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CONTENTS

EDITOR'S NOTE

Background: Following on a tradition begun with* Microbicides 2004[1] *and continued with* Microbicides 2006,[2] *this issue of* The Microbicide Quarterly *is dedicated to coverage of the* Microbicides 2008 *conference, held 24-27 February 2008 in New Delhi, India.

Objective: In an attempt to condense what was an expansive conference program into a summary report, we have identified and written to a selection of cross-cutting themes, thus "highlights as we see them."

Organization and Style: Writing to these themes has allowed us to create a synthesis of the conference through clustering of microbicide research across and within tracks. Each presentation covered in this synthesis is footnoted and includes its respective abstract number as listed in the conference program. The sequencing of the article topics follows the progression of a product through the microbicide pipeline: from preclinical testing, to clinical trials, to product introduction and use.

Further Information: As we are reporting on information presented at a public meeting earlier this year, some numbers may have changed since. Therefore we ask our readers to contact the presenter identified in the footnotes for more up-to-date information as needed.

SCREENING TOOLS AND COMMON ALGORITHMS FOR ASSESSING PRECLINICAL COMPOUNDS AS POSSIBLE CANDIDATES FOR CLINICAL TRIALS

Elaine A. Richman, Richman Associates

Microbicides could prevent HIV infection in several ways. They could present the virus with a physical barrier that blocks its passage into epithelial tissues. They could boost the natural defenses of the vagina or rectum against the pathogen. They could disable the virus (viral disruption) or create a barrier between the virus and target cells (fusion/entry inhibition). They could prevent HIV from replicating inside the target cells (replication inhibition). Or they could work through a combination of approaches.

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[1] *The Microbicide Quarterly* 2(2): 1-23, 2004.
[2] *The Microbicide Quarterly* 4(2): 1-32, 2006.

SCREENING TOOLS AND COMMON ALGORITHMS *(Continued from p.01)*

Any candidate compound must undergo preclinical assesment to determine the feasibility of its further development as a potential microbicide. Researchers are investigating a number of new approaches for assessing compounds and it is possible that common screening tools and algorithms will emerge. This is very important because of the copious number of compounds for testing, the many variables that affect detection of biomarkers, and dependence on a relatively small number of scientists experienced in drug development who understand needs and potential problems. Microbicides must have acceptable potency, toxicity, and metabolic profiles. Their impact on the normal physiologic and biochemical processes of innate cells must be understood. They must be stable and able to be integrated into a carrier for delivery. It is important to assess such characteristics early in order to save time, money, avoid duplication of effort, and move candidate products efficiently and appropriately along the development pathway.

Screening tools for studying preclinical compounds as possible candidates for clinical trials include tissue explants, cell lines, polarized cell cultures, dual compartment cultures, bioengineered tissues, and microflora-colonized epithelium.

Below are examples, presented at both *Microbicides 2008* and at a pre-conference symposium on rectal microbicides, of assays being tested for evaluating potential microbicides:

- An algorithm for testing rectal microbicides that progresses from formulation testing to human studies was presented by the Microbicide Trials Network (MTN) in the Rectal Microbicides Update Symposium.[3] The researchers advocated for validation and standardization of all *in vitro* and *ex vivo* testing in order for comparisons to be made between products and formulations.
- Researchers described a potential pre-clinical screening tool for microbicides that assesses HIV replication in human tissue explants in the presence of possible microbicidal agents.[4] The screening tool was tested using unformulated PRO 2000 and cervical, rectal, and tonsil tissue explants. PRO 2000 is thought to work by blocking the entry of HIV into target cells. Virus replication was determined by measuring p24 levels (pg/mL) in explant cultures every two to three days. Overall, a reduction of HIV replication occurred regardless of tissue type. However, replication was affected by isolate type, PRO 2000 concentration, and the laboratory where the screening tool was tested. This reinforces the need for standardization of screening tools and techniques for the preclinical screening of potential microbicides.
- A full-thickness human vaginal-ectocervical tissue culture model is being studied, ultrastructurally and immunohistochemically, to evaluate it for possible use for preclinical screening of topically applied microbicides.[5] The researchers observed the effect of reproductive hormone status on the tissue's microvilli, tight junctions, glycogen-filled cells, desmosomes, and estrogen and progesterone receptors, and found all to be structurally and histochemically similar to *in vivo* tissues. They also examined the impact on the cultured tissues of topically-applied nonoxynol-9 (N-9) and benzalkonium chloride. Exposure to N-9 at concentrations > 0.02% or benzalkonium chloride at concentrations > 0.125% for 24 hours was toxic to the tissue and resulted in release of inflammatory factors during different stages of the menstrual cycle.
- *In vitro* release testing (IVRT) is commonly used for measuring the liberation of a drug from a polymer matrix. Researchers from the International Partnership for Microbicides (IPM) have applied this test to evaluating release of dapivirine (TMC120) from different vaginal gels.[6] Dapivirine is a non-nucleoside reverse transcriptase inhibitor designed to prevent or interrupt HIV replication in human cells. Each of the gels tested contained a different FDA-approved excipient (e.g., propylene glycol, poloxamers, antimicrobial preservatives) plus dapivirine concentrations ranging from 0.02%

[3] Dezzutti C. Rectal microbicides update: Nonclinical evaluation. Rectal Microbicides Update Symposium. 24 February 2008.
[4] Cummins JE. A standardized pre-clinical evaluation of HIV-1 growth and microbicide efficacy in tissue explants. Abstract AP56-395.
[5] Ayehunie S. Long-lived, organotypic vaginal tissue model for microbicide and endocrine hormone studies. Abstract AP91-623.
[6] Bryla PM. *In-vitro* release rate testing (IVRT) as a performance test for dapivirine (TMC-120) vaginal gels. Abstract AP3-154.

to 0.1%. The drug concentration in the receiving medium of a diffusion cell was assessed by reversed-phase high-performance liquid chromatography. The researchers found that the release of dapivirine was dependent on the physical properties of the expedient and on the concentration of dapivirine. They recommend IVRT as a useful screening tool for testing and formulating vaginal gels containing anti-HIV compounds.

- A preclinical *in vitro* screening tool has been designed for studying the effect of seminal fluid on HIV infectivity of cells and the integrity of prospective microbicidal compounds.[7] (This is important because HIV is often transmitted because of unprotected [condom-free] vaginal or anal receptive intercourse.) Researchers evaluated prospective microbicides for anti-HIV activity in the presence of pooled human seminal plasma (SP) using the cell-free and cell-associated CCR5-specific cell-based HIV-1 transmission assay of the NIAID topical microbicide screening algorithm.[8] They found that a concentration of 25% SP does not interfere with the infection of cells by HIV and that the SP assay is a reproducible way of assessing the anti-HIV activity of potential microbicides. They also identified a class of compounds (quinobines) that remain active in a non-SP assay but are consistently inactivated in the presence of 25% SP, making quinobines a control for assessing the assay's performance. This *in vitro* screening tool is another that could be useful for narrowing the choice of compounds for eventual testing in animal models and, ultimately, in clinical trials.
- The protein DC-SIGN (dendritic cell-specific ICAM-3-grabbing non-integrin) is expressed on the membranes of dendritic cells. It serves as a ligand that efficiently binds, concentrates, and mediates transfer of HIV-1, HIV-2, and simian immunodeficiency virus (SIV) from mucosal surfaces to CD4+ T-cells. A microbicide that targets this cell surface molecule could possibly prevent infection with HIV.
- Researchers have developed a novel quantum dot-based high-throughput assay for screening inhibitors that would block the interaction of HIV with DC-SIGN.[9] They are using the assay to screen a large library of molecules that were selected by computational algorithms for their diversity, solubility, and drug-like qualities. Molecules that show evidence of an ability to prevent binding to DC-SIGN will be further examined for their effect on HIV transmission.

Each of these assays, if validated in the hands of others and standardized to allow comparisons between or among products, adds an element of dependability to the testing of compounds as microbicides for preventing HIV infection. Some, or all, could possibly contribute to a new microbicide testing algorithm for selecting a range of preclinical candidates for advancement to clinical trials.

NEW PRECLINICAL MODELS FOR ASSESSING PRODUCT SAFETY

Elaine A. Richman

Any potential microbicide must be subjected to rigorous preclinical testing for safety (e.g., pharmacokinetic studies, pharmacodynamic studies, *in vitro* studies, *ex vivo* studies, animal studies) to assure that it is not only efficacious but safe, since in the case of microbicides, safety and efficacy are so tightly intertwined.

Existing preclinical assays to test microbicide safety have not proven to be satisfactory predictors of outcomes in clinical trials, as evidenced by an inflammatory response and increased HIV infectivity related to the use of nonoxynol-9 (N-9) and, possibly, cellulose sulfate (CS).

Continued on p.04

[7] Lackman-Smith CS. Evaluation of potential topical microbicides in cell-based assays in the presence of human seminal plasma. Abstract AP49-350.
[8] Lackman-Smith CS, Osterling C, Luckenbaugh K, et al. Development of a comprehensive human immunodeficiency virus type 1 screening algorithm for discovery and preclinical testing of topical microbicides. *Antimicrob Agents and Chemother* 52(5): 1768-81, 2008.
[9] Jain P. DC-SIGN as a potential target for novel microbicide development. Abstract AP87-603.

NEW PRECLINICAL MODELS *(Continued from p.03)*

Murine and Dual Chamber Models

NEW MODELS FOR ASSESSING MICROBICIDE SAFETY

Balb/c mouse. This laboratory animal was treated intravaginally with N-9 gel, PRO 2000 gel, or tenofovir gel and monitored for signs of infection.

Dual chamber system. The chamber contains a layer of human epithelial cells atop constituted vaginal tissue. It has been used to test the ability of HIV to migrate across the tissue and the effect on tissue of the microbicides PRO 2000, tenofovir, and cellulose sulfate.

Bone marrow/liver/thymus (BLT) mouse. The antiretroviral Truvada® was introduced into this mouse which was engineered to have a susceptibility to intravaginal and intrarectal HIV infection. Protection against HIV transmission was seen.

Balb/c mouse

In this model the animal is treated intravaginally with a microbicide. Following treatment, the response of inflammatory mediators is measured and the migration of virus across the vaginal epithelium is quantitated.[10] The microbicidal agents used to test this model were N-9 gel, PRO 2000 gel, and tenofovir gel, and the virus introduced was herpes virus (HSV).

N-9 increased the inflammatory response in the vaginal tissue of these mice and also increased their susceptibility to HSV. However, PRO 2000 triggered a significantly smaller inflammatory response and had no effect on HSV susceptibility. Tenofovir-treated mice showed no inflammatory response or HSV infiltration into vaginal tissue.

Additional analysis of tissues in this study indicated that N-9 could be enhancing infectivity by causing a release of calcium from cells, which would interfere with adherence of vaginal epithelial cell junctions and facilitate passage of HSV through gaps in the vaginal mucosa. The researchers suggested that HSV infection in these mice could be used as a biomarker for increased HIV susceptibility in microbicide testing.

Dual chamber system

Another model for testing microbicide safety uses a "dual chamber system" that contains a layer of polarized human epithelial cells (HEC-1-A) atop constituted vaginal tissue, mimicking the normal multilayered vaginal epithelium.[11] Candidate microbicides and HIV are introduced into the sealed chamber above the tissues and measured in the chamber below. The integrity of the cells is evaluated by confocal microscopy, by monitoring transepithelial electrical resistance (TER), and gene expression. A drop in TER correlates with disruption of cell attachments. Adding HIV to the apical chamber allows for measurement of the ability of the virus to migrate across the tissues into the lower compartment.

In tests of PRO 2000 and tenofovir, the researchers found that PRO 2000 and tenofovir neither disrupted epithelial integrity nor enhanced passage of HIV. Cellulose sulfate, however, significantly affected TER and tight junction proteins, and led to increased HIV migration across the membrane. CS also increased the release of inflammatory cytokines and interfered with cell secretion of a protease inhibitor that is protective against HIV.

BLT mouse

Yet another newly proposed mouse model for testing microbicidal agents is the BLT mouse. (BLT is an acronym for humanized bone marrow/liver/thymus.) The mouse was engineered to have susceptibility to intravaginal and intrarectal HIV infection and was constructed by implanting human liver and thymus stem cells into the kidney capsule of a non-obese diabetic (NOD)/SCID-immunodeficient mouse. The mouse is then irradiated and transplanted with autologous fetal liver CD34+ cells.[12,13]

Researchers found robust populations of human lymphoid cells (e.g., B-cells, T-cells, monocytes, macrophages, and dendritic cells) in the BLT mouse peripheral blood, vaginal tissue, ectocervix, endocervix, uterus, small intestine, large intestine, colon, rectum, lung, liver, pancreas, skin, and all other tissues tested.

[10] Herold B. Safety of tenofovir gel in a comprehensive murine model. Abstract AO9-389.
[11] Mesquita P. Disruption of the epithelial barrier by cellulose sulfate: Development of a model to assess microbicide safety. Abstract AO10-415.
[12] Garcia V. Faithful reconstitution of the entire female reproductive tract of humanized BLT mice with human lymphoid cells renders them susceptible to vaginal HIV transmission. Abstract AP80-589.
[13] Othieno FA. Evaluation of microbicides in BLT humanized mice. Abstract AP85-600.

A large proportion of the human T-cells in the BLT mouse expressed the HIV receptor CCR5. When the researchers challenged the animals with a single exposure to HIV, they saw a histological and chemical depletion of CD4+ and CD8+ cells. And when prior to exposure, they prophylactically introduced an antiretroviral—the nucleoside reverse transcriptase inhibitor Truvada® (tenofovir + emtricitabine)—they witnessed complete protection against HIV transmission.

Protection was defined to include all of the following four parameters:

1) Lack of viral RNA or antigenemia in plasma at all times measured
2) Lack of viral DNA in peripheral blood at any time analyzed and in all tissues after harvest
3) Lack of productively-infected cells in all tissues as determined by *in situ* hybridization
4) Lack of rescuable virus from any tissue by co-culture with activated allogeneic peripheral blood mononuclear cells (PBMC).

The BLT mouse is seen as a plausible preclinical animal model for studying microbicides for preventing sexual transmission of HIV. As a new model, it remains to be validated in the presence of other infections and at different stages of hormonal cycles.

All three of these models are potentially promising for achieving accurate and comparable results in early microbicide safety and efficacy studies. The field would benefit by having a standardized model for testing parameters such as microbicide dosage, formulation, and viral challenge.

ENGINEERING VAGINAL COLONIZATION OF MICROBICIDE-PRODUCING BACTERIA

Elaine A. Richman

The mucosa of the healthy vagina is populated with bacteria dominated by lactobacilli. The depletion of lactobacilli has been associated with increased risk of HIV infection. One of the main lactobacillus species of the vaginal mucosa is *Lactobacillus jensenii* (*L. jensenii)*, which colonizes the vaginal mucosa and acts as a natural biofilm (likely through its production of hydrogen peroxide) to protect against infection.

Scientists are genetically engineering *L. jensenii* to produce microbicides to block HIV. The goal is to develop a self-renewing vehicle for delivery of a protein-based microbicide. One group is exploring a strategy that involves enhancing secretion by *L. jensenii* of the HIV-suppressive chemokine RANTES and a derivative, C1C5 RANTES, to block HIV binding to CCR5 receptors of HIV target cells.[14] The wild-type RANTES produced by their engineered *L. jensenii* is similar to RANTES produced in an earlier *E. coli* model. These researchers are about to test the C1C5 RANTES-producing *L. jensenii* in vaginal colonization studies. They are also exploring the production by lactobacilli of RANTES-derived short peptides, which function as potent CCR5 antagonists and have the advantage of not activating the receptor, thereby preventing tissue inflammation.

Other researchers are working on engineering human *L. jensenii* to produce the HIV-entry inhibitor cyanovirin-N (CV-N), which works by binding to the gp120 molecule on the outside of the viral envelope.[15] *In vitro*, the engineered *L. jensenii* potently inhibits HIV infectivity and retains its activity in the presence of seminal fluid. In rhesus macaques, it has successfully colonized the vagina for more than three months and, histologically, shows no evidence of causing inflammation. In a Phase 0 study, the researchers plan to determine colonization and safety of the modified microbacilli in human volunteers.

Re-engineering PSC-RANTES for Affordability and Delivery

PSC-RANTES is an engineered human protein that competes with HIV for the

Continued on p.06

[14] Vangelista L. Expression of RANTES derivatives in lactobacilli: A novel strategy for development of vaginal microbicides. Abstract AO18-235.
[15] Xu Q. Development of a live topical microbicide for women. Abstract AO17-221.

ENGINEERING VAGINAL COLONIZATION *(Continued from p.05)*

CCR5 receptor on immune cells. A problem with PSC-RANTES as a universal anti-HIV microbicide is its high cost of production. However, by re-engineering the PSC-RANTES molecule, researchers have found several other products that could be low-cost alternatives.[16] One is 6P4-RANTES. The other is 5P12-RANTES. The antiviral activity of these two proteins, demonstrated in explants of human cervical and penile tissue, is very close in activity to the parent molecule. The researchers are conducting exploratory work on production of 6P4-RANTES and 5P12-RANTES in commensal bacteria.

Another approach being investigated for engineering the delivery of PSC-RANTES is one that encapsulates the protein in biodegradable nanoparticles.[17] This would provide a sustained and controlled microbicide release. In permeability studies, the encapsulated PSC-RANTES demonstrated greater uptake by human cervical tissue than non-encapsulated PSC-RANTES.

COMBINATION MICROBICIDE PRODUCTS

Elaine A. Richman

Infectivity with HIV is extremely complex and multi-staged. Conceivably, barriers to prevent HIV infection could be established at different points within the process to help assure that a person does not become infected. This could involve combinations of products that function as entry or fusion inhibitors, reverse transcriptase inhibitors, or integrase inhibitors. For controlling HIV infection and AIDS in people who are already infected, combination therapy (highly active antiretroviral therapy, HAART) has been highly successful. HAART uses a combination of three or more antiretroviral drugs.

Advantages of combination microbicides could be better potency, less drug resistance, and better protection of a larger variety of body tissues. In addition to proof of principle and formulation, challenges in developing combination microbicides include delivery of the synergistic products and regulatory hurdles.

Combination Products Being Tested

Several combination microbicidal products are being tested in preclinical studies. One combines an entry cascade inhibitor (DS003; DS001) + the nucleotide reverse transcriptase inhibitor PMPA + the non-nucleoside reverse transcriptase inhibitor TMC120 (dapivirine).[18] In all testing situations, researchers found that the combination of products provided better protection against HIV replication than single products. PMPA + TMC120 appeared to enhance protection against HIV infection by decreasing pyrophosphate-mediated excision of nucleotide incorporation during reverse transcription. No antagonism among products was observed.

PMPA, TMC120, and a second non-nucleoside transcriptase inhibitor UC-781 have also been combined to inhibit HIV infection. These were tested in colorectal explants where HIV had been added. In all cases, the antiviral efficacy of the three combined compounds outmatched the inhibitory effect of each alone and separately.[19]

In another study, researchers compared the inhibition of HIV infection of macrophages using a gp120 inhibitor (lectin HHA), a fusion inhibitor (T20), and a non-nucleoside reverse transcriptase inhibitor (KRV2110), alone and in combination.[20] They also looked at the toxicity of each toward three different epithelial cell lines. All combinations provided better antiviral potency than the single molecules.

Other combinations with possible synergistic and complementary effects against HIV infection being tested include the following:

[16] Fletcher P. Anti-HIV activity of RANTES analogues in human genital tissue. Abstract AO7-282.
[17] Ham AS. A biodegradable nanoparticle drug delivery system of PSC-RANTES for the prevention of HIV. Abstract AO31-406.
[18] Schader SM. Better protection against HIV-1 infection *in vitro* with candidate microbicides in combination. Abstract AO20-273.
[19] Herrera C. Reverse transcriptase inhibitors as potential colorectal microbicides. Abstract AO24-498.
[20] Belec L. *In vitro* synergistic activity against R5-tropic HIV of the candidate microbicide molecules HHA, KRV2110, and T20 combinations. Abstract AO23-340.

- Cellulose acetate 1,2-benzenedicarboxylate (CAP) and TMC120.[21] CAP blocks HIV entry by targeting gp120 and gp4. TMC120 is a non-nucleoside reverse transcriptase inhibitor.
- Entry inhibitors CMPD-167, T1249, and AMD3465. CMPD-167 and AMD3465 showed activity against R5 and X4 virus, respectively. T1249 was active against both phenotypes.[22] Combinations may be most effective.
- ISIS 5320 (also known as IQP-0831) and other entry or reverse transcriptase inhibitors. ISIS 5320 inhibits gp120-CD4 interactions, thereby preventing attachment of HIV to target cells and cell-to-cell fusion. In anti-HIV combination assays, ISIS 5320 acted synergistically with AZT and UC-781. It was well tolerated in a Phase 1 human clinical trial as a therapeutic anti-HIV agent.[23]
- NB325 or PSMA with efavirenz, tenofovir, or cyanovirin.[24] Software programs CalcuSyn and MacSynergy showed that efavirenz (a non-nucleoside reverse transcriptase inhibitor), tenofovir (a nucleoside reverse transcriptase inhibitor), and cyanovirin (a fusion inhibitor) might be suitable partners in a combination microbicide.

It will be important to assure the vaginal and rectal safety of any combination microbicide. In macaque testing, some combinations (e.g., a dendrimer in an acid-buffering gel) have shown different toxicity profiles from single products.[25] The researchers suggest that assessment with rectal lavage may be sufficiently sensitive to evaluate the toxicity of combination strategies.

DEVELOPMENT AND ACCEPTABILITY OF RECTAL MICROBICIDES

Elaine A. Richman

Vaginal and rectal anatomy and their respective sexual practices pose different problems for the development and formulation of safe and effective microbicides. For one, the cellular structure of the anal canal, rectum, and vagina differ substantially in ways that are reflected in their absorptive and secretory properties and susceptibility to HIV infection. Receptive anal intercourse is associated with the highest risk for sexually transmitted HIV, yet much remains to be understood about transmission processes and structures and how these might be intervened by topically-applied microbicides.

Presentations at *Microbicides 2008* included questions about transmission dynamics, models for understanding those dynamics, the safety and potential efficacy of candidate microbicides, new candidate categories, formulation issues, acceptability, and the status of rectal microbicide clinical research.

- Because semen is frequently present during receptive anal intercourse, it is necessary to determine its effect on the infectivity of HIV and on the activity of microbicides. In cell cultures using the indicator cell line TZM-bl, researchers combined HIV with semen and found that semen increased the infectivity of the cells compared to control. Semen did not, however, alter the antiviral activity of tenofovir.[26]
- Radioisotope studies show that permeability of the rectal epithelium is affected by the chemical composition of the applied compound and by tissue manipulation.[27] Comparing levels of radioisotope in plasma and urine of men in whom isotonic saline solution or 2% nonoxynol-9 (N-9) gel was administered rectally showed that N-9 is absorbed through rectal tissue at a significantly greater rate than saline. Permeability was further increased when receptive anal intercourse was simulated. *Ex vivo* studies of rectal epithelium confirm that damaged tissue

Continued on p.08

[21] Jiang S. Synergistic anti-HIV effect of CAP and TMC120 combination. Abstract AP37-283.
[22] Harman SJ. Characterization of small molecule entry inhibitors in human cervical and penile tissue models. Abstract AP70-542.
[23] Buckheit RW. The preclinical development of the oligonucleotide ISIS 5320 as a single or combination anti-HV topical microbicide. Abstract AP84-599.
[24] Pirrone V. Achieving cooperative inhibition of HIV-1 using microbicidal agent combinations that include the biguanide-based molecule NB325 (PEHMB) or the copolymer PSMA. Abstract AP97-638.
[25] Patton DL. A combination microbicide shows differential toxicity compared with standalone products. Abstract AP32-267.
[26] Dezzuti C. Impact of semen on HIV-1 infection and *in vitro* antiviral activity of topical microbicides. Abstract AP17-215.
[27] Fuchs E. Detecting rectal epithelial disruption using radioisotopes: A simple test to identify potential HIV microbicide toxicity. Abstract AO6-209.

DEVELOPMENT AND ACCEPTABILITY OF RECTAL MICROBICIDES *(Continued from p.07)*

increases HIV risk. Simulated receptive anal intercourse also shows that ejaculate is deposited in the distal rectum and that CD4 cells and HIV-sized particles pass through the epithelium and into surrounding tissue.[28]

- The colorectal explant appears to be a suitable model for screening potential rectal microbicides, including those based on reverse transcriptase inhibitors (RTI).[29] The tissue used is from patients who a few hours earlier have had bowel resection surgery for a non-inflammatory disorder. When the antiviral efficacy of three non-formulated reverse transcriptase inhibitors—the nucleoside RTI PMPA and the non-nucleoside RTIs UC-781 and TMC120—was tested in colorectal explants where virus was added and infection determined, inhibition of clade B HIV-isolates occurred. When these two RTIs were combined, a boost in the dose-response curve was detected.
- Absorption, permeability, safety, and HIV efficacy of the candidate microbicide VivaGel® are also being tested in colorectal explants.[30] Researchers report that VivaGel® is generally non-toxic to colorectal tissue and protective against infection by HIV.
- The pigtailed macaque is another model being used to study the safety and efficacy of repeated rectal microbicide application.[31] Studies have revealed similarities in rectal histology and microflora between humans and pigtailed macaques. Using rectal lavage techniques, the researchers have been able to retrieve rectal epithelium for analysis and detect the presence of blood and stroma cells. This model has been used to evaluate several products, including UC-781 and BufferGel®. The researchers believe that the pigtailed macaque is a clinically relevant model for assessing the rectal safety of microbicides and that rectal lavage is sufficiently sensitive for identifying toxicity.
- Therapeutic use of live rectal microbicides is being studied as a possible way to effectively and inexpensively prevent HIV infection.[32] Researchers have genetically engineered a probiotic strain of *E. coli* to colonize the gastrointestinal tract and secrete antiviral peptides onto the surface epithelium. The anti-HIV peptide alters the structure of the p41 envelope protein of HIV and, *in vitro*, has subsequently prevented fusion of the virus with T-cells, macrophages, and immature dendritic cells. In rhesus macaques, the engineered *E. coli* colonized the lower intestine and protected a small number of animals against simian HIV infection. By increasing production of the anti-HIV peptide, it may be possible to enhance protection.
- Others are examining HIV-1 aptamers to inhibit HIV infection in colorectal tissue[33] or human recombinant lactoferrin.[34]
- An ongoing study conducted under the U19 Microbicide Development Program is one of the first to examine the safety of the NNRTI UC-781 tested rectally in men and women.[35] Data were presented based on results from 19 seronegative subjects enrolled in a Phase 1 study of two doses (1% and 2.5%) of UC-781 in a gel formulation compared to placebo. The researchers are using a battery of tests looking for signs of toxicity and inflammation, including taking biopsies of rectal tissues and samples of rectal fluids. The early results indicate that the UC-781 microbicide gel appears to be safe. No obvious differences appeared between the experimental and placebo groups in terms of gross or microscopic cell damage, and cytokine and chemokine levels revealed no unusual inflammatory response.
- The formulation of safe and acceptable rectal microbicides is also critically important. Researchers have generated a panel of potential lipid- and aqueous-based rectal microbicide formulations by testing nearly 200 "placebo" compounds for toxicity, long-term stability, physical characteristics, and compatibility with

[28] Nimmagadda S. Colonic luminal and tissue distribution of lymphocytes and HIV-sized particles suspended in seminal plasma in healthy men following simulated receptive anal intercourse. Abstract AO1-441.
[29] Herrera C. Reverse transcriptase inhibitors as potential colorectal microbicides. Abstract AO24-498.
[30] Dezzutti C. Rectal microbicides update: nonclinical evaluation. Rectal Microbicides Update Symposium. 24 February 2008.
[31] Patton DL. Pigtailed macaques as a model for rectal microbicide use. Rectal Microbicides Update Symposium. 24 February 2008.
[32] Wang T. Development of a live rectal microbicide. Abstract AO22-306.
[33] McGowan IM. HIV-1 aptamer inactivation in the colorectal explant model of HIV-1 infection. Abstract AP65-494.
[34] Cho DD. Prevention of HIV infection in large intestinal explants utilizing human recombinant lactoferrin. Abstract AP42-314.
[35] Anton P. Phase 1 rectal microbicides study. Rectal Microbicides Update Symposium. 24 February 2008.

condoms.[36] The outcome was 10 acceptable formulations eligible for evaluation in clinical trials.

- In addition to being efficacious, rectal microbicides need to be acceptable to potential users.[37] Surveys asking about formulation and packaging suggest a preference for easy-to-use, attractive packaging that dispenses a full dose consistently and smoothly through an enema-like applicator with a smooth and rounded tip. The dispenser should be attractive (non-clinical-looking), require no user assembly, and inexpensive and disposable after one use. Prototypes are under development. This will be important for clinical trials to assure consistent dosing and acceptance by study participants.
- Several Phase 1 microbicide safety studies are planned and one—a trial of UC-781—is ongoing. In the planning phase are studies that will test a polyanion and PRO 2000 along with two other trials that are under development by the MTN. In addition, a Phase 1 trial testing a rectal formulation of UC-781 is possible. See the following table of ongoing and planned studies *(Table 1)*, from a presentation[38] at the Rectal Microbicides Update Symposium that preceded *Microbicides 2008*, also in New Delhi, India.

TABLE 1. PHASE 1 RECTAL MICROBICIDE SAFETY STUDIES[38]

Product/Trial	Status	Timeline	Sponsor
UC-781	Ongoing	N/A	NIAID/DAIDS
Polyanion	Planned	Q3 2008	NIAID/DMID
PRO 2000	Planned	Q2 2008	MDP MRC-UK
MTN-006	Planned	Q3 2008	NIAID/DAIDS
MTN-007	Planned	Q3 2008	NIAID/DAIDS
UC-781	Possible	Q4 2010	TBD

CLINICAL TRIALS: COMMUNITY ENGAGEMENT

Betsy M. Finley, Alliance for Microbicide Development

The growth of the biennial *Microbicides* conferences parallels the growth of the microbicide field overall in terms of interest, attendance, and the variety of topics and issues covered in depth. Expansion of the conference was seen at *Microbicides 2006* in Cape Town with the inauguration of a new track, named "Community and Advocacy." At *Microbicides 2008* this new track grew still further to encompass "Policy, Advocacy, and Community."

Such growth demands greater coordination across disciplines. This was expressed at *Microbicides 2008* in the form of cross-track sessions to encourage conference attendees to attend sessions they might not have considered otherwise.

This report focuses on several key topic areas discussed in the "Policy, Advocacy, and Community" Track as well as complementary research presented in Tracks B ("Clinical") and C ("Socio-behavioral").

Maximizing Recruitment and Retention of Study Participants

Clinical trials present challenges to researchers, participants, and communities alike, and must be addressed with a range of strategies, some tried and true, some novel. Following are examples of community-

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[36] Ferguson LW. Development of a panel of rectal microbicide formulations. Abstract AP24-425.
[37] Carballo-Diéguez A. Importance of the right microbicide delivery device for rectal microbicide acceptability. Rectal Microbicides Update Symposium. 24 February 2008.
[38] McGowan IM. An overview of rectal microbicides. Rectal Microbicides Update Symposium. 24 February 2008.

CLINICAL TRIALS: COMMUNITY ENGAGEMENT *(Continued from p.09)*

supported approaches for maximizing the recruitment and retention of study participants in microbicide trials.

> "WORKING WITH COMMUNITY-BASED ORGANIZATIONS AND WITH PARTICIPANT LEADERS HAS PROVED TO BE AN EFFECTIVE APPROACH TO ENHANCE RECRUITMENT AND RETENTION IN [CLINICAL] TRIAL[S]."
>
> – VINCENT BASAJJA, MEDICAL RESEARCH COUNCIL/UGANDA RESEARCH UNIT ON AIDS

Recruitment

The Masaka, Uganda, site of the Microbicides Development Programme (MDP) study MDP 301 used several strategies to improve recruitment, all involving the respective local communities. Initial recruitment methods consisted of identifying HIV-negative women who were in HIV-discordant or -concordant relationships, through Voluntary Counseling and Testing (VCT) centers and household surveys. Additional approaches included using community-based AIDS care and support organizations, general community meetings, and participant leaders. The participant leaders (one female and one male from each community) formed an advocacy network with the goal of increasing participant recruitment. Upon completion of leadership and communication training, the leaders mobilized couples for VCT, provided support visits, and coordinated communication around participant concerns about the trial. Recruitment of women who had previously declined VCT requests demonstrated the success of the "participant-leader" strategy.[1,2]

Similar recruitment strategies were used at the Pune, India, site of the HPTN 059 study. The three-tier program included the following components: 1) study information was given to potential participants and their partners during presentations at women's group community meetings and home visits; 2) prior to scheduling a study screening visit, an eligibility questionnaire was administered and completed; 3) informed consent was explained; and 4) an assessment was made of participant comprehension of the informed consent form.[3]

At the Makarere, Uganda, site of the CONRAD Phase 3 trial of cellulose sulfate (CS), an extensive community-based recruitment program was used *(see Table 1)*. This involved appointing and training non-study "peer leaders" from high-risk groups in the community to lead the efforts alongside the study team. Despite challenges, for example, peer leaders asking trial participants for their study gel, the study team concluded that "the peer leader approach helped in providing for the needs and expectations of the study participants and addressing their concerns."[4]

TABLE 1. RECRUITMENT STRATEGIES EMPLOYED AT THE MAKERERE, UGANDA, SITE OF THE CONRAD PHASE 3 TRIAL OF CELLULOSE SULFATE[4]

Strategies used by research team

- Identified and contacted "peer leaders" from among potential trial participants
- Conducted sensitization of peer leaders about trial
- Informed and trained peer leaders about their roles and responsibilities

Strategies used by peer leaders

- Mobilized high-risk groups
- Identified meeting points to hold information sessions conducted by research team
- Identified candidates and recruited trial participants
- Communicated trial participant misconceptions and myths to research team
- Reminded trial participants about their respective scheduled visits
- Assisted research team in tracing trial participants who missed scheduled visits
- Promoted trial in respective communities and encouraged candidates to participate

[1] Basajja V. Strategies to recruit and retain couples in a vaginal microbicides trial of PRO 2000/5 in a rural community, SW Uganda. Abstract DO16-333.
[2] Kasse MJ. Recruitment and retention in a vaginal microbicide efficacy trial: Experiences with HIV-negative women living in discordant couple relationships in rural SW Uganda. Abstract BO13-321.
[3] Das SS. Strategies for recruitment and retention of women in the HPTN 059 Phase II expanded safety and acceptability study of the vaginal microbicide 1% tenofovir gel in Pune, India. Abstract BO14-110.
[4] Nakimuli M. Community involvement in microbicide clinical trial through peer leader approach: Experiences from Makerere/Mulago/CONRAD Microbicide Centre. Abstract DO15-326.

Retention

Retention of study participants is essential to the success of a clinical trial. Attrition must be kept to a minimum in order to retain study validity and statistical power and to ensure successful assessment of trial endpoints.[5,6] As challenging as this is, several microbicide trials have attained nearly perfect retention rates, ranging from 95% to 100% *(see Table 2)*.

As in the case of strategies designed to enhance recruitment, many studies used community-based interventions to achieve maximum participant retention, for example:

- Distributing cards, making phone calls, and visiting homes to remind participants of upcoming appointments
- Increasing study-specific education
- Creating commitment-based incentive awards
- Establishing participants as peer educators
- Allowing weekend appointments
- Educating and involving participant partners.[6]

One study developed focus groups to discuss trial-related information and perceptions at baseline. Individuals not enrolled in the study but from nine communities in which trial participants lived, were selected to attend 15 focus group discussions. Focus group topics included information about the trial and the gel, risk of contracting HIV, intravaginal practices, and partner involvement. The focus groups revealed both misconceptions and positive perceptions about the trial among the community. Based on these results, the study team opted to continue the community-based informational program in order to address misconceptions. The program has been effective, since "participation and cohort retention in the ongoing study seem to be unproblematic."[7]

In cultures where men are the primary decision-makers, their involvement and support of clinical trials in which their female partners are enrolled is key to participant retention and, ultimately, the success of the study. Strategies to encourage male partner involvement have been used in clinical trials including HPTN 035,[8] HPTN 059,[3] MDP 301,[7,9] and MIRA (Methods for Improving Reproductive Health in Africa).[6] In addition to utilizing strategies to increase male partner involvement and support, HPTN 035—a Phase 2/2B trial assessing the safety and effectiveness of PRO 2000 and BufferGel®—analyzed the impact of male partner clinic visits on participant retention. With motivations such as seeking HIV testing and STI treatment, male partner clinic visits resulted in consistently higher participant retention rates compared to the group without male partner visits (quarterly rates of 98%, 95%, 97%, 94% versus 93%, 91%, 89%, 88%, respectively). Based on the higher retention rates in the group with male partner clinic visits, the study team concluded that involvement of male

Continued on p.12

CHALLENGES COMMONLY REPORTED AND ASSOCIATED WITH RETENTION[6]

- Not wanting to be tested for HIV
- Long wait times at clinics
- Lack of support of trial from participant families and local community
- Relocation of some trial participants

TABLE 2. RETENTION RATES FROM A SELECTION OF MICROBICIDE CLINICAL TRIALS

Trial Code	Candidate Product	Phase	Site Retention	Rate
HPTN 059	Tenofovir/PMPA gel	2	Pune, India	100%[3]
MDP 301	PRO 2000/5	3	Masaka, Uganda	96%[1,2]
MIRA	Diaphragm and Replens® gel	3	Durban, South Africa	95%[6]
N/A	Cellulose sulfate	3	Makerere, Uganda	97.5%[4]

[5] Chandrasekaran V. Reducing attrition in cohorts of young reproductive age women: An Indian experience. Abstract DO13-252.
[6] Gappoo S. Strategies implemented to increase participant retention in a community-based HIV prevention efficacy trial in Durban, South Africa. Abstract CO25-135.
[7] Nalukenge W. Community perceptions of vaginal microbicides Phase III trial in rural SW Uganda. Abstract DO10-324.
[8] Hoffman IF. The impact of male partner clinic visits on retention, gel and condom adherence among women participating in a microbicide trial: Lilongwe, Malawi, HPTN 035. Abstract BO15-303.
[9] Buthelezi S. Giving trial participants a voice! Experiences from the MDP 301 clinical trial site in the Umkhanyakude district of northern KwaZulu-Natal. Abstract DO17-348.

CLINICAL TRIALS: COMMUNITY ENGAGEMENT *(Continued from p.11)*

TABLE 3. RETENTION IN A COHORT OF SEXUALLY ACTIVE WOMEN AGED 15-30 IN MYSORE, INDIA[5]

Retention influences

- Family
- Local leader motivation
- Peer group decisions
- Recruitment area

Reasons for attrition at first follow-up	
Changed residence	17.8%
Incorrect contact address	13.3%
Lack of family support	13.3%
Pregnancy	13.3%
Reasons for attrition at second follow-up	
Fear of blood draws	23.9%
Changed residence	13.1%
Pregnancy	13.1%
Lack of family support	8.7%

partners seemed to have a positive effect on retention of female study participants.[8]

Novel strategies to increase participant retention were also used in a prospective cohort study[5,10] examining the relationship between reproductive tract infections (RTIs) and acquisition of herpes simplex virus 2 (HSV-2). The study team was presented with a unique set of challenges with regard to minimizing attrition in a cohort of 898 women, aged 15-30, many of whom had children. Through approaches including child-friendly sites, strategies to lessen wait times, partner and family outreach, and low-literacy materials, the study achieved a 90% retention rate at final follow-up. Reasons for attrition between first and second follow-up were essentially the same, with the exception of "fear of blood draws," which was the primary reason for attrition at second follow-up *(see Table 3)*.[5]

Additional Models for Community-based Leadership

Several microbicide clinical trials of various candidate products in various phases encountered negativity and difficulties in the wake of the early closure of the Phase 3 trial of cellulose sulfate, causing wide-spread confusion and disruption within trial communities. Study teams took measures to resolve the situation through a range of community-based approaches.

At the Africa Centre for Health and Population Studies site of the MDP 301 trial, when study participants requested a forum for sharing their trial experiences, the study team formed a participant stakeholder group composed of a former and current study participant from each of three sites to plan a "theatre-sketch, song, and dance" event. The event, held in August 2007, drew 476 enrolled study participants and 94 male partners. The sketches provided information on many important topics: testing for HIV; the unknown efficacy of the study gel (PRO 2000); condom use; accurate self-reporting; partner support; study retention; and attending scheduled appointments. With 64% of enrolled study participants at the event, the study team concluded that community events led by former and current participants provided an appropriate and effective platform to reduce confusion.[9]

The Masaka, Uganda, site of the MDP 301 study also used participant leaders to clarify misleading information. By opening lines of communication between the community (via selected leaders) and the research team, many misconceptions resulting from the premature closure of the CS trial were resolved in an effective manner.[1]

The Microbicide Trials Network VOICE trial (MTN-003) offers another example of the value of community engagement. The study team chose a model that

> "TRIAL SITES HAVE A RESPONSIBILITY TO PROTECT THE CONFIDENTIALITY OF PARTICIPANTS, BUT ALSO PROVIDE A SAFE PLATFORM ON WHICH PARTICIPANTS CAN EXPRESS THEIR VIEWS OF TRIAL PARTICIPATION AND GEL USE…."
>
> – SIBONISO BUTHELEZI, AFRICA CENTRE FOR HEALTH AND POPULATION STUDIES

[10] Krupp K, Madhivanan P, Karat C, et al. Novel recruitment strategies to increase participation of women in reproductive health research in India. *Global Public Health* 2(4): 395-403, 2007.

involved the community for the first time from the earliest possible stage, i.e., the development of the research protocol. Among their first objectives was to obtain buy-in from local researchers and the Community Advisory Board (CAB). They also facilitated communications between the principal investigator and the MTN Community Working Group (CWG) which included community advisors, educators, and advocates from microbicide organizations, to describe the study concept and collect comments for further discussion. Discussions were also held among the trial sponsor, principle investigator, and the CWG. The CWG helped the MTN obtain feedback from local community members that supported MTN's request to the US National Institutes of Health for funding. Based on the MTN-003 experience, MTN leadership supports future engagement of community from trial concept throughout protocol development and implementation. This particular example shows that this concept is both feasible and worthwhile.[11]

The examples from the clinical trials covered in this summary offer models for engaging communities, as well as useful strategies for the recruitment and retention of clinical trial participants—not just for future microbicide trials, but for trials of other technologies whose purpose is to prevent HIV transmission.

CLINICAL TRIALS: ISSUES AND INNOVATIONS

Stephanie N. Tillman, Alliance for Microbicide Development

First-Time Reports on Microbicide Clinical Trials

Results from microbicide clinical trials were released officially for the first time in three presentations at the *Microbicides 2008* conference. The first described the results of the Phase 3 trial of Carraguard® vaginal gel. The second reported on a Phase 2 trial of tenofovir vaginal gel, and a third provided preliminary results from a Phase 1 trial of UC-781 gel applied rectally. The social, political, and economic impact of the cellulose sulfate trial in Nigeria was also discussed.

Results of the Phase 3 Carraguard® trial

The completion by the Population Council of the Phase 3 trial of Carraguard® topical gel marked a milestone for the field as the first completed Phase 3 microbicide trial. The results were much anticipated and, despite the fact that the gel was shown not to protect against HIV infection, it was shown to be safe at the levels of use reported.[1]

Carraguard® is an entry/fusion inhibitor derived from a seaweed extract that blocks HIV *in vitro* and was shown in animal models to protect against gonorrhea, herpes simplex virus (HSV), and human papilloma virus (HPV). It does not impede conception and is compatible with latex. It is generally recognized as safe (GRAS), is widely used in food and cosmetics and, due to its large molecular size, is believed to be non-absorbable. This trial studied the safety and efficacy of Carraguard® in protecting women from HIV infection. The trial began in March 2004; exit interviews and follow-up were completed in March 2007. Over 6,000 women participated at three sites[2] in South Africa: Medunsa, the Microbicide Research Council (MRC), and the University of Cape Town. Women were eligible for enrollment if they were HIV-negative, sexually active but not pregnant, and between 16 and 40 years of age. The lower age limit allowed enrollment of adolescents, and the upper age limit excluded ages for which seroconversion rates in the target population were minimal. The mean age of trial participants was 30.7 years and 63% defined their current relationship status as single.

Continued on p.14

[11] Ukpong M. Community engagement in research concept development: Lessons from the microbicide trials network (MTN). Abstract DO9-88.

[1] Johansson E. Population Council: Results of the Phase 3 Carraguard® trial. Plenary lecture. 27 February 2008.

[2] Setshaba Research Centre, through the University of Limpopo/Medunsa campus; the Empilisweni Centre for Wellness Studies, through the University of Cape Town; and the Isipingo Clinic, through the Medical Research Council of South Africa. *http://www.popcouncil.org/pdfs/Media%20Center/News_CarrResults_A4.pdf.*

CLINICAL TRIALS: ISSUES AND INNOVATIONS *(Continued from p.13)*

Baseline enrollment statistics were essentially similar across the three sites, with comparable rates of marriage and weekly sex acts. However, the MRC site encountered a higher incidence of uncircumcised partners and higher HIV-positive rates at screening, which led researchers to theorize that participants at the MRC site would demonstrate higher rates of HIV incidence by trial's end compared to the other sites.

The Carraguard® trial achieved lower than expected participant retention, despite persistent efforts to keep participants involved: 13% of trial participants were lost to follow-up, 9% of which was attributable to pregnancy. Although researchers had expected 80% retention, only 68% of the sample remained in the study, with a consequent decrease in study power.

This trial employed a novel approach developed by the Council to measure compliance with product use. Gel applicators were pre-treated with a special coating and, after return by participants as requested, laboratory-tested with a blue dye to detect presence of vaginal mucus, which would indicate that vaginal insertion had occurred. However, evaluation halfway through the trial found that just 61% of the opened applicators returned by participants tested positive for insertion. The success of subsequent attempts to encourage more compliance is being analyzed.

There were several significant issues around adherence to protocol. First, over the course of the trial, perhaps in response to prevention counseling, condom use increased by 31%. While objectively desirable, this outcome generates a lack of confidence in gel effectiveness data, especially due to high reports of covariance of condom and gel use: 62% of the condom users claimed to have used the gel in combination with condoms. Second, assessment of participants' potential HIV exposure was further complicated by reports of oral and anal sex in 8% and 2% of sex acts, respectively. Third, while participants reported 96% adherence to study protocol, comparison of their reports of gel use with the number of sex acts they reported in the same time period found that vaginal gel had, in fact, been used in only 43.4% of sex acts in the Carraguard® arm and 45.4% in the placebo arm. These averages may be somewhat misleading since they include a substantial number of outliers at the extreme ends of the gel-use spectrum (women reporting never having used product and those reporting always using it). Subgroup analyses will be performed to help explain these results.

No adverse events were related to product use. Prevalence of sexually transmitted infections (STIs) was lower throughout the trial than at baseline, but there was no difference between the placebo and active arms. However, women with an STI had 70% higher seroconversion rates than women without an STI, adding support to the growing body of research indicating that STIs enhance HIV acquisition.

The study's seroconversion data demonstrated no statistically significant differences between the seroconversion rates in the Carraguard® and placebo arms across all trial sites *(see Table 1)*. However, there were a few more seroconversions at the MRC site in the Carraguard® arm than in the placebo arm (48 and 42, respectively). This difference between arms was reversed at the other two sites, which totaled 86 seroconversions in their combined Carraguard® arms and 103 in their combined placebo arms. Though these between-site differentials cannot support a contention that Carraguard® gel may be protective against HIV, they do reveal site-specific differences among trial populations that would seem to merit such

TABLE 1. CARRAGUARD® SEROCONVERSION RATES

	Carraguard®	Placebo
Seroconversion (%)	3.4%	3.8%
Seroconversion (number)	134	145
Seroconversion (number, excluding MRC site)	86	103
Seroconversion (number, MRC site only)	48	42

attention as intensified counseling efforts and tailored measurement of protocol adherence at individual sites in future trials.

The Population Council developed three key messages to summarize the trial findings:
1) Carraguard® is safe and well accepted by the user.
2) Low adherence to protocol reduced the effective sample significantly.
3) Intent-to-treat analysis did not show any significant differences.

The presentation concluded with the observation that these findings, together with those likely to emerge from further analysis, should enrich the microbicide field with useful lessons learned. The Population Council will continue toward its goal of developing a safe and effective microbicide and has authored a report on the Carraguard® study to appear in *The Lancet*.

Results of the tenofovir study

The results of the Microbicide Trials Network (MTN) Phase 2 expanded safety trial of 1% tenofovir gel (daily versus coital use in vaginal application) showed this candidate microbicide to be safe and acceptable among trial participants.[3]

Beginning in August 2006, 200 women were enrolled at two sites in the United States (Birmingham, AL; Bronx, NY) and one site in India (Pune). Study participants were divided among four arms: daily use of tenofovir gel; daily use of a placebo gel; coitally-dependent use of tenofovir gel; and coitally-dependent use of a placebo gel. The primary study objective was to examine the local and systemic safety of the study product; the secondary objective was to compare acceptability of, and adherence to, two different study regimens. Safety and acceptability data were gathered at baseline and at one, three, and six months.

Follow-up of 198 women identified no statistically significant differences between study arms with respect to incidence of genital symptoms. The most frequently reported side effects among women using daily tenofovir were vaginal itching and burning. Rates of candidiasis ranged from 13% to 20% among all participants. No trial participants acquired gonorrhea, hepatitis B, or HIV during the study. One woman became infected with herpes simplex virus type 2 (HSV-2) and three tested positive for chlamydia. Women's reports of social harm (i.e., emotional issues) were minimal.

Six months into the study, participant retention was 96% with only one pregnancy, and self-reported adherence rates were high. Participants in the daily-use arm used the gel in 83% of total study days, with menses their most common reason for missing a dose. In the coitally-dependent arm, 80% of all sex acts were covered by gel within two hours of sex. These high rates of self-reported adherence were corroborated by pharmacokinetic (PK) testing, which found low but detectable plasma tenofovir levels in 79% of women who reported using the gel within the 12-hour period prior to testing. Participants found the gel acceptable with respect to appearance, smell, ease of use, and making sex more pleasurable. When asked if they would use the gel again if it proved to protect against HIV, 90% of women using the gel with each coital event and 96% of those using the gel daily reported positively.

In sum, the trial showed both daily and coitally-dependent use of 1% tenofovir gel to be safe compared to placebo. These results, together with high adherence rates and gel acceptability, and the results of earlier studies of tenofovir, will help pave the way for the Phase 3 VOICE (Vaginal and Oral Interventions to Control the Epidemic) trial, projected to begin enrollment in the third quarter of 2008.

Results of the UC-781 trial

Preliminary findings from an ongoing Phase 1 safety trial of UC-781 gel used rectally are encouraging.[4] This first clinical study of a vaginal microbicide tested for rectal use was supported under the NIH Integrated Preclinical/Clinical Program (IP/CP). The study seeks to evaluate the safety and acceptability of the non-nucleoside reverse transcriptase inhibitor (NNRTI) UC-781 gel at two concentrations—0.1% and 0.25%—in

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[3] Hillier SL. Safety and acceptability of daily and coitally dependent use of 1% tenofovir over six months of use. Abstract BO12-655.
[4] Anton P. A Phase 1 safety and acceptability study of the UC-781 microbicide gel applied rectally in HIV seronegative adults: An interim safety report at 50% completion. Abstract BO5-290.

CLINICAL TRIALS: ISSUES AND INNOVATIONS *(Continued from p.15)*

single- and seven-day use. The trial site is the University of California, Los Angeles (UCLA). The sample includes 36 seronegative men and women with histories of receptive anal intercourse (RAI), monitored for Grade 2 or higher adverse events and asked for feedback on product acceptability.

A unique feature of this study is use of biopsies to evaluate product safety after single- and seven-day exposures. The challenge for researchers is how best to distinguish side effects commonly associated with biopsy procedures, e.g., bleeding and diarrhea, from adverse events produced by the gel itself. To address this, the UCLA research team collaborated with NIH staff to apply the recently updated Division of AIDS (DAIDS) Toxicity Grading Tables to help avoid miscategorization of side effects.[5]

Analysis at the trial's halfway point showed UC-781 to be safe and well tolerated. Of 64 adverse events reported, none were Grade 3 or 4; seven were Grade 2 and unrelated to the biopsy procedure. Retention so far is 100%, all participants have adhered to the study protocol, and no participants have withdrawn due to biopsy-related concerns. This suggests that biopsy is acceptable to participants and therefore potentially useful for other microbicide studies. This study should be completed in March 2008.

Results of the cellulose sulfate trial

Although the Phase 3 trial of cellulose sulfate in Nigeria closed early, preparations for implementing the trial resulted in several positive outcomes:[6]

- *Individual:* 120 people were trained in all aspects of clinical research, leading the way to a variety of other career opportunities.
- *Community:* Health care facilities already in place were upgraded, and trial recruitment procedures brought HIV/AIDS awareness issues to the forefront of local attention.
- *National:* Trial planning and approval procedures increased communication among citizens, politicians, and the research community.
- *International:* Nigerian researchers have become involved in the international HIV/AIDS research effort.

Similar positive effects could occur in other communities in which microbicide trials take place. These outcomes should be taken into account in tallying successes in the HIV-prevention field.

New Approaches to Clinical Trials: Participant Registries

A new topic at the *Microbicides 2008* conference was the development of participant registry systems to accomplish different important objectives. One presentation described a registry approach to help researchers monitor the safety of participants who become pregnant while in an HIV prevention trial. The other described a registry for individuals interested in participating in rectal microbicide trials, the purpose of which was to expand and streamline enrollment in the future.

Registry of women who become pregnant during trials

When a microbicide becomes widely available, it is likely that women will use it either prior to knowing of a positive pregnancy, especially in areas with high fertility rates and low contraceptive use, or it will be used to provide protection during sexual interactions during pregnancy. Thus, any candidate microbicide will need to be tested in a pregnant population if it is to be labeled as safe during pregnancy; absent such testing, products will have to be labeled unsafe for use by pregnant women. Thus far, the microbicide field has avoided including these women in any trial due to concerns about teratogenesis, or harm to the fetus.

To address these concerns and their implications, the MTN has established an HIV Prevention Agent Pregnancy Exposure Registry (designated as MTN-016).[7] The registry's primary goal is to evaluate the safety and teratogenic risk

[5] National Institutes of Health. Division of AIDS table for grading the severity of adult and pediatric adverse events. Published December 2004, updated November 2007. Available at *www3.niaid.nih.gov/research/resources/DAIDSClinRsrch/PDF/Safety/DAIDSAEGradingTable.pdf.*

[6] Obunge O for McNeil LK. Microbicide research in Nigeria – Other than scientific successes. Abstract DO20-513.

[7] Beigi RH. Pregnancy in HIV prevention research: The MTN approach. In Symposium on Moving Microbicides into Vulnerable Populations. 26 February 2008.

of investigational products and to monitor the prevalence of structural abnormalities in fetuses and infants. Its secondary goal is to provide evidence-based assurance of lack of teratogenic risk when a given test product is used during pregnancy. Women who enroll will have been exposed to a microbicide or an oral pre-exposure prophylaxis (PrEP) agent when they become pregnant while participating in an HIV prevention trial. More specifically, the registry will include:

- Women who become pregnant in a trial testing HIV prevention methods, including those participating in HPTN 035, an ongoing Phase 2/2B study of the microbicides PRO 2000 and BufferGel®
- Women who have a planned exposure to a microbicide late in gestation, including those enrolled in MTN-002, a planned Phase 1 trial testing the absorption and drug activity of a single dose of tenofovir gel given prior to caesarean section.

Until researchers are able to define safety parameters for using these products in pregnant women, the registry will continue to enroll and monitor participants.

Rectal microbicide participant registry

Almost all candidate microbicides have been formulated and tested solely for vaginal use. Whether or not these products will be applied rectally or whether there are to be microbicides designed explicitly for rectal use, formulation and testing for rectal application is essential *(see summary on rectal microbicides on pages 7-9 of this issue)*. However, recruitment of participants for such testing has sometimes been hampered by stigma and cultural taboos, and is likely to continue to be challenging, particularly as research moves into late-stage testing and requires larger samples.

Thus, some researchers have started registries of individuals willing to participate in future rectal microbicide trials. One such registry—part of a larger registry of men in the Los Angeles, California, area interested in participating in rectal microbicide trials[8]—has already been used in a Phase 1 safety trial of UC-781[9] *(see summary of preliminary trial results on pages 8 and 15 of this issue)*. A forthcoming study of "Barriers to enrollment in a registry for microbicide trials" will compare demographics, risk behaviors, and drug use in the larger registry population among those either choosing or declining enrollment.[10]

Special Trial Populations

Populations not regularly included in microbicide clinical trials are referred to as "special populations" because they have unique biological or behavioral characteristics that require special consideration. Two such populations are female adolescents and women who test HIV-positive. Though both have been included in various early-stage microbicide trials, ethical and biological considerations may affect their inclusion in the future.

Female adolescents

For a variety of biological, behavioral, and socio-cultural reasons, adolescents are typically protected by ethical and legal policies with respect to participation in research. Parameters of adolescence vary from country to country. Clinical trials must therefore be designed to respond to such regulations as country-specific guidelines about independent age of consent and requirements for parental consent. While these may represent hurdles for trials of HIV prevention technologies, ways must be found to overcome them because regulatory authorities, perhaps somewhat paradoxically, may require that such technologies be tested in adolescents, who may be arguably at risk of HIV infection.

Two microbicide trials have included participants defined as adolescents: the recently completed Phase 3 Carraguard® trial, which enrolled women as young as 16 years of age, and the ongoing Phase 3 PRO 2000 trial, which enrolled women as young as 18 years of age.

Ethical-legal issues in adolescent microbicide and HIV vaccine trials

Ethical and legal concerns around inclusion of adolescents in trials of HIV vaccines and microbicides motivated

Continued on p.18

[8] Anton P. Personal communication. 8 May 2008.
[9] Anton P for Elliott JE. *Ex vivo* challenge of *in vivo* exposed colorectal explants may be an important predictor of microbicidal effectiveness *in vivo*. Abstract BO4-241.
[10] Gorbach P. Personal communication. 9 May 2008.

CLINICAL TRIALS: ISSUES AND INNOVATIONS *(Continued from p.17)*

an international consultation in 2007.[11] A major conclusion of the consultation was that, in order to fully understand the complex behavioral issues that could affect microbicide trials involving adolescent participants, further data are needed on adolescent sexual behavior, especially the potential for increased risky behavior. The consultation also discussed informed consent by adolescents, sexual empowerment, and the autonomy that might ensue from microbicide use, and the need for parental consent for adolescent participation versus adolescents' rights to confidentiality and privacy. The consultation developed four key areas of focus:

- Justification for adolescent enrollment
- When and how to include adolescents as trial participants
- Potential for "behavioral disinhibition" and possible stigma
- Ethical-legal audits for adolescent trial populations.

The consultation closed with agreement that more attention must be paid to adolescents as a special population in HIV prevention research.[12]

Another presentation provided a report-back from a 2007 consultation, "Making HIV Trials Work for Women and Adolescent Girls," which had dealt with the barriers, challenges, and opportunities for inclusion of women and adolescent females in clinical trials. That consultation recommended advocacy for feasibility studies of sensitive behavioral questions and issues around accrual, retention, community engagement, acceptability, and evaluation and improvement of consent processes.[13]

Challenges to inclusion of adolescent females in the Carraguard® Phase 3 trial

Inclusion of females under age 18 challenged the ingenuity of the designers of the Carraguard® Phase 3 trial, worried about possibly promoting promiscuity or encouraging premature sexual debut.[14] To avoid these possibilities, recruitment targeted participants who were already sexually active. Trial designers also addressed parental consent, participant confidentiality, conflicts between school hours and clinic visit schedules, and participant retention. To ensure participant safety, multiple regulatory bodies approved the trial protocol, and the trial's Data Safety Monitoring Board (DSMB) reviewed data for this age group separately from the data on the rest of the trial population. Females aged 16-17 were permitted to give informed consent or, in the case of the MRC site, request consent from a parent or guardian.

The results of these inclusions and distinctions are noteworthy. Of the 4.2% of trial participants aged 16-17, 16% became pregnant during the trial, compared to 11% in the group over age 18. This would seem to indicate low condom use and the need for more condom counseling in this age group in future trials.

Building a platform for HIV prevention for adolescent girls

Engagement and support of adolescent females in clinical research will require a multifaceted approach that combines strategies for protection, health services, and access to social power and economic opportunities.[15] Such a "platform" will have to be built with careful application of the term "adolescent," so as to avoid homogenizing the age group rather than recognizing its heterogeneity. Females in this age group are notably diverse: they may be in or out of school, married or unmarried, married and in school, or in other combinations of status and situation.

Still, researchers must elicit the same information from adolescent females that they seek from adults:

- Do you perceive yourself at risk of HIV infection?
- How do you construct notions of risk?
- What actions do you take to protect yourself?

Research on microbicides must somehow include all populations that might eventually

[11] Slack C. Ethical-legal issues in adolescent microbicide and HIV vaccine trials: Report on an international consultation, Durban, South Africa. In Symposium on Moving Microbicides into Vulnerable Populations. 26 February 2008.

[12] A draft of the meeting conclusions, "Towards a roadmap: A summary of identified ethical-legal complexities in adolescent HIV vaccine and microbicide research," is available on the South African AIDS Vaccine Initiative (SAAVI) website: *www.saavi.org.za.*

[13] Hankins C. Making HIV trials work for women and adolescent girls. Report-back session.

[14] Ratlhagana M for Skoler S. Challenges and results of including 16-17 year old women in the Carraguard® Phase 3 efficacy trial. Abstract CO33-645.

[15] Brady M. Building the platform for HIV prevention for adolescent girls. Abstract DO6-465.

use them. Inclusion of adolescents in early-phase clinical research can provide valuable qualitative feedback on product use and acceptability, and lessons learned about this special population from trials and subsequent consultations will both strengthen and streamline the design and execution of trials to come.[16]

Microbicides and women who test positive for HIV

Women who test positive for HIV constitute a special subpopulation of prospective microbicide users to whom special consideration must be given *(see Table 2)*. HIV-positive women typically want to protect their partners from infection, yet their involvement in clinical research entails critical biological and immunological considerations to which attention must be paid.[18] Women on highly active antiretroviral therapy (HAART) or hormonal contraceptives, and HIV-positive women who are pregnant, require special attention in

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TABLE 2. MICROBICIDE CLINICAL TRIALS INCLUDING HIV-POSITIVE (HIV+) WOMEN[17]

Candidate and Mechanism of Action	Phase	Status	Title of Study	Exclusively HIV+ Participants	HIV+ Women	HIV+ Couples
Carraguard® Entry/fusion inhibitor	1	Completed	Randomized, controlled, double-blind cross-over trial of safety, effect on genital tract shedding, and acceptability of Carraguard® among HIV-infected women	X	X	
	1	Completed	Safety and acceptability study of Carraguard® among HIV-positive women and men	X	X	
Dapivirine (TMC120) Replication inhibitor	1	Completed	Safety and tolerability of TMC120 gel in HIV-negative and HIV-positive women (TMC120-C127)		X	
	N/A	Planned	Seroconverter protocol (IPM 007)		X	
PC-815 (Carraguard® + MIV-150) Entry/fusion inhibitor and Replication inhibitor	1	Funded	Probing study: infectivity of vaginal lavages from HIV-positive women after vaginal administration of PC-815	X	X	
PRO 2000 Entry/fusion inhibitor	2	Completed	Randomized vaginal microbicide trial assessing safety of PRO 2000/5 Gel (P) versus vehicle placebo, in Uganda		X	X
	1	Completed	Multi-center dose-escalation safety and acceptability study (HIVNET 020)		X	
Tenofovir/PMPA Gel Replication inhibitor	1	Completed	Safety and acceptability study of PMPA gel		X	X
UC-781 Replication inhibitor	1	Ongoing	Safety and acceptability study of UC-781 topical vaginal microbicide in heterosexual women and their male partners		X	X*

* *The UC-781 trial does not specify whether the male partners included in the study need to be HIV+.*

[16] Mensch B. The contribution of behavioral research to microbicide trials: Taking stock. Plenary lecture. 25 February 2008.
[17] Alliance for Microbicide Development. *Microbicide Research and Development Database (MRDD).*
[18] El-Sadr W. HIV-infected individuals: The new frontier for microbicides. Original title: Issues related to HIV positive women — What is so unique about safety? In Symposium on Microbicides and HIV-Positive Women. 27 February 2008.

CLINICAL TRIALS: ISSUES AND INNOVATIONS *(Continued from p.19)*

> "WE CANNOT DIVIDE THE WORLD NEATLY INTO PEOPLE WITH HIV AND PEOPLE WITHOUT HIV. WE ARE ALL ONE PEOPLE, AND WE HAVE TO THINK BROADLY ABOUT THE FUTURE RESEARCH OF MICROBICIDES, OF HOW THESE PRODUCTS ARE GOING TO BE USED, AND HOW CAN WE REALLY HAVE AN IMPACT THAT IS WIDE AND FOR THE BROADER POPULATIONS AT RISK AS WELL AS INDIVIDUALS WHO HAVE A MAJOR IMPACT ON THE SUCCESS OF OUR STRATEGIES."
>
> – WAFAA EL-SADR, COLUMBIA UNIVERSITY

trial design. Women who are or become HIV-positive during a trial have a higher prevalence of vaginal symptoms, suffer from more adverse events from placebo gels, and have higher rates of laboratory abnormalities at baseline. Co-morbid conditions such as tuberculosis must also be taken into account. There is also the potential for drug resistance among HIV-positive microbicide users. All of this entails multiple levels of responsibility and monitoring that must be integrated into the design and implementation of trials, including (but not limited to) monitoring of blood plasma and levels of mucosal absorption of active drug product. Another variable to be taken into account is the fact that ARV-based candidates are not contraceptive, an attribute that may be of prime importance to HIV-positive women.

Attitudes toward microbicide testing among women who are HIV-positive

Women who test positive for HIV also have many concerns about microbicide testing in and eventual use by their community.[19] In 2006, the International Partnership for Microbicides (IPM) and the International Community of Women Living with HIV/AIDS (ICW) convened a series of conference calls that included HIV-positive women, scientists, clinicians, and researchers. Questions addressed during the calls focused on the safety of testing an investigational product in a community with individuals who are HIV-positive, access to care by those who seroconvert during a trial, potential for bi-directional compounds, and concerns about investigational product use by women during pregnancy. A separate roundtable session discussed additional concerns: continued inclusion in trials of HIV-positive women, potential implications for HIV-positive women in evaluations of ARV-based microbicide candidates, and the desire for continued research on non-ARV-based microbicides, both contraceptive and non-contraceptive.[20]

ARV-based microbicides: Implications for trial design and product use

ARV-based microbicides and their potential for fostering drug resistance represent challenges for two categories of HIV-positive individuals: those participating in trials of ARV-based microbicides who seroconvert in the period between routine HIV tests, and those who will use ARV-based microbicides once they are licensed and available for use.[21] Both categories and eventualities must be accounted for when candidate compounds are selected for further development.

There are essentially three levels of ease with which different ARV drug classes might generate drug resistance. Each has implications for microbicide design and development *(see box)*.

Non-nucleoside reverse transcriptase inhibitors (NNRTIs) are a drug class to which individuals most easily become resistant. They also foster "cross-class

EASE OF DEVELOPING RESISTANCE TO AN ARV CLASS[21]

Easiest →	More difficult →	Most difficult
NNRTIs (Dapivirine, MIV-150, UC-781)	NRTIs (Tenofovir)	Protease Inhibitors (PIs) (No product in testing)

[19] Forbes AS. HIV positive women and community. In Symposium on Microbicides and HIV-Positive Women. 27 February 2008.
[20] Microbicides and HIV+ women. Roundtable.
[21] Lacey C. How product characteristics and delivery may influence clinical trial design. Plenary lecture. 27 February 2008.

resistance:" individuals who develop resistance to one NNRTI are subsequently resistant to all drugs in that class, which includes many first-line therapies and drugs used to prevent mother-to-child transmission (PMTCT). The NNRTIs dapivirine, MIV-150, and UC-781 are being developed as possible microbicides.

NRTIs as a drug class are less likely to generate resistance than NNRTIs, but more likely to do so than protease inhibitors. The NRTI tenofovir has been formulated for both oral and topical use and is being tested in both formulations.

Protease inhibitors appear to only rarely produce drug resistance. None are in active development as microbicides. However, they would seem to merit attention, for that reason and because long-term use of NNRTI-based and, possibly, NRTI-based microbicides may generate resistance. Microbicide researchers might also consider ARVs with long half-lives, which would allow high drug-tissue levels and extended protection even when doses are missed.

Standards of Care and Prevention: Current and Evolving Thinking

As new HIV prevention methods currently in testing show effectiveness and are subsequently approved by regulatory bodies, microbicide researchers may question whether these strategies should be integrated into clinical trial standard of care. Though the introduction of an expanded standard of care package might complicate trial protocol, counseling procedures, and statistical analysis, the safety of clinical trial participants is nonetheless paramount. Another consideration for integrating new methods into international clinical trials is the variability in country-specific risk-benefit analysis.[22]

Impact of other HIV prevention trials

Male circumcision

Future microbicide trials may need to contemplate the possibility of offering circumcision to the male partners of female trial participants.[23] The premise here would be that female partners of circumcised males would be less likely to be infected. Microbicide trials might offer a unique opportunity to collect data on the circumcision status of participants' partners and capture insights into the positive effects of male circumcision on women. However, at present this entire issue raises more questions than can be readily answered.

Diaphragms

The MIRA (Methods for Improving Reproductive Health in Africa) trial found that the diaphragm used with lubricant gel was not protective against HIV, even in the context of a comprehensive HIV prevention package that included condoms.[24] Interest in this trial was high, since diaphragms are among the few available female-controlled health technologies and cervical barriers with associated gels are in testing as combination methods. While the MIRA trial results were disappointing, future trials of combination methods should not be ruled out. Diaphragms are still reasonably effective contraceptives and could be included in the mix of contraceptive products offered to trial participants.

HSV-2 suppressive therapy

A recently completed Phase 3 study (HPTN 039) was designed to determine whether twice-daily treatment of HSV-2 with acyclovir would decrease HIV

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> "HOW WOULD IT CHANGE OUR SAMPLE SIZE ESTIMATIONS IF WE MADE WOMEN'S PARTNERS LESS LIKELY TO ACQUIRE HIV INFECTION THEMSELVES? DO WE HAVE AN OBLIGATION TO OFFER MALE CIRCUMCISION, REFER FOR MALE CIRCUMCISION, SIMPLY DISCUSS IT WITH OUR WOMEN STUDY PARTICIPANTS, OR NOT SAY ANYTHING AT ALL?...THE WAY WE ANSWER THESE QUESTIONS WILL HAVE IMPLICATIONS FOR HOW WE DEAL WITH FUTURE PROVEN EFFECTIVE HIV PREVENTION TECHNOLOGIES."
>
> – CATHERINE HANKINS, UNAIDS

[22] Farley T. Report-back from ICMR/WHO/CONRAD/IPM Regulatory Meeting. Feedback session.
[23] Hankins C. Male circumcision. Impact of Other HIV Prevention Trials. Panel discussion.
[24] Blanchard K for Padian N. Diaphragms. Impact of Other HIV Prevention Trials. Panel discussion.

CLINICAL TRIALS: ISSUES AND INNOVATIONS *(Continued from p. 21)*

acquisition in HSV-2-positive individuals. While acyclovir did reduce the incidence of genital ulcers in HSV-2-positive individuals, it did not prove protective against HIV infection.[25] This result raises the question of whether or not to provide HSV-2 suppressive therapy to HIV-negative/HSV-2-positive trial participants as standard of care in microbicide trials; however, this approach is not yet recommended. The trial also demonstrated success in having women take a drug twice daily, which inspires some hope for microbicide trials comparing daily dosing with coitally-dependent regimens.

Discussion during a panel on "Confronting the 'Evidence' in Evidence-Based HIV Prevention" *(see full summary on page 32 of this issue)* raised the possibility of a comparative trial that would assess the acceptability of various prevention strategies including some mix of the following: male condom, female condom, diaphragm, daily preventative or suppressive therapy, vaginal rings, and topical microbicide gels. Its purpose would be to identify which methods relevant populations would select as most preferable. One such design might include preference arms, one of which would allow individuals to select a preferred product while the other arm would randomize participants to multiple products. Another design might seek to demonstrate one product as more effective than another in preventing pregnancy or HIV. When and if international regulators approve microbicides for use, such comparative models and user preference studies could be useful as the basis for developing standards of care and introduction strategies.

BEHAVIORAL AND SOCIAL SCIENCES: SPOTLIGHT ON ACCEPTABILITY AND ADHERENCE RESEARCH

Latifa Boyce, Alliance for Microbicide Development

Researchers who conduct microbicide clinical trials face many challenges. Among them is the acceptability of test compounds to potential or actual study participants and adherence by participants to study protocols. Some challenges may arise from misinformation and misperceptions about the trials and compounds. Others may be due to problems related to product ineffectiveness, or closures of HIV prevention trials in other communities. And sometimes the root of the problem may be the design or execution of the trial itself. All these factors are being addressed in some way by scientists involved in behavioral and social science research.

Track C of *Microbicides 2008* focused on this research. Several reports were essentially continuations of research presented in the Social Sciences Track[1] of the *Microbicides 2006* conference in Cape Town, South Africa. Others have emerged from recent Phase 2 and 3 microbicide clinical trials.

In her keynote plenary address, *Barbara Mensch (Population Council)* provided an inventory of the contribution made by behavioral research to microbicide trials.[2] She argued that, to understand recent clinical trial challenges—such as over-reporting of adherence and misreporting of sexual activity—more behavioral research is needed to help predict interpersonal and contextual factors that influence adherence, and to identify factors that influence and link women's acceptance of a given microbicide and adherence to protocol.

The tables that follow summarize the studies reported at *Microbicides 2008* that addressed behavioral and social science issues related to microbicide acceptability and adherence in clinical trials.

[25] Celum C. Effect of HSV-2 suppressive therapy on prevention of HIV acquisition (HPTN 039). Abstract BO22-310.

[1] Harrison PF. Acceptability research: Outcomes and future directions. *The Microbicide Quarterly* 4(2): 10-2, 2006.
[2] Mensch BS. The contribution of behavioral research to microbicide trials: Taking stock. Keynote address.

TABLE 1. EMPIRICAL (QUALITATIVE AND QUANTITATIVE) STUDIES ON MICROBICIDE ACCEPTABILITY

Type of Study	Description
Non-clinical setting	■ Researchers identified potential person-, product-, and context-related factors that predict willingness to use vaginal microbicides.[3] ■ Behavioral measures of user perception and acceptability were linked to biomechanical properties of gels.[4] ■ Preferences for rectal microbicide formulations were assessed in men who have sex with men.[5] ■ Researchers assessed attitudes among health care providers toward intravaginal rings as a delivery device for microbicides.[6]
Clinical setting	■ The acceptability of vaginal gels—BufferGel®,[7] PRO 2000/5[7,8], Carraguard®,[9,10,11,12] cellulose sulfate,[13] and 1% tenofovir[14]—has been assessed in the following groups: - Clinical trial staff[13] - Community stakeholders[13,15] - Female participants who used gel during Phase 2 and Phase 3 trials[7,8,9,13,14,15] - Female trial participants at high risk for HIV acquisition[13] - Health professionals[15] - HIV-infected women (not taking antiretrovirals) in Thailand[11] - HIV-negative women in India and United States[14] - Low-risk, HIV-negative couples in Thailand[10] - Male partners of female trial participants[15] - Non-trial participants, non-gel users in communities hosting trials[15,16,17] - Female sex workers[13] - Women who refused to use gel during trials[15] - Women who were ineligible for trials[15] ■ Other researchers assessed the acceptability of Praneem polyherbal vaginal tablet in a Phase 2 trial in India.[18] ■ A theoretical framework was used to integrate behavioral and social science research into clinical trials and guide acceptability research in clinical settings.[15] ■ Contextual and interpersonal influences on acceptability in a clinical trial setting were assessed.[7,12,19,20] ■ A theoretical construct was used to generate a culture-specific understanding of gel acceptability within trial settings.[21]

[3] Morrow KM. A contextual model of microbicide acceptability. Abstract CO9-557.
[4] Morrow KM. Co-optimizing vaginal microbicide gel acceptability and vaginal deployment. Abstract CP61-560.
[5] Carballo-Diéguez A. Gel or suppository? Results of a rectal microbicide preference trial. Abstract CO18-210.
[6] Wakasiaka SN. Perceptions of health care providers regarding the acceptability of intravaginal rings as a potential method of delivering microbicides for HIV prevention in Nairobi, Kenya. Abstract CO1-203.
[7] Woodsong C. Multiple perspectives on acceptability of microbicides in the HPTN 035 clinical trial sites in Lilongwe and Harare. Abstract CO19-239.
[8] Dhookie J. An assessment of the acceptability of a PRO2000/5 microbicide gel in the MDP 301 trial in Johannesburg. Abstract CO3-391.
[9] Friedland BA. Impact of acceptability on adherence in the Carraguard Phase 3 trial. Abstract CO16-570.
[10] Blanchard K. Acceptability of the vaginal microbicide Carraguard® among couples in Chiang Rai, Thailand. Abstract CP41-411.
[11] Whitehead SJ. Acceptability of Carraguard® vaginal gel among HIV-infected women—Results from a randomized, controlled, crossover trial, Thailand. Abstract CP35-358.
[12] de Kock AE. Exploring microbicide acceptability in terms of socio-cultural norms, relationships and product attributes in the Carraguard Phase 3 trial in South Africa. Abstract CO8-552.
[13] Wong CM. Acceptability of the cellulose sulfate vaginal microbicide among HIV-negative women in the CONRAD Phase 3 effectiveness trial. Abstract CP59-550.
[14] Hillier S. Safety and acceptability of daily and coital dependent use of 1 percent tenofovir over six months use. Abstract BO12-655.
[15] Alleman P. Pleasure and power: Impact of microbicides on the sexual encounter and sexual partnership. Abstract CP28-312.
[16] Lees SS. Perceptions of the MDP microbicides clinical trial in Mwanza, Tanzania and Masaka, Uganda: Views of participants and people from the wider community. Abstract CP29-319.
[17] Tolley EE. What predicts adherence in a safety trial—Is it generalizable beyond the trial setting? Abstract CO10-590.
[18] Joglekar NS. Acceptability and adherence: Findings from Phase 3 study of a candidate vaginal microbicide, Praneem polyherbal tablet in Pune, India. Abstract CO5-467.
[19] Seoka SP. Cleansing, curing and exciting: Unanticipated attributes of a microbicide gel in the MDP trial, South Africa. Abstract CO7-540.
[20] Phillip JL. Impact of disclosure of gel and trial participation to male partners on gel adherence among women in the Microbicide Development Programme (MDP) 301 Phase 3 trial. Abstract CO11-338.
[21] Montgomery CM. Emic perspectives on microbicides and sexual health: A new approach to acceptability. Abstract CO4-403.

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TABLE 2. LESSONS LEARNED FROM RESEARCH ON GEL ACCEPTABILITY, BY TOPIC

Topic	Lessons Learned
Overall acceptability of gel use	■ Topical microbicides appeared to suit diverse needs for HIV prevention in different populations, settings, and socio-cultural contexts.[13,22] ■ Microbicide gels were found to be highly acceptable to most users, including HIV-negative trial participants[8,13,21] and heterosexual couples,[10] HIV-infected women,[11] most clients of sex workers,[13] men who have sex with men,[5] and some male partners of female users.[13] ■ Some female users perceived their overall health and wellbeing to have been improved by study gels.[21] ■ Non-gel users were concerned that gel use would negatively affect sex.[15]
Product attributes	■ Some male partners reported preferences for gels with a more pleasing smell, though most described gels as odorless.[10] ■ Some users preferred smaller volume and thicker consistency.[10,11] ■ Some users suggested making applicators softer, more compact, and discreet.[10,11] ■ Some health care providers were concerned with the size of the vaginal ring and potential side effects of the gel.[6]
Sexual intercourse attributes	■ Gel use rarely had a noticeable effect on sex.[23] ■ For some users, gel provided extra lubrication, increased sexual pleasure for self and partner, increased comfort, reduced pain, or made the vagina feel tight.[8,10,11,13,15,21] ■ Perceptions of gel effect on sex may differ for gel users and non-users.[15] ■ Reports of "improved sex" with gel use may have different meanings among users in different populations.[11,13,21]
Partner dynamics and product use	■ Trial participants reported that vaginal gels were easy and convenient to use.[8,11,13] ■ Ease of insertion and perceived convenience of gel use are likely to improve with continued use over time.[8] ■ Female users' perceptions about gel use may be influenced by disclosure of gel use and trial participation to male partners.[20] ■ Clandestine use may be unimportant, difficult, or disadvantageous in certain contexts (e.g., married women). In fact, disclosure of gel use and trial participation by married women to male partners helped build trust and intimacy in relationships and has been empowering for women.[21] ■ Women's control of gel use is important, but there are concerns that it may increase promiscuity or violate norms for decision-making within marriages.[7] Socio-cultural and interpersonal influences may affect sentiments within couples and communities regarding whether women can and should use microbicides.[12,17]
Interpersonal and contextual influences	■ Individual willingness to use gels may be influenced by social and cultural norms, health care delivery systems and providers, partner dynamics, and community perceptions.[3,7,12,15] ■ One's willingness to use a specific microbicide to protect against HIV infection is affected by both those individual and dyadic elements.[3] ■ Perceived HIV risk, male partners, cultural notions about sex and sexuality, motivations for participation in trials, and social perceptions of HIV research are important factors influencing acceptability of microbicide gels.[1,2] ■ Microbicide gel use integrates well with broader concepts of sexual health, vaginal hygiene, cleansing the body of polluted substances, and concepts of sexual desire and pleasure.[21]
Protective effect, contraceptive effect, male microbicides	■ Heterosexual Australian men reported some reluctance to use a microbicide that has less protective efficacy than condoms.[24] ■ There is strong support for a microbicide with contraceptive effect, but this may differ by gender (i.e., men less supportive) and relationship status (e.g., women in stable relationships are more supportive than those who are not).[7,10] ■ Support for male topical microbicides was reported, mostly by men.[10]
Promotion, marketing, and introduction strategies	■ Different marketing and introduction strategies will likely be needed for different populations, within and across diverse socio-cultural contexts.[7] ■ Beyond trial settings, perceived protective efficacy of gels may influence patterns of gel use.[17] Strategies should balance potential users' need for a protective product with their insecurity about partner trust and reactions, and should be considered within socio-cultural and gender/power norms and other relationship dynamics.[10] ■ For married couples, monogamous partners, or other non-sex worker populations, promoting potential microbicides as contraceptives, as a way to increase sexual pleasure, or as an occasional preventive method that can be used without partner participation might be an effective marketing strategy.[10] ■ For potential users in non-stable relationships, marketing strategies that emphasize gels' sexual pleasure attributes might be more appealing and effective.[10] ■ Some investigators suggested positioning microbicide gel use within the overall picture of sexual health by promoting it as a way to facilitate pleasure, excitement, empowerment, intimacy, and overall health and well-being.[8,21] ■ People will likely look to health professionals and community leaders for recommendations about use of microbicide gels. ■ Some religious groups may not support gel use.[7]
Willingness to pay	■ Vaginal gels should be moderately priced (not too expensive so as to prevent access, but not so inexpensive that quality is questioned).[10] HIV-infected women expressed willingness to buy an effective gel for a condom-equivalent price.[11]

[22] Pati S. A biosocial perspective on microbicide acceptability as women controlled HIV prevention method in Indian context. Abstract CP66-580.
[23] Whitehead SJ. Will microbicides feel good as well as preventing HIV? Maximising pleasure and prevention. Abstract CP36-359.

TABLE 3. RESEARCH CONCERNING ADHERENCE TO MICROBICIDE GEL USE IN CLINICAL SETTINGS

Study Purpose	Topic
Analysis of levels of adherence	■ New reports on levels of adherence were presented for the following clinical trials: - Phase 3 Carraguard® [2,9] - Phase 2/2B HPTN 035 (BufferGel®, PRO 2000/5)[2,25] - Phase 3 MDP 301 (PRO 2000/5)[20,25,26] - Phase 2 Praneem polyherbal vaginal tablet[18]
Assessment of reliability of self-reports	■ Studies assessed reliability of self-reported gel use compared to used applicator returns[26] and to determine if self-reported sexual behavior at last sex act is a reliable indicator of behavior at all sex acts.[27]
Assessment of predictors of adherence	■ Investigators studied relationship between female users' gel adherence and disclosure of gel use and trial participation to male partners.[20] ■ A mixed-model approach was used in India to assess acceptability and sustained use of vaginal microbicides among trial and non-trial participants to determine if predictors of adherence among women in microbicide safety trials can be generalized to non-clinical trial populations.[17] ■ The impact of acceptability on adherence was assessed in the Carraguard® Phase 3 trial[9] and in the Phase 2 trial of Praneem polyherbal vaginal tablet.[15] ■ Researchers studied factors affecting product adherence among HPTN 035 participants in Hlabisa, South Africa.[28]
Strategies for improving adherence and its measurement	■ Studies are looking at which mode of inquiry [e.g., audio computer-assisted self-interviews (ACASI) or face-to-face interviews (FTFI)] produces more accurate self-reports on adherence and sexual activity.[2] ■ The feasibility of using pictorial ACASI is being studied in the HPTN 035 microbicide study in Malawi and South Africa.[2] ■ Researchers described methods used to improve the accuracy of self-reported data on adherence.[29] ■ Used applicators were collected in some trials to determine the reliability of self-reported gel use.[27] Researchers also assessed whether sexual behavior at last sex act was a good indicator of behavior at all sex acts.[25] ■ The design, development, and implementation of approaches used to enhance product use during the Phase 2B clinical trial of tenofovir gel were described.[30] ■ Researchers evaluated the effectiveness of a strategy to improve compliance in gel use among trial participants.[27]

TABLE 4. SELF-REPORTED ADHERENCE IN MICROBICIDE PHASE 2 AND 3 TRIALS (% OF SEX ACTS COVERED)

Clinical Trial/Candidate	Phase	Condom Use (%)	Gel Use (%)	Gel Use, No Condom Use (%)
Carraguard®[2]	3	64 (self-report)	96 (self-report); 44 (tested applicators)	34 (self-report)
MDP 301[25]	3	78	84	83
HPTN 035[25]	2/2B	65	83	78
CS CONRAD	3	96	86	45
CS FHI (Nigeria)[31]	3	88	82	53
Savvy™ (Nigeria)[31]	3	87	78	62
Savvy™ (Ghana)[31]	3	90	79	45

[24] Rosenthal SL. Acceptability of microbicides to Australian men. Abstract CP1-103.
[25] Hillier S. Update from clinical trials of microbicide effectiveness. Plenary lecture. 26 February 2008.
[26] Gilbert C, Crook AN, Nunn A, McCormack S. Is self reported sexual behaviour at the last sex act a good indicator of behaviour at all recent sex acts? Abstract BP37-401.
[27] Crook AN, Nunn A, Gilbert C, McCormack S. Assessing the reliability of self-reported gel use compared to used applicator returns in the ongoing MDP 301 Phase 3 trial. Abstract BP38-402.
[28] Dladla-Qwabe AN. Factors affecting product adherence among HPTN 035 participants in Hlabisa. Abstract CO15-528.
[29] Pool R. Increasing the accuracy of adherence data in the Microbicides Development Programme 301 trial. Abstract CO12-368.
[30] Mansoor LE. Development of materials and tools for the adherence support program in CAPRISA 004 Phase 2B tenofovir trial. Abstract CI14-497.
[31] Van Damme L. Phase 3 microbicide trials update. IAS Conference, Sydney, Australia, July 2007. WEBS103.

Continued on p.26

TABLE 5. LESSONS LEARNED ABOUT ADHERENCE: SUMMARY

Topic	Lessons Learned
Adherence estimates	■ Several early-generation Phase 2 and 3 trials reported lower than expected or poorly measured adherence to product use and protocols, which ultimately can affect measurement of product effectiveness.
Adherence measurement and its challenges	■ Trial investigators are using different measurement approaches and modes of inquiry (e.g., self-reports using coital diaries, face-to-face interviews, ACASI, applicator tests, human semen markers) to collect data on adherence. Varying self-reported adherence measurements have been obtained using these different measurement approaches, suggesting that wording, meaning, timing of questions, and mode of inquiry may be important and need to be improved.[2,32] ■ Self-reported estimates of adherence in some trials differed from adherence estimates obtained using clinical biomarkers (e.g., applicator tests).[2]
Factors that influence or predict adherence and/or non-adherence	■ Sexual frequency was a significant predictor, with higher levels of adherence to gel use reported among women having sex less often.[9] ■ Perceived risk of HIV infection may influence adherence to gel use.[9] ■ Gel effect on partner's sexual pleasure was a stronger predictor of adherence than gel effect on participant's own sexual pleasure.[9] ■ Two clinical trials reported high acceptability (willingness to use microbicides), but general willingness to use products in those trials did not translate into/predict sustained and consistent product use.[2,18] ■ Contextual factors may influence the relationship between acceptability of gels and adherence.[17] ■ Certain aspects of acceptability may predict adherence among trial participants, but not among people from the same communities who are not enrolled. Psychosocial factors (e.g., couple harmony, protection efficacy, positive attitudes toward condoms, perceived partner infidelity, male involvement in trials, and disclosure of gel use and trial participation to male partners) were predictors of consistent use within the clinical trial setting. Protection efficacy was a significant predictor of consistency of condom use beyond the trial setting.[17,20,28]
Strategies used to improve adherence and its measurement in clinical trials	■ Several trials cross-checked and validated self-reported data with biomarker data (e.g., applicator tests, human semen detector tests).[2,26,27,29,32] ■ Researchers are hoping to improve data collection by determining which modes of inquiry produce the most accurate and reliable self-reported adherence estimates. They are also integrating strategies that enhance adherence to product use into clinical trials.[2] ■ Researchers are trying to improve adherence during clinical trials by using local staff for data collection and evaluation,[30,33] and by integrating intensive education and adherence counseling support programs.[28,30] ■ Others used staff feedback to improve counseling messages[34] or incorporated strategies to increase male partner involvement in clinical trials.[35,36]

[32] Littlefield SA. An analysis of varying measures of adherence among women enrolled in the Carraguard Phase 3 trial. Abstract BO18-533.
[33] Tolley EE. Track C Rapporteur Summary.
[34] Mansoor LE. Staff opinions and perceptions of the adherence support programme in CAPRISA 004 Phase 2B tenofovir gel trial. Abstract CP53-503.
[35] Makhanya NL, Palanee T, Ramjee G. Strategies to increase male involvement and product adherence in the Phase 3 Carraguard® trial in Durban, South Africa. Abstract CP80-658.
[36] Busari OA. Novel strategies for securing male involvement and partner consent in microbicide trials: Our experience in a resource-limited West African setting. Abstract CP8-119.

Participants in this Track suggested future directions for studying and encouraging acceptability of microbicide candidates and adherence to their recommended use *(see Table 6)*.

TABLE 6. FUTURE DIRECTIONS

- Continue to integrate behavioral and social science research into microbicide clinical trials. Some researchers recommend full integration.[37]
- Determine contextual factors or circumstances that may enhance or prevent use of microbicides. Understand whether acceptability and adherence are context-specific, and if so, determine the most appropriate contexts for enhancing acceptability and adherence within and outside clinical settings.[2]
- In current trials of diverse populations, directly assess the relationship between the product's effect on sexual experience, subsequent product use, and negotiations with partners.[23]
- Continue development and use of theoretical frameworks and models to examine acceptability.[33] Conduct more research to determine predictors of adherence (versus predictors of acceptability).[2]
- Understand influences on adherence and acceptability (e.g., contextual factors, perceived risk) and the use of these influences to enhance acceptability and adherence within and beyond clinical trial settings.[2,33]
- Use of new technologies (e.g., interactive voice response surveys, Blackberry® devices, and web-based behavioral assessments) may improve adherence measurement.[2]
- Use mixed-method approaches (qualitative and quantitative) to enhance acceptability assessments.[33]
- Use multiple approaches and techniques within a single trial to collect and validate adherence data.
- Assess feasibility and effectiveness of new techniques and strategies.[33]
- Improve behavioral questions so that wording and timing are clear and unprompted. Reduce bias in self-reports.[2]
- Validate behavioral self-reports of adherence.
- Integrate new strategies for improving adherence and its measurement in clinical trials.
- Collect empirical data on interpersonal and contextual factors that might influence adherence during trials.[3]
- Continue to measure behavior change (e.g., changes in risk behavior and condom use) during trials.[33]
- Increase male involvement in trials from the outset.[35,36]
- To improve adherence during ongoing clinical trials, continually assess and adapt recruitment and retention procedures.[38] Post-licensing studies should evaluate approaches to promotion that include the enhancement of pleasure.[23]

As behavioral and social science research continues to make significant contributions to the field of microbicides, it will help explain some unanswered questions about acceptability and adherence. However, because microbicide basic science, clinical science, behavioral and social science, and advocacy are intertwined, full integration of social sciences into microbicide research and coordination among all research tracks is essential to advancing microbicide development and enhancing eventual use.

[37] Abbott S. Challenges implementing behavioral research in microbicides clinical trials. Abstract CO32-641.
[38] de Kock E. Engaging participants in a Phase 3 study of the efficacy and safety of the microbicide Carraguard® in preventing HIV sero-conversion in women. Abstract CP60-558.

AFTER THE TRIALS: INTRODUCTION AND USE

Betsy M. Finley, Alliance for Microbicide Development

Marketing, Modeling, Access to, and Use of Microbicides

History has shown that we can learn from the successes, failures, and struggles of other reproductive health technologies. Rather than "reinvent the wheel," these lessons can then be applied to the microbicide field.

What have we learned?

There has been discussion within the microbicide field and other relevant disciplines about which previously-introduced reproductive health method offers the best model for microbicide marketing and introduction. Some feel that the analogies between the female condom and microbicides make that a "natural" for microbicides; however, there have been problems with this technology on several levels, including strategies for roll-out. Experience with the female condom has provided lessons about outreach, community involvement, and cost *(see Table 1)*.

The example of the female tampon is also instructive. Microbicide researchers have illustrated this point by presenting results from a 1939 provider survey from which emerges the following quote: "It is our opinion that inefficacy of the method, common sense, and fear would limit the use of this procedure to a relatively small number and that the fad should die of its own weight, were it not for the constant new crop of neophytes in schools and colleges gullible to attractive advertising and sampling." Quite the contrary occurred; over an extended period of time, use far exceeded expectation.[2,3]

TABLE 1. LESSONS LEARNED FROM THE FEMALE CONDOM[1]

Lessons *from* female condoms	Lessons *for* microbicides
Capacity building is pivotal to acceptance.	Education on use will be key.
Outreach by peers sustains use in difficult settings.	Consider peer outreach as a strategy for introduction.
Community involvement is key for implementing successful strategies.	Community involvement is, and will continue to be, important.
Cost was too high.	Examine pricing strategies now.
Social marketing has been effective.	Social marketing could be effective in increasing access and use.

Modeling impact and use

The successful introduction of a product in any setting is directly related to "the product profile, country epidemiological profile, introduction strategy, and individual use patterns."[4] Mathematical modeling programs have been designed to predict the impact and potential use of a microbicide within different populations and under different circumstances. Evaluating behavioral measures (e.g., adherence rates) and product efficacy will tell us what potential impact a microbicide might have on the HIV epidemic.[5]

Product efficacy must also be factored in, because it is likely that a microbicide will have only partial efficacy. A model developed to compare protection from a low-efficacy/high-use microbicide to a high-efficacy/low-use microbicide showed that researchers should be aiming to develop a microbicide that will be well accepted and well used because of the likelihood of low-level efficacy. One approach that has been proposed for increasing use is the development of a product that enhances sexual pleasure.[6]

The way a product is introduced to potential users will be key for successfully marketing a microbicide. To the question, "Are microbicides good enough?", a reasonable answer could be that

[1] Kundu P. Our host country: Microbicides and female condom advocacy in India. Compiled jointly by Global Campaign for Microbicides and Hindustan Latex Family Planning Promotion Trust. Pre-Conference Workshop.
[2] Rees H. Reproductive health/HIV technologies research and introduction: Lessons for microbicides policy and advocacy. Plenary lecture. 27 February 2008.
[3] Magid MO, Geiger J. The intravaginal tampon in menstrual hygiene. *West J Surg Obstet Gynecol* 51:150-2, 1943.
[4] Foss AM. Phasing introduction—What is the impact? Examination of potential microbicide introduction strategies in India. Abstract CO36-416.
[5] Blower S. Modeling the impact of microbicide introduction. Keynote address.
[6] Watts C. Microbicide modeling to inform policy. Keynote address.

especially in situations where women have no options to protect themselves from HIV transmission, even a partially effective microbicide would be better than no protection at all.[7]

Access to microbicides

Advocates have reported difficulty in explaining to politicians the rationale behind making the cost of female condoms low, given the fact that there is already a low-cost option in the male condom. Since the objective for developing a technology such as the female condom (or a microbicide) is for that technology actually to be used, more than simple political will is required—the products must be available and accessible to those populations most in need.

Researchers from the Microbicides Development Programme surveyed over 1,000 women in Johannesburg, South Africa, about their preferences for site and method of distribution of microbicides, advertising, and price *(see Table 2)*.

Multinomial logit model analysis revealed that the women favored distribution at a pharmacy, in a private room, with messaging for women's empowerment, and free of charge. The least-favored distribution strategy was in a township store, from behind the counter, with messaging for pleasure, and costing 20 South African Rand.[8]

In another study, in Botswana, researchers who interviewed a total of 76 health care providers, traditional healers, non-governmental organizations, and female sex workers, to evaluate access and use of condoms among female sex workers, found that the more distribution channels there were and the lower the cost, the better the access.[9]

Additional studies of potential users of microbicides and other reproductive health technologies, to assess their preferences for distribution, will help development of successful strategies, and assist researchers in developing the best possible products and ensuring their availability for the maximum number of potential users.

TABLE 2. MICROBICIDE DISTRIBUTION PREFERENCES FROM THREE COMMUNITIES IN JOHANNESBURG, SOUTH AFRICA[8] *(first preference is bolded in each column)*

Distribution Channel	Collection Method	Messaging	Price
▪ Clinic	▪ **In private room**	▪ HIV	▪ 20 South African Rand
▪ Township store	▪ Behind counter	▪ Pregnancy	▪ 15 South African Rand
▪ **Pharmacy**	▪ From shelf	▪ **Women's empowerment**	▪ 5-10 South African Rand
▪ Supermarket	▪ Dispensing machine	▪ Enhanced pleasure	▪ **Free**

MDS CIVIL SOCIETY WORKING GROUP PUBLISHES *THE FIRST 55 STEPS*

Anna Forbes, Global Campaign for Microbicides

As reported in this publication a year ago,[1] the Global Campaign for Microbicides convened an international Civil Society Working Group in 2006-07 to develop a clearly articulated plan for moving the microbicides field from where it is now regarding civil society engagement—which is minimal, scatter-shot, and under-resourced—to where it needs to be.

This project was undertaken to provide an additional chapter to the *Microbicide Development Strategy (MDS)*, a document created at the behest of the Microbicide Donors Committee to serve as a prioritization framework for decision-making by funders, researchers, and

Continued on p.30

[7] Watts C. Apples and oranges? Interpreting success from contraceptive and HIV prevention research. Abstract DO7-518.
[8] Terris-Prestholt F. Facilitating microbicide use in South Africa: Using women's preferences to design distribution strategies. Abstract CO35-247.
[9] Sharma A. Microbicide provision strategies that may reach female sex workers in Botswana. Abstract CO34-65.

[1] Forbes A, Yassky R. *MDS* Civil Society Working Group. *The Microbicide Quarterly* 5(1): 19-22, 2007.

MDS CIVIL SOCIETY WORKING GROUP *(Continued from p.29)*

developers. The *MDS* was generated by four Working Groups: Basic Science and Preclinical Development; Clinical Trials; Manufacturing and Formulation; and Commercialization and Access. Funding was subsequently provided to convene the Civil Society Working Group to undertake a parallel process. *The First 55 Steps: A Report of the Microbicide Development Strategy's Civil Society Working Group* was unveiled at the *Microbicides 2008* conference in New Delhi on 25 February 2008 and is acknowledged by the authors of the *MDS* as a companion document to their original report.

The *Report* identifies the barriers to full civil society engagement in the microbicide field and lays out pragmatic steps to remedy them. To achieve a tightly-focused analysis of the existing situation and clear priorities for action, the Working Group identified the seven issues that are *both* of greatest concern to civil society *and* that—if addressed with targeted energy and resource investments—could result in immediate benefit to the field. It also described the seven priority actions needed to address those gaps, as follows:

HIGHEST-PRIORITY GAPS	PRIORITY ACTIONS
1. Insufficient investment in building sustainable research capacity and health care delivery infrastructure in trial communities	1. Use microbicide trial site development investments as opportunities to ratchet up local health care infrastructure and expand human capacities for research and health care delivery in ways that provide durable local benefit
2. Lack of formal mechanisms and opportunities for civil society engagement and transparent communication with researchers throughout the research process	2. Develop mechanisms to increase civil society's engagement across the entire arc of research, development, and product introduction, and to improve communication among researchers, sponsors, developers, and civil society
3. Inadequate civil society participation in monitoring and accountability across the field	3. Create more structural opportunities and build capacity for civil society participation in the monitoring bodies that guide microbicide research and development
4. Insufficient investment in science-focused microbicide advocacy	4. Invest in initiatives to increase advocacy participation by microbicide scientists and the scientific expertise of microbicide advocates
5. Lack of widespread, timely dissemination of results to microbicide stakeholders and the general public	5. Improve systems for rapid and user-friendly dissemination of trial results and their implications to stakeholder groups and the general public through multiple communications channels
6. Lack of civil society involvement in defining plans for acceptability, affordability, sustainable access, and marketing work to maximize microbicide uptake among key populations	6. Utilize the existing expertise of civil society actors in current efforts to develop product introduction, distribution, and marketing plans
7. Lack of effective civil society influence on product regulatory bodies	7. Create structural opportunities and build capacity for civil society to have meaningful input into regulatory processes

Early in its deliberations, the Working Group decided not to produce a "laundry list" of aspirational ideas and recommendations but, instead, a practical tool comprised of actionable and measurable objectives. The report challenges each sector in the microbicide field—government and policy-makers; researchers and scientists; funders, trial sponsors and research institutions; and the civil society organizations themselves—to take on assigned tasks that, collectively, could bring about full civil society integration into the field at all levels.

To identify these tasks specifically, the Working Group broke its seven priority actions down into 55 interlocking implementation steps—concrete activities that, if undertaken, should generate real progress toward the goal. The action steps needed to accomplish Priority 2, for example, are as follows:

EXAMPLE: ACTION STEPS BY SPECIFIC SECTOR FOR PRIORITY ACTION #2: DEVELOPING MECHANISMS TO INCREASE CIVIL SOCIETY'S ENGAGEMENT

Civil Society	Governments/Policy-makers	Researchers/Principal Investigators	Funders/Sponsors/Research Institutions
Work to develop the knowledge base needed to serve on peer review committees, advisory and planning boards, institutional review boards, etc., and effectively request such opportunities	Increase the number of dedicated civil society seats on national planning and regulatory bodies	Identify civil society actors who can impact the achievement of research goals and establish transparent opportunities for ongoing communication with them	Fund mechanisms to facilitate communication between researchers and civil society, including efforts by civil society to build their own science literacy and, thus, capacity for productive participation in the microbicide development and access process

The *Report* also takes an unflinching look at the "money problem." The life blood of civil society engagement is money, capacity, and access. Most civil society entities simply cannot afford to "skill up" and "staff up" to the extent necessary for greater engagement. To maintain their current workloads and follow through on their share of the activities outlined in this report, they need more leaders, more managers, more staff training and development (especially in the area of "research literacy"), and enhanced access to communications technology. Without these, they will fail, even if offered every opportunity for full participation in the microbicide research and development process. They are simply too over-stretched and under-prepared to take on the additional work.

Unfortunately, very limited support is available through foundations and other funders for HIV prevention advocacy. Access is also compromised by the fact that funders are understandably drawing away from giving small grants to small and medium-sized NGOs and moving toward the much more efficient process of making large grants to well-established, highly professionalized organizations.

In some other fields, this problem is being addressed by establishing intermediary grant-making entities capable of accepting large grants from funders and using them to support a wide range of projects proposed by smaller NGOs. Such a "funding window" could be established and capitalized to funnel resources to those civil society groups committed and well-positioned to pursue HIV prevention advocacy.

One has only to contrast the budget of the average civil society NGO with that of entities in the other sectors (research institutions, funders, and governmental policy-makers) to see why truly balanced collaboration among the sectors cannot be achieved without additional investment in NGO capacity-building. Groups with the "on-the-ground" expertise and connectedness are often the best qualified and situated to serve as authentic civil society voices and many of them want to participate in the microbicide enterprise. But, if the field sincerely wants their full participation, it must first find a balanced way to invest in building their capacity.

In the last section of the *Report*, the Working Group described the "value added" that will only be fully realized when civil society is accepted and integrated into the microbicide field. Civil society actors, working hand-in-hand with research institutions, industry, and governments, play a critical role in creating an enabling environment for microbicide research and development. The *Report* describes an enabling environment as one in which:

- Government policies and regulations facilitate research
- Science professionals from the relevant disciplines are available in sufficient numbers
- Adequate clinical research facilities exist
- A pool of properly trained staff is on hand for recruitment
- Public awareness of and support for microbicide research and development exists, as does consumer demand
- Media coverage of trials is supportive, balanced, and well informed.

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MDS CIVIL SOCIETY WORKING GROUP *(Continued from p.31)*

Adequate financial resources, political will, and public support are all essential to creating and maintaining this enabling environment. Civil society entities have the leverage, positioning, and political legitimacy needed to generate these ingredients.

These groups also serve an essential bridging and cultural translator function between research institutions (especially those based in the Global North) and trial host communities and governments (especially those in the Global South). As trial host communities and end-users develop greater expectations and make ever greater demands on the research establishment, researchers' need for civil society to help ensure positive, meaningful, productive collaborations also grows. But civil society cannot and will not carry out these essential functions fully if it is not appropriately integrated into the field at every other level as well.

The *Report* is posted at *http://www.global-campaign.org/clientfiles/GCM-MDS-CSWG-FinalReport2008.pdf*. The Executive Summary is at *http://www.global-campaign.org/clientfiles/GCM-MDS-CSWG-Flyer2008.pdf*. For more information, please contact Anna Forbes, Deputy Director, Global Campaign for Microbicides, *asforbes@path.org*.

WHAT IS EVIDENCE IN HIV PREVENTION RESEARCH?

Bob Roehr

There is a convergence in HIV prevention research that, increasingly, is tying together behavioral, physical, and biomedical interventions into a single matrix. It is fostered by the understanding that no single intervention is likely to be a "silver bullet" that does the entire job of blocking infection. Rather, as with therapy, the most effective prevention is likely to be a "cocktail" of interventions tailored to the needs of individuals.

A common and crucial theme in this convergence is the matter of what constitutes evidence. For example, how does one measure outcomes in an environment where the traditional randomized controlled trial (RCT) does not always or fully apply, or where trial outcomes are murky? This was the focus of a special conference panel at *Microbicides 2008*.

"We need an inclusive yet very rigorous notion of evidence that encompasses biological, behavioral, and social sciences, and the lived experiences of individuals and communities affected by HIV and AIDS," said Judy Auerbach, Deputy Executive Director for Science and Public Policy at the San Francisco AIDS Foundation. Auerbach introduced the session noting that it would focus on the gathering and interpretation of evidence from biomedical technology trials, including but not limited to microbicides.[1]

The evidence-based public health approach in HIV prevention is modeled after evidence-based medicine, which "valorizes the randomized controlled trial as the gold standard of evidence and suggests [that] it above all other methodologies can produce evidence that really matters." That is one of four trends influencing prevention research that Auerbach discussed.

Another is that the Centers for Disease Control and Prevention (CDC) increasingly has used a "tiers of evidence" approach to fund research and programs, which gives primacy to the RCT and relegates other methodologies to lower status. However, most community-based organizations (CBOs) lack the capacity to conduct, implement, or evaluate those types of interventions.

The CDC-sanctioned "Diffusion of Effective Behavioral Interventions (DEBI)" programs "have to be adapted to be applicable to their population and community group to have cultural relevance and situational relevance," said Auerbach. The question becomes, "How much adaptation is okay before you lose fidelity in these very rigorously designed interventions?"

[1] Panelists: Dickson K, Padian N, Warren M. Moderators: Auerbach J, Solomon L. Confronting the "evidence" in evidence-based prevention. Feedback session.

She said HIV prevention research has come to recognize the importance of cultural variables and social institutions in fueling or stemming the HIV epidemic. But there are serious questions as to how relevant the RCT and clinical methodologies are "for addressing those type of questions and developing those kind of social policy interventions. We keep saying the question should guide the methodology, not the other way around," but too often do not follow that principle.

With interventions such as microbicides, where the RCT at first glance appears to be more relevant, how does one interpret null or negative findings, and separate the contribution of the new intervention from the counseling for condom use that has become the prevention equivalent of optimized background therapy in treatment studies? "Even when we can do the rigorous kind of research, we often can't answer the very questions we need to answer," Auerbach said.

Political and ideological considerations are another strong current in HIV prevention. Auerbach cited efforts by social conservatives in the United States to promote "abstinence-only until marriage" education programs, domestically and in US-funded programs abroad, despite "no evidence of the efficacy or effectiveness of those programs." These same forces have restricted syringe exchange programs despite solid evidence that they reduce the risk of HIV transmission in injection drug-using communities.

What is the Appropriate Standard of Proof?

Counseling to reduce risk behavior and thereby acquisition of HIV, the provision of condoms to reduce transmission, and the treatment of sexually transmitted infections to reduce transmission and acquisition, have all been adopted as cornerstones of HIV prevention activities based upon levels of evidence lower than what is expected from randomly controlled trials, said Ward Cates, President of Research at Family Health International (FHI).

"All of the things we're using now as part of our trials that we consider ethical do not have Level 1 evidence to support them. So, the question is, what is the appropriate standard of proof?"

He went on to say that the only prevention interventions with the highest level of evidence supporting their use are male circumcision, antiretroviral therapy to reduce mother-to-child transmission, and contraception. But even when those interventions have been folded into prevention guidelines, even over years, their adoption into widespread use has lagged in many settings.

Microbicide research has produced five negative or inconclusive outcomes—from the trials of nonoxynol-9, Savvy™, cellulose sulfate, 2% PRO 2000, and Carraguard®—and for some that might be enough evidence to kill the concept of microbicides overall. However, Cates said that at least some of the data from these trials might also be interpreted as supporting product efficacy in certain contexts and populations.

Another example of a similar possibility was the diaphragm study[2] concluded in 2007 which found standard prevention measures plus diaphragms and gel as a preventive intervention to be no more effective than male condoms. But the data from that trial could also be interpreted another way, he said. "When you have lower male condom use, diaphragms are at least as good as male condoms in reducing risk of transmission. Now that's blasphemy to scientific purists. But at the same time, it is an interpretation that we ought to keep in mind as we are thinking through creative interpretations of available data."

"A [self-identified] card-carrying statistician" (Tim Farley, WHO) would later rise from the audience "to come to the defense of the randomized controlled clinical trial. It is very good to look at efficacy, but the moment you try to measure effectiveness, as for example with the Carraguard® trial, you lose power, you lose clarity of interpretation." He added that the trials involving treatment of sexually transmitted infections to which Cates referred randomized the intervention to communities, not to individuals. "I think we have got to be very careful with distinguishing these different levels" of aggregation in discussing and interpreting studies.

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[2] MIRA. *http://pub.ucsf.edu/newsservices/releases/200707125/*

WHAT IS EVIDENCE IN HIV PREVENTION RESEARCH? *(Continued from p.33)*

Cates closed by observing that the field of HIV prevention as a whole needs to develop and adopt a new lexicon that adequately captures what will be occurring as microbicides research moves into next-generation trials that include comparisons of oral versus topical products.

Cultural Differences

Kim Eva Dickson, Medical Officer in the HIV department of the World Health Organization (WHO), drew on her experience with interpreting outcomes of the male circumcision trials to conclude that "the level of evidence really depends on who is looking at the evidence. If that person is a clinical trialist, then the randomized controlled trials are good enough. If they are social scientists, they want all behavioral research. But if they are policy-makers, it depends on the culture of the society, it depends on how much money they've got, etc. So the level of evidence depends on a number of factors."

She advised that researchers attempt to better understand cultural and community factors that may influence a given study, and how people incorporate the various realities around HIV into their lives. Cultural norms inevitably differ. For example, in Uganda, people will volunteer for studies without compensation, but few people in Nigeria will do so. Pregnancy can be an exclusionary factor in trial design and can complicate the conduct and analysis of a trial, yet discussion of pregnancy, including intent to become pregnant and even being pregnant, is taboo in some cultures.

Another variable fraught with implications is risk and its perception. "Either people don't perceive themselves at risk, or they do not fully understand the concept of effectiveness or partial effectiveness [in the context of risk]." Dickson said researchers must better understand this dynamic and thus be better able to educate study participants.

Institutional Factors

"Statistical significance may have little or nothing to do with community significance," said Mitchell Warren, Executive Director of the AIDS Vaccine Advocacy Coalition (AVAC). He expressed dismay and frustration at the pace with which male circumcision is being rolled out as a prevention intervention in many of the nations with the highest incidence of new infections.

The continued enthusiasm and willingness of study participants to remain in the study process, in the face of failed trials and slow implementation of well-documented interventions, has been all the more amazing.

One audience member commented on the circumcision trial in South Africa, suggesting that had it been a vaccine trial, groups such as WHO and funders would have been unlikely to have waited for results from a confirmatory study before moving forward.

Warren returned to the framework that Dickson had offered: "Feasibility, the potential for adverse outcomes, acceptability, the potential size of the effect, and the potential health and social benefits. These are very different for a vaccine than they are for male circumcision, and hence the greater caution required in wanting to see more than one randomized controlled trial to move ahead with that."

But that thinking also was influenced by the knowledge that additional circumcision studies already were underway and that there would be only a relatively short delay until their outcomes would become known. Perhaps the dynamic would have been different if confirmatory trials had had to be initiated from scratch.

Evidence and Expectations

A central dilemma is how to balance existing scientific knowledge, public health needs, ethical imperatives, and community needs in deciding what HIV prevention technologies to advance, said panel moderator Liza Solomon, Deputy Director of the Alliance for Microbicide Development.

WHO's Dickson elaborated on other major considerations: the cost of an intervention and the feasibility of its implementation. Sometimes the potential for side effects or acceptability issues in the intended populations can be major factors affecting whether or not an intervention is embraced. All these factors

go far beyond the medical efficacy of any intervention.

The prevention research community needs to do a better job at managing expectations and educating people as to what trial results will and will not tell us, even before that trial is completed, said Warren. "I'm continually amazed at the expectation that we all have, even those deeply involved in the research, that somehow one of any of these trials is going to answer all of our questions."

"We lose a lot of time after the result comes out trying to explain why we don't know what it is. I think we've done a disservice to some of the communities we work with [in not adequately explaining] what the trial is going to do and what it won't do. The degree [to which] we can bring everybody up to speed in a similar way about the research process, and what we expect and don't expect, will serve us well in the future."

He went on to argue, "The nature of public health is that we make decisions with the best available evidence at any given moment. We have a lot of unanswered questions about male circumcision, we have a lot of unanswered questions about other things, and no one trial answers all of the questions. But you still make decisions. And I think we need to do a better job of communicating in advance [about] what the trial will tell us and what it won't tell us."

Solomon elaborated further, noting that given the ethical need to include a standard prevention package in the intervention under study, it becomes difficult to ascertain which intervention works better.

Risk-benefit

Speaking from the audience, Louise Binder, Chair of the Canadian Treatment Action Council, said, "What we need to do here is start to look much more closely at risk-benefit. And look more closely at what the communities consider to be appropriate risk-benefits, and a little bit less at what the scientists think is an appropriate risk-benefit given the nature of the disease."

Drawing on 15 years' experience in the field of drug development for treatment of HIV, she said, "One of the tradeoffs that we made in order to take more risks was really strong post-approval surveillance. I would like to suggest we think about that as we think about these [trials and approval of microbicides], so we can get moving faster with the microbicide stuff, and stop wringing our hands quite so much."

Binder also expressed concern with "niche thinking." "In treatments we were busy worrying about saving the baby and forgot about the mothers. I would suggest to you that while you're busy saving the men [with circumcision], you are forgetting about the women. A lot of women in countries [with the higher rates of infection] are not hurrahing male circumcision. So I think you've got to bring everyone into the picture. When we talk about risk-benefit, let's talk about everyone's risk-benefit in the context of the intervention."

Warren lamented fixation on the "new" that seems to cut across cultures. "So much effort and emphasis is put on developing the new. And then we get the new and it's no longer the new, we move on to the next new." As great as the challenges are in conducting prevention studies, they often pale in comparison to the difficulty of rolling them out into applications broad enough to impact the course of the epidemic.

He recalled the slogan used for years by gun advocates in the United States—"guns don't kill people: people kill people"—and adapted it to HIV prevention, saying: "I'm a firm believer that none of these technologies—vaccines, condoms, microbicides—none of them prevents infection. People using them will prevent infections."

A member of the audience from the US Agency for International Development (USAID) raised the example of maternal mortality. He said post-partum hemorrhage accounts for 55% of maternal deaths in some countries, and there are interventions that dramatically reduce those rates. "But we don't roll them out. Our entire field of reproductive health and HIV is stuck with having lots of

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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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WHAT IS EVIDENCE IN HIV PREVENTION RESEARCH?

(Continued from p.35)

good things to do, and we need to learn how to roll them out very quickly, have impact quickly."

Warren closed by saying: "We need to recognize that prevention alone won't end the epidemic, treatment won't end the epidemic, and research won't end the epidemic. We really need to be creative in coming up with new solutions [for] how we integrate these pieces." Adding circumcision to the existing package of prevention activities will increase the complexity, number of participants, duration, and cost of conducting studies. Given that complexity, "We need to spend much more time thinking about new creative trial designs to try to get to some of these answers faster," he said.

Making Decisions

So how does the HIV prevention field decide which products to advance from early development into large, expensive Phase 3 trials? "We want the best product to go forward, and we think we are going to assemble some combination of esteemed, wise people that are going to sit around the table and look at all the evidence—[Carraguard®, TMC120, BufferGel®]—and divine which to move forward," said FHI's Cates.

"In my view, what the last few years have taught us is, we don't have a clue about what will eventually work. I was really surprised, to tell you the truth. I thought that based on all the epidemiological evidence and the acquisition-type risks, acyclovir [to reduce herpes simplex outbreaks and the risk of HIV transmission and acquisition] was going to show some effect. I certainly thought the diaphragm was going to show an effect." His interpretation of the data is that it probably did, but "How do we show it is as effective as our current methods? I think that's what we as evidence-based advocates need to focus our advocacy on."

Cates wrapped up with the following: "We have to acknowledge the uncertainty, make our best guesses, and move on." His bottom line was that ultimately "the funders are going to be the ones who are going to decide what product goes forward. We can put forth all of our best guesses, but it's the person or collective that writes the check that's going to get things going forward."

EDITOR'S NOTE: At the XVII International AIDS Conference in August in Mexico City, the Caucus for Evidence-Based Prevention will host a satellite session, "Weighing the evidence: Prioritizing HIV prevention in the fight ahead" that will further discuss these and ancillary matters. Stephen Lewis, Co-director of AIDS-Free World, will moderate.