARE FAR MORE DANGEROUS THAN SERIAL MONOGAMY BECAUSE THEY LINK PEOPLE UP IN A GIANT WEB OF SEXUAL RELATIONSHIPS THAT CREATES IDEAL CONDITIONS FOR THE RAPID SPREAD OF HIV."
—Helen Epstein in *The Invisible Cure: Africa, the West and the Fight Against AIDS*

"THE STUDY OF DRUGS DURING PREGNANCY CONTINUES TO BE ONE OF THE MOST NEGLECTED AREAS OF BIOMEDICAL RESEARCH...AS FOR MICROBICIDES, WHEN THE VERY POPULATION AT RISK FOR HIV IS THE SAME POPULATION OF WOMEN MOST LIKELY TO BECOME PREGNANT, WE HAVE A CLINICAL AND ETHICAL OBLIGATION TO PURSUE STUDIES INVOLVING THE USE AND SAFETY OF MICROBICIDES IN PREGNANCY."
—Richard Beigi, Assistant Professor, Department of Obstetrics, Gynecology, and Reproductive Sciences, University of Pittsburgh