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CONTENTS

AIDS 2008: SPOTLIGHT ON MICROBICIDE POSTERS

Latifa M. Boyce, Alliance for Microbicide Development

Introduction

Poster presentations at large conferences are often buried in the program book and overshadowed by oral presentations, even though they may offer novel ideas and fresh research. And even the most diligent conference attendee may be unable to juggle poster sessions, the demands of concurrent events, and simply too many posters to visit and absorb in any logical way.

More than 70 microbicide-specific abstracts were presented at the August 2008 *International AIDS Conference* in Mexico City. All were listed in the Alliance for Microbicide Development's daily coverage of that meeting and are now posted on the Alliance website at: *http://www.microbicide.org/cs/meetings_events/events/aids_2008.*

The purpose of this article is to feature 22 abstracts that employ particularly innovative tools, strategies, methods, or approaches to understanding aspects of microbicide research and development. Each illustrates new approaches to evaluating candidate microbicides across the product development pipeline, or utilizes inventive data collection and validation approaches and new techniques for developing and evaluating targeted introduction strategies, in some cases in totally new population categories, for example, refugees. Collectively, these abstracts constitute advances in the field of microbicide research and development that we believe merit attention.

The abstracts that appear here are grouped by common theme and referenced by abstract title, authors, and conference abstract number.

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A New Lexicon for Prevention

Biomedical interventions for HIV prevention: re-thinking the way forward (Abstract MOPE0434)

Padian N, Buvé A, Balkus J, Serwadda D

For each method of biomedical prevention (microbicides, STD treatment to prevent HIV, vaccines, diaphragms, and male circumcision), the study authors described the biological plausibility of the method; reviewed outcomes of trials evaluating the method; and presented challenges relevant to evaluation, implementation, and scale-up.

They concluded that a new lexicon for prevention is required—one that integrates partially effective biomedical methods with other modes of prevention, including behavioral, social, and structural interventions, in the conviction that a more integrative approach would help increase adherence and avoid sexual disinhibition during trials. They suggested that the prevention field would advance more rapidly if more attention were focused on the *type of method* (e.g., antiretroviral-based prevention) rather than on *mode of administration* (e.g., microbicide preparations, pre-exposure prophylaxis). They also recommended that new prevention methods be compared to prevention activities currently or potentially available in communities, rather than methods that are unavailable or whose availability and use are unsustainable.

EDITOR'S NOTE: The authors published a more extensive version of this research in the 16 August issue of* The Lancet *(Padian NS, Buvé A, Balkus J, Serwadda D, Cates W. Biomedical interventions to prevent HIV infection: evidence, challenges, and way forward.* Lancet *372: 585-99, 2008.)

Approaches to Candidate Discovery and Preclinical Evaluation

Variations in antimicrobial components in relation to STIs and HIV neutralization in cervicovaginal fluid of HIV-uninfected Kenyan sex workers (Abstract WEAA0205)

Levinson P, Kaul R

Results from the first comprehensive analysis of cervicovaginal innate immune factors with anti-HIV activity in a sizeable high-risk population were presented. Levels of antiviral innate immune components in cervicovaginal fluid samples from 113 HIV-uninfected female sex workers from Kenya were measured to assess their HIV-neutralizing capacities and relationship to prevalent sexually transmitted infections. Innate factors quantified were secretory leukocyte protease inhibitor (SLPI), the antimicrobial cathelicidin LL-37, regulated upon activation normal T-cell expressed and secreted (RANTES), interferon-alpha (IFN-alpha), beta-defensins 2-3 (HBD2-3) and alpha-defensins 1-3 (HNP1-3). The IgA1-depleted secretion samples were subsequently tested for neutralizing capacity using primary HIV-1 isolates to determine biological relevance of the measured molecules. Data regarding risk factors and concomitant STIs were also collected.

Results showed that 23 of 113 IgA1-depleted samples evaluated neutralized a clade A primary isolate and 13 neutralized both clade A and C primary isolates. HIV neutralization against clade A and C isolates was significantly correlated with increased levels of HNP1-3 and LL-37. Prevalent infection by chlamydia or gonorrhea was associated with significantly higher levels of HNP 1-3, LL-37, and HBD 2-3, but not with changes in levels of RANTES or SLPI. The authors suggested that such innate immune factors may show utility in developing an anti-HIV vaccine or microbicide, but additional research in this area will be needed.

EDITOR'S NOTE: The authors published a more extensive version of this research in the 28 January issue of* Journal of the International AIDS Society *(Levinson P, Kaul R, Kimani J, Ngugi E, the Kibera HIV Study Group, Moses S, MacDonald K, Broliden K, Hirbod T. Levels of innate immune factors in genital fluids: association of alpha defensins and LL-37 with genital infections and increased HIV acquisition.* JAIDS *23(3): 309-17, 2009.)

Evaluation of molecular mechanisms of mucosal immunity in the genital tract on exposure to NisCar gel (Abstract THPDA103)

Gupta S, Aranha C, Reddy KVR

This study investigated the impact of NisCar gel on mucosal immunity in the genital tract by evaluating the expression of Toll-like receptors (TLRs), cytokines, and CD-markers in rabbit vaginal epithelium. *In vitro* model systems for monitoring undesirable pro-inflammatory effects of NisCar gel were also identified. Immunofluorescent microscopy, flow cytometry, RT PCR, ELISA, and other molecular methods were used. Results show that after intravaginal application of NisCar gel, no alteration in TLRs, cytokines, and CD-markers was observed in cervicovaginal epithelium of rabbits. Additionally, no alteration in NF-kB activation and defensin-1 gene expression was observed in cervicovaginal epithelial cells after administration of NisCar gel.

The authors concluded that TLRs, cytokines, and CD profiles in cervicovaginal cells may be useful *in vitro* model systems for monitoring undesirable pro-inflammatory effects of NisCar gel and predicting the vaginal inflammatory potential of microbicides. In summary, NisCar gel did not cause adverse effects on the mucosal immune system, suggesting its suitability for further testing as a microbicide.

Development and characterization of a humanized-cervicovaginal murine model for the study of HIV-1 transmission and infection (Abstract MOAA0104)

Kish-Catalone T

The NOD/SCID-hu immunocompromised murine model reconstituted with human peripheral blood mononuclear cells (PBMC)—a small animal (mouse) model currently being developed to evaluate preclinical safety and efficacy of biologically active anti-HIV-1 agents—was used to evaluate the relationship between cervicovaginal toxicity and susceptibility to HIV infection and to examine the cell populations involved in establishing HIV-1 infection. Cervicovaginal tissues of mice engrafted with human PBMC showing immune cell populations circulating in the blood after fluorescence-activated cell sorter (FACS) analyses were harvested. They were further analyzed using immunohistochemical methods to determine specific human immune cell populations present. Microbicide-induced inflammation and toxicity and the recruitment of human PBMC into the cervicovaginal epithelia were observed:

- Human immune cell populations were detected in the peripheral blood of PBMC-reconstituted NOD/SCID-hu mice, and also detected moving into the cervicovaginal mucosa;
- CD45+ cells were present in the mouse spleens for at least two months after reconstitution.

Given these observations, the authors concluded that the NOD/SCID human xenograft model may be a useful small animal system for studying HIV-1 transmission in tissue with human immune target cells, and for examining initial cell populations involved in the establishment of HIV-1 infection.

In-vitro *evaluation of antibacterial efficacy of Nisin and NisCar gel formulations in human cervicovaginal lavages: a randomized pilot study (Abstract TUPE0004)*

Aranha C, Gupta S, Meherji P, Reddy KVR

The objective of this study was to investigate the antibacterial efficacy of Nisin and NisCar gel formulations in human vaginal fluid and to evaluate their effect on vaginal flora. A combination gel of Nisin (0.1%) and carrageenan (1%) was used and its effect on vaginal pH, cytokine levels, and levels of bacteria present in human vaginal fluid was assessed.

The results suggest that human cervical vaginal fluid provides an appropriate source for testing the efficacy of microbicides against potential pathogens

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in the human reproductive system before proceeding to clinical trials. In the presence of the gel combination, vaginal pH was restored to normal in patients with bacterial vaginosis (BV). Cytokine levels increased to normal range in women with BV infections. The Nisin and carrageenan acted synergistically in combination. Growth of certain strains of lactobacilli was also inhibited by the gel formulations.

Future research by these authors will identify the strain of Lactobacillus inhibited by Nisin/NisCar gels, evaluate whether these gel formulations could be used to treat BV, and determine whether the experimental protocol used in this study is appropriate for comparing and prioritizing different candidate products.

Models for Clinical Evaluation of Candidate Microbicides

A Phase 1 safety and acceptability study of the UC-781 microbicide gel applied rectally in HIV seronegative adults: an interim safety report at 86% completion (Abstract CDA0041)

Anton P, Saunders T, Adler A, Siboliban C, Khanukhova E, Price C, Elliott J, Tanner K, Cho D, Johnson E, Klein J, Dominguez A, Watson S, Boscardin J, Mauck C, McGowan I

Blinded, interim results from a Phase 1 rectal microbicide study of the vaginal formulation of UC-781 gel suggest that the microbicide is safe and well-tolerated by participants when applied to the rectum. The study, the first to test UC-781 gel in the rectum of humans, is being conducted by the University of California, Los Angeles, National Institute of Allergy and Infectious Disease (NIAID), and CONRAD to obtain data on the product's safety and acceptability when rectally administered to 36 HIV-1 seronegative adults.

Participants (adult men and women) who have completed the trial thus far attended five visits, during which they 1) were screened; 2) participated in baseline evaluation; 3) were randomized to one of three groups: 0.1% UC-781 gel, 0.25% UC-781 gel, or a placebo gel (12 per group); 4) administered a single dose of study gel to which they were assigned, and clinically evaluated; 5) self-administered single daily doses of their assigned study gel for seven consecutive days; and 6) returned to the study clinic for final follow-up and evaluation. Investigators also collected data from participants that would allow them to evaluate potential surrogate markers of safety and efficacy (e.g., mucosal cytokine profiles, secreted mucosal immunoglobulins, fecal calprotectin assessing mucosal inflammation, and explant infections for direct HIV challenge of mucosa *ex vivo*).

Results of the study at 86% completion (31 of 36 intended participants have completed the study) were presented at the conference. At the time of presentation, no participant withdrawals had occurred, and according to the investigators, participants were highly compliant and coped well with trial procedures. Among the 31 participants included in this analysis, 82 adverse events (AEs) were reported, 91% of which were Grade 1 (Mild). Four participants reported seven Grade 2 (Moderate) AEs. No procedure-related AEs or AEs of Grade 3 (Severe) or higher were reported. The investigators, also the first to incorporate use of new Division of AIDS (DAIDS)/NIAID-approved toxicity tables for rectal safety studies into a clinical trial, reported that the grading tables appear sensitive enough to distinguish procedure-related expected AEs from others, which is an important distinction to make when assessing and reporting AEs in clinical trials.

Comparing and Prioritizing Candidate Microbicides

Evaluating the use of non-nucleoside reverse transcriptase inhibitors in carrageenan-based microbicides (Abstract THPDA102)

Fernandez-Romero J, Maguire R, Zydowsky T, Mawson P, Chudolij A, Begay O, Ford B, Phillips DM

Four different non-nucleoside reverse transcriptase inhibitors (NNRTIs) were evaluated in this study—MV007662-1, MV008216-1, MV012403-1, and

MV2531-1—in an effort to find suitable candidates to combine with carrageenan-based microbicides. Cytotoxicity, antiviral, and virucidal activities (including combination effects with carrageenan), resistance, and antiviral activity against multidrug-resistant HIV-1 primary isolates were assessed. The results suggest that MV2531-1 may be a promising microbicide candidate since, compared to the other three NNRTIs evaluated, it:

- was the least cytotoxic when evaluated in neutralizing antibody assays, TZM-bl, and PBMCs;
- showed the best antiviral activity (using the MAGI antiviral assay);
- had the best Therapeutic Index;
- retained antiviral activity in the presence of seminal fluid;
- had the strongest virucidal activity of the candidates tested;
- had the best resistance profile (development of resistance against it was considerably delayed compared to the other compounds);
- demonstrated an additive effect when combined with carrageenan; and
- was able to block the multidrug-resistant HIV-1 strains significantly better than any of the other compounds tested.

A systematic review of the clinical safety of candidate vaginal microbicides in women (Abstract WEPE0270)

Poynten IM, Millwood I, Falster M, Andresen D, Van Damme L, Kaldor J

A systematic review of published human safety trials of potential vaginal microbicides was conducted, in which design features of studies were summarized and meta-analyses performed for endpoints of urogenital symptoms, genital signs with disrupted epithelium, genital signs with intact epithelium, and bacterial vaginosis (BV). Fourteen trials of seven products met study inclusion criteria. Only a small number of products had more than one eligible trial that could be included in the analyses. A total of 1,104 women participated in the 14 trials. The mean study sample size was 62 women (range 24–180). The mean study duration was 14 days (range 5–365). Most trials were generally short in duration; only three trials reported that participants were exposed to study products for longer than two weeks.

The authors concluded that most trials included in the analysis had small sample sizes and few events, and statistical power that was too low to detect treatment differences. Confidence intervals were often too wide to draw sound conclusions about whether an outcome was affected by a particular trial product. The authors noted the limitations to their analysis.

In summary, the review highlights the lack of published safety data for candidate microbicides. It also points to the need to 1) standardize endpoints measured across safety trials of similar and different products so that cross-comparisons can be made, and 2) conduct longer and larger safety trials.

Mixed-Method Approaches to Behavioral and Social Science Research

Assessing the impact of acceptability on adherence in the Carraguard Phase 3 trial (Abstract THPE0120)

Katzen L, Friedland B, Littlefield S, de Kock A, Palanee T, Gehret M, Morar N, Skoler S, Mehlomakulu V, Williams M, Abbott S

Acceptability and its impact on adherence were assessed during the Population Council's Phase 3 trial of Carraguard® conducted in South Africa. Multivariate regression analyses were used to determine predictors of adherence among a subsample of women participating in the trial from three South African trial sites [South African Medical Research Council (MRC), University of Cape Town in Gugulethu, and University of Limpopo in Medunsa]. Adherence was measured using vaginal applicator tests and self-reported sex acts. The study showed that being from the MRC site (the trial site with the highest HIV prevalence rates of the three sites included in the trial) was a statistically significant predictor of higher adherence levels. Higher coital frequency (measured as average weekly sex acts) predicted lower levels of adherence, as

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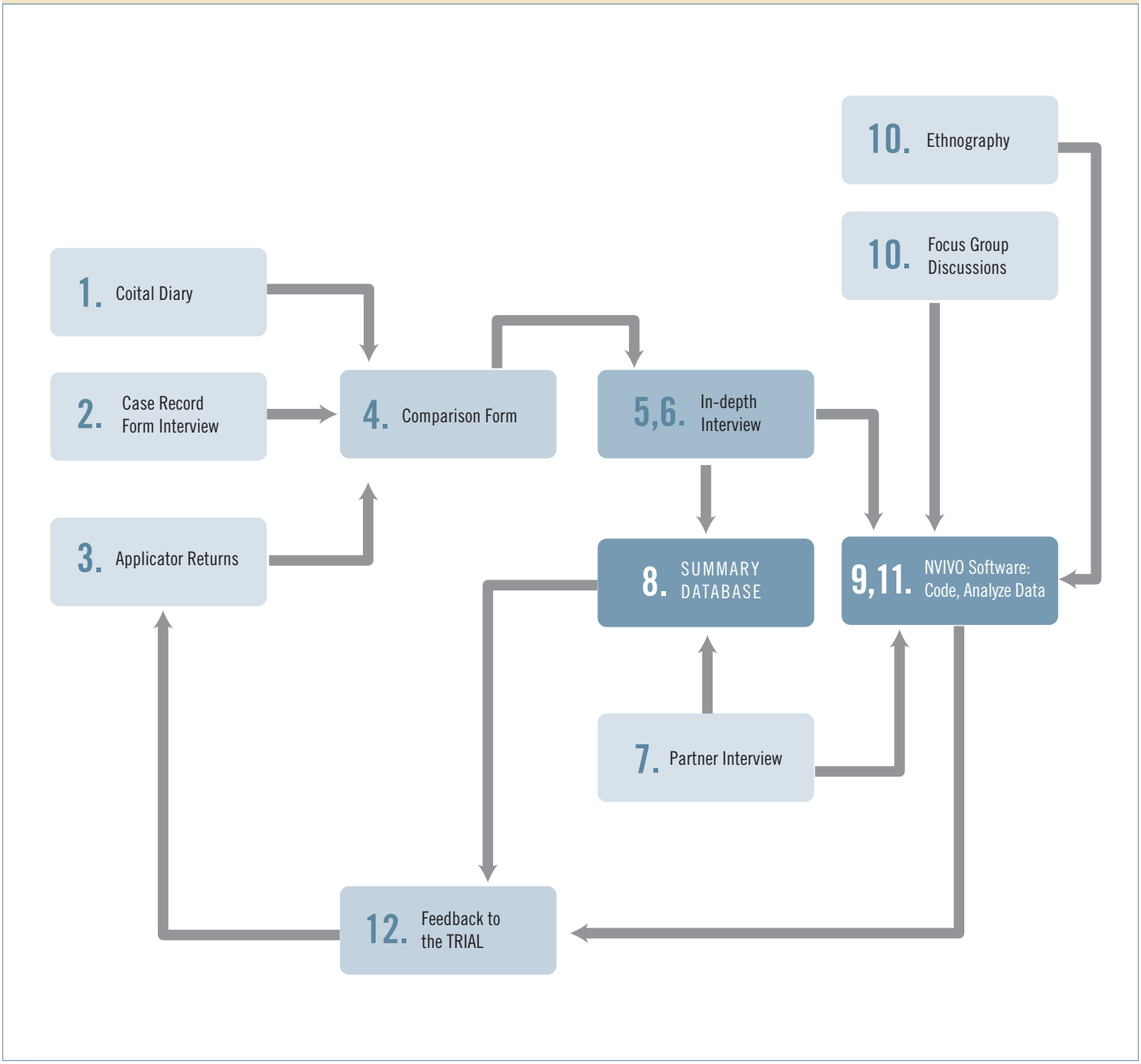
FIGURE 1. TRIANGULATION PROCEDURES USED IN THE MICROBICIDES DEVELOPMENT PROGRAMME (MDP) PHASE 3 TRIAL OF A VAGINAL MICROBICIDE



did reporting joining the study for the purpose of testing a gel that might prevent HIV. Participant age, education, and reported partner pleasure from gel use (based on self-reports only) were not statistically significant predictors of adherence. The study suggests that microbicide trial participants in higher-risk areas may adhere more to product use compared to those from lower-risk areas. The authors concluded that products should be designed so that women with different sexual frequencies can adhere to product use, and that questions related to acceptability should be integrated into ongoing clinical trials to improve understanding and interpretation of adherence and other trial data.

Towards a new model for mixed-method research in HIV-related clinical trials: the example of the Microbicides Development Programme (Abstract MOPE0437)

Pool R, Montgomery C, The MDP Team

Issues associated with using different approaches to mixed-method research in large-scale clinical trials of vaginal microbicides to prevent vaginally-acquired HIV transmission were discussed. Drawing from experiences conducting a large-scale Phase 3 microbicide clinical trial, the authors cited reasons for moving toward a mixed-method approach to data collection:

- They reported instances where data collected through qualitative methods were more accurate than data collected quantitatively, which countered assumptions that quantitative data are more accurate than qualitative data.
- Their experiences suggest the research process is not as neutral as it is assumed to be. Instead, it influences study participants' perceptions, which in turn influence participants' answers to study questions.
- They displayed how questions from different methods may have different meanings and interpretations for trial participants, and concluded that it was insufficient to simply combine methods without first reflecting on the implications that their respective underlying paradigms have for the interpretation of the data.

In summary, there is need instead to develop a mixed-model approach that moves beyond simply combining different methods within the assumptions of a single paradigm and comparing how the results they produce differ. Such a mixed-model approach would be more likely to increase convergence and resolve inconsistencies in data sets. The example given was the "triangulation" process used in the Microbicides Development Programme (MDP) Phase 3 trial of PRO 2000 (MDP 301) *(see Figure 1)*. Integration of information from various methods and sources using the data triangulation method provided more insightful and useful information than using isolated data collection methods. Using the triangulation process, MDP researchers were able to reconcile substantial inconsistencies between sets of data acquired from the same participants through different quantitative and qualitative methods, and 80% of such inconsistencies were resolved through in-depth interviews.

Secrets, pleasure, and vaginal microbicides: implications for adherence (Abstract TUPE0768)

Woodsong C, Alleman P, Musara P, Chandipwisa A, Chirenje M, Salima C, Hoffman I, Martinson F

An ancillary study of a clinical trial of two microbicide gels was conducted in Malawi and Zimbabwe to investigate differences in participant pre-use expectations and use experiences. A "Comprehensive and Flexible" conceptual framework, which employs a range of qualitative research methods, including guided data collection, was used.

Study participants included women participating in the clinical trial (primarily those in stable sexual relationships), male partners of trial participants, health professionals, and community leaders. The study compared pre-use expectations and use experiences for three gel characteristics: side-effects; effects on sex; and secret use. It found that most participants expected

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TABLE 1. REASONS FOR JOINING THE CARRAGUARD® PHASE 3 TRIAL REPORTED IN AN EXIT SURVEY AMONG A SUBSAMPLE OF TRIAL PARTICIPANTS FROM SOUTH AFRICA (Number of participants in subsample = 1,601)

Reasons for joining the trial	% of participants
HIV testing/counseling	56%
Help test a product that may prevent HIV	21%
Free exams	16%
Other (compensation, chance to use/be protected by gel, STI treatment)	8%

male partners to notice their gel use, which in turn influenced them to disclose gel use to their male partners prior to use. Most women and men using gels found them to either increase sexual pleasure or have no effect on sex. The most commonly mentioned pre-use concern among female trial participants and their male partners was fear of side effects; however, this disappeared as a concern during use experiences. For most participants, side effects from gel use did not occur, or were short-lived or minor.

The authors concluded that adherence to use requirements of a proven effective microbicide may be improved by strategies that:

- introduce products previously shown to have minimal side effects on both women and men;
- disclose possible effects of product use on sexual experiences within the context of local social and cultural norms for sexual pleasure; and
- in comparable sociocultural settings, do not emphasize microbicides as something women can secretly use without a partner's knowledge.

What motivates women to enroll in vaginal microbicide clinical trials: results from the Phase III Carraguard trial (Abstract WEPE0272)

Abbott S, Friedland B, Katzen L, de Kock A, Madiba S, Cishe S

In-depth interviews, focus groups, and exit interviews were conducted with a subsample (N=1,601) of Carraguard® Phase 3 trial participants from trial sites in South Africa to examine motivations to participate in a clinical microbicide trial. A modified grounded-theory approach was used to code and analyze participant responses.

Among the participants sampled, HIV testing (the desire to know one's HIV status) and counseling was the predominant motivator, both for joining *(see Table 1)* and remaining in the trial. Helping to test a product that could prevent HIV and free examinations were other lesser motivators for trial participation. The low ranking of financial compensation may have been a function of "social desirability" among participants reluctant to disclose compensation as a primary motivation. The authors noted that while the overall impression from these responses is that provision of the higher-quality health services via clinical research may be a significant motivator to join and remain in future trials, more research is needed to understand why women appear more willing to test at study clinics rather than VCT clinics.

What is HIV research telling us about women's sexuality? Exploring the construction of sexuality during the Phase III clinical trial of a microbicide gel in Mwanza, Tanzania (Abstract WEPDD103)

Lees S

Various methods, including semi-structured depth interviews (SSDIs), focus group discussions (FGDs), participant observation, case studies, and modified participatory learning activities (PLA) (e.g., body mapping) were used to explore concepts of sexuality among women participating in the Microbicide Development Programme Phase 3 trial of PRO 2000/5 gel (MDP 301) in Mwanza, Tanzania. Data collection methods were also compared to determine which of these might provide useful knowledge about sexuality in the context of medical research.

The study showed that SSDIs and FGDs conducted with trial and non-trial participants provided information about gel and trial experiences, but since these methods focus on behaviors, they revealed limited information about sexuality (except for pleasure associated with the gel). The PLA and participant observation methods, however, produced more in-depth descriptions of sexuality and how it relates to perceived HIV risk than was the case for SSDIs and FGDs. The study author modified the PLA method for use in future FGDs and plans to conduct a critical analysis of data produced by SSDIs and FGDs. The purpose of this analysis would be to determine what types of research questions about sexuality can be most informative in the context of the HIV pandemic.

Preparatory Studies

Estimating HIV incidence in high-risk women and VCT clients in Kigali, Rwanda, in preparation for microbicide trials (Abstract THPE0247)

van de Wijgert J, Ingabire C, Braunstein S, Ntirushwa J, Geubbels E, Kestelyne E, Gahiro AE, Ford K, Umulisa MM, Vyankandondera J

Cross-sectional surveys and a prospective cohort study were conducted to estimate HIV incidence among high-risk women and VCT clients in Kigali, Rwanda to determine if microbicide trials were feasible in this population. Women enrolled in the cross-sectional and cohort studies were tested for HIV-1, HIV-2, and HSV-2 antibodies, and pregnancy. Those enrolled in the cohort study were also tested for other STIs, vaginal infections, and HPV. Data collected were used to estimate HIV, STI, and pregnancy prevalence rates and cumulative HIV incidence. The cohort study was still ongoing at the time of the *AIDS 2008* conference, so only preliminary results were presented.

Based on 100 women-years of follow-up, cumulative HIV incidence among the cohort of high-risk women was 3.8 per 100 woman-years of follow-up. HIV prevalence among high-risk women was approximately three to four times as high; among female VCT clients, prevalence was two to three times as high as the most recent estimate of HIV prevalence in the general adult female population in Kigali (6.6% in 2005).

The study supports the conduct of microbicide trials in Kigali and concludes that it is possible to successfully recruit and retain women at high risk of HIV infection for clinical trials in this region.

Knowledge about HIV/AIDS and willingness to participate in New Preventive Technologies trials (NPT) among a Nigerian refugee population (Abstract CDD0025)

Akinyemi O, Onigbogi O

The purpose of this study was to determine if refugees in Nigeria might constitute a suitable population for clinical trials of new HIV prevention technologies. Questionnaires were administered to a random sample of 252 refugees in Nigeria to evaluate their knowledge of HIV/AIDS and willingness to participate in clinical trials of new HIV prevention technologies. Survey responses, analyzed using SPSS®, yielded the following results:

- Demographics: Survey respondents were both female (51%) and male (49%); mean age was 27.7 years; and most were either Liberian (60.7%) or Sierra-Leonean (30.7%). A large proportion of respondents (48.8%) had lived in the refugee camp for five or more years prior to taking the survey. Most respondents reported having at least some secondary education (88.1%); 55% reported having a tertiary education or its equivalent.
- Knowledge of HIV/microbicides: Most respondents who reported having at least some secondary education believed that HIV/AIDS could be cured using local herbs (p=0.021).

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Respondents with less than a secondary school education were significantly less likely to have ever heard of microbicides compared to those with a tertiary education or its equivalent (p=0.04).

- Willingness to participate in NPT: Those who had used an illicit drug in the past one month (69.7%) were willing to participate in clinical trials for HIV vaccines (p=0.06).

The authors concluded that more research is needed to evaluate this population's suitability for NPT research, and that more work is needed to educate this vulnerable population about HIV/AIDS and NPT research.

Approaches to Navigating Trial Closures and Completions

The impact of the premature closure of an HIV prevention Phase III clinical trial on human capital in South Africa (Abstract MOPE0813)

Narain N, Morar NS

This poster described procedures used by the Medical Research Council (MRC) to minimize effects of the closure of the Phase 3 trial of cellulose sulfate on skilled staff (e.g., clinical trial workers) in South Africa.

As mandated by the Labour Relations Act of South Africa, the MRC followed a series of steps to ensure that trial staff were appropriately informed of the status of the study and the possibility of staff retrenchments and redeployment. Although most members of the trial staff were eventually redeployed, premature trial closure did adversely affect the mental health of some trial staff as expressed in reduced motivation and anxiety and concerns about job security. MRC minimized the negative impact of the closure by developing and consistently using open communication and providing counseling and face-to-face discussion to staff; this proved essential to preventing resignations and further declines in morale and motivation. Staff retention and redeployment strategies were developed and acted on quickly and after redeployment, new staff were immediately retrained and realigned with new study teams, protocols, management, and work environments.

The authors advised that the best approach in such situations is to closely adhere to all labor processes and regulations, and to develop (in advance, if possible) and maintain open and effective communication strategies and policies between employees and employers.

Concerns on end of study—a case for women completing 52 weeks in the MDP 301 study in Mazabuka (Abstract MOPE0852)

Mazunda C, Mundia K, and Community Mobilization

This study explored the concerns of women who completed follow-up in the Microbicide Development Programme (MDP) Phase 3 trial of 0.5% PRO 2000 vaginal microbicide gel (MDP 301) and highlights their perspectives on gel use and study outcome. Women who completed all study procedures were given an incentive (a wall clock) and asked to participate in a survey of their views of the trial and its outcome. Most women completing the 52 weeks of follow-up reported liking the gel and many were concerned about how they would cope without it since:

- some reported it increased their sexual pleasure;
- some liked using vaginal gel as a lubricant; and
- others felt that without the gel, they would be vulnerable to HIV since they believed gels were protective.

Some women questioned whether it was safe for them to have children after participating in the study. Others felt they should have been better rewarded by trial staff for taking part in the study.

Modeling: Introduction and Access

The implications of inadequately modeling AIDS mortality for the expected impact of microbicides: a modeling study (Abstract MOPE0259)

Delva W, Vansteelandt S, Claeys P, Annemans L, Temmerman M

This study explored the implications of using different models for HIV-related mortality to estimate HIV incidence from HIV prevalence data. National HIV prevalence data for Kenya from 1980 to 2006 were employed to estimate time trends in past HIV incidence. Four different models for the cumulative distribution function of mortality after HIV seroconversion were used and modeled trends in HIV incidence were compared.

The researchers suggested that methods traditionally used to model the HIV epidemic may inadequately account for HIV-related mortality. Further, epidemiological models that poorly reflect the survival of HIV-positive individuals are likely to produce biased estimates of the impact of new or scaled-up HIV prevention programs. The observed differences in the implied HIV incidence rates appeared to be directly related to differences in implied HIV-related death rates. The authors instead proposed application of stochastic, discrete-event simulation methods to estimate HIV incidence from HIV prevalence data and use of more recent estimates of HIV incidence as a proxy measure for the maximal short-term potential to avert new HIV infections.

In summary, choice of model structure and parameter estimates used to estimate AIDS mortality for the expected impact of microbicides should be based on comprehensive statistical analyses of the full survival distribution rather than on the mean durations of the different states of HIV infection.

Microbicide uptake likely to be higher among women not using condoms: results from a discrete choice experiment in Johannesburg, South Africa (Abstract WEPE0269)

Terris-Prestholt F, Kumaranayake L, Macphail C, Rees H, Watts C, HIV Tools Research Group

A discrete-choice experiment was conducted among 1,017 women in three Johannesburg townships to determine the impact of different potential microbicide HIV-efficacies on the probability of women switching from what they did last time they had sex. Women were presented with different choice scenarios:

- different barrier methods (microbicides, diaphragms, female condom);
- "what I did last time I had sex" (used "a male condom" or "no condom");
- different HIV-efficacies (35%, 55%, 75%, 95%);
- pregnancy prevention efficacies (0%, 55%, 75%, 95%); and
- prices (free, 5 Rand, 10 Rand, 20 Rand).

A multinomial logit model was used to estimate preferences for products and attributes, and to calculate women's choice probabilities for the different scenarios:

- Among women who had not used a male condom in their last sex act, the probability of choosing the baseline microbicide (one 55% HIV effective, not protective against pregnancy, and costs 10 Rand) over the female condom or neither was 10%.
- For a microbicide with 95% HIV-efficacy (with costs and pregnancy prevention at baseline levels), the probability of switching would increase to 31%; if the microbicide were also 95% effective against pregnancy, the probability would double to 60%. If the 95% HIV-effective microbicide were free, the probability of switching would be 65%.
- The highest choice probability (65%) was for a microbicide that could be used in secret with 95% efficacy against HIV and pregnancy and was free; the lowest choice probability (5%) was for a microbicide that could not be used in secret, had no pregnancy effectiveness, was just 35% effective against HIV, and would be sold at 20 Rand.

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The study proposes that product efficacy is critical in women's choices and that predicted uptake of microbicides with poor effectiveness would be low, especially among women already successfully using condoms. Women able to use male condoms in their last sex act reported that they were less likely to choose microbicides than those for whom male condom use was not possible; therefore, the authors concluded that migration away from condoms to microbicides is a less likely concern. They also noted that product potential to prevent pregnancy might enhance microbicide attractiveness and eventual use and that while price could be used to enhance use among women unable to use condoms, it might be persuasive for women for whom condom use is possible.

Effectiveness of community integration strategies for HIV microbicide delivery in Gauteng province of South Africa (Abstract CDC0386)

Cox SP, Foss A, Kumaranayake L, Vickerman P, Terris-Prestholt F, Chimbwete C, Okonji E, Moyes J, Delany-Moretlwe S, Rees H, Watts C

Comparing the impact of alternative strategies for introducing microbicides into a Southern Indian setting (Abstract CDC0384)

Foss A, Cox A, Vickerman P, Ramesh BM, Reza-Paul S, Kumaranayake L, Demers E, Vyas S, Guinness L, Lowndes C, Alary M, Moses S, Watts C

Researchers at the London School of Hygiene and Tropical Medicine utilized an innovative approach to identifying future introduction strategies, ascertaining their potential impact at the country level, and identifying factors that influence their impact. Country-level workshops to elicit potential strategies for future introduction of microbicides were held in two settings: 1) Gauteng province of South Africa, and 2) Mysore in Karnataka, India.

Three future introduction strategies from each workshop were evaluated for their potential impact.

For South Africa, the strategies evaluated were:

- integration into public and private provision of contraceptives;
- targeted distribution to youth, through youth-friendly services, social marketing, and family planning providers; and
- integration into services providing HIV testing.

For southern India, they were:

- marketing as a vaginal health product for all women;
- provision through sex worker programs, promoted for use as a fall-back to condoms; and
- provision through sex worker programs, promoted for use in non-commercial sex.

Mathematical models that incorporated epidemiological and economic data from each setting were used to estimate the potential impact of each introduction strategy over a three-to-five-year and 10-year period. Each strategy was evaluated using four different assumptions for HIV-efficacy and consistency of use when condoms are not used:

- 35% per sex act HIV-efficacy used with 50% consistency;
- 60% per sex act HIV-efficacy used with 65% consistency;
- 85% per sex act HIV-efficacy used with 80% consistency; and
- 35% per sex act HIV-efficacy used with 80% consistency.

Sensitivity analyses were used to evaluate how impact is related to HIV-efficacy and consistency, STI-efficacy, and bi-directional effects. This strategy appears to be a particularly useful approach to identifying future strategies and evaluating their potential impact in country-specific contexts.

Modeling: HIV/STI Interactions

Exploring the interactions between HSV-2 and HIV: model predictions for a southern Indian setting (Abstract MOPE0360)

Foss A, Vickerman P, Mayuad P, Weiss H, Ramesh B, Reza-Paul S, Washington R, Lowndes C, Alary M, Watts C

How much HSV-2 contributes to HIV transmission, and vice versa, was estimated for a cohort of female sex workers (FSWs) in southern India using a model that describes interactions between the two viruses, and assumes one-way transmission from clients to FSWs and constant client prevalence over a five-year period. Model parameters were set using published literature and epidemiological and behavioral data collected from FSWs and clients from or nearby Mysore, Karnataka, India, as part of the India AIDS Initiative. Population attributable fractions (PAFs) of HIV infections due to HSV-2 infections, and vice versa, were determined, and multivariate sensitivity and multilinear regression analyses were conducted. The model, run on 10,000 parameter sets, produced 401 models fits (based on prevalence).

The results suggest that within this southern Indian context, each virus appears to substantially contribute to the other's epidemic. Specifically, approximately one-third (36%; 95% CI 22-62%) of HIV infections among FSWs in this population were due to HSV-2, mostly attributable to increased HIV susceptibility among HSV-2 positive/HIV-negative FSWs and increased HIV infectivity among co-infected clients.

Additionally, HIV may have increased HSV-2 incidence among FSWs by approximately 44%, mostly attributable to increased shedding rates and heightened HSV-2 infectivity among co-infected clients. Asymptomatic HSV-2 shedding appeared to contribute substantially more to HIV transmission than symptomatic shedding recurrences. Sensitivity analyses showed that PAFs for HIV incidence were most sensitive to co-factors that increased the per-sex act probability of transmission of HIV in the presence of HSV-2, and PAFs for HSV-2 incidence were most sensitive to co-factors for increased HSV-2 shedding rates among those co-infected with HIV.

STAKEHOLDERS IDENTIFY NEXT STEPS FOR MICROBICIDE ACCESS AT INTERNATIONAL FORUM

Youssef Tawfik and Vimala Raghavendran, International Partnership for Microbicides

The second *Microbicide Access Forum* held in Mexico City on 3 August 2008 helped advance the way forward for microbicide access by bringing together more than 40 representatives from microbicide development, government, research and science, HIV/AIDS advocacy, the pharmaceutical industry, and reproductive health to evaluate the current state of access planning and draw on lessons learned from the introduction of health technologies in developing countries.

Hosted by the International Partnership for Microbicides, Population Council, and World Health Organization, with funding from the US Agency for International Development and the European Community, the event was held in advance of the 18th *International AIDS Conference*.

Forum participants assessed recent progress in microbicide development and new data on microbicide acceptability. The London School of Hygiene and Tropical Medicine discussed preliminary findings from a recent mathematical modeling study designed to forecast the impact of microbicide introduction in India and South Africa. The research clearly illustrates how factors such as efficacy, distribution channels, and speed of regulatory approval could act together to play a critical role in determining eventual microbicide uptake.

Continued on p.14

STAKEHOLDERS IDENTIFY NEXT STEPS *(Continued from p. 13)*

Participants also explored the pharmaceutical industry's experience introducing antiretroviral therapy in developing countries, with a focus on the crucial role partnerships play in providing access to new products there.

Recent efforts to introduce human papillomavirus (HPV) vaccines for preventing cervical cancer into government programs were also examined, along with the criteria policymakers use at the country level to decide whether and how to introduce new health products.

Forum participants adopted the strategic next steps outlined below:

- **Encourage regulatory strengthening and harmonization:** Weak regulatory capacity in developing countries and the absence of clear regulatory guidelines create major delays in clinical study implementation. The microbicide field needs to work with governments hosting studies as well as donors to consider initiatives that will strengthen and harmonize regulatory systems.
- **Plan for access financing:** The experience of introducing new health technologies—from the female condom, antiretroviral therapy for AIDS treatment and, more recently, the HPV vaccine—point to the importance of developing global financing sources to support the introduction and scale-up for future microbicides.
- **Engage civil society:** The microbicide field has received significant support from grassroots advocates both in developed and developing countries. In fact, advocates played a crucial role in building early support for the microbicide field by highlighting the increased vulnerability of women in the HIV epidemic and making the case for female-initiated HIV prevention tools such as microbicides. Advocates in developing countries could also play a central role in facilitating support for clinical research among policy-makers and communities. The microbicide community must examine its global advocacy strategy and meaningfully engage advocates and grassroots supporters while managing expectations.
- **Build capacity for social science research:** As the microbicide field gets closer to proof-of-concept, marketing and product positioning will become increasingly important. Social science research can make significant contributions to understanding product acceptability, use, and context of use.
- **Develop product-specific introduction strategies:** As microbicide product developers get closer to licensure, the field will need a product-specific introduction strategy that identifies countries in which the product would be initially launched, and country-specific strategies for manufacturing, financing, distribution, community engagement, marketing, and evaluation. The microbicide community must synchronize these activities with progress in clinical trials.

The *Microbicide Access Forum* is an annual event that provides an opportunity for stakeholders to share information, discuss timely issues, and examine new evidence to plan for the future introduction and use of microbicides. The first forum was held in Nairobi, Kenya, in 2007.

Presentations from the 2007 and 2008 *Microbicide Access Forums* can be downloaded from *http://www.ipm-microbicides.org/ensuring_future_use/english/microbicides_access_forum.htm.* For more information, please contact IPM Senior Policy Associate Vimala Raghavendran at *vraghavendran@ipm-microbicides.org.*

MICROBICIDE CANDIDATES IN ONGOING CLINICAL TRIALS *Summary as of September 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
2	Tenofovir gel	RI	Adherence and pharmacokinetics study of oral and vaginal preparations of tenofovir (MTN-001)	MTN	South Africa, Uganda, United States
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	United States
	Tenofovir gel	RI	Pharmacokinetic study of the vaginal microbicide agent 1% tenofovir gel (A04-095)	CONRAD, IPM/USAID	Dominican Republic, United States
	Tenofovir gel	RI	Maternal pharmacokinetics and placental perfusion of tenofovir/PMPA gel (MTN-002)	MTN	United States
	Tenofovir gel	RI	Effect of repeated applications of tenofovir gel on mucosal mediators of immunity and intrinsic antimicrobial activity of cervicovaginal secretions	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	South Africa, Tanzania (ongoing sites); Kenya (follow-up)

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), and Surfactant (S)

**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 is ongoing but pending enrollment.
***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 September 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
	Dapivirine (TMC120)	RI	Dapivirine efficacy study (IPM 009)	IPM	
2/3	Invisible Condom®	EFI	Effectiveness of Invisible Condom® in high-risk women		
2/2B	Tenofovir	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	Sites in Africa TBD
1/2	Dapivirine (TMC120)	RI	Safety and acceptability of dapivirine gel, conducted using daily monitored adherence in healthy HIV-negative women (IPM 014A)	IPM	TBD
	Dapivirine (TMC120)	RI	Safety and acceptability of dapivirine gel, conducted using daily monitored adherence in healthy HIV-negative women (IPM 014B)	IPM	TBD
	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	TBD
	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
	VivaGel® (SPL7013 gel)	EFI	Assessment of local retention and duration of activity of SPL7013 following vaginal application of 3% SPL7013 Gel (VivaGel®) in healthy volunteers	Starpharma, NIAID, NIH	Australia
1	CAP vaginal soft tablet	C	Safety and acceptability of CAP vaginal microbicide soft tablet	New York Blood Center, NIAID	United Kingdom
	Dapivirine (TMC120)	RI	Dapivirine gel male tolerance study (IPM 010)	IPM	TBD
	Dapivirine (TMC120)	RI	PK study in healthy HIV-negative women to assess delivery of dapivirine from intravaginal rings (IPM 013)	IPM	Belgium
	Dapivirine (TMC120)	RI	Study to evaluate effect of dapivirine gel on vaginal flora (IPM 023)	IPM	Belgium
	Duet®	C	Duet® acceptability and safety study	ReProtect, RTI International, IPM	Zimbabwe
	PC-815	C	Randomized, double blind, crossover safety study of two microbicide formulations: PC-815 and Carraguard®	Population Council	Dominican Republic, South Africa
	PRO 2000	EFI	Postcoital anti-viral activity of cervicovaginal secretions following intravaginal application of 0.5% PRO 2000/5 Gel (P)	AECOM, Indevus, NIH	United States
	Tenofovir gel	RI	Device for Vaginal Drug Delivery (DVD2) with tenofovir gel vs. plain tenofovir gel	FHI	
N/A	Placebo ring	Placebo	Expanded safety and acceptability study of a non-medicated intravaginal ring (MTN-005)	MTN, IPM	India, United States
	No product	N/A	Seroconverter protocol (IPM 007)	IPM	
	Placebo	Placebo	Pilot study to evaluate the accuracy of the Smart applicator for microbicide clinical trials (IPM 022)	IPM	South Africa, United States

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

Definition of acronyms used in this table: Combination (C), Entry/Fusion Inhibitor (EFI), Mechanism of Action (MoA), Replication Inhibitor (RI), Vaginal Defense Enhancer (VDE), Vaginal and Oral Interventions to Control the Epidemic (VOICE)

**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.
‡This study includes an observational cohort study (MTN-003B), entitled "Bone Mineral Density Substudy," which will explore the effects of oral study products on bone mineral density.

THIS QUARTER IN MICROBICIDES

7 JULY *PUBLICATION:* Wilson DP, Coplan PM, Wainberg MA, Blower SM. The paradoxical effects of using antiretroviral-based microbicides to control HIV epidemics. *Proc Natl Acad Sci USA* Epub ahead of print, 2008. "Surprisingly, we show that reducing a participant's risk of resistance during a trial could lead to unexpectedly high rates of resistance afterward when microbicides are used in public health interventions. We also find that, paradoxically, although microbicides will be used by women to protect themselves against infection, they could provide greater benefit to men."

9 JULY The Microbicide Trials Network (MTN) announces the launch of MTN-001, the first trial to compare absorption of and acceptability and adherence to oral and vaginal forms of tenofovir. This Phase 2 trial involves 120 sexually active, HIV-negative women at six sites in South Africa, Uganda, and the United States.

10 JULY The Alliance begins compilation and distribution of monthly *Pipeline Updates*. Each *Update* includes information summarizing critical pipeline numbers, such as a tally of candidates and trials, along with a section on "Pipeline Changes" that alerts readers to what is going on in this critical area of microbicide research and development. *Pipeline Updates* will also be posted regularly on the Alliance website.

17 JULY Robin Maguire and David Philips announce retirement from the Population Council. Among his accomplishments, Phillips identified candidate compounds for vaginal microbicides, including carrageenan, the active ingredient in the Council's first-generation microbicide candidate Carraguard®. Maguire was instrumental in the nonclinical testing and development of Carraguard® and collaborating with Council colleagues on studies of its pharmacological effects, toxicology, and chemistry. Both Robin and David were active and dedicated members of the Alliance from its earliest days.

21 JULY The Alliance initiates work toward a comprehensive inventory of topical lubricating products, including spermicides, that are on the US domestic and international markets. This *Topical Products Inventory* will seek to include detailed information on regulated products, such as those available over-the-counter (OTC) and by prescription, with ingredients and safety (preclinical and clinical) data where available. All unregulated products will be compiled by country in a separate list, and distributors will be contacted for follow-up information.

25 JULY *PUBLICATION:* Grant MR, Hamer D, Hope T, et al. Whither or wither microbicides? *Science* 321(5888): 532-34, 2008. "After disappointing results from all efficacy trials conducted to date, the field of microbicides research now faces substantial challenges. Poor coordination among interested parties and the choice of nonvalidated scientific targets for phase III studies have hampered progress and created mistrust about the use of microbicides as a method to prevent HIV-1 sexual transmission. Although new promising strategies are available, there will need to be serious reappraisals of how decisions are made to advance the next generations of candidates into clinical trials, and the use of appropriate animal models in this process will be critical."

31 JULY *PUBLICATION:* Van Damme L, Govinden R, Mirembe FM, et al. Lack of effectiveness of cellulose sulfate gel for the prevention of vaginal HIV transmission. *N Engl J Med* 359(5): 463-72, 2008. "Cellulose sulfate did not prevent HIV infection and may have increased the risk of HIV acquisition."

1 AUGUST ImQuest BioSciences, located in Frederick, MD, USA, receives a grant for development of pyrimidinedione inhibitors as topical microbicides to prevent the sexual transmission of HIV. The two-year Small Business Innovative Research Phase 2 grant is worth $442,156 for the first year.

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THIS QUARTER IN MICROBICIDES *(Continued from p.17)*

3-8 AUGUST *CONFERENCE:* The 18th *International AIDS Conference (AIDS 2008)* takes place in Mexico City, Mexico. Over 20,000 people attend this first conference in a Latin American country. *(See page 1 of this issue of* TMQ *for coverage of* AIDS 2008.*)*

5 AUGUST HIV Vaccines and Microbicides Resource Tracking Working Group releases annual report, *Sustaining the HIV Prevention Research Agenda: Funding for Research and Development of HIV Vaccines, Microbicides and Other New Prevention Options (2000 –2007)*, at the *International AIDS Conference* in Mexico City. According to the annual report—which reviews funding from governments, private philanthropy, and industry—the total 2007 global investment in HIV vaccine R&D was $961 million and total investment in microbicides was $226.5 million, representing a 2 to 3 percent increase in funding from 2006 to 2007, but a tripling of funding over 2000 levels.

5 AUGUST *PUBLICATION:* Cranage M, Sharpe S, Herrera C, et al. Prevention of SIV rectal transmission and priming of T cell responses in macaques after local pre-exposure application of tenofovir gel. *PLoS Med* 5(8): e157, 2008. "These results indicate that colorectal pretreatment with ARV drugs, such as tenofovir, has potential as a clinically relevant strategy for the prevention of HIV transmission. We conclude that plasma tenofovir concentration measured 15 min after rectal administration may serve as a surrogate indicator of protective efficacy. This may prove to be useful in the design of clinical studies. Furthermore, *in vitro* intestinal explants served as a model for drug distribution *in vivo* and susceptibility to virus infection. The finding of T cell priming following exposure to virus in the absence of overt infection is provocative. Further studies would reveal if a combined modality microbicide and vaccination strategy is feasible by determining the full extent of local immune responses induced and their protective potential."

13 AUGUST The International Partnership for Microbicides (IPM) receives 1.5 million contribution from Spain, the country's first contribution to the international effort to develop a microbicide. This contribution is part of a larger €10.2 million commitment that also includes €3 million for the International AIDS Vaccine Initiative (IAVI).

15 AUGUST *PUBLICATION:* Ramjee G, Doncel GF, Mehendale S, et al. Microbicides 2008 Conference: From discovery to advocacy. *AIDS Res Ther* 5: 19, 2008. "The biannual Microbicides conference took place in New Delhi, India from 24-27 February 2008. The conference was open to delegates from the scientific and medical fields, as well as communities and advocates. In addition to microbicide research and development, the conference afforded the opportunity for the discussion of key issues such as ethics, acceptability, access, and community involvement. In this conference report we provide brief summaries of recent advancements made and challenges experienced in microbicide research and development, including updates on basic and clinical science, social and behavioural science, and community mobilisation and advocacy activities pertaining to clinical trials."

20 AUGUST Mary K. Howett, an internationally-renowned virologist, dies at the age of 60 from complications related to leukemia. Her work at Pennsylvania State, supported by the Jake Gittlen Cancer Research Institute, led to the discovery of a method for propagating HPV, which contributed to the development of vaccines to prevent cervical cancer, including Gardasil®, recently released by Merck Pharmaceutical Company. Her more recent studies involved the development of microbicides to prevent sexual transmission of HPV and HIV as well as other sexually transmitted pathogens.

21 AUGUST The Microbicides Development Programme (MDP) announces successful completion of enrollment in MDP 301, the Phase 3 safety and efficacy trial of PRO 2000/5 gel, being conducted across six sites in South Africa, Tanzania, Uganda, and Zambia. The follow-up of participants should be completed by the end of August 2009 and the final results of the Phase 3 trial are expected to be available by the end of 2009.

24 SEPT. Elias Zerhouni, Director of the National Institutes of Health, announces that he will end his tenure at the end of October. Dr. Zerhouni, a physician scientist and world-renowned leader in radiology research, has served as NIH director since May 2002. He led the agency through a challenging period that required innovative solutions to transform basic and clinical research into tangible benefits for patients and their families. He plans to pursue writing projects and explore other professional opportunities.

QUOTABLE QUOTES

"WE HAVE TO BE UNAFRAID OF FAILURE. SCIENCE IS NOT A STRAIGHT LINE."

—Alan Bernstein, Director of the Global HIV Vaccine Initiative, as quoted in "Back to basics in search for HIV vaccine, conference told," *Agence France Presse*, 4 August 2008.

"LET'S BE PERFECTLY CLEAR: FAILURE TO ENACT A COMPREHENSIVE, SUSTAINED AND MULTIPRONGED ATTACK ON THE PANDEMIC REPRESENTS A CRIME AGAINST THOSE INFECTED, THOSE AFFECTED AND THOSE SUSCEPTIBLE. INDEED, IT REPRESENTS A CRIME AGAINST HUMANITY."

—Julio Montaner, President of the International AIDS Society, as quoted in "Human rights at the core of AIDS control, conference told," *Globe and Mail*, 9 August 2008.

"IN BOTH THE VACCINE AND MICROBICIDE FIELDS, RESEARCHERS ARE WORKING WITHOUT VALID ANIMAL MODELS, KNOWN CORRELATES OF PROTECTION, OR A COMPLETE UNDERSTANDING OF THE IMMUNE SYSTEM AND ITS DEFENSES AGAINST HIV."

—HIV Vaccines and Microbicides Resource Tracking Working Group in *Sustaining the HIV Prevention Research Agenda: Funding for Research and Development of HIV Vaccines, Microbicides, and Other New Prevention Options, 2000 to 2007*, 5 August 2008.

"...CLINICAL RESEARCH OR RESEARCH IN GENERAL IS NOT A MATTER OF SUCCESS OR FAILURE. IT IS A MATTER OF WHAT WE LEARN ON THE ROAD TO SUCCESS...NINE OUT OF TEN CANDIDATE DRUGS OR VACCINES THAT GO INTO STUDIES IN HUMANS THAT HAVE PASSED THE TESTS OF SAFETY, FORMULATION, MANUFACTURE, AND GONE INTO HUMAN TRIALS...FAIL. ONLY ONE IN TEN SUCCEEDS. BUT THESE FAILURES INFORM FUTURE SUCCESSES. SO THE INDUSTRY CONTINUES TO INVEST..."

—Tachi Yamada, President of Global Health, Bill & Melinda Gates Foundation, in session "Vaccines and microbicides: where do we go from here?" at *AIDS 2008*, 4 August 2008.

THE MICROBICIDE QUARTERLY

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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.

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