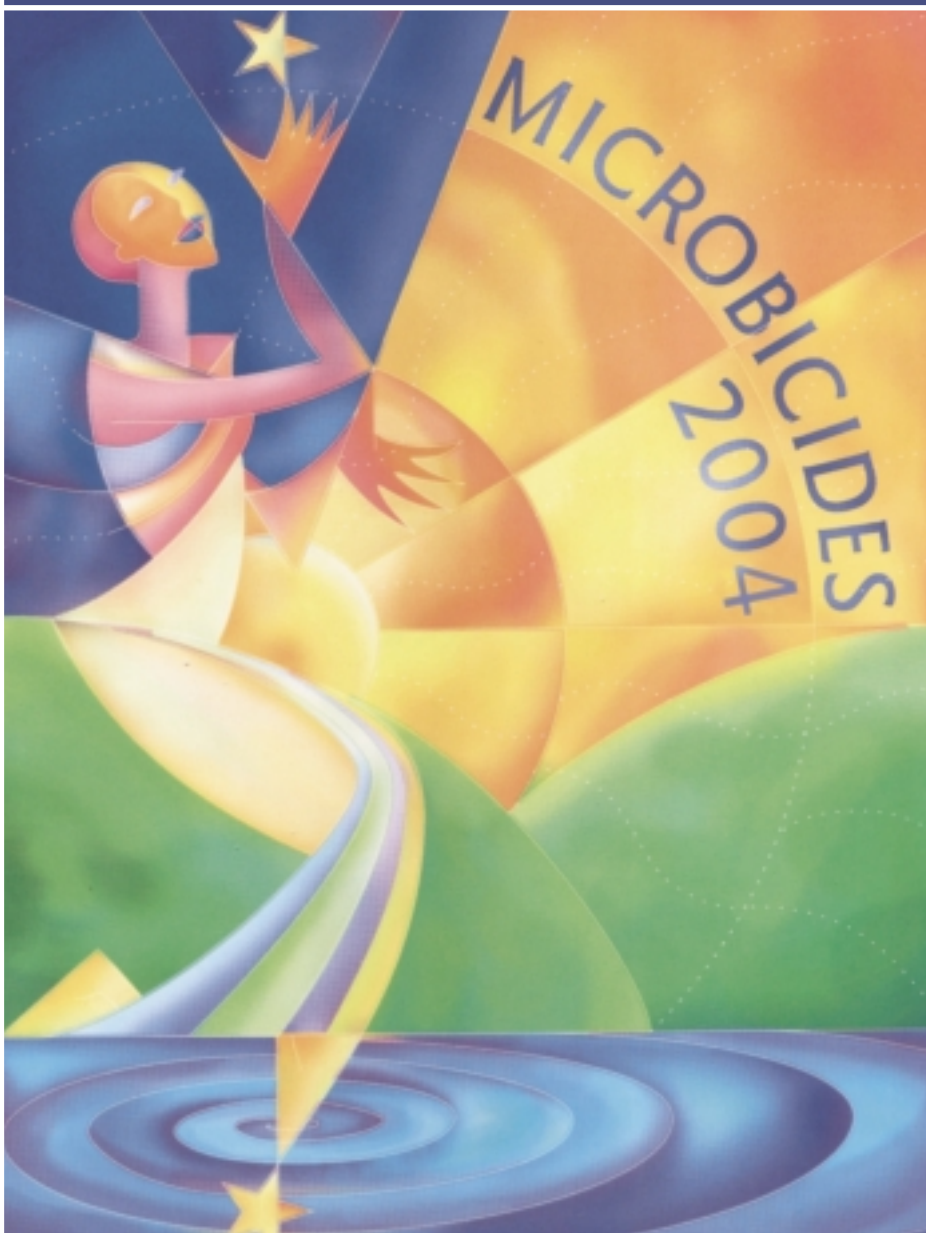
Microbicides 2004

28-31 March 2004
Hilton London Metropole

Conference abstracts



MDP
Microbicides Development Programme

Imperial College London

MRC Medical Research Council

Co-chaired by
Janet Darbyshire, Medical Research Council Clinical Trials Unit | **Robin Gorna**, UK Department for International Development | **Jonathan Weber**, Wright-Fleming Institute, Imperial College London

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PLENARY PRESENTATIONS

MONDAY 29 MARCH

PL-01 MECHANISM OF SEXUAL TRANSMISSION OF HIV-1

Pope, Melissa
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Understanding the earliest events of HIV infection and how the virus breaches the mucosal barriers are essential to advance microbicide development. It is still unclear whether virus crossing the mucosae does so as free virions and/or in cell-associated forms. Either way, viruses that penetrate the epithelial barriers (through breaks in the tissue, infecting the epithelial cells, or transcytosing the cells) access white blood cells that can serve as targets for virus capture and/or infection – dendritic cells (DCs), macrophages, T cells. DCs positioned within and just beneath the epithelia are one of the first leukocytes that encounter HIV and likely contribute to the efficient dissemination of virus to neighboring lymphocytes/macrophages that then rapidly amplify the incoming viruses. In addition, virus-carrying DCs can migrate to the draining lymphoid tissues to further exacerbate HIV dissemination. Infection of target cells is largely dependent on CCR5, but virus capture (most adeptly by DCs) is independent of CCRs, but involves CLRs, with some contribution from CD4 and other receptors. Newly produced virus as well as that entrapped by cells is efficiently transmitted to T cells driving virus spread. Blocking agents that target specific virus-cell interactions can limit these events, but typically work most effectively if multiple receptor-virus interactions are impeded. Alternatively, agents with more broad acting activities like sulfated polysaccharides may work more effectively by preventing the virus binding to any of the cell surface receptors to block infection and/or entrapment. Continued advances in defining the first events of HIV infection are critical to assist in designing more effective preventative strategies to limit sexual transmission of HIV.

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PL-03 STANDARDS OF CARE IN RESEARCH: RESPONDING TO THE CHALLENGE

Benatar, Solomon R
University of Cape Town

This presentation begins with the claim that acknowledging the current global context within which health research is conducted is the starting point from which to argue for a new and visionary conception of what the standard of care in research should mean. After briefly outlining the controversy about the 'standard of care' initiated by placebo studies of PMTCT of HIV infection I shall suggest that a broader concept of a universal 'standard of care' in research is possible and can be justified. Ongoing challenges for HIV prevention research will be mentioned and a schema offered for working towards higher standards of care in research that could contribute to improvements in health care and sustainable development.

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MT-01 NOVEL LOW-DOSE VAGINAL EXPOSURE STRATEGY TO STUDY HIV MICROBICIDE INTERVENTIONS IN NON-HUMAN PRIMATE

Otten, Ron; Adams, Debra; Kim, Caryn; Jackson, Eddie; Lee, Kemba; Grohskopf, Lisa; Monsour, Michael; Butera, Sal; Folks, Thomas
Centers for Disease Control and Prevention, Atlanta; Emory University, Atlanta.

A nonhuman primate model for HIV-1 infection that more closely mimics human sexual transmission by multiple, weekly low-dose exposures is critical to better evaluate intervention strategies using microbicides or vaccines. In this report, we describe such a system using female pig-tailed macaque monkeys exposed vaginally to a simian-human immunodeficiency virus (SHIVSF162P3) at weekly intervals. Dose titration experiments indicated that three weekly exposures of 10 tissue culture infectious doses of SHIVSF162P3 resulted in consistent virus transmission and establishment of systemic infection. Using this virus dose, efficacy of cellulose acetate phthalate (CAP) as a vaginal microbicide was evaluated by applying product 15 minutes before each weekly SHIVSF162P3 exposure in monkeys (n=4). Significantly, three of four CAP-treated monkeys (75%) remained uninfected through 12 exposures. Similar to control results, one of four CAP-treated monkeys (25%) was infected after only three exposures. Our findings provide a basis to refine monkey models for HIV-1 transmission which may be relevant to pre-clinical evaluation for therapeutic interventions.

MT-05 MECHANISMS OF HIV RESISTANCE IN EXPOSED SERONEGATIVE SUBJECTS

Rowland-Jones, Sarah
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A central question in HIV vaccine design is what is actually needed to provide protective immunity against HIV infection. One approach is to study potential protective immune responses in individuals who escape persistent HIV infection despite repeated HIV exposure. We have studied mechanisms of HIV resistance in a cohort of female prostitutes in Nairobi, Kenya, with very intense HIV exposure, over 80% of whom are HIV-infected. This cohort includes an "HIV-resistant" group, who remain persistently seronegative despite frequent HIV exposure over many years. Many of these women have circulating HIV-specific cytotoxic T lymphocytes (CTL), largely directed towards regions of the virus conserved between different HIV clades. A striking finding is that the specificity of the CD8+ T-cell response differs between resistant and HIV-infected women for those class I HLA molecules that are associated with HIV resistance in this cohort, which raises the possibility that some CTL epitopes may be more "protective" than others. Although many members of the "resistant" subgroup have remained uninfected despite years of exposure, a few women have undergone late seroconversion following a break from sex-work or a reduction in client numbers. In other women, reduced HIV exposure leads to a fall in detectable HIV-specific CD8+ T-cell responses, suggesting that it may be important to maintain persistent effector T-cell responses for protection against HIV infection. Similar studies in a cohort of HIV sero-discordant couples in London will also presented, in which the responses can be more clearly be related to exposure. These observations have led to strategies to test a CTL-inducing vaccine using a prime-boost approach which is currently in phase I trials in Nairobi and Oxford.

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SC-01 JUSTICE AND THE STANDARD OF CARE

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Justice is essential to determining the standard of care for clinical research. As part of research, people cannot be denied medical services that they are entitled to, except in specific cases. This entitlement determines the kind of interventions that must be included as standard of care in research. However, what people are entitled to cannot simply be based on what services they actually receive, because this could result from injustice. Determining what they are entitled to is based upon considerations of distributive justice. Conflicts of the standard of care can be traced to conflicts in conceptions of justice.

London's Global Egalitarianism claims that "international medical research [itself] is not morally permissible until…a more equal distribution of global resources" occurs. Thus standard of care is not even an issue, because any clinical research is currently unethical. This seems untenable for empirical reasons about the source of inequality, witness India and China, and because it would only worsen the 90-10 divide, focusing all research on diseases of the rich.

Rawls's Law of the People's contends that great wealth is not required for a just flourishing society, only a hospitable political culture matters, witness Kerala; most societies in the world are not so poor that they cannot become just. Thus, the duty of foreign assistance is limited to helping establish a just society; since this does not require substantial wealth, aid beyond eliminating grinding poverty is not required. Rawls's view of justice suggests that people are entitled to what they are currently receiving, and the appropriate standard of care would be the current care people are receiving in the host country.

At the opposite pole is a radical equality view that holds that all people, regardless of country, are entitled to about the same well-being. Justice requires people to transfer their wealth as long as it can increase the well-being of others more than it decreases their own. This is a Singer type version of utilitarianism. It would mean people everywhere should be entitled to the best care available anywhere and would endorse the Declaration of Helsinki's "best proven method" anywhere in the world view.

Finally, limited cosmopolitanism holds that we are required to create institutions that give other individuals the opportunities for a flourishing life; there is no demand for equality of well-being or resources. We need not develop a full theory of justice, but focus on justice in health alone. The well known relationship of increases in life span compared to health spending has an asymptote at $500 per person per year, provides guidance on what is necessary in health given people and opportunity to flourish. That is, the health care people are entitled to in an international order that complies with the limited cosmopolitan view of justice is the services they would get for $500 per person per year. In 1997, long course AZT cost $800 per person and would not have been the standard of care. Today, triple ARV therapy costs under $300 per year making it standard of care. This limited cosmopolitan conception of justice provides a way to both justify and operationalize the notion of highest attainable and sustainable standard of care.

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SC-02 THE "STANDARDS OF CARE DEBATE": SOME PERSPECTIVES FROM THE DEVELOPING WORLD

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The issue of a universal standard of care for research subjects in developing countries was brought to the fore by the controversy surrounding the HIV using ACTG 076 triple therapy versus placebo. This resulted in an acrimonious global debate and a review of exiting ethical review guidelines on the issue. While it can be argued that the principle of beneficence dictates that all research subjects must maximally benefit from planned interventions, the most pervasive arguments supporting the continued use of placebos are based on efficiency and economics. Also the "tyranny" of the randomized controlled trial precludes any learning from alternative methods of evaluation such as quasi-experimental designs.

The standard of care may be seen as the global rather than local standard of care, although others have questioned this. What constitutes a standard therapy in one health system with profligate expenditure on medical practice based on defensive medicine, may be totally inappropriate in another system with limited resources. Thus a reasonable compromise may be seeking the highest attainable local standard rather than an impossible alien and unsustainable alternative. Nevertheless there is a legitimate debate as to what constitutes an acceptable standard? Is it a prevalent local standard or one that is ideal in any given circumstance i.e. a local de-facto versus de-jure standard? Thus the standard of care does not necessarily relate to the most expensive or sophisticated treatment regimen but those that perform best given the local conditions and health systems. Another important issue around the standard of care argument is that it is frequently interpreted in the narrow context of medications or dugs used in trials alone rather than the overall care within the health system.

It must be emphasized that the current safeguards and guidelines were largely devised to prevent undue exploitation of vulnerable populations and developing countries. The need is to develop pragmatic and flexible approaches that marry the fundamental principles of beneficence with a public health approach that allows the possibility of incremental benefits.

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SC-03 ADDRESSING TREATMENT AND CARE IN HIV PREVENTION TRIALS: IN-COUNTRY CONSULTATIONS

L. Camille Massey
Anjali Nayyar, Sam Kalibala
International AIDS Vaccine Initiative

Issues: A pressing challenge facing those involved in HIV-1 prevention trials is the provision of treatment and care for trial participants, including those who, despite counselling, become HIV-1 infected during the trial. In many countries where clinical trials are being considered, expenditures on general primary health care remain extremely low. Therefore, the discussion about treatment cannot focus solely on the availability of highly active antiretroviral therapy (HAART).

Description: A priority must be to ensure that participants in clinical trials have access to basic, comprehensive primary health-care, including antiretrovirals if needed. IAVI is eager to collaborate with other trial sponsors, including those working on microbicide trials, to explore funding options and opportunities to prioritize research host communities in ARV scale-up plans and to link constructively trials with testing and treatment programmes.

Lessons Learned: Recent IAVI-sponsored meetings in Uganda and India brought together HIV prevention researchers, government officials, service providers, community representatives, and other national stakeholders to begin to develop locally agreed guidelines and explore partnership opportunities for providing treatment and care to trial volunteers.

Recommendation: It is critical that governments, donors, and trial sponsors share responsibility to ensure maximum benefit from trial investments and to sustain healthcare improvements over the long-term. It is recommended that researchers carefully consult and coordinate with national and local stakeholders to develop and implement the treatment and care policies for trial participants and host communities.

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SC-04 STANDARD OF CARE IN AFRICA IN RELATION TO CLINICAL TRIALS OF VAGINAL MICROBICIDES

Kamali, Anatoli
Medical Research Council Programme on AIDS in Uganda /MDP

Health care delivery in Africa is largely provided through the peripheral health facilities within public health system and to a limited extent in the private sector with marked variations in access and options across communities. HIV/AIDS care in particular is limited to treatment of opportunistic infections, counselling and social support through AIDS support organisations and no access to antiretroviral treatment (ART). These are challenges to forthcoming clinical trials planned in rural populations where "best locally available care within country" might be inadequate.

Further to these challenges in Africa is care to participants who seroconvert during the trials. They will require continued counselling on safe sex, couple counselling where possible, treatment of STIs and opportunistic infections and referral to support organizations. These services need to be established, where they are non-existent and strengthened where they are weak.

Many countries in Africa now plan to access ART from international funding agencies. However this access will initially be through large hospitals mainly located in district capitals with specialist staff and better facilities. The success of this initial phase will determine expansion of access at peripheral health units in communities where most trial participants live. Women who seroconvert will require ART possibly several years later and very likely after the trials have been completed. In this aspect responsibility to microbicide trials would be to facilitate the public health systems to ensure well coordinated ART access and assist to put in place necessary infrastructure for the planned expansion for providing ART to peripheral health units within easy reach to the participants when they eventually require ART.

All clinical care should be provided through the existing health facilities that provide services to the wider community. This will ensure sustainability after completion of the trial, avoid "inducement" to participation and prevents re-infection of infectious diseases such as STIs within communities and pill sharing.

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REG-01 REGULATORY PATHWAYS FOR MICROBICIDES: A DIALOGUE

CHAIRS: SALIM S. ABDOOL KARIM & POLLY F. HARRISON, PhD
Facilitators: Y.K. Hamied, Frances Rotblat, Tim Berridge

Microbicides face many of the same challenges as do other "economically orphan medicines", i.e., medicines for conditions in developing countries that are "orphaned" primarily by market considerations rather than prevalence or burden of disease. Among those challenges are matters around drug regulatory approval and the delays that can be associated with approvals in the case of products whose greatest need and utilization will be developing countries. Because microbicides are intended to prevent HIV infection, and because of the ever increasing rates of new HIV infections worldwide, unnecessary delays in the availability of any valid prevention technology are not acceptable. The same is, of course, true of HIV vaccines, and there is active ongoing dialogue with that community on how to grapple with the dilemmas that plague potential access to both technologies. The position of the USFDA, whose mandate is to protect the well-being of the US population, is that there should be no "double standard" with respect to drug safety and quality for developing world populations. This session will begin to explore possibilities for innovative ways to accelerate regulatory approvals of products whose primary consumer populations are in resource-constrained countries where risk-benefit ratios diverge substantially from those in industrialized countries.

Speakers will be:

Teresa Wu, MD - Medical Office, Center for Drug Evaluation and Review, US Food and Drug Administration Considerations for clinical development of topical microbicides: A US regulatory perspective

Timothy M.M. Farley, PhD - Coordinator, Controlling Sexually Transmitted and Reproductive Tract Infections, Department of Reproductive Health and Research, World Health Organization. Oversight of microbicide research and registration

N.K. Ganguly, MBBS, MD - Director-General, Indian Council of Medical Research The Indian environment for development, registration, and distribution of microbicides

John Purves (tbc) - European Medicines Evaluation Agency, Head of Sector, Quality of Medicines, Pre-authorisation Unit Current and new issues for Europe

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TUESDAY 30 MARCH

PL-01 MATCHING MECHANISMS WITH MICROBICIDES

Robin J Shattock PhD
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Heterosexual transmission is the leading mode of HIV-1 infection worldwide, with women particularly vulnerable to HIV-1 infection as they often cannot control sexual encounters or insist on condom use. In the absence of an effective vaccine there is an urgent need to develop alternative prevention strategies. It is only now, more than 20 years into the epidemic, that immediate events between exposure to infectious virus and the establishment of infection are becoming clear. Defining the mechanisms of HIV-1 transmission, the target cells involved and how the virus attaches to and fuses with these cells is revealing new ways to block the sexual spread of the virus. Initial efforts to develop vaginal microbicides focused on killing the virus through membrane disruption using surfactants,

and blocking viral entry using polyanionic compounds that interact with the positively charged areas of the viral envelope proteins, many of which are currently entering phase II/III trials. However recent advances in HIV pathogenesis and therapeutics are now bringing a wide range of new products into the development pipeline that specifically target different stages in the viral life cycle. Rigorous pre-clinical evaluation of candidate microbicides is now required to select the best compounds for clinical trials, since this will provide savings in costs and time, given the expense and length of formal efficacy trials. Selection criteria include: high activity against viral clades predominant in the areas where clinical trials are to be conducted; low irritation potential based on a range of preclinical irritation assays; high in vitro activity in the presence of semen; and effectiveness in animal models using challenge virus that is relevant to sexual HIV transmission. In addition assessment of product formulation, stability, cost, acceptability and ease of manufacture are important in candidate selection. This presentation discussed how our increasing knowledge of the ways in which HIV-1 is transmitted will shape the development of new, more sophisticated intervention strategies based on the application of vaginal or rectal microbicides, the major hurdles in the development of different biologic approaches and likely timescales for providing an effective microbicide to protect those most at risk of infection.

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PL-02 MICROBICIDE PREVENTION AND RESEARCH IN THE OVERALL CONTEXT OF HIV/STI PREVENTION RESEARCH

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Background: Previous reviews of interventions to prevent sexually transmitted infections (STI) focused largely on HIV infection. Here, we review trials of interventions to prevent sexual transmission of any STI, employing a multi-level perspective. Methods: We searched MEDLINE, the Cochrane CENTRAL Registry, and recent unpublished presentations through 2003 to identify randomized controlled trials of STI prevention interventions having systematic, objective measurement of STI outcomes. Included trials were classified according to intervention target (individual, group, or community); impact target (acquisition, transmission, or complications of STI); and intervention modality. Results: Of 88 trials identified, 41 met inclusion criteria, including 27 individual-level, 9 group-level, and 5 community-level interventions. Among individual- and group-level interventions, 31 targeted acquisition, 4 transmission, and 1 complications of STI; community-level interventions had multiple impact targets. The four intervention modalities most often used included behavior change interventions (11 studies), vaccination (7), topical microbicides (10) and prophylactic, curative, or suppressive therapy (10). Two community intervention trials employed multiple modalities (2). Only one intervention showed efficacy against sexual transmission of HIV, but 22 (53.7%) reported effectiveness against other STIs. Conclusions: Despite many interventions found effective against STI, few have been replicated, widely implemented, or carefully evaluated for effectiveness in other, non-research settings.

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MMM-01 ENTRY INHIBITORS AS TOPICAL MICROBICIDES

John P. Moore; Ronald S. Veazey, Dennis R. Burton, M. Lu, M. Springer

Progress in the evaluation of entry inhibitors in the rhesus Macaque vaginal transmission Model will be reviewed, including studies of inhibitors aimed at viral targets and others directed towards cellular receptors.

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MMM-02 TOPICAL ESTROGEN PROTECTS AGAINST SIV VAGINAL TRANSMISSION WITHOUT EVIDENCE OF SYSTEMIC EFFECT

Marx, Preston A; Stephen M. Smith(1), Megan Mefford (2), Zachary Klase(1), Donald Sodora(3), Nancy Alexander(4), David Hess(5)
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Accumulating evidence suggests that the state of the vaginal epithelium affects a woman's risk of HIV vaginal transmission. Several human and non-human primate studies have established that the rate of HIV or SIV vaginal transmission is decreased when estrogen is dominant. Women treated with depo-medroxyprogesterone acetate (DMPA), an estrogen antagonist, have low levels of estrogen and are at increased risk of HIV vaginal transmission. Moreover, women, who become infected with HIV through the vaginal route while on DMPA, have more viral variants and higher viral loads than women not on a contraceptive agent. In this study, we examined the protective efficacy and safety of vaginal estriol in ovariectomized macaques against SIV vaginal transmission. Vaginal estriol, in a cream form approved for human use, applied twice weekly resulted in minimal serum estriol levels and had no effect on serum LH levels, which decline rapidly in the presence of systemic estrogen and serve as the most sensitive marker for systemic estrogen effect. Vaginal epithelia cornified and thickened significantly in response to topical estriol therapy. Twelve macaques on vaginal estriol and eight control animals on placebo cream were challenged vaginally with pathogenic SIVmac251. 1 of 12 estriol treated became infected after this s ingle challenge, while 6 of 8 control animals became infected (p= 0.0044). These data demonstrate that topical vaginal estriol can strongly protect against SIV vaginal transmission, while having no detectable systemic effect. The effect of estriol on the vaginal epithelia persisted for over 12 days after the last treatment. These results support the study of topical vaginal estriol in preventing HIV vaginal transmission in at-risk women. Topical estriol therapy will have no systemic effect in women, who can use the treatment twice per week (or less) and remotely from sexual encounters. Further, topical estriol therapy may be used in conjunction with an effective microbicide. This therapy should be studied in high-risk women, especially those who are on DMPA, as a means to reduce the rate of HIV vaginal transmission.

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MMM-03 THE PROSPECT FOR RT INHIBITORS AS TOPICAL MICROBICIDES

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Reverse transcriptase inhibitors are generally divided into two categories: non-nucleosides (NNRTIs) and nucleosides/nucleotides (NRTIs). The former have a major advantage over the latter in terms of rationale for microbicide development, since they do not require metabolism in order to achieve an active antiviral state. Hence, these compounds might be directly active against HIV within the vaginal cavity. Furthermore, considerable progress has been achieved in regard to such products as UC781, that act as tight-binding inhibitors to the RT enzyme. In this context, such a molecule is expected to inactivate RT enzymatic activity in a highly efficient manner, hence eliminating the ability of the virus to initiate a new round of infection. Considerable data is now available from both tissue culture and animal experimentation in support of this hypothesis. In contrast, other NNRTIs, such as nevirapine, that do not have the ability to bind to RT with as high affinity as UC781, do not have rationale for development as microbicides, and indeed have failed to show microbicide activity in monkey experiments performed in a SHIV model, in which the RT was derived from HIV.

In addition to UC781, a number of other NNRTIs being developed have strong rationale as microbicides and these include TMC 125 and calanolide A, among others. Interestingly, almost all second generation NNRTIs that possess favourable drug-resistance mutational profiles, in the sense that they retain activity against viruses resistant to nevirapine and efaverenz, are tight-binding inhibitors of RT that have rationale as microbicides.

Although NRTIs do not have the same rationale for development as microbicides, due to their requirement for metabolism to an active state, the fact remains that intra-vaginal administration of tenofovir (TDF) has been shown to protect against infection by SIV in a simian model. Further studies will be necessary to definitely address this subject; also the use of TDF in pre-exposure prophylaxis studies in healthy human volunteers is a compelling concept.

Finally, the RT enzyme of HIV-1 includes a number of potential targets in addition to the viral polymerase function, that might also have rationale for microbicide development. These include viral RNaseH activity as well as the potential use of reagents that might disrupt RT dimers.

MIH-01 INHIBITION OF VIRAL STD INFECTION BY PEPTIDES CONTAINING PROTEIN TRANSDUCTION MOTIFS

Brandt, Curtis R.
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Protein-protein interactions are fundamental in biology. Because of their importance, interfering with these interactions is a potentially powerful strategy for drug development. In the past few years, a number of publications have shown that peptides that match the sequence of a protein-protein interface will compete for the interaction and disrupt the complex. Such peptides have also been used to map protein-protein interaction sites. One problem with the use of peptide inhibitors is their inefficient entry into cells. However, the use of peptides to block activities at the cell surface does not suffer this limitation. During studies to improve the delivery of antiviral peptides into cells, we discovered that peptides that contain membrane-transiting motifs (e.g., tat, homeodomain, FGF4 signal sequence) were potent antivirals. We have identified peptides that inhibit Herpes simplex virus Type 1, Influenza virus, Human Immunodeficiency virus, Human Papilloma virus, and Vaccinia virus. Studies in animals show the peptides block HSV-induced disease and Influenza virus even post-exposure. We will briefly discuss the evidence showing that some of these peptides are virucidal, rendering virions permanently non-infectious. In studies where virions were added to cells at 4°C followed by peptide addition and subsequent shift to 37°C, we showed that the peptides inhibited viral entry. Finally, we will discuss more extensively new data showing that some of the peptides

induce a state in cells whereby they are resistant to viral infection. Toxicity studies showing the peptides are non-toxic in vivo after corneal or vaginal instillation will also be discussed. The fact that we can prevent infection of cells by the three major viral STD's with only one or two peptides represents a novel approach for microbicide development.

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MIH-02 TOPICAL MICROBICIDES FOR THE PREVENTION OF GENITAL HERPES: A MAJOR CO-FACTOR FOR HIV INFECTION

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Genital herpes is one of the most prevalent STI worldwide and is the most common cause of genital ulcers. Studies in developing countries reveal HSV-2 seroprevalence rates ranging from 60-80% in young adults. What makes HSV so difficult to control is that most sexual and perinatal transmission occurs during unrecognized or asymptomatic shedding. The impact of genital herpes as a public health threat is amplified because of its association with enhanced HIV acquisition. Epidemiological studies consistently demonstrate that genital herpes enhances the transmission and acquisition of HIV. Although the cellular mechanisms underlying the link between HSV and HIV/AIDS have not been elucidated, studies from our laboratory indicate that HSV may facilitate HIV acquisition by modifying the mucosal environment leading to the release of pronflammatory cytokines, which may enhance HIV replication and/or activate target cells for HIV acquisition. Using a three-tiered strategy characterized by in vitro human culture systems, small animal models, and pilot clinical studies, we are evaluating candidate topical microbicides, including sulfated or sulfonated polymers (PRO 2000 5 Gel (P), polystyrene sulfonate, cellulose sulfate, and polymethylenehydroquinone sulfonate), a chemically distinct anionic compound (SAMMA), defensins, and acid-buffering gels alone and in combination. Compounds are assessed for spectrum of anti-HSV activity, mechanism of action, and safety using human cell culture systems and clinical isolates. Results indicate that the sulfated/sulfonated polymers and SAMMA inhibit HSV infection 10,000 fold, are active against clinical isolates, form stable complexes with the HSV envelope glycoprotein B, and inhibit HSV binding, entry and cell-to-cell spread. These compounds retain anti-viral activity in the presence of cervical secretions and over a broad pH range. Using a murine model of genital herpes, we found that PRO 2000/5 Gel (P) prevents genital herpes infection and may block the HSV-induced proinflammatory response. Pilot human clinical trials are in progress to examine the effects of 0.5% PRO 2000/5 Gel (P) on mucosal immunity and to evaluate the anti-HSV activity in cervicovaginal fluid obtained 1-h after a single application. These comprehensive pre-clinical and pilot human studies will lay the groundwork for future large-scale clinical trials with optimal microbicides alone or in combination.

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MIH-03 ACCEPTANCE AND TOLERANCE OF THREE MALE MICROBICIDES AMONG MEN ATTENDING AN STD CLINIC

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Nairobi, Nairobi, Kenya, 6,Department of Medicine, University of Washington, Seattle, Washington, USA. * Current Affiliation, University of California, San Francisco.

Background: Men possibly carry the microorganisms that initiate and perpetuate bacterial vaginosis (BV), a risk factor in HIV acquisition. Postulating that use of topical microbicides could stem the initiation and recurrence of BV, we evaluated the safety and tolerability of three topical microbicide formulations (Purell-62% ethyl alcohol in a gel emollient and 1% and 4% benzalkonium chloride on a sanitary wipe) for use on male genitalia.

Methods: This triple randomized cross over study among men attending a referral STD clinic in Nairobi, Kenya, required individuals without clinical STD to use the 3 products in a pre-determined random order for 2 weeks each and compare them for safety and acceptability. Each 2-week cycle was followed by a one-week washout period. The men recorded possible side effects in a study diary and dermatological changes found during a physical examination were recorded at the end of every 2-week cycle.

Results: Thirty-nine men with a mean age 27 years were recruited and 33 completed the study. At enrolment, all participants reported sexual activity in the preceding week and a mean of 8 sexual partners in their lifetime. Over 80% found the products easy to use, and almost all (90%) were willing to use the products again and would recommend it to a friend. Men used one of the products for 60% of the days, with the greatest compliance recorded for Purell (76%). Use of one of the formulations before sex ranged from 19-24%. No significant dermatological complaints resulting from the use of the products were documented on examination during follow-up.

Conclusions: Although all three products were safe and well tolerated by this group of men, Purell emerged as the preferred formulation.

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LT-01 AFFORDABLE HIV DIAGNOSIS AND MONITORING: THE NEXT CHALLENGE FOR THE DEVELOPING WORLD…

Stevens W
University of Witwatersrand and the National Health Laboratory Service

Affordable laboratory diagnosis and monitoring of HIV is essential to parallel programs such as the Global AIDS initiative of UNAIDS and WHO proposing to treat 3 million individuals in developing countries with ARV therapy by 2005. Most developing countries are under-resourced with annual health expenditure per capita frequently less than the cost of a single monitoring visit. This paper addresses the laboratory dilemmas facing countries such as South Africa where approximately 5 million individuals are currently estimated to be infected with HIV.

On the diagnostic front, considerable debate is ongoing regarding algorithms for rapid HIV testing, the appropriate confirmatory HIV testing strategies and the relevant QA programs needed for monitoring such programs. Other challenges in this environment will be addressed such as the timing and methodology appropriate for cost-effective early diagnosis of HIV in the vertically exposed infant. Emerging public health issues include the techniques and algorithms that may be required to diagnose acute primary infection in high risk clinical populations.

In the arena of monitoring of patients on ARV therapy, innovative strategies used in South Africa for CD4 and viral load monitoring will be described. This will include presentation of local data on the "Panleucogated" CD4 assay which represents an affordable solution on a high-end platform. In addition, data on the evaluation of assays on analysers such as the Guava instrument (a middle of the

range solution) will be provided. Alternative viral load testing strategies that will be presented include data on the performance of the heat-denatured p24 antigen quantitation assay, the Cavidi reverse transcriptase enzyme activity assay and an in-house real-time PCR assay designed for the LightCycler analyser, in HIV-1 subtype C infected individuals. In addition, preliminary data on affordable drug resistance testing approaches using assays such as the Oligonucleotide Ligation assay (OLA) will be discussed.

A universal solution for all resource constrained environments is unlikely due to significant differences that can be identified in each setting. Facilitated informed decision making for implementation of appropriate technology is thus essential and should be made based on available technical skills and laboratory resources, anticipated volume of samples to be conducted, supplier support and the availability of quality control initiatives and training programs.

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LT-02 BED-CAPTURE EIA: A TOOL TO ESTIMATE HIV-1 INCIDENCE FOR PREVENTION TRIALS AND M&E

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We have devised a simple laboratory assay, BED-Capture EIA, for detection of recent HIV-1 infection among HIV-seropositive individuals infected with diverse subtypes. Two key aspects of this approach are: 1) the use of a chimeric HIV-1 antigen derived from multiple HIV-1 subtypes, and 2) IgG capture format of the assay that captures and measures relative proportion of HIV-1 IgG present in the serum. A branched peptide that included gp41 immunodominant sequences from multiple subtypes was used to detect HIV-specific antibodies. Due to competitive nature of the capture format of the assay, a gradual increase in the proportion of HIV-1 specific IgG in total IgG present in the serum was observed for more than 2 years following seroconversion. This was in contrast to the conventional enzyme immunoassay using the same antigen coated wells, which plateaus soon after seroconversion. The assay has been used to test longitudinal specimens from incident cases in U.S. (subtype B), Thailand (B & E), Ethiopia (C), Kenya (A & D) and Zimbabwe (C). Statistical and empirical analyses indicated that a threshold cutoff of 1.0 OD-n represents about 150 to 200 days since seroconversion (mean period 190 days) among different subtypes. The assay has been successfully used in selected cross-sectional populations to estimate HIV-1 incidence, identify behavioural risk factors and assess incidence trends over time. The BED-CEIA can be an important laboratory tool for identifying cohorts for prevention trials (e.g. microbicide, vaccine) and for monitoring and evaluation programs.

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FADS-01 FORMULATING SEMI-SOLID TOPICAL DELIVERY SYSTEMS

David Fairhurst

Topical delivery systems(TDS)are many and varied; they range from ointments to creams/lotions and gels. Each TDS was originally formulated for a particular application and so has its own specific advantages and limitations in terms of performance. Current microbicides are based exclusively on simple water-based polymer gel formulations that are suboptimal for many actives/purposes. TDS are multicomponent, heterogeneous compositions that require much iteration to attain the final desired

formulation; many factors play a role in determining the outcome. Formulation is often thought of as a black art rather than an exact scientific discipline based on established physicochemical principles. This paper will outline and review the relevant factors affecting formulation of a TDS and lay out some basic principles and methods, especially as they apply to microbicide application.

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FADS-02 INTRAVAGINAL RINGS FOR THE LONG-TERM CONTROLLED DELIVERY OF HIV MICROBICIDES

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It is likely than the first-generation vaginal microbicides for the prevention of heterosexual HIV transmission will make use of traditional semi-solid formulations, such as gels or creams. While such formulations have certain advantages when it comes to issues of expense and manufacture, they also suffer from serious disadvantages that may limit their clinical effectivness. These disadvantages include poor vaginal retention (even for so-called bioadhesive formulations), messiness in their application, requirement for applicator use, poor user acceptability, stability issues, and the requirement for application prior to every act of intercourse. In addition, it is unlikely that they can be used without the knowledge of the male partner.

Intravaginal rings are elastomeric drug delivery devices that provide controlled release of substances to the vagina for up to a year from a single device. Various rings have already been marketed for the controlled delivery of steroids for contraception and hormone replacement therapy. Importantly, they overcome many of the disadvantages associated with semi-sold formulations, and may therefore offer a more clinically effective approach to delivering HIV microbicides.

The aims of this presentation will be to provide a background to controlled drug delivery and intravaginal ring technology, to compare patient compliance and acceptability issues as they relate to both rings and semi-sold formulations, and to highlight the potential for using microbicide-releasing rings to prevent heterosexual HIV transmission.

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WEDNESDAY 31 MARCH

PHIII PHASE III TRIAL DESIGNS

H Rees, L Van Damme, A Colletti, D Waldron
On behalf of, respectively; Microbicides Development Programme, Conrad, HIV Prevention Trials Network, Population Council

Representatives of the four major academic groups conducting effectiveness trials of new microbicides will present their overall trial designs. They will very briefly review their trial sites, any

demographic differences between sites, baseline data from the sites documenting HIV incidence, STD prevalence, condom use, pregnancy factors, and cohort retention rates.

They will then summarise their trial design (including numbers of subjects, length of follow-up, assumptions of product effectiveness, loss to follow-up, and power calculations), active products (with brief details of applicator and delivery volume), and control arms. Any pilot study data and rationale for their design will be briefly reviewed.

Then Professor Peter Smith, London School of Hygiene and Tropical Medicine, will present a discussion of the presenatations.

IA-02 ROLE OF TOLL LIKE RECEPTORS IN MEDIATING IMMUNE ACTIVATION IN THE FEMALE GENITAL TRACT

Landay, Alan L.; Spear, Gregory T.
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The development of microbicides for prevention of HIV infection in women requires basic knowledge of the local environment of the female genital tract. Our laboratory has identified a factor in cervicovaginal lavage (CVL) samples that is heat stable, protease sensitive and activates HIV replication via NFKß. This activity, that we have termed HIV inducing factor (HIF), is found to be closely associated with CVL samples from subjects with bacterial vaginosis (BV). We recently explored the mechanisms by which BV stimulates inflammatory responses and show it is mediated through Toll like receptor 4 (TLR4). Similarly, infection with Trichomonas vaginalis stimulates cells via TLR4. CVL obtained from subjects treated for these infections was significantly reduced in their ability to induce cellular activation. TNFa, LPS, or B2 defensins do not mediate this activity. CVL from women with BV also upregulate expression of TLR4 on mononuclear cells. These studies provide important basic information about the inflammatory/activation status of the local genital tract environment that will be critical in the design of effective microbicide strategies

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OHPT CLINICAL AND PUBLIC HEALTH EFFECTIVENESS OF CONDOMS: LESSONS FOR MICROBICIDES

Hearst, Norman
University of California, San Francisco

Two decades of experience and research give substantial insight into both the clinical and public health effectiveness of condoms for AIDS prevention. Prospective (but not randomized) observational studies in known discordant couples have established that condoms, when used consistently, are about 90% effective for preventing HIV transmission. When used inconsistently, they provide little or no protection. Despite their clinical effectiveness, the public health effectiveness of condoms has only been demonstrated in settings of concentrated transmission, such as commercial sex and among men who have sex with men. After years of effort, condom promotion as a principal strategy to curb the generalized AIDS epidemics of sub-Saharan Africa has not had a measurable impact, despite high rates of reported condom use in many of these countries. In countries like Uganda that have successfully reduced HIV transmission, reducing the numbers of individuals' sex partners appears to have been more important than promoting the use of condoms. The public health impact of condoms may be limited by inconsistent use, low use among those at highest risk, and negative interactions with other strategies. The experience with condom research, both in terms of

methodological issues and results, gives important lessons for future research on microbicides and other strategies to prevent the transmission of HIV.

CT-01 CONTRACEPTIVE EFFECTIVENESS AND SAFETY OF FIVE NONOXYNOL-9 SPERMICIDES: A RANDOMIZED TRIAL

Raymond, Elizabeth Gray ; Chen, P L1; Luoto, J2; Rountree, R W1; Barnhart, K T3; Bradley, L4; Creinin, M D5; Heine, M W6; Poindexter, A7; Wan, L8; Martens, M9; Schenken, R10; Nicholas, C F11; Blackwell, R12; Archer, D F13; Holmes, M14
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Objectives: To estimate and compare the contraceptive effectiveness and safety of five spermicides over 6-7 months of use. The spermicides included 3 gels containing 52.5 mg, 100 mg, and 150 mg of nonoxynol-9 per dose and a film and a suppository each containing 100 mg of nonoxynol-9 per dose.

Methods: Healthy, sexually active women aged 18-40 years who were at low risk for sexually transmitted infections and who were willing to accept a moderate risk of pregnancy were enrolled. Each participant was randomly assigned to use one of the five spermicides with emergency contraception back-up. Participants were followed for up to 30 weeks after admission.

Results and Conclusion will be presented.

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CT-02 CRITERIA FOR ADVANCING MICROBICIDES BEYOND PHASE I

Moench, Thomas R.
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Criteria are needed to prioritize candidates to advance to larger studies since an increasing array of microbicides will compete for Phase II & III tests in a limited clinical trial infrastructure. These criteria, based on both preclinical and Phase I standard safety and efficacy data, should also include product characteristics that may influence adoption, compliance, and other public health benefits. Safety: Since microbicides are a preventive technology intended for prolonged use by healthy individuals, safety is of even greater importance than for most drugs. Well-established assessments of each candidate's effect on genital tract epithelium and vaginal flora will be useful to rank products. Also, techniques for quantitation of proinflammatory cytokines in cervicovaginal secretions have been developed that may help reveal potentially harmful inflammatory effects of microbicides. Similarly,

animal models are being developed that detect and quantitate toxic effects that actually increase susceptibility to bacterial and viral STD pathogens.

Efficacy: Activity against HIV is a fundamental requirement, and the ideal microbicide would have potent and long-lasting activity against a broad range of isolates, and against both cell-free and cell-associated isolates. Broad activity against other STDs is an important advantage, both due to the direct morbidity of these diseases, and their augmentation of HIV transmission.

Other: HIV and STDs are highly stigmatized conditions that potentially limit social acceptability of microbicides. Thus, broad-spectrum benefits of microbicides in the realm of vaginal hygiene (BV, yeast, UTI) as well as for contraception, may provide socially acceptable (non-stigmatizing) motivations for method uptake and adherence. Also, candidate agents that might accelerate the development of microbicide-resistant HIV, such as agents that are absorbed systemically, or are being used for HIV therapy, should be viewed with caution. Finally, the panel of microbicides chosen for advanced-stage development should be diverse both in mechanism of action and other characteristics, due to our lack of knowledge of which approaches will ultimately prove effective.

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CT-03 CRITERIA FOR ADVANCING INTO PHASE III

Nunn, Andrew

Traditionally drug development follows a clinical trial path starting with Phase I and proceeding through Phase II to Phase III. Phase II trials are generally expected to include data on both safety and evidence of activity. This approach is considered by many to be inappropriate for microbicides since to demonstrate evidence of activity requires substantially greater numbers of participants than would normally be recruited to such a study. In the absence of any validated data on surrogates for efficacy of microbicides and in order to facilitate the development process most efficiently a number of alternative strategies have been proposed. The advantages and disadvantages of these approaches will be discussed. Knowledge of such factors as the safety profile of the product, HIV-incidence rates in the target population, the state of preparedness of the sites for Phase III trials, regulatory requirements and not least the availability of funds are all likely to influence the final choice of study design.

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TRACK A ORAL PRESENTATIONS

02114_2 SPECTRUM OF HIV-1 INHIBITORY ACTIVITY OF SULFONATED POLYMERS, CANDIDATE TOPICAL MICROBICIDES

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A number of candidate topical microbicides under development are within the same class of sulphated or sulfonated polysaccharides and include cellulose sulfate (CS), polysterene sulfonate (PSS), polymethelenehydroquinone sulfonate (PMHS) and Pro2000. In order to better understand the potential of this class of compounds, we compared these four compounds for their anti-HIV activity, cytotoxicity, activity in cervical lavage fluids and their antiviral mechanism(s) of action.

METHODS: Primary macrophages and T-cells as well as U87 cells engineered to express single co-receptors were treated with CS, PSS, PMHS and Pro2000 and challenged with laboratory-adapted or primary HIV-1 isolates as well as replication defective viruses carrying the luciferase indicator gene. The latter challenges were done with the addition of the compounds or AZT or small molecule entry inhibitors either at the same time as viral infection or varying amounts of time following infection. Finally, compounds were tested for their ability to block gp120 binding to the cell and for their ability to bind directly to gp120 using surface plasmon resonance (SPR) analyses with a BIAcore 3000 system.

RESULTS: All four compounds blocked HIV-1 replication in primary macrophages and CD4+ T-cells in the range of 10-100 ug/ml. The majority of the anti-HIV affect was during virus entry although there were some post-entry affects, particularly with PSS and CS. Each compound blocked binding of gp120 to CD4+/coreceptor positive U87 cells. PSS, CS and PMHS showed similar stable, high affinity binding to gp120 while CS could not be tested in this assay. Finally, all four compounds showed significant antiviral activity in the presence of cervical lavage fluid.

CONCLUSIONS: The compounds CS, PSS, PMHS and Pro 2000 all inhibit HIV-1 in primary macrophages and CD4+ cells in the presence of cervical lavage fluid. Consistent with their blocking of HIV-1 entry is their ability to block gp120 binding to the cell and their high affinity stable binding to gp120.

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02342 ESTABLISHING A CHLAMYDIA + SHIV CO-INFECTION MODEL IN NONHUMAN PRIMATES: PRELIMINARY DATA

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Prevention of human immunodeficiency virus (HIV) remains a primary goal in Topical Microbicide product development. Preclinical studies designed to test a product's ability to prevent infection in the face of viral challenge are essential for product advancement to clinical trials. Conducting such studies in nonhuman primates (NHP) may provide results most apt to translate to the human experience. We have initiated model development studies to establish a reliable SHIV infection model

in Macaca nemestrina monkeys. In this model, animals are pre-exposed to infection with Chlamydia trachomatis (CT). With a heightened anti-CT immune response, animals undergo a single mucosal challenge (intravaginal) with SHIV, chimeric SIV/ HIV which has been molecularly constructed for macaque infection.

The initial series of six-animal experiments are completed in which 3 animals were pre-exposed to chlamydia cervical infection prior to mucosal challenge with 500 TCID50 SHIV89.6P, while the remaining three underwent SHIV inoculation without prior CT exposure. All three of the pre-exposed animals became infected with SHIV, while one of three SHIV-only animals has developed viral infection, as of week 10 post-SHIV challenge. These results indicate that CT pre-exposure may have enhanced SHIV transmission and/or infection, and constitute the basis for a new, CT/SHIV co-infection model in non-human primates.

This work supported by CONRAD MSA-02-315 and U of WA National Primate Research Center RR-00166.

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02381 BLOCKADE OF ATTACHMENT AND FUSION RECEPTORS INHIBITS HIV-1 INFECTION OF HUMAN CERVICAL TISSUES

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Identification of cellular factors and primary target cells involved in mucsoal HIV-1 infection are crucial for understanding viral pathogenesis and development of effective prevention strategies. Accordingly, HIV-1 entry inhibitors were used to investigate the first line coreceptors for HIV-1 infection of human cervical tissue, the role of migratory cells and attachment receptors in HIV-1 dissemination in both cellular and mucosal infection. Blockade of CD4 alone, or CCR5 and CXCR4 together, inhibited localized mucosal infection. However, simultaneous blockade of both CD4 and mannose C-type lectin receptors (MCLR) including, but not limited to, DC-SIGN, was required to inhibit HIV-1 uptake and dissemination by migratory cells. In contrast, the direct targeting of HIV-1 by neutralizing mAb b12 and sCD4 fusion protein CD4-IgG2 was sufficient to block both localized infection and viral dissemination pathways. The observations were further confirmed in monocyte-derived dendritic cells and DC-SIGN+ cell line. Flow cytometric analysis and immunostaining of migratory cells revealed two major populations, CD3+CD4+HLA-DR- and CD3-CD14-HLA-DR+, with a significant proportion of the latter population also positive for DC-SIGN expression. The findings in current study provide the first demonstration that HIV-1 infects human cervix via CCR5 and CXCR4, and that both CD4 and MCLR on migratory cells may be involved in dissemination of infectious HIV-1 to other tissue sites. These studies have identified key targets for developing topical microbicide.

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02414 SAFETY AND EFFICACY OF CELLULOSE ACETATE PHTHALATE (CAP) AGAINST VAGINAL TRANSMISSION OF SIMIAN/HUMAN IMMUNODEFICIENCY VIRUSES IN RHESUS MACAQUES

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Cellulose acetate phthalate (CAP), a pharmaceutical excipient designed as a coating material for tablets or granules, has been demonstrated to be effective against herpes simplex virus type 2 (HSV-2) infection in mice, and to protect four of six rhesus monkeys from vaginal challenge with simian immunodeficiency virus SIVmac251. Formulated CAP applied vaginally to rhesus macaques was not irritating as determined by colposcopy. Serum chemistries, vaginal biopsies, bacterial cultures and vaginal pH were all within normal limits. No obvious changes in peripheral CD4:CD8 ratios or levels of inflammatory cytokines/chemokines in plasma and vaginal fluids were detected. Thus, CAP appears to be safe in vivo. Magnetic resonance imaging (MRI) revealed that CAP was evenly distributed after application and 20 min thereafter, but was found absent 24h after application. To assess whether CAP confers protection against primary viral strains that are transmitted in humans, infections with simian/human immunodeficiency viruses (SHIVs) expressing the envelopes of X4 and R5 HIV-1 strains (SHIVSF33A and SHIVSF162P3, respectively) were performed. Replication of SHIVSF33A and SHIVSF162P3 in vitro can be efficiently blocked by CAP, with ID50 concentrations of 180 and 25 mg/ml respectively. Preliminary findings in rhesus macaques challenged with a mixture of X4-SHIVSF33A and R5-SHIVSF162P3 suggest that CAP is efficacious against both X4 and R5 SHIV viruses in vivo, and should therefore be considered as a viable topical microbicide candidate in the prevention of HIV-1 infection.

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02435 GP340: A NOVEL MICROBICIDE FROM THE INNATE IMMUNE SYSTEM

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Gp340 is a high molecular weight sialyated glycoprotein that inhibits HIV-1 infectivity in vitro. This protein is a member of the scavenger receptor cysteine-rich (SRCR) family found on the surface of many epithelial cells, and also secreted into bronchial alveolar lavage, tears, and saliva. Secreted forms lack a transmembrane domain. Gp340 appears to play a broad role in the innate immune system. We reported that gp340 inhibits a wide range of HIV-1 strains by interacting with viral gp120 in a calcium-dependent reaction. Gp340 binds to gp120 with a KD of 10-7 – 10-10 M, comparable to gp120-sCD4, but this binding occurs at a site distinct from CD4. The binding reaction is specifically inhibited by antibodies to gp340. We have now identified the binding sequence on the V3 loop of gp120 as a highly conserved site that is part of the CCR-5 binding region.

We now report that while high level of gp340 are secreted at some locations (lung, eye, salivary gland), only modest levels are found in cervical-vaginal lavage. It appears that in cells of the reproductive tract, gp340 is expressed as a membrane associated protein. Our studies suggest that cell surface gp340 could function to concentrate and perhaps transmit virus, while soluble gp340

functions as an inhibitor of HIV-1 infectivity. We are currently exploring the possibility that truncated forms of soluble gp340 could be the basis for a novel microbicide.

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02437 HIV NEUTRALIZING IGA OBTAINED BY SCREENING A PHAGE-DISPLAY FAB IGA LIBRARY DERIVED FROM HEPS WOMEN

Bomsel, Morgane
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Backgound: Rare individuals remaining uninfected despite unprotected sex with HIV+ partners, i.e. Highly Exposed Persistently IgG Sero-negative (HEPS), contain in their secretions anti-HIV envelope secretory IgA (S-IgA), suggesting that these S-IgA are involved in protection. Accordingly, such IgA, the major effector molecule of the mucosal immune system, have been shown to inhibit CD4+ cell infection as well as one pathway of HIV entry across mucosa, i.e. transcytosis through an epithelial barrier. Aims: To produce human monoclonal S-IgA targeting conserved HIV envelope epitopes with neutralizing activities. Methods & Results: Cervical secretions from 56 HEPS originated from Cambodia were tested for HIV-envelope glycoprotein S-IgA: 22 contained a high level of anti-HIV envelope gp41 S-IgA. Mucosal B cells of these 22 HEPS were used to construct a combinatorial phage display library expressing Fabs of IgA. Selection for HIV envelope specific Fab was carried out by panning the Fab librairy on immobilized HIV envelope proteins gp41 and peptides covering conserved region of gp41. Several tenth of positive clones were obtained as measured by ELISA and were induced to produce soluble Fab. The Fab were tested for their capacity to block: i) HIV interaction with and trancytosis across epithelial cells; ii) HIV infection of CD4+ cells by different viral strains. Several Fab clone were found to block efficiently HIV transcytosis and infection of CD4+ T cells. Neutralizing Fab will be then used to reconstruct human d-IgA or S-IgA and their precise epitope specificity will be determined. Perspectives: These studies could permit to characterize new neutralizing epitopes on HIV envelope glycoprotein and to dispose of HIV envelope specific IgA clones blocking HIV mucosal entry that could be included in a topical microbicide formulation to prevent mucosal transmission of HIV.

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02465 NATIVE VAGINAL LACTOBACILLI ENGINEERED AS A DELIVERY VEHICLE FOR ANTI-HIV PROTEIN MICROBICIDES

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The predominant mode of HIV transmission worldwide is via heterosexual contact, with the cervico-vaginal mucosa serving as the main site of viral entry in women. The mucosal surfaces are naturally lined with commensal bacteria, primarily lactobacilli. A deficiency of vaginal lactobacilli is associated with increased HIV acquisition. To address the urgent need for female-controlled approaches to block the heterosexual transmission of HIV, Osel is actively pursuing a novel approach, termed MucoCept. This approach involves genetic modification of a preferred vaginal strain of Lactobacillus,

to express HIV-binding proteins. Intravaginal colonization of the MucoCept bacteria should replenish flora and serve to trap and inactivate HIV, thus reducing the efficiency of viral transmission.

To date, Osel has expressed the biologically active HIV receptor, human two-domain CD4, as either a secreted or cell wall anchored molecule in a vaginal isolate of L. jensenii, and progressed to have the expression cassettes stably integrated into preferred sites of the bacterial chromosome. The resolved integrants retain the wild-type phenotype. Osel is currently advancing Lactobacillus-based expression systems for anti-HIV protein microbicides, including CD4, cyanovirin-N, and HIV entry inhibitors, as a basis for selecting an optimised MucoCept product for eventual clinical testing.

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02508 CELLULOSE ACETATE PHTHALATE INHIBITS HIV-1 INFECTION VIA DIFFERENT CLADES IN CELLULAR, DENDRITIC CELL AND HUMAN CERVICAL EXPLANT MODELS

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Background
Cellulose acetate phthalate (CAP) is a cheap and effective compound exhibiting good activity against HIV-1 and a number of other STD's with a long history of safe usage in humans. We have investigated CAP as a potential microbicide both as a base compound and a formulated gel against a range of HIV-1 strains and clades using cellular and human cervical explant models and in combination with zinc finger inhibitors.

Methods
Anti-HIV-1 activity of CAP and nucleocapsid p7 zinc finger inhibitors (zfi) alone and in combination was determined by *in vitro* assays and in *ex vivo* human cervical explant models. THP-1/DC-SIGN transfectants and monocyte derived dendritic cells were used to investigate the action of CAP against dendritic cell medicated infection. Biocompatibility was assessed by viability assays and cytokine profiles from mucosal tissue exposed to both compounds and N-9 as a control.

Results
Our results show that CAP strongly inhibits the activity of a number of different cell free and cell associated strains and clades of HIV-1. It inhibits viral transfer via DC-SIGN and by migratory cells emigrating from cervical explants. Furthermore, it is biocompatible and is effective in the presence of seminal plasma and across a wide pH range. Preliminary studies with zfi showed some promise for development of a combination microbicide.

Conclusions
CAP has shown strong anti-viral activity across a spectrum of HIV strains and clades in cellular, dendritic cell and cervical explant models and is biocompatible at all concentrations tested. Therefore, it shows good potential for development as a topical microbicide.

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02560 SYNERGY BETWEEN POTENTIAL HIV MICROBICIDAL AGENTS

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Polyanionic microbicides such as Dextrin-2-sulphate (D2S) and PRO2000 are currently in Phase II trials. However, it is unlikely that microbicides will be used alone to prevent HIV infection due to the problem of resistance seen in monotherapy. The aim of this work was to study the anti-HIV-1 interactions of D2S and PRO2000 with other known antiretroviral agents in vitro. Combinations of D2S and PRO2000 with the neutralising monoclonal antibody IgG1B12, the peptide-based fusion inhibitor DP178, the CCR5 antagonist TAK779 and the bacterial anti-HIV-1 agent Cyanovirin-N were assessed for their ability to act in synergy against HIV-1JR-FL, HIV-1HxB2 and HIV-1W61D pseudoviruses. These pseudoviruses have the luciferase gene inserted into nef allowing quantitative analysis of viral infection 3-5 days post infection, and are only capable of a single round of replication. The data were analysed for synergy using Calcusyn software. Results using HIV-1JR-FL indicate that PRO2000 acts synergistically with IGG1B12 and PRO2000 acts in synergy with DP178 at high concentrations of both drugs. These findings suggest that it may be beneficial to use PRO2000 in combination with other known antiretroviral agents. By contrast, combinations of D2S with IgG1B12 and DP178 are antagonistic for inhibition of HIV-1JR-FL infectivity. These data suggest that polyanionic microbicides can exhibit synergistic anti-HIV-1 activity in combination with other types of inhibitor, but that combinations must be studied on a case by case basis.

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02573 DEVELOPING AN HIV MICROBICIDE BASED ON RNA INTERFERENCE

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Sexual transmission of HIV occurs when cell-free or cell-associated virus infects cells primarily via the CCR5 coreceptor, expressed on macrophages, dendritic cells and activated T lymphocytes. A microbicide that could be used vaginally to prevent sexual transmission would make a substantial contribution to controlling the spread of HIV. We are exploring the hypothesis that RNA interference (RNAi) can form the basis of an effective anti-HIV microbicide.

RNAi is an ancient, evolutionarily conserved, host defense against viruses and transposable elements, which uses small double-stranded RNAs, called small interfering RNAs (siRNA), to silence gene expression with exquisite specificity by targeted degradation of homologous mRNAs. There has been a lot of excitement about the therapeutic potential of RNAi to treat viral infection. A major obstacle is how to deliver siRNAs into cells in vivo. Duplex siRNAs targeting CCR5 and HIV gag delivered to monocyte-derived macrophages and activated T cells lead to prolonged gene silencing, lasting for weeks in macrophages, that completely inhibits de novo infection and suppresses viral replication in already infected cells. This suggests that duplex siRNAs might serve as the active component in a microbicide that might not need to be administered directly before sexual intercourse.

Many steps are needed to determine whether an siRNA-based microbicide is possible. These include in vivo delivery of siRNAs to dendritic cells, macrophages, and (if possible) lymphocytes in the genital mucosa of small animals, and demonstration that delivered siRNAs effectively inhibit HIV production. Delivery methods have to be safe and compatible with a formulation suitable for vaginal delivery that does not induce inflammation at the mucosa. Early proof-of-principle studies eventually need to

be complemented by formal pharmacokinetics, toxicity and efficacy studies in small animals and primates. We will discuss our first steps to develop methods to deliver duplex siRNA to macrophages and dendritic cells in vivo in mice.

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02663 HUMAN VAGINAL-ECTOCERVICAL TISSUE MODEL FOR MICROBICIDAL IRRITATION STUDIES

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Infection through the vaginal-ectocervical (VEC) tissue is believed to be the main route for the heterosexual transmission of the human immunodeficiency virus (HIV) in women. Recently, a tissue culture based model of the VEC has been developed. Normal, human ECV epithelial and dendritic cell co-cultures were used to form a three-dimensional tissue using specially formulated medium. The in vitro engeneered tissue reproduces many of the histological and ultrastructural features including basal, parabasal, glycogenated intermediate, and the superficial cell layers. Preliminary experiments showed the use of this tissue model and the MTT tissue viability assay for predicting VEC irritation of microbicides. Different concentrations of Nonoxynol-9 (N-9), carrageenin-I, and methyl cellulose were dosed topically and the viability of the VEC tissue was determine by MTT. Following 24 hr exposure to N-9 (0.1%) tissue viability was reduced to 51%. In contrast, carrageenin-I (20%) reduces viability to 77% and no effect was observed for methyl cellulose (up to 20%). H & E staining showed irritation of epithelial lining following N-9 treatment ≥ 0.1%. Experiments also showed that HIV virions do not pass freely through the tissue but they infect cells in the reconstructed VEC tissue model containing dendritic cells. In conclusion, the tissue model is likely to serve as a useful tool to screen new or existing microbicides/formulations for vaginal toxicity and microbicidal efficacy.

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02671 EROSION OF SURFACE COATING OF MICROBICIDE FORMULATIONS DUE TO SHEARING & CONTACT WITH VAGINAL FLUIDS

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A new in vitro assay analyzed erosion of microbicide formulation surface coating due to interactions with ambient vaginal fluids and shearing. Contacting layers of test formulations and fluid were subjected to defined external shear histories. Persistence of the formulation layer, and physical properties of both layers, were assessed vs. time. 4 vaginal formulations were tested: Carraguard (carrageenan); Replens (polycarbophil); KY Jelly (cellulose); Conceptrol (cellulose). 2mm layers of our vaginal fluid simulant or a new semen simulant were applied. Low shear viscosities modeled pre/post coital and high shear viscosities reflected coital conditions. Very significant differences occurred across gels. For example, rank orders for vaginal fluid contact were: gel layer viscosity retention KY > Carraguard > Conceptrol > Replens; fluid layer viscosity increase Conceptrol > Replens > Carraguard > KY. These were relatively independent of contact time (≤ 70 min) and shear rate in the initial vaginal fluid testing series. Retention of microbicide coating is essential for function. Formulation

composition and structure produce properties that govern the complex biophysics of coating retention. This new assay is being applied to a spectrum of biologically relevant conditions that model the natural history of formulation residence in the vagina. Initial results suggest differences in vaginal retention by these four test formulations. These putative differences can be tested by direct in vivo imaging of formulation retention. Supported by NIH AI48103.

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02686 IN VITRO ANTI-HIV-1 ACTIVITY OF MICROBICIDE FORMULATIONS AGAINST NON-SUBTYPE B PRIMARY STRAINS

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In vitro analyses to assess the anti-HIV-1 efficacy of microbicide formulations should include primary virus strains from geographic regions where clinical studies are being proposed. In this study, microbicide formulations of CarraguardTM, cellulose acetate phthalate (CAP), KY plus nonoxynol-9 (KY-N9), PRO 2000 (0.5% and 4%), UC781 (0.1% and 1%), and Vena GelTM were tested against primary HIV-1 strains (subtypes A, C, and CRF01_AE) representing predominant circulating strains in southern Africa and southeast Asia. Microbicides (highest non-toxic concentrations) were added to peripheral blood mononuclear cells (PBMCs) along with HIV-1 strains. Virus infection of the PBMCs was monitored by HIV-1 p24-antigen in culture supernatants at days 1, 3, and 7 post-challenge, and anti-viral activity of microbicides was measured as log10 reduction of p24 production in the presence of microbicides versus controls (no microbicides). CAP, PRO 2000, and UC781 effectively blocked the infection by the three subtype strains (1.3- 4.5 log10 or 95-100% reduction). KY-N9 completely blocked infection by the subtype A and CRF01_AE strains (2.4-2.8 log10 or 100% reduction) and had a smaller effect on the subtype C strain (0.9 log10 or 88% reduction). CarraguardTM did not block infection by the three subtype strains (-1.3-0.38 log10 or 185-59% reduction). The effect of Vena GelTM on the three subtype strains was variable: a 1.36 log10 (96%) reduction for the subtype C strain but only a 0.2 log10 (38%) and a –0.02 log10 (-4.1%) reduction the subtype A and CRF01_AE strains, respectively. Differences in microbicide efficacies against primary viruses belonging to different subtypes highlight the importance of including primary HIV-1 strains in pre-clinical microbicide testing algorithms.

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02756 INDUCTION AND INHIBITION OF THE HIV-1 VIROLOGICAL SYNAPSE IN T CELLS

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HIV-1 can spread either by release of cell-free virions or by direct cell-cell spread. Cell-cell spread has advantages for the virus such as production of new viral RNA and proteins that is more rapid than that observed after cell-free virus infection, and potential escape from elements of humoral immunity and inhibitors of viral entry. We have established a model system, based on conjugate formation between HIV-1-infected (effector) T cells and uninfected (target) T cells to analyse the molecular events taking place during cell-cell spread. Using this system we demonstrate that HIV-1 induces

actin-dependent recruitment of the viral receptors, CD4 and CXCR4, and the adhesion molecue LFA-1, to the interface between effector and target cells. This has been termed a 'virological synapse'. Formation of this synapse is followed by rapid transfer of viral Gag into the target cell, a process that probably takes place via directed fusion of virions with the target cell membrane. We have tested a number of inhibitors of this process and report that agents with potential for use as HIV-1 microbicides, including neutralising antibodies, anti-CD4 antibodies and small molecule inhibitors of the HIV-1-coreceptor interaction, are effective at preventing cell-cell transfer of HIV-1. These data are encouraging as they demonstrate that this mode of viral spread is susceptible to microbicidal intervention.

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TRACK B ORAL PRESENTATIONS

02002 A SAFETY STUDY OF DEXTRIN SULPHATE VAGINAL MICROBICIDE

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Background
We perfomed a randomised placebo controlled trial to assess safety of 4% intravaginal dextrin sulphate gelat a hospital in Kampala, Uganda.

Methods
Sexually active females of reproductive age were screened for eligibility of the study. Those found to have sexually transmitted infections were treated before entry. Consentig females were allocated toactive gel or its matched vehicle placebo, pre sex active gel and observation only arm. Total follow up lasted 8 weeks during which women were interviewed, examined by colposcopy and labaratory tests(HIV test, STD screening, haematology, coagulation and clinical chemistry) perfomed.

Results
A total of 109 females were enrolled(71 HIV negative & 38HIV positive); 80 to use gel twice a day[65active gel, 15 placebo], 9 active gel pre sex and 20 observation only arm. In 7/322(2.2%) colposcopy exams, abnormalities were documented among females using active gel, and in 11/74(14.9%)within the placebo group. Only 2 of the 18 abnormalities were thought to be gel related. 6/65(9%) participants on active gel twice daily reported mild intermenstrual spotting, compared to 2/15(13%) using placebo, and 3/20(15%) using no gel. 8/65(12%) participants on active gel reported excessive thirst during the first week of gel use. No excess genital irritation, no evidence of change in vaginal flora, no evidence of systemic toxicity were observed as a result of gel use.

Conclusion
The results indicate a satisfactory safety profile of dextrin sulphate 4% gel in sexually active African population. In particular colposcopic abnormalities did not appear more frequent in the active gel arm. Temporary occurrence of excessive thirst may require further research.

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02092_3 VAGINAL HYGEINE PRACTICES IN A LONDON, UK POPULATION

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Background
Vaginal hygiene practices such as douching or washing the vagina have been linked to presence of bacterial vaginosis, pelvic inflammatory disease and HIV infection. We know that hygiene practices vary between women of different countries and ethnicity. Such hygiene practices may be linked to the acceptability of a vaginal study product, and might influence outcomes in safety or effectiveness microbicide trials. This study assessed vaginal hygiene practices amongst women in West London.

Methods
Interviews were conducted at the sexual health clinic, Jefferiss Wing, St Mary's Hospital. The main variables analysed were the nature and frequency of vaginal hygiene practices, any products used for such, and other demographic variables. Willingness to use an intravaginal gel in a microbicide study was also assessed.

Results
Initial analysis of the first 50 questionnaires revealed that 58% of women practised some form of intravaginal hygiene. Of the subjects who practised vaginal washing, 86% do so during a shower or bath, while 45% do so after sex or menses, 45% wash at least once a day, 28% once a week and 24% once a month. Of the subjects who practised vaginal washing using fingers or flannels water only was used in 50%, soap in 40%, bubble bath products in 30%, antiseptics in 5% and douching products in 5% of the subjects. Of all subjects 24% used commercially available douching appliances, 10% only to introduce water and 14% to introduce a douching product. 46% of the subjects were taught the hygiene practices by their mother, while 36% were self motivated. The completed database will be analysed for the associations of vaginal hygiene practices with age, ethnicity, educational history, smoking and past history of STI's.

Conclusions
58% of women attending a sexual health/STD clinic practiced some form of intravaginal hygiene. This could influence studies of vaginal microbicides. Hence the prevalence and nature of vaginal hygiene practices in a population is an important factor in the design and implementation of microbicide clinical trials.

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02104 A PHASE-TWO SAFETY STUDY OF PRO 2000/5 GEL IN SEXUALLY ACTIVE FEMALES IN UGANDA

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Background:A phase-two study to assess the safety of PRO 2000/5 gel is being carried out in Kampala, Uganda. The objective of the study is to assess systemic and local safety of PRO 2000/5 gel inserted vaginally, as part of research conducted to identify a safe and effective vaginal microbicide to prevent HIV acquisition.

Methodology:The study is a randomised placebo controlled trial being conducted in a cohort of 100 sexually active females of reproductive age in a busy hospital in Kampala. Participants are screened for sexually transmitted infections and HIV and are randomised to either PRO 2000/5 gel or its matched vehicle placebo twice daily for 4 weeks, or to an observation-only arm. Participants are reviewed fortnightly. Evidence of systemic adverse events is sought using various laboratory procedures, which include haematology and biochemistry done at screening and at 4 weeks after randomisation. Local adverse events are assessed every two weeks using a structured questionnaire, clinical examination, colposcopy, and Nugent score on Gram stained specimens based on vaginal swabs.

Results:A total of 65 women have been screened so far, 35 of whom have been randomised into the trial (5 in the observation-only arm and 30 in the gel arms). To-date, 20 participants have completed the study, 16 in the gel arms and 4 in the observation-only arm. None of the women randomised to gel use has indicated any difficulty in inserting the gel and no withdrawal of consent has been observed. One participant in the gel arm was lost to follow up.Two out of the sixteen participants in

the gel arm reported mild vaginal itching and three reported thirst in the first week of gel use. Two participants were found to have superficial epithelial disruptions. There were no other cervico–vaginal epithelial disruptions, no significant changes in vaginal flora and no evidence of systemic toxicity related to gel use observed.

Conclusion: We have observed a good acceptability of gel use and preliminary results based on the first 20 participants seem to suggest a satisfactory safety profile of PRO 2000/5 gel.

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02249 PHASE 1 MULTI-DOSE SAFETY AND ACCEPTABILITY STUDY OF 6% CELLULOSE SULFATE (CS)

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Primary Objective: To assess the local effect of four times daily vaginal applications of 3.5 ml 6% CS gel or K-Y® Jelly for 14 consecutive days.

Methods: Women were randomized to receive either CS or K-Y Jelly. Follow-up visits were conducted on days 8 and 15. Colposcopy assessed epithelial disruption, a wet mount assessed bacterial vaginosis and candidiasis, and a questionnaire assessed acceptability.

Results: 134 women were referred for screening and 75 of them were screened for enrolment. Twenty-seven women were enrolled in each group and 25 women from each group completed the 15 days of follow-up. During follow-up, 2 women in each group had epithelial disruption, 1 woman in each group had candidiasis, and 1 woman in the K-Y group had bacterial vaginosis. Adverse event frequencies were similar in both groups. The products were equally acceptable to the participants.

Conclusion: There was no evidence that 6% CS was different from K-Y Jelly with respect to epithelial disruption, candidiasis, bacterial vaginosis, and acceptability when used four times per day for 14 days.

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02417 VAGINAL FLUID SLPI IS RELATED TO VAGINAL FLORA AND HORMONAL CONTRACEPTION

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SLPI is a serine protease inhibitor which is found on mucosal secretions including vaginal fluid, semen, breast milk and saliva. SLPI is thought to protect epithelial surfaces from damage due to

release of proteases from inflammatory cells. SLPI may also act as a endogenous microbicide. Although the in vitro activity of SLPI against HIV has been inconsistent, recent data suggests that women having elevated vaginal levels of SLPI have decreased mother to child transmission of HIV, and that infants having higher SLPI levels in the saliva have decreased HIV acquisition during breatfeeding. The goal of this study was to assess the effects of vaginal microflora constituents and hormonal contraception on vaginal fluid SLPI levels. A group of 245 reproductive aged women were evaluated for SLPI by ELISA. SLPI levels were not correlated with ethnicity, age, or day in menstrual cycle. However, the median SLPI concentration was decreased among 36 women using Depo Provera for contraception compared to 52 women using oral contraceptives (244 vs 378 ng/ml, p = .03) and 146 women not using hormonal birth control methods (244 vs 305 ng/ml, p = .08). Further, the 98 women having bacterial vaginosis had significantly decreased levels of vaginal fluid levels SLPI compared to women having normal or intermediate flora (256 ng/ml versus 341 ng/ml and 384 ng/ml, respectively, p = 0.01). These data suggests that hormonal contraception and microbial constituents of the vaginal flora may influence vaginal fluid levels of SLPI, which may, in turn, impact susceptibility to sexually transmitted infections including HIV.

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02420_1 INTRA-VAGINAL DISTRIBUTION OF CELLULOSE SULFATE

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Introduction: A microbicide formulation of 6% sodium cellulose sulfate (CS) has been demonstrated to be safe for human subjects, although the optimal applied volume of gel is not known. Larger volumes (5 ml) of gel lead to increased leakage, and smaller volumes (2.5 ml) of gel may provide insufficient vaginal epithelial coverage. Given concern that a dose volume of 2.5 ml may not provide sufficient vaginal coverage to prevent sexually transmitted diseases, including HIV, this study was performed to evaluate intravaginal gel spread and gel leakage in patients who used 2.5 ml and 3.5 ml dose volumes of CS.

Methods: Blinded crossover study of CS gel delivered in 2.5 ml and 3.5 ml volumes to 6 women, three parous and three nulligravid. Each woman was imaged using three-dimensional MRI with gadolinium chelate contrast added to the gel.. Imaging was performed at baseline, and at 5, 20, 35 and 50 minutes after product insertion. Each woman used both gel volumes twice: once with ambulation following insertion and once without ambulation. The sequence was determined by randomization.

Results: Most linear gel spread took place in the first five minutes after insertion, although some continued spread was seen when ambulation took place. Lateral spreading appeared to continue after linear spreading had slowed or stopped. Ambulation also increases gel spread. At times greater than 5 minutes, ambulation had a greater effect on gel distribution than did gel volume. The degree of spreading achieved at 5 and 20 minutes was approximately 60% of both linear distance and surface contact in any group. By 50 minutes, coverage ranged from 53.1% to 84.5% of the linear distance covered and surface contact ranged from between 61.7% - 85.9%. Using a larger volume of gel increased linear spreading but had less consistent effects on lateral spread as measured by surface contact. Within ambulating groups, use of the larger volume increased linear spreading by 4-23% at each time point and increased surface contact by 5-46% at all time points. The greatest linear spreading (49.2 mm) and surface contact (85.9%) 50 minutes after product insertion were in the group of women who used 3.5 ml of gel and ambulated. There was no clear pattern of effect by parity. Most of the women had bare spots in coverage, particularly in the proximal vagina. Leakage was not a severe problem in any of the groups.

Conclusions: The spreading of CS in the absence of intercourse did not result in complete vaginal coverage, even when observed 50 minutes after product insertion. The use of 3.5 ml compared with 2.5 ml, and the practice of ambulation, generally increased gel spread. Results are generally consistent with other MRI studies of vaginal products. This research was funded by CONRAD.

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02436 SAFETY, ACCEPTIBILITY AND EFFICACY OF A PENILE MICROBICIDE WIPE

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Innovative, low cost and practical preventive measures are needed to reduce acquisition of STIs. Two studies were conducted in Malawi to determine safety, acceptability and potential efficacy of a topical penile microbicide wipe, 0.4% bezalkonium Chloride (BZK). The first study was a phase I dose escalating clinical trial to assess safety and acceptability of pre- and post-coital penile cleaning. After obtaining consent, 27 uncircumcised and 24 circumcised low-risk, HIV negative men were enrolled. These men were followed for 8 weeks with penile wipe use escalating from none to a maximum of 3 a day. Compared to events during the first 2 weeks when no wipe was used, there were no changes in reported or confirmed adverse events (AEs) with escalation of dose during subsequent weeks. Adherence and acceptability were high (~90%) and did not differ with increasing dose. Among female partners of these men there were no reports of AEs. The second study assessed the efficacy of 0.4% BZK wipe to decrease the frequency of pathogens found on the mucosal surface of the penile foreskin. After consenting, 27 uncircumcised men were recruited from an STD clinic. The presence of pathogens before and after cleaning the penis with the wipe was quantitatively scored using wet mount, gram stain and culture. The frequency of almost all pathogens, including N. gonorrhoeae, significantly ($p<0.05$) decreased after cleaning with the wipe compared to rates before cleaning. These results suggest that this topical penile microbicide wipe is safe and acceptable. It was effective in reducing the frequency of several pathogens. A phase III trial is planned to further evaluate this wipe.

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02440 VAGINAL HYGIENE AND USE OF INTRAVAGINAL PRODUCTS AMONG WOMEN IN RURAL SW UGANDA

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Background: The success of phase II/III microbicide safety and efficacy trials will largely depend on acceptability of intravaginal products. Vaginal hygiene and vaginal products other than microbicides could be related to HIV acquisition and may influence outcomes of a phase III trial. This study assessed use of intravaginal products and vaginal hygiene among women in a feasibility study of phase III microbicide.

Methods: Focus Group Discussions (FGDs) for both sexes and individual interviews for women only were conducted among men and women (in regular sexual relationships) participating in an ongoing microbicide feasibility study. Themes investigated were: perceptions of HIV/AIDS; acceptability of couple counselling; male involvement in a trial investigating a female product; condom use; sexual practices, vaginal hygiene and use of vaginal products. A total of 12 FGDs (6 with women, 6 with men) each with 8-12 participants were conducted.

Results: Participants in Focus group discussions expressed that vaginal products are used, primarily to lubricate or tighten the vagina before sex to increase sexual pleasure. The men were not well informed about products used. Main products used were herbs and gels such as vaseline and creams for lubrication, and detergents, soft beverages and herbs for tightening. A few people mentioned vaginal drying but no specific product was mentioned. 79% of 98 women reported use of both water and soap, and 18% use water only for vaginal hygiene. Of these 80% did so more than once a day, 13% once a day, 5% less than once a day but once a week and 1% less than once a week but more than once a month. Women were asked about washing during menses, before or after sex. 90% of 86 who answered these questions wash during menses, 99% before sex and 97% after sex. Specific time for washing the vagina before or after sex was not discussed.

Lessons learnt: Vaginal hygiene practices are frequent in this population and understanding this would be important in the design and implementation of a phase III microbicide trial. Use of intravaginal products implies that vaginal microbicides in phase III trials will not be a new concept.

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02454 THE EFFECT OF THE UNPROTECTED INTERCOURSE ON THE VAGINAL ENVIRONMENT: COLPOSCOPY AND OTHER MARKERS

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OBJECTIVE: To evaluate the effect of unprotected intercourse on the vaginal environment through colposcopy and other laboratory markers. METHODS: During the control cycle of a phase I blinded, randomized, clinical study with ACIDFORM, 20 women were evaluated on the 12-14o day of a cycle through vaginal colposcopy (CONRAD-WHO), pH, Gram stained smear (Nugent criteria), H2O2 producer lactobacillus growth, and leucocytes counts and IL-6 (Biotrak®) in vaginal lavage. Colposcopy was re-evaluated 2-3 hs, and other parameters 72hs after an unprotected intercourse. Women were asked not to duch during the evaluation period. Only women with a regular partner, not pregnant, having tubal ligation, regular menstrual cycles, not using hormones, the couple having no current or previous STI, and using condoms in all previous intercourse were selected for participation. Wilcoxon's test (means) and McNemar tests (proportions) for paired samples were used for data analysis. RESULTS: No differences on defined colposcopic findings, neither in vaginal pH (4.35 x 4.28), Nugent score (1.4 x 1.5), IL-6 (1.44 x 2.15 pg/mL), H2O2 lactobacillus growth (30 x 25%) were observed. There was a significant difference in leucocyte's means (53.8 x 155.7, p=0.048). CONCLUSION: In regular, monogamous partners, unprotected sex does not altered vaginal environment, except for an increase in inflammatory cells in vaginal lavage which is possibly due to the ejaculate.

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02463 SAFETY OF CARRAGUARD® AMONG HIV-POSITIVE WOMEN AND MEN IN SOUTH AFRICA

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Background: Ideally, microbicides will be available over-the-counter. It is likely that microbicides will be used by women and men who are not aware of their HIV status. HIV-infected persons may also use a microbicide to avoid sexually transmitted infections, or to protect their partners. It is important to know whether HIV-positive women and men can safely use a potential microbicide.

Methods: We conducted a Phase I study to assess the safety and acceptability of Carraguard", the Population Council's lead candidate microbicide, among HIV-positive women and men in Durban, South Africa. Twenty healthy HIV-positive sexually abstinent women and men, and 20 HIV-positive sexually active women were recruited from health service and community centers in Durban, South Africa. Eligibility criteria included CD4 count >200, menstrual regularity, and absence of STIs or symptomatic vaginal infection. Consenting participants were randomized to use Carraguard, placebo (methyl-cellulose), or condoms only. Women inserted one dose of gel vaginally every evening for 14 intra-menstrual days, and men applied one dose of gel directly to the penis every evening for 7 days. Participants underwent clinical exam (including colposcopy for women) and laboratory testing for infections per protocol at follow-up visits.

Results: Preliminary, blinded findings for sexually abstinent women and men only are included; results for sexually active women will be included in the final presentation. Sixty percent of women reported current contraceptive use, with hormonal injectables and male condoms being the two most common methods. At baseline, 70% of women and 60% of men reported condom use in the last month. Eighty-five percent of women and 80% of men had previously been HIV tested; one woman and two men reported an STI in the prior 3 months; and few participants reported an AIDS-related illness in the previous 5 years. At baseline, 46% of women and 36 % of men were taking medication for HIV (none were using anti-retroviral therapy); during the study, 24% of women and 8% of men took medication(s) for HIV. No serious adverse events occurred during the study. A total of 117 adverse events (AEs) occurred, 103 in women and 14 in men. Among women, AEs were generally equally distributed across study arms, and the majority (79%) were mild. Sixty percent were related to the reproductive system (e.g. vaginal discharge, itching, burning); none of these were severe, and two (both mild) were considered probably related to product use. Nine women ever reported a genital symptom. Of the 5 genital exam findings for women during follow-up, 3 had superficial epithelial disruption and none had deep disruption. Among men, the majority of AEs were unrelated to the reproductive system (79%), mild (86%), occurred in the condoms-only arm (79%), and none were considered probably related to product use. Three men ever reported a genital symptom, and there were no positive tests for inflammation or genital findings with epithelial disruption in men.

Conclusion: Preliminary blinded results show that the product and the placebo appear to be safe in HIV-positive sexually abstinent men and women.

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02534 QUANTITATIVE AND QUALITATIVE DETERMINATION OF THE VAGINAL MICROBIAL FLORA BY REAL TIME PCR

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In each ecological niche of the human body, including the vagina, the microbial commensal flora is composed of about 100 to 600 different bacterial species. While a minority of these organism grows well in vitro, the vast majority is not cultivable by standard laboratory techniques. Since it is of great importance to asses the variation of the microbial flora connected with the use of microbicides, as well as in specific pathological conditions, we developed an efficient new method based on quantitative real-time PCR. Aim of this work is the development and validation of a novel molecular diagnostic approach for characterisation vaginal flora, both for cultivable and uncultivable bacterial species. Real time PCR is used as a culture-independent tool for characterisation of the shifts in the composition of microbial population of the vagina. After construction of a database, several PCR primer sets, able to amplify defined groups of bacteria, were designed. Three different sets of primer were designed to identify/quantify the predominant species of the human vagina flora which correlated to "normality" (Lactobacillus crispatus, Lactobacillus gasseri, Lactobacillus jensenii). For the recognition/quantification of the major phylogenetic groups of bacteria a series of 10 primer sets were designed. For few pathogens specific primer sets were designed (Chlamydia trachomatis, Trichomonas vaginalis, Candida albicans). The PCR assays have been validated on controls of cloned DNA and specificity and sensitivity were checked. The quantitative real time PCR assay developed was shown to be able to quantify efficiently selected species in spiked samples over a wide range of serial dilutions.

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02603 EFFECT OF 0.5% PRO 2000/5 GEL ON INFECTIOUS HIV-1 AND INFLAMMATORY MEDIATORS IN CERVICOVAGINAL SECRETIONS

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PRO 2000/5 has been shown to inhibit HIV and other STI in cell culture and in animal models. However, there is as yet no data showing that any microbicide exhibits anti-viral activity in vivo. We are conducting a prospective double-blind placebo-controlled study among 20 HIV-infected women to assess whether a single 2-g intravaginal dose of 0.5% PRO 2000/5 Gel (P) reduces levels of infectious HIV present in cervicovaginal lavage (CVL) fluid collected one hour after application. A secondary objective is to assess the acute inflammatory response to a single application of 0.5% PRO 2000/5 Gel (P) by testing the CVL for inflammatory cells, IL-1b and IL-8. Inclusion criteria include age between 18 and 45, HIV-1 RNA ≥ 50,000 copies/ml, and a normal Pap smear within 6 months of screening. Exclusions include pregnancy, recent UTI or STI, and sexual intercourse or use of other vaginal products within 48 h of screening. Given the variability in the ability to reproducibly recover a subject's own infectious HIV from CVL, the anti-viral activity in CVL will be assessed by spiking with serial dilutions of HIV and quantifying the virus recovered. Serial two-fold dilutions of CVL supernatants collected at screening (2-3 days before) and 1h after application of PRO 2000/5 or placebo gel will be spiked with dilutions of HIV-1 and then inoculated onto susceptible cells. A dilution of CVL that inhibits or neutralizes virus will be determined. Additionally, the subject's own virus will be cultured directly from supernatant and cell pellets obtained before and after PRO 2000/5 or placebo gel application. A peroxidase test on the cell suspension will be used to quantify PMNs; IL-

1b and IL-8 will be measured using commercial ELISA kits. In preliminary studies, infectious virus has been reproducibly and successfully recovered after spiking CVL samples with serial dilutions of virus. In addition, the anti-HIV activity of serial two-fold dilutions of PRO 2000/5 diluted in vitro in CVL has been established starting with an initial concentration of 500 mg/ml and spiked with 20 ng of p24/ml of replication defective JRFL-pseudotyped virus expressing a luciferase indicator gene. A 1:512 dilution or 0.977 mg/ml of PRO 2000 in CVL inhibited infection by the JRFL-pseudotyped virus. This strategy is a mechanism for testing in vivo the efficacy of a microbicide before embarking on large-scale clinical trials.

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02655 VAGINAL TENOFOVIR GEL TOLERABILITY IN HIV-UNINFECTED WOMEN AND ABSTINENT HIV-INFECTED WOMEN:HPTN 050

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Objective: To establish the highest tolerated dose and frequency of once daily or twice daily 0.3% and 1% Tenofovir (PMPA) vaginal gel in abstinent HIV-uninfected (HIV-) women and to evaluate this dose in sexually active HIV- women and abstinent HIV-infected (HIV+) women. To describe systemic pharmacokinetics (PK) of Tenofovir vaginal gel in a subset of participants.

Methods: Safety labs and pelvic exams were completed at screening, enrollment, Day 2-3, Day 7 and Day 14 visits with colposcopy at enrollment and the Day 14 visit. Women used study product for 14 consecutive days. PK samples were collected after a single application and on Day 13.

Results: Seventy-two women were enrolled. Since 1% BID was as well tolerated as lower doses/frequencies, it was evaluated in the sexually active HIV- and abstinent HIV+ cohorts. Adverse events (AEs) were reported in 66 women. Most were mild genital AEs such as erythema(n=15), ecchymosis/petechiae(n=13), or pruritis (n=12). One severe adverse event (abdominal pain) possibly related to product was reported. Ten of 19 women in the PK subset had low but detectable tenofovir serum concentrations (lower level of quantification=2.99 ng/ml, Cmax ranged from 3.01 – 25.83).

Conclusion: Tenofovir (PMPA) vaginal gel 1% BID is well tolerated in HIV- women and abstinent HIV+ women with minimal systemic absorption. Evaluation of sexually active HIV+ women is underway. Phase II extended safety and effectiveness testing is planned.

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02674 REACHING CONSENSUS: DEVELOPING AN AGREED CLINICAL TRIAL PROTOCOL FOR A MULTI-CENTRE MICROBICIDE RCT

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Background: Since the MDP started in October 2001, Feasibility Studies have been initiated in six sites: Durban, Johannesburg and Mtubatuba (South Africa), Masaka (Uganda), Mazabuka (Zambia) and Mwanza (Tanzania) in preparation for a RCT of two microbicides. In parallel, working groups (Clinical Trial, Laboratory, Social Science and Community) were established to review and address issues relevant to the development of the protocol and implementation of the trial.

Objectives: The objectives of the Feasibility Studies include: to collect data on HIV incidence and prevalence, sexual behaviour including anal sex and condom use and determine ability to recruit and retain women in follow-up. The objectives of the Clinical Trial Working Group are to address issues relevant to the trial design.

Methods: Six cohorts have been established and details are presented elsewhere. A timetable of topics to be addressed by the Clinical Trials Working Group was drawn up. The group included at least one member from each site, and a central group including the facilitators of the other working groups. An overview of each topic was circulated to all members by email with clear timelines for response, which were summarised prior to review by conference call in order to reach consensus.

Results: Although there is international debate about the control group(s) for microbicide RCTs, investigators were unanimously in favour of a single control group (placebo gel) due to concerns with regard to differential behaviour between women allocated to 'gel' or 'no gel' and consequent difficulty in interpreting the trial result. The advantages and disadvantages of various lengths of follow-up (6, 9, 12 and 24 months) were considered and will be presented. HIV testing, support and care are not readily available in the participating communities, and as a result HIV-positive women are not excluded from the research in all sites. Nonetheless, it was agreed that only HIV negative women would be eligible for the trial. Limiting the upper age limit in order to select women at highest risk was also discussed, but in the interests of generalisability of the trial result it was decided not to have an upper age restriction. For similar reasons, and because of the difficulty in collecting robust data on the subject, it was decided not to exclude women who reported practising anal sex or use of vaginal products to enhance sex at screening.

Conclusion: Effective communication between the members of this large group was achieved using the strategy described. All the sites and investigators have contributed actively towards the development of the randomised placebo-controlled trial protocol to be implemented in 2004.

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02676_1 SAFETY OF CARRAGUARD USE BY HETEROSEXUAL MEN IN A SIX MONTH CLINICAL TRIAL IN THAILAND

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In phase II trials Carraguard use has been shown to be safe and acceptable in women. We conducted a six-month, randomized, triple-blinded trial of Carraguard (3% carrageenan) compared to 2.5% methyl cellulose placebo in Chiang Rai, Thailand, to evaluate safety and acceptability among heterosexual couples. We enrolled 55 low-risk couples who were in good health, were monogamous, did not use condoms regularly, and were free of HIV/STI. Couples were randomized to Carraguard or placebo gel and were asked to use the gel each time they had vaginal sex. Men and women came for monthly follow-up visits including genital/pelvic exams, STI testing, interview and counseling.

Follow up and adherence with gel use instructions were >90% at each scheduled visit. During follow up four men in group I (15%) and five men in group II (18%) ever reported any genital itching, burning or pain; one man in each group reported that the gel ever caused itching, burning or pain, and one man in each group reported the gel caused other (mild) symptoms. Four men in group I (15%) and six men in group II (21%) ever had a (small) superficial epithelial disruption during the study. There were no cases of deep epithelial disruptions in any men during the study, nor were there any cases of balanitis or urethral discharge. These data indicate that Carraguard did not cause significant irritation or harm to the male genitalia when used by low-risk heterosexual couples during vaginal intercourse.

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02685 IMAGING THE DISTRIBUTION OF A RECTAL MICROBICIDE GEL AND SEMEN SURROGATE IN THE LOWER GI TRACT

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Background: Understanding distribution of microbicide gel and HIV-infected semen within the rectum and lower gastrointestinal (GI) tract is critical to furthering the development of effective microbicides for rectal use. No data are available to describe this distribution, especially in the setting of coital behaviors that might notify distribution.

Objective: To evaluate the feasibility of imaging the distribution of a microbicide or semen surrogate using Single Photon Emission Computed Tomography/Computed Tomography (SPECT/CT) and Magnetic Resonance Imaging (MRI) at baseline and 4 hours post-administration.

Study Design: A KY-Jelly-based microbicide surrogate or viscosity-matched semen surrogate, labelled with Gadolinium-DTPA (MRI contrast) and 500?Ci Technetium sulphur colloid (SPECT contrast), was administered to 3 subjects using 4 different experimental conditions. SPECT/CT and MR images were obtained immediately after simulated intercourse, and repeated 4 hours later.

Main Outcome Measure: Lower GI distribution of microbicide or semen surrogate over time.

Results: MR and SPECT/CT images of gel distribution initially localized to the rectum and sigmoid colon. 4 hours post–administration, the signal had migrated cephalad in 12/12 studies, with the most distant migration distributing to the splenic flexure (top of the descending colon).

Conclusion: SPECT/CT and MRI can be used to successfully determine the distribution of a microbicide or semen surrogate in the lower GI tract. Using the parameters for simulated coitus in our study, gel distribution was seen as far as the splenic flexure. MRI and SPECT/CT may be useful tools to study distribution and clearance of rectal microbicides and of HIV-infected semen to facilitate rational development of microbicides for rectal use.

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TRACK C ORAL PRESENTATIONS

02148 CHALLENGES IN CONDUCTING MICROBICIDE PREPAREDNESS STUDIES IN URBAN AND RURAL SOUTH AFRICA

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HPTN GRANT NO: 1 UO1 A148008

Background:
Developing countries with high HIV prevalence rates are obvious sites for HIV prevention studies. Funding for these trials largely comes from developed countries committed to curbing the spread of the virus. Implementing protocols developed in the sponsor countries poses a great challenge for researchers in developing countries, primarily because these countries lack the basic health care and research infrastructure and clinics. Further, there is a strong divide between urban and rural communities based on socio-economic status, health care provision and health seeking behavior.

We describe the challenges faced in:
Obtaining ethical and regulatory approval
Community education and awareness and site development
Implementing the protocol specific activities
Challenges of high HIV prevalence rates
Recruitment and retentions strategies
Challenges of conducting laboratory tests

Results:
The unit had to seek approval from Provincial Health Department and the Ethics Committee. The ethics committee requested that a paragraph on the results of N9 be included in the informed consent form. Community education and awareness was a long process with several meetings between traditional leaders, service providers, women's groups and the community at large. The high prevalence rates detected at both urban (Durban) and rural (Hlabisa) sites of 29.6% and 35.8% respectively, resulted in the need for extra study staff such as nurses, counselors and community educators. HIV positive women requested the need to be counseled by clinical staff and were reluctant to be referred elsewhere. The recruitment and retention to date has been successful at both Durban and Hlabisa sites having no participants lost to follow-up in the first 3 months of operations.

Multi-site study protocols can be implemented in developing countries provided there is adequate research infrastructure, trained and skilled staff, and community health care support.

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02152 MICROBICIDES AND THE DEVELOPING WORLD: SOCIO-ECONOMIC AND ETHICAL CHALLENGES IN THE INDIAN CONTEXT

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Each day 16,000 people contract HIV, 90% of whom live in developing countries" Fight against dreadful and devastating diseases like HIV/AIDS, and many others, contemplates concerted efforts on the part of developed and developing countries. Microbicides hold vast promise as a preventive tool

against STDs and HIV/AIDS and also as a contraceptive device. Development of a suitable Microbicides therefore constitutes an effective strategy in combating these diseases, and also in the direction of population containment. In order to utilize the potential of developing world and to make a lasting contribution in this global pursuit it is necessary to appreciate their inherent concerns such as free and informed consent, safety and accuracy of the product, affordability, proper selection of the users and cultural and religious compatibility. In the area of microbicides research certain additional precautions have to be taken such as, relevance of the research for the host population, care of the research subjects in the event of research induced injuries, accessibility of the research product, confidentiality, and freedom from stigmatisation and isolation. The concerns of the developing countries are thus wide-ranging and complex, at times, displaying conflicting perspectives. The strategies evolved by the Western world have to be suitably modified — at times fresh approaches have to be evolved — in order to respond to the peculiar circumstances of the developing countries. "There is considerable potential of ethical disputes to arise where clinical research, supported by developed countries, takes place in developing countries" (The ethics of research in developing countries: a discussion paper by Nuffield Council of Bioethics, 1999, p3) Implementation, not the policy alone is the challenge in the developing countries. The acceptance of a product contemplates great degree of education and counselling. Developing countries are a major stakeholder in microbicides research and use. This paper is an attempt to identify characteristic features such as overpopulation, social inequalities, poverty, illiteracy, genderization, cultural pluralism, religious sensitivity, infrastructural constraints, legislative inadequacy and a host of other factors dominating most of the developing countries, particularly India and to suggest an ideal strategy of microbicidal development, consistent with socio-economic, moral and ethical imperatives.

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02158 MICROBICIDE TRIALS AND EDUCATION: STRATEGIES AND COMMUNITY PREPAREDNESS AT NIGERIAN OIL LOCATIONS

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Background: Transactional Sex Workers (TSWs) and Women settlers are more vulnerable to HIV/AIDS in the face of sexual network with Field-Based Oil Workers (FBOW) at oil locations in Nigeria. Recent evidence suggests that Vaginal Microbicides may reduce women's susceptibility to sexually transmitted infections including HIV/AIDS.

Methods: Using Key informant Interview, FGD, participatory engagements and AIDS awareness campaigns targeted at TSWs, Community Women and FBOWs, the unmet needs, challenges to and preparedness for Microbicide Trials for these settlers were explored. Findings were used to develop strategies to prepare this vulnerable community for effective partnership in Microbicide Trial and Education.Program.

Results: Post-program revealed more informed settlers responding to the challenges of HIV/AIDS and taking responsible decisions on their reproductive health and rights. Ninety-two percent will use the vaginal microbicides if available, cheap and found effective against STIs and HIV. Eighty-five percent were ready to be recruited into a trial. Potentiality to accept trials in these communities was found to be more with the offer of free access to a product when one is found to be effective.

Conclusions: There is still poor information on Microbicide as a potential prevention option amongst Communities at Oil Locations in Nigeria. A sustained gender-sensitive AIDS education and community involvement will facilitate community mobilization towards effective preparedness for Microbicide trials in Nigeria.

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02244 WOMEN'S AUTONOMY AND INFORMED CONSENT IN MICROBICIDES CLINICAL TRIALS RESEARCH

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Internationally accepted principals of bioethics research include recognition of the autonomy of individuals to make decisions about participation in research, yet potential participants and community leaders in many research settings consider that enrolling women in microbicide trials without involving male partners potentially violates cultural norms. This paper presents data from two recent studies conducted in conjunction with a multi-national microbicides clinical trial (HPTN 035). These studies provide a range of views on participation in microbicide research, including the contentious issue of partner involvement. Data were collected from community leaders, health providers, and female and male research participants in 7 countries.

In addition to considerations of the ethical principal of respect for persons, the host of issues surrounding partner involvement that were raised in the studies include (1) influence on adherence to study protocol, (2) forfeiting the potential for covert use, (3) distrust and/or lack of familiarity with the biomedical research process, and (4) access to trial care and treatment resources.

The authors propose that adopting a comprehensive approach to the informed consent process can facilitate resolution of some of these issues, and this approach is summarized in the paper.

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02276 ENGAGING GAY MEN IN MICROBICIDE ADVOCACY

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The rise in HIV and STD rates among gay and bisexual men in some communities illustrates the limits of condom promotion and the impact of "condom fatigue" among these populations. Despite the fact that microbicides may offer an acceptable risk reduction alternative, little has been heard about microbicide research and development in the gay press or among gay men's health promoters. In a recent UK survey, a substantial numbers of gay men identified themselves as potential microbicide users. The survey also showed, however, that pre-survey awareness of microbicides as a potential prevention technology was relatively low among respondents.

Gay men's voices were at the forefront of successful activist pressure for new HIV drugs a decade ago and are prominent now in the "global access to treatment" advocacy that is changing pharmaceutical pricing and distribution policies. A burgeoning gay men's health movement is also emerging in the Global North. Men engaged in these two advocacy fronts constitute a natural, although previously untapped, constituency for microbicide advocacy. The Global Campaign for Microbicides has undertaken efforts to engage this constituency, using a range of techniques including (1) promotion of the topic in the gay-focused media, (2)participation in treatment advocacy and gay men's health

conferences and campaigns and (3)outreach via a web site designed to present information on microbicide research and development in the context of gay men's needs and interests. This presentation examines the progress of these efforts, challenges encountered and emerging successes.

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02284 MICROBICIDE FEASIBILITY STUDY, MWANZA, TANZANIA: PRIORITISING & RESPONDING TO COMMUNITY CONCERNS

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OBJECTIVES: To explore strategies for effective community liaison & participation in the context of a feasibility study for a phase III clinical trial of vaginal microbicides in a high-risk occupational study population in Mwanza City, Northern Tanzania.

STUDY POPULATION: 2,400 women working as mamalishe (in makeshift eating places selling food cooked outdoors), or in bars, guesthouses, video halls, vilabu (shops selling locally brewed beer), hotels, restaurants and disco halls ("facilities") in Mwanza City.

METHODS: A community-based sexual & reproductive health service has been established in 10 city wards. Field staff conduct mobilisation activities at facility level. Participants are enrolled and followed-up at mobile clinics conducted at guesthouses and hotels. Wards were divided into geographical clusters of facilities with 20-30 women per cluster. Cluster and ward-level representatives were elected in a process facilitated by the project's Community Liaison Officer. Criteria for the selection of representatives were developed by the community e.g. ability to maintain confidentiality, willingness to attend meetings and to represent others. Orientation workshops and community meetings have explored project-related concerns using tools adapted from participatory learning and action (PLA) and related techniques e.g. Venn diagrams, matrices, pair-wise ranking. Development of a city-level Community Liaison Board comprising ward representatives is on-going.

RESULTS: 32 facility clusters each with one elected representative have been identified in four study wards up to end-Sep 03. Mamalishe and vilabu found in pre-existing geographical clusters (e.g. market places) share concerns and experiences that differ from women working in other facilities. Key clinic-related concerns included waiting times, incentives and speculum examination.

CONCLUSIONS: The Mwanza feasibility study was designed around a high-risk occupational cohort in which traditional community development concepts such as general community mobilisation, representation, liaison and participation are difficult to apply. Representation was tackled by using clusters of facilities as core units in a community defined by eligibility to join a study cohort. Adopting community development approaches that made use of participatory methodologies was key to developing meaningful dialogue.

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02391_3 SEXUAL BARRIER METHOD ACCEPTABILITY AMOUNG HIV- POSITIVE US AND ZAMBIAN WOMEN

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HIV-positive Zambian (n = 359) and US (n = 232) women were assessed and the effects of a culturally tailored cognitive-behavioral based intervention on sexual risk behavior and sexual barrier acceptability and preference were compared. Vaginal lubricants were provided as surrogates for vaginal chemical barriers (VCBs) in addition to male and female condoms. Mean ages (Zambia 29, US 39) and average education level 8 (Zambia) and 12 (US) years at both sites were comparable. Women at both sites were multiethnic (US, African American, Hispanic, Creole speaking; Zambia, over 15 ethnic groups). Most were unemployed (Zambia 78%, US 85%) and sexually active (Zambia 79%, US 72%).

At baseline, 6 and 12 months post-intervention, Sexual Activities and Acceptability Questionnaires were administered to assess frequency of product use, acceptability and preference. Among Zambians, use of male and female condom use increased post-intervention ($F = 14.5$, $p = .001$) while US women did not experience a similar increase ($F = .789$, $p = .463$). Both US and Zambian participants identified ease of use and comfort as the most important characteristics of sexual barrier products and the potential to use a product secretly as the least important following trial use. In both samples, product acceptability predicted use of gels and suppositories and acceptability of VCBs increased post-intervention. Suppositories (Zambia) and gels (US) were most popular. Results suggest increased acceptability predicted use in both US and Zambian women Findings suggest cognitive behavioral interventions can be translated from US to African urban settings. Study supported by NIMH R01-MH63630.

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02405 NEW RESOURCES FOR THE FIELD: THE MICROBICIDE RESEARCH AND DEVELOPMENT DATABASE

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Objective: To introduce the new Alliance Microbicide Research and Development Database (MRDD) to the microbicide community as an authoritative, thorough, up-to-date, and reliable source of information on the microbicide pipeline.

Methods: Since early 2003, with funding from the International Partnership for Microbicides, the Alliance has converted and integrated the existing Microbicides Products Database, Clinical Trials Information Center, and Compendium of Bibliographic Abstracts into an on-line interactive, searchable database with different levels of access and maximum on-line security.

Results: The MRDD was completed in October 2003 and is linked to the Alliance website, www.microbicide.org. Authorized Researchers and Developers can submit, review, edit, and up-date all information about their products, and can view only non-proprietary information on products submitted by others. Guest Users are restricted to viewing only non-proprietary information about all products, which includes a profile of each developer/researcher, general product description, pathogen activity profiles, and pre-clinical and clinical status for each candidate. All Users will have access to all information in the "Abstracts Compendium" and "Supportive Research" sections. A novel report feature permits all users to print reports based on non-proprietary information.

Conclusions: The MRDD permits developers to provide information via the web with maximum security and allows the Alliance to more readily compile, up-date, and analyze data. It also offers a richer, sturdier basis for partnering and funding decisions.

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02406 DETERMINING THE COST: GETTING TO PROOF OF CONCEPT

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The objectives of this research are to: (1) Ascertain the costs for taking a single microbicide candidate to proof of concept; (2) Determine the costs of advancing all microbicide candidates in the pipeline to proof of concept. Methods: The number of microbicides in the current pipeline was taken from the Microbicide Research and Development Database (MRDD). Developers with candidate microbicides were contacted to collect data on their calculations of the costs of imminent, planned, and projected clinical trials. We then obtained illustrative numbers for the minimal pre-clinical requirements for IND submission, which were then used to construct two profiles. The first profile is an estimate based on the average costs for pre-clinical and clinical phases to ascertain the cost of taking a single microbicide to proof of concept. The second profile is an estimate for moving all microbicide candidates in the pipeline to proof of concept. As there is no adequate basis for determining fallout, all candidates were assumed to advance and it was also assumed that each candidate would fulfil minimal pre-clinical and early clinical requirements and one trial in each of phases 2 and 3. Results: Results of these analyses are being cleaned and will be provided as the conclusions of this abstract. Implications: A major challenge for microbicide research and development is identifying and securing sufficient funding commitments. For present and prospective funders, having a clear picture of what is needed will be essential to wise judgments about forthcoming allocations and, possibly, collaborative decision-making.

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02462 DEVELOPMENT OF A RECRUITMENT VIDEO FOR A PHASE 3 TRIAL OF CARRAGUARD

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Ensuring truly informed consent and voluntary participation is one of the major challenges in conducting microbicides clinical trials. To address this, researchers at the Population Council, the University of Cape Town (UCT), and the Medical University of Southern Africa (MEDUNSA) developed a 20-minute video for a Phase 3 trial of Carraguard, as part of a holistic approach to the informed consent process, which also includes a study booklet and the actual informed consent form. The video's primary purpose is to introduce the trial, explain difficult concepts ("microbicide," "randomisation," "blinding") visually, and address several "themes" – voluntary participation, HIV testing, partner issues, gynaecological exam – that were identified as key to truly informed consent

and voluntary participation. These key themes emerged from focus groups conducted with study staff and participants after a Phase 2 expanded safety study at the same sites. A short portion of the video, filmed in three languages (Tswana, Xhosa and English), was pre-tested in focus group discussions (FGDs) in the recruitment communities (Gugulethu, Ga-Rankuwa and Soshanguve) and was also shown to the local community advisory groups (CAGs). Based on feedback from the FGDs and CAGs, the video script was revised and submitted for approval by the Ethics Committees/IRBs the study sites and the Population Council. This led to further revisions before completion of the video in December 2003. We will present the process of developing the video and show the video.

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02556 ADVOCATING FOR MICROBICIDES USING A SEXUAL RIGHTS FRAMEWORK: LESSONS FROM SOUTH AFRICA

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As Microbicides advocacy accelerates, debates are opened up and positions taken on issues related to culture and the implications of cultural practices on the process of decision making and access to microbicides. One such issue that is eliciting strong debate is that of the role of men in hereosexual relationships about whether a microbicide will be used or not.

The Gender AIDS Forum has been working on community mobilisation for microbicide advocacy since 1999 in KwaZulu Natal, South Africa and have now started working nationally on this issue. We are gender activists using a gender justice framework and in relation to Microbicides have found a sexual rights framework for planning, implementation, monitoing and evaluation critical to ensure that the culture debate – linked to patriarchy - does not lead to regression in relation to the gains made by activists on the rights of women to equality, dignity, freedom and erode the atonomy of women, especially in the South and in Africa in particular.

This paper shows how a sexual rights framework has been used to plan and implement a capacity building and an Advocacy campaign plan for Microbicides in South Africa and shows clearly how the cultural (patriarchy) barriers that are been stacked up against the vision of Microbicides can be dealt with.

Key lessons learnt are that when we show those who resist the notion of Microbicides as a women contolled technology that safety trials will ensure that male sex partners whose female partners are using Microbicides are safe, the only issue that remains is that of men's control over womens sexuality or the flip side – the removal of womens right to autonomy. This can then be dealt with by looking at a set of International and national instruments where clear positions have been taken on these issues. By appealing to the sense of justice in people in South Africa in relation to racial inequality, the imperatives for gender equality can be emphasised and the links to sexual rights made and accepted. Furthermore, when a few men who are unthreatened by womens autonomy are mobilised to lead the way in Microbicides discussions, resistence is more likely to be reduced.

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02590 HOW IMPORTANT IS THE STI EFFICACY OF A MICROBICIDE: MODEL PREDICTIONS FROM TWO SETTINGS

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Background: STIs are cofactors for HIV infection. However, the distribution of STIs varies from setting to setting and so the degree to which they drive different HIV epidemics must vary. The extent to which the efficacy of a microbicide against different STIs determines its impact on HIV transmission is investigated in Cotonou, Benin and Johannesburg, South Africa. The settings are different with respect to their underlying risk behaviour, and prevalence of STIs and HIV.

Methods: With data from each city, a mathematical model is used to estimate the amount STIs drive the HIV epidemic in each setting, and the impact of introducing microbicides with different HIV and STI efficacies. Model simulations are compared to determine how the STI efficacy of a microbicide affects the impact of the microbicide in settings with different STI distributions.

Results: The impact of introducing a microbicide in a specific setting is determined by the microbicides efficacy against HIV and other STI. The amount attributable to the STI efficacy of the microbicide depends on the distribution of STIs and the amount STIs drive the HIV epidemic.

Conclusions: A microbicide can reduce HIV transmission even if it is not efficacious against HIV. The impact of a microbicide with specific STI efficacy will vary depending on the setting. This highlights the importance of estimating the efficacy of microbicides against STIs other than HIV in intervention trials, so that unbiased estimates of HIV efficacy can be made and the impact of introducing it in different populations can be investigated realistically.

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02617 MICROBICIDE APPLICATOR RESEARCH FOR USE IN LOW-RESOURCE SETTINGS

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Program for Appropriate Technology (PATH) conducted a systematic assessment of applicators being used in microbicide clinical and preclinical trials to determine their possible benefits and limitations for use in low-resource settings. First, information was gathered through a literature review to determine appropriate interview domains. Subsequently, seventeen semi-structured interviews were conducted with investigators from 7 clinical trials, 4 preclinical trials, and 6 acceptability research studies. The 7 applicator designs represented in the assessment were two reusable and two single-use applicators, an intra-vaginal ring, a rectal applicator, and a new applicator currently under development. The key parameters explored were rationale for applicator choice, acceptability, cost, reuse vs. single use, size of the applicator, and dosage delivery. Results showed that there was a need for further research on issues of safety, cost, and reuse, primarily in the context of low-resource settings.

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02618_1 MEASURING DESIGN TRADE-OFFS FOR MICROBICIDE APPLICATORS IN THE DOMINICAN REPUBLIC AND SOUTH AFRICA

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Program for Appropriate Technology in Health (PATH), Profamilia, and the Reproductive Health Research Unit conducted a survey-based study in the Dominican Republic and South Africa to characterize and prioritize women's needs as they relate to vaginal applicator features. The specific parameters explored were cost, reuse, and perceived safety, with specific attention to how these features related to one another and affected women's preferences for microbicide applicators. Conjoint analysis, a quantitative method utilizing structured surveys and close-ended interviews, was used to allow for statistical analysis in estimating preferences among potential microbicide user groups in the two populations sampled. Respondents were randomly sampled from clinic populations in the Dominican Republic and South Africa. 450 interviews were conducted with selected women in each country. Results of this study will be discussed, including the priorities for applicator design and their implications for microbicide clinical trials and future introduction of microbicide products. Recommendations for appropriate design criteria for applicators used in low-resource settings will also be discussed.

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02638 DISCLOSURE OF STUDY PARTICIPATION AND HIV STATUS AMONG WOMEN IN A MICROBICIDE FEASIBILITY STUDY

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Background: We hypothesize that women who feel unable to tell their partners that they are particpating in a study that involves testing for HIV and other STDs, may experience difficulties in negotiating the use of a microbide gel in a Phase III trial. We consider the advantages of using such factors to identify women who may need additional support during the trial around gel use.

Objectives: To investigate whether women in a microbicide feasibility study, in rural KZN, S. Africa, disclose their study participation and HIV status to partners and family and to explore characteristics of that disclosure. In addition, we will explore demographic and socio-economic data, and data on individual knowledge and awareness of HIV, associated with disclosure.

Methods: Women returning for their follow up visits are interviewed by counsellors about disclosure of their study participation and HIV status using questionnaires. Approximately 10% of the women enrolled are HIV positive. Logistic regression will be used to explore associated factors with disclosure.

Results: Data will be available for 300 women, currently available for 82 women. Preliminary results suggest that after 2 weeks, 15% of HIV negative women had not told anyone they were participating. An additional 27% had not told their partner but had told someone else. Meanwhile, the majority of women choose to disclose their HIV status immediately. HIV negative women are more likely to disclose than positive women, they also tell more people. Of the positive women that have disclosed

(5/9) to date, there were no reports of blame, violence or abandonment, suggesting positive women who choose to disclose seem able to correctly assess suitable confidants.

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02653 ADVOCATING FOR MICROBICIDES IN THE GLOBAL SOUTH: APPROACHES AND METHODS

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As the number of clinical trial sites in the global south increases, the need for advocacy to create awareness about microbicides is becoming ever more important. Advocacy is needed not only to build political support and mobilise resources but also to increase knowledge, support and demand amongst community members and those with influence over policymakers.

International Family Health is working in partnership with the Global Campaign for Microbicides and with a range of other collaborating partners on a microbicides advocacy project aimed at raising awareness of microbicides. The project is funded by the European Union, the Department for International Development and the International Partnership for Microbicides.

This paper compares microbicide advocacy efforts of non-governmental organisations working with International Family Health in different settings in the global south, including South Africa, Thailand and Uganda. Key lessons learnt include the need for a multi-sectoral approach; the need to bridge the gap between civil society and the research community; and, the need to engage different constituencies, including women living with HIV and men, in advocacy efforts. The paper compares the different issues faced in each setting and examines advocacy objectives and strategies, including audiences targeted, messages chosen and materials developed.

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02668 THE PROCESS OF FORMING A COMMUNITY ADVISORY GROUP: EXPERIENCES FROM A FEASIBILITY STUDY IN SOWETO

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Introduction: Community involvement is critical to the success of community-based research projects, and increased community participation is likely to result in improved understanding and informed consent among participants. A specific attention was focused on the process of increasing community participation in a feasibility study in Soweto prior to the introduction of a microbicide trial in 2004.

Key activities: The process involved the description of the community, the identification of key organizations and structures within that community and the formation of a community advisory

group (CAG) which could meet regularly to represent and give and receive feedback from the community on the research processes. In addition, workshops were conducted with a range of community members to provide information about the study, as well as to gain information about the community response to AIDS. Currently the focus is on monitoring community responses to the project.

Outcomes: A CAG of 16 people representing 16 organizations in Soweto meets on a monthly basis to discuss and provide input on the research activities related to the microbicide feasibility study. A total of 10 meetings and 2 1-day workshops have been held. A standard operating procedure was agreed and has since been amended based on input from CAG members. The CAG has provided significant insights into the community attitudes to HIV, sexual practices, the role of men in microbicide research and referral of research participants for HIV care.

Conclusion: The establishment of an identifiable community representative group has been invaluable in the process of the Microbicides feasibility study because it has facilitated interaction with the community on key issues affecting recruitment and retention.

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02669 IS HIV TESTING IN HIV PREVENTION TRIALS ACCEPTABLE? RESULTS FROM A STUDY IN SOWETO

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Introduction: HIV remains a public health priority in South Africa, and interventions to prevent the spread of HIV, particularly in young women, are urgently needed. Microbicides represent one possible option for a female-controlled method of HIV prevention. In order to demonstrate that an intervention is effective in preventing HIV, trials are required to recruit large number of HIV negative participants. There are concerns that the requirement for HIV testing at enrolment may discourage participants from participating in these trials. A feasibility study was conducted among family planning clients in Soweto to determine factors which might influence enrolment in a Phase III clinical trial.

Methods: Socio-demographic and behavioural data was collected during a screening visit conducted in the community to identify persons eligible for HIV testing and subsequent enrolment at the study clinic. This data was analysed to determine particular factors which might be responsible for influencing women's attendance for voluntary counselling and testing at the study clinic. Significant variables associated with willingness to test were combined in a multivariate analysis using logistic regression to identify factors which predict willingness to test for HIV.

Results: Over 1974 participants have been screened to date, 89% of whom were eligible for further screening. Despite concerns that the requirement for HIV testing would be a disincentive for enrolment in trials, 95% of those interviewed said that they were willing to test for HIV. 43% had previously been tested for HIV. The main reason for willingness to test was that participants wanted to know their HIV status (89%) because they felt at risk for HIV (57%). The main reason that participants felt at risk was because they did not use condoms all the time. Most of those that did not want to test (5%) were afraid of the result (68%). Type of housing and having at least one child were associated with a willingness to test for HIV in a multivariate analysis.

Discussion: These results suggest that women are interested in HIV prevention research, and are willing to test for HIV because they consider themselves to be at risk for HIV. Women who have children may be more willing to test because they wish to plan for the future. Type of housing may be an indicator of social stability, hence the finding that those that live in formal housing were more likely to want to test for HIV. However, high risk populations like young women or economically disadvantaged women may be missed by current approaches.

Conclusion: Although HIV testing appears to be widely acceptable to women in Soweto, there may be sub-populations at higher risk for HIV who may be less willing to test for HIV. Alternative recruitment and testing strategies need to be developed to include these higher risk groups.

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02675 HOW RELIABLE DOES SELF-REPORTED SEX BEHAVIOUR NEED TO BE FOR VALID MICROBICIDE EFFICACY ESTIMATION?

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Objective: The primary objective of randomised clinical trials for microbicides is to determine effectiveness of protection against HIV. Observed effectiveness will be a function of several unknown parameters including the biological efficacy, consistency of use (compliance) and possibly epidemiological interaction between HIV and other STIs. If compliance can be accurately determined from sexual behaviour questionnaires, there is an opportunity to estimate biological efficacy. We examine to what extent misreporting in sexual behaviour data can be tolerated in validly estimating microbicide efficacy.

Method: A stochastic mathematical model simulating microbicide clinical trials where biological efficacy, compliance and self-reported behaviours vary is employed. Two types of misreporting are assumed for compliance: random over/under-reporting (type 1) or over-reporting (type 2).

Preliminary Results: If type 1 misreporting is not more than 30%, then efficacy of a microbicide conferring 40% reduction in susceptibility per act can be validly determined, otherwise efficacy is strongly underestimated. The effect of type 2 misreporting at low level is considerably worse than type 1 but equally underestimates at high levels. Further results will seek to quantify a minimum level of questionnaire validity.

Conclusion: If sexual behaviour questionnaires can be developed to provide accurate data on microbicide compliance (as well as condom use, partners, etc), they will enhance ability to estimate product efficacy which, in conjunction with effectiveness estimates, will enhance interpretation of randomised controlled trials

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02688 NIAID TOPICAL MICROBICIDE STRATEGIC PLAN: DISCOVERY, DEVELOPMENT AND EVALUATION

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The long-term goal of the NIAID is to identify safe, effective and acceptable microbicides to prevent HIV/AIDS and other sexually transmitted infections. A five-year strategic plan has been implemented following approval by a Blue Ribbon Panel of extramural scientific experts. The objective of the plan is to support the near-term goal of establishing proof-of-clinical efficacy for at least one microbicide candidate. The plan is configured to simultaneously address, through integrated basic and applied programs and workshops, the scientific challenges that span basic, preclinical, clinical, and behavioral research while providing targeted support to advance the development of priority products of public health import. Preclinical development resources have been established to help address needs in the key areas of in vitro screening, in vivo safety and efficacy testing, chemical synthesis, formulation development, and clinical product manufacture. Project management and regulatory documentation capabilities will be added, upon availability of funds. To assure efficient use of NIAID resources, priorities have been set at specific junctures in the development process. Well-defined in vitro and in vivo criteria serve as the basis for advancement of the most promising candidates into Phase I trials. In addition, considerations for progression of the highest priority candidates into effectiveness trials will be discussed.

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02694 HIV TREATMENTS, MICROBICIDES AND VACCINES: ADVANCING A RIGHTS-BASED AGENDA FOR RESEARCH, DEVELOPMENT AND ACCESS

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Objectives: To engage key advocates from the global HIV treatments, microbicide and vaccine movements in a dialogue regarding joint agendas for action; to resolve challenges and obstacles to collaborative advocacy, and to develop and launch an action plan on priority issues for joint work.

Description: Since 2000 the organization has explored commonalities between HIV vaccine and treatment advocates (and, more recently, microbicides), drawing on international law and the right to health to advance respective agendas. Initiatives have included satellite meetings at international AIDS conferences in Durban (2000) and Barcelona (2002), as well as an international expert meeting on HIV vaccines in Montreal in April 2002. Commonalities include: human rights arguments for assuring developing world access to effective HIV treatments, vaccines and microbicides as they are developed; increasing political will to address the epidemic; assuring increased overall funding; resolving intellectual property issues that may impede private sector investment in treatments and prevention technologies and that may impede access to technologies developed, particularly in developing countries; improved regulatory and approval mechanisms for new treatments and prevention technologies; improving the distribution of and access to medications and existing vaccines; improved community understanding of HIV/AIDS treatments and prevention technologies; and treatments for persons infected in the course of clinical trials.

Results: In November 2003 a research paper which identifies opportunities for collaboration on priority issues was presented at an international expert consultation in Montreal. At this meeting participants prepared a model advocacy action plan with methods and issues for joint work in 2004-2006. In early 2004, the finalized discussion paper and the action plan will be disseminated widely in English, French and Spanish, including to 500 organizations working on related issues in both developed and developing countries.

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02696 PROJECTIONS OF THE RESOURCE REQUIREMENTS FOR PROMOTING AND DISTRIBUTING MICROBICIDES

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Introduction The identification of the resource requirements for microbicides have focused on product development. There is limited discussion on the future resources required to promote and distribute microbicides. For different assumptions about the unit cost of a microbicide, this study estimates the resource requirements associated with adding a microbicide to existing prevention interventions in 73 low and middle-income countries. These are compared with estimates the associated HIV impact and economic benefits of the widespread use a 60% efficacious microbicide

Design Mathematical and economic modeling using demographic, behavioral, epidemiological and economic data.

Methods The analysis builds upon the framework used in the Rockefeller Public Health Impact analysis in 2002. For different assumptions about the unit costs of a microbicide, and estimates of the national level incremental costs of promoting microbicides and incorporating their distribution into existing HIV prevention interventions, estimates of the overall distribution costs of microbicide distribution are obtained. The findings are compared with updated estimates of the projected impact on HIV transmission of the use of a 60% efficacous microbicide by inconsistent and non-condom users and the associated health care costs avoided and productivity savings gained.

Results The analysis is ongoing, and will be completed by January 2004. Key findings will be projections of the future promotion and distribution costs of microbicide and a comparison of the costs and benefits of widespread microbicide distribution.

Conclusion As part of preparations for ensuring widespread microbicide access, it is important that adequate financial resources are committed to microbicide promotion and distribution.

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TRACK A POSTERS

02008 WATER DISPERSIBLE MICROBICIDAL CELLULOSE ACETATE PHTHALATE FILM

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Background: Cellulose acetate phthalate (CAP) has been used for several decades in the pharmaceutical industry for enteric film coating of oral tablets and capsules. Micronized CAP, available commercially as "Aquateric" and containing additional ingredients required for micronization, used for tablet coating from water dispersions, was shown to adsorb and inactivate the human immunodeficiency virus (HIV-1), herpesviruses (HSV) and other sexually transmitted disease (STD) pathogens. A gel formulation of micronized CAP was shown to have potential as a topical microbicide for prevention of STDs including the acquired immunodeficiency syndrome (AIDS). The objective of endeavors described here was to develop a water dispersible CAP film amenable to inexpensive industrial mass production.

Results: The prerequisites for producing CAP films which are soft, flexible and dispersible in water, resulting in smooth gels, are combining CAP with hydroxypropyl cellulose (HPC), and casting from organic solvent mixtures containing ≈50 to ≈65% ethanol (EtOH). The films are ≈100 ? thick and have a textured surface with alternating protrusions and elevations revealed by scanning electron microscopy. The films, before complete conversion into a gel, rapidly inactivated HIV-1 and HSV and reduced the infectivity of non-viral STD pathogens >1,000-fold.

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02114_1 EFFECTS OF CANDIDATE MICROBICIDES PRO2000 AND SAMMA ON DC-SIGN MEDIATED INFECTION OF CD4+ T-CELLS

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Dendritic cell C-type lectins, including DC-SIGN, have been shown to bind to HIV-1 gp120 and play a role in virus transfer to T-cells. Dendritic cells expressing these molecules at mucosal surfaces may play a role in virus transmission. The candidate microbicides, SAMMA and Pro2000 both have been shown to block HIV-1 infection of susceptible CD4+ cells and to bind directly to HIV-1 gp120. We therefore tested the ability of these compounds to block either binding of HIV-1 to DC-SIGN or transfer of the virus from DC-SIGN expressing cells to susceptible T-cells.

METHODS: DC-SIGN expressing THP-1(DC-THP-1) cells were incubated with HIV-1 in the presence or absence of microbicide. After washing, THP-1 cells were co-cultured with susceptible CD4+ T-cells in the presence of absence of the microbicide. Both DC-THP-1 cell and T-cell supernatants were monitored for HIV-1 infection by measuring p24 antigen.

RESULTS: DC-THP-1 cells did not produce significant HIV-1 p24 in the presence or absence of microbicide. However, when the DC-THP-1 cells were then co-cultivated with activated T-cells, significant HIV-1 p24 was detected in the supernatants. Both Pro2000 and SAMMA blocked this production when the compounds were present at the time of the co-cultivation. However, neither

compound blocked the successful transfer of the virus if only present during the initial infection of DC-THP-1 cells.

CONCLUSIONS: The topical microbicides successfully blocked transfer of HIV-1 from DC-SIGN bearing cells to susceptible T-cells however; they did not appear to block the initial binding of the virus to the DC-bearing cell.

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02183 CELLULOSE ACETATE PHTHALATE INHIBITS INFECTION BY CELL-FREE & CELL-ASSOCIATED PRIMARY HIV-1 STRAINS

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Background: Cellulose acetate phthalate is a pharmaceutical excipient with a long history of use in humans as an enteric coating agent, and is produced on an industrial scale. We previously demonstrated that CAP has potent inhibitory activity against infection by several laboratory-adapted HIV-1 strains. In the present study, we evaluated its inhibitory activity on infection of peripheral blood mononuclear cells (PBMCs) and CEMx174 5.25M7 cells by 15 representative primary HIV-1 strains of distinct genotypes (clades A to G and group O) and phenotypes (R5, X4 and R5X4) and on transmission of these primary HIV-1 strains from dendritic cells (DCs) to PBMCs, and from PBMCs to CEMx174 5.25 M7 cells.

Results and conclusions: CAP inhibited infection by all these cell-free HIV-1 strains tested with 50% inhibition concentrations ranging from 2 to 130 µg/ml and also blocked transmission of the cell-associated primary HIV-1 strains from DCs to PBMCs, and from PBMCs to CEMx174 5.25M7 cells. The inhibitory activity of CAP on infection by the cell-free and cell-associated primary HIV-1 strains is independent of virus subtypes and coreceptor usage. These results suggest that CAP is an ideal microbicide candidate, which may be further developed for global application to prevent sexual transmission of HIV-1.

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02202 STRUCTURAL STUDIES OF APTAMERS THAT NEUTRALIZE R5 SRTAIN OF HIV-1

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Human Immunodeficiency Virus 1(HIV-1) has evolved various strategies in response to the current anti-retroviral drugs and the selection pressure of humoral and cellular immunity. In particular, the R5 strains of HIV that is central to Acquired Immune Deficiency Syndrome (AIDS) pathogenesis are resistant to neutralization by antibodies. The recessed nature of the binding pockets on the surface glycoprotein (gp120), masking by hypervariable loops, conformational changes in the core gp120 molecule and a 'glycan shield' mechanism of neutralization escape allow HIV-1 persistence in the face of an evolving antibody repertoire. We hypothesized that RNA aptamers, in contrast to antibodies, by

virtue of their small size and slow dissociation rates, might be able to bind to the occluded neutralization sites on the gp120. Accordingly, using Systematic Evolution of Ligands by EXponential Enrichment (SELEX), we have isolated specific 2'Fluoro-pyrimidine RNA aptamers that bind to monomeric HIV-1BaL gp120 with affinities in the order of 10-9 M. The aptamers not only neutralize HIV-1BaL in human Peripheral Blood Mononuclear Cells (PBMCs) by 1,000- to 100,000-fold but also neutralize clinical isolates from multiple clades efficiently. Secondary structure analysis, in conjunction with ribonuclease footprinting studies, revealed the probable region essential for gp120-binding. Truncating the aptamer to this smaller region retained its binding to monomeric gp120. The binding affinity and the neutralization potency of the truncated aptamer and the parental aptamer have been found to be similar. Further investigation of the structure of the truncated aptamer might lead to alternative anti-HIV-1 drugs and help us understand the molecular interaction between the viral gp120 and host cellular receptors that facilitate HIV-1 entry.

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02225 ANTI-HIV AND OTHER STD PATHOGEN ACTIVITIES OF A COMBINATIONAL MICROBICIDE CANDIDATE, PL40

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Combinational microbicide targets at two or more sites in fighting against HIV-1 infection and is expected to be more powerful than single compound. We designed a combinational microbicide candidate, PL40, which is composed of PS20 and LN43. PS20 with high anti-HIV activity is a plant-derived polysaccharide sulfate, and was reported in the last conference (A017). LN43 is a rare earth compound with small molecular weight. The anti-HIV activity of LN43 was detected by syncytial formation inhibition assay for HIV?B and by p24 ELISA assay for R5 strain (HIVAda-M), and its effective concentration (EC50) was 23.0 mg/ml and 23.8 mg/ml, and its therapeutic index?TI?was 97 and 76, respectively. EC50 of PS20 in anti-HSV activity detected by plaque reduction assay was 68 mg/ml. The minimum inhibition concentration (MIC) of LN43 defined as ≥ 90? inhibition compared to growth control was 1.17 mg/ml for Candida albicans using an improved MTT test. Both compounds had no inhibition activity for either Neisseria gonorrhoeae or Ureaplasma urealyticum. The time-of-addition experiment showed that both compounds may target at early stage (binding/fusion) of HIV-1 replicate cycle. Furthermore, when combined usage of PS20 with LN43 at concentration ratios of 1:1, 1:4 and 1:11 and at ECs50, 70 and 90, their means of anti-HIV-1 combination indeces (CIs) measured using mixed dose effect analyses and the CalcuSyn package were less than 0.5, and the strong synergism was shown.

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02229_1 SEX HORMONE RECEPTOR, ADHESION MOLECULE AND ANTIBODY PRODUCTION IN ANTIBOBY-SECRETING CELLS

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Local immunity in the genital tracts is important in protection from sexually transmitted pathogens, and in immunological fertility regulation. Our previous study showed that sex hormones play an important role in regulation of the migration of circulating antibody-secreting cells to genital tracts. This regulation may be caused by complementary adhesion molecules expressed on the antibody-secreting cells and on the endothelium of venules. To understand the mechanism that sex hormones regulate the migration of antibody-secreting cells to genital tracts and the effect of sex hormones on antibody production in mucosal associated tissues, we selected mouse SG2 and PA4 hybridoma cells respectively secreting IgG2b and polymer IgA, and used RT-PCR for detecting expression of sex hormone receptor and CXCR4 mRNA in the SG2 and PA4 cells. The expression of surface molecular markers was measured by flow cytometry, and antibody production of SG2 and PA4 cells was determined by ELISA. Androgen receptor (AR), estrogen receptor? and CXCR4 mRNA were found in SG2 and PA4 cells, but CD31 were not expressed on these cells. The effects of sex hormones on the expression of surface molecular markers and antibody production in SG2 and PA4 cells were not obviously demonstrated. These results suggest that the adhesion molecules on the antibody-secreting cells are not associated with sex hormone regulation on the migration of these cells to genital tracts. Therefore, the migration regulation by sex hormones is most likely expected to be caused by the addressins on endothelial cells.

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02229_2 SECRETORY COMPONENT IS DISTRIBUTED IN MOUSE PROSTATE EPITHELIA, AND UP-REGULATED BY TESTOSTERONE

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Secretory IgA (sIgA) is composed of polymer IgA (pIgA) and secretory component (SC). Distribution of SC in genital tracts has been widely investigated in many species (such as mouse, rat and human) by several groups. Their different distribution patterns have been observed in various species. Our previous study showed that the transport of sIgA from serum to secretory fluids in prostate glands of mice was up-regulated by testosterone treatment in orchiectomized mice (JI 156:1014, 1996). In order to understand the distribution of SC in male BALB/c mouse genital tract and whether testosterone influences the disribution, the expression of SC in the tract was detected by immunohistochemical technique. The specific distribution of SC was only observed in epithelia of prostate gland, but not in the other tissues of male genital tract. The reduced expression of SC in prostate was found in the orchiectomized mice, and the increased expression of SC was obviously observed in the protates of testosterone-treated mice. The results are consistent with our previous study on pIgA transport in mouse prostate, and suggested that testosterone may up-regulate the expression of SC in mouse prostate gland.

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02230 IN VITRO SAFETY EVALUATION OF A COMBINATIONAL MICROBICIDE CANDIDATE, PL40,

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In order to evaluate the safety of a combinational microbicide candidate, PL40, which is composed of PS 20 and LN 43, their cytotoxicities to human cervical cancer cell lines ME-180 and HeLa, and to primary foreskin keratinocytes (PFK) were detected by MTT assay. The activity of anti-Lactobacillus debrueckii, a member of normal vaginal flora, was measured by microdilution method. Inhibition concentrations (IC50s) of PS20 were 3.2 mg/ml for ME-180, 2 mg/ml for HeLa, 1.5mg/ml for PFK cells, and IC50s of LN43 were 4.6 mM, 4.3 mM and 1.2 mM, respectively. All IC50s are several hundreds times of effective concentrations (EC50s) of both compounds for inhibiting HIV-1 infection. The minimal inhibition concentrations (MICs) of both PS20 and LN43 for Lactobacillus debrueckii were more than 20 mg/ml, and are almost 1000 times of EC50s of the compounds for their anti-HIV-1 activities. These results suggest that the components of PL40 have very low toxicity to cells of human genital tracts as well as to normal bacteria in the above in vitro tests.

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02243 EVALUATION OF ANTIMICROBIAL AND CONTRACEPTIVE ACTIVITIES OF NISIN: IN VITRO AND IN VIVO STUDIES

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A number of vaginal microbicides are currently undergoing preclinical or clinical trials to assess their acceptability, safety and efficacy in protecting women from STI/HIV infections and unintended pregnancies. Since the best known microbicide, Nonoxynol-9 causes vaginal toxicity, a major challenge is to design mechanism based microbicides that are highly effective against infections and unwanted pregnancies while lacking detergent-type effects. Therefore, we evaluated Nisin, a known naturally occuring antimicrobial peptide.

Nisin is a 34 amino acid peptide having a molecular weight of ~3.5 kDa. The peptide is produced by bacteria, Lactococcus lactis and is being used as a food preservative.

Nisin (400 ?g)is found to inhibit sperm motility in a dose and time dependent manner. Intravaginal administration of a single dose of Nisin blocked conception in rats (200 ?g) and rabbits (1 mg/ml). Repeated intravaginal application of Nisin (50 mg/day/14 consecutive days) was found to be safe and did not cause local, systemic or reproductive toxicity. In addition, Nisin inhibits the growth of STI causing pathogens at a concentration of 200 ?g.

In conclusion, under the conditions of its intended to use as a dual function spermicidal microbicide, Nisin has a unique advantage that may greatly enhance its prophylactic capability against conventional STIs.

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02321 A POTENTIAL ANTI-HERPES SIMPLEX VIRUS AGENT FROM A KENYAN MEDICINAL PLANT

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Herpes simplex virus types one and two (HSV-1 and HSV-2) are among the most common opportunistic infections in immunosuppressed persons especially those with HIV/AIDS. The emergence of resistant strains of HSV to drugs and the high cost of these drugs has worsened the situation. There is therefore need to identify new agents that can be developed for the management of HSV infections.

An extract from a Kenyan medicinal plant, *Acacia mellifera* (Vahl)Benth, has showed activity on both wild type and resistant HSV. The extract exhibited *in vitro* anti-HSV activity by plaque reduction assay against wild type strains, 7401H HSV-1 and Ito-1262 HSV-2 with EC_{50} of 100 and 87.1 µg/ml respectively. The extract also showed activity against acyclovir resistant strain, AP^r 7401H HSV-1 with EC_{50} of 130.8 µg/ml. In the *in vivo* studies, the extract exhibited efficacy in Balb/c mice cutaneously infected with a lethal titre of wild type strain 7401H HSV-1. On oral administration of the extract to HSV infected mice, there was delayed onset of skin lesions and progression of infection to zosteriform lesion. Also the mean survival times of the treated animals were prolonged. The detailed results will be presented

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02337 CYTOKINE EXPRESSION IN CERVICOVAGINAL COMPARTMENT OF INDIAN WOMEN

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Genital tract infections as well as asymptomaticidiopathic genital tract inflammation are thought to be major cofactors promoting the sexual transmission of HIV-1. It is largely believed that the inflammation associated with genital tract disease is immunologically mediated. Genital tract infection and the resulting cytokines regulates the recruitment of specific subsets of lymphocytes to distinct parts of genital tract and thereby cytokine secretion by activated T-cells. To evaluate to what extent the female genital tract represents source of these cytokines, we determined by flowcytometry the levels of TNFa, IFN-g, IL-10 and IL-12 concentrations in the cervicovaginal washings of 17 women attending with varied symptoms of genitourinary related illness including complaints of vaginal discharge and attending Gynaecology clinic at Safdarjung Hospital, New Delhi. In our study, we found high levels of IFN-g, in cervico-vaginal lavage, however, other

cytokines (TNFa, IL-10 and IL-12) were in the normal range. Data from this study indicate that soluble mediators of inflammatory and immunological responses are measurable in genital tract secretions and their levels are dynamic. More studies are required to know the detailed cytokine profile in cervico-lavage in symptomatic and asymptomatic patients as high levels of genital tract cytokines may enhance local HIV replications on exposure resulting in increased transmission.

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02343_1 PRECLINICAL EVALUATIONS OF DENDRIMER FORMULATIONS IN THE NONHUMAN PRIMATE MODEL

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In developing dendrimers as pharmaceuticals, Starpharma (Melbourne, Australia) has focused on the prevention of human immunodeficiency virus (HIV) and sexually transmitted infections (STIs) with the development of microbicide candidates. An optimized dendrimer-based microbicide, SPL7013 has emerged as a lead candidate and clinical studies are in progress under an Investigational New Drug application (IND) submitted to the United States Food and Drug Administration (FDA).

Three gel formulations of SPL7013 (1%, 3% and 5% w/w) have been assessed in our nonhuman primate (NHP) model for safety studies with repeated vaginal application. Each product was applied to six animals daily for 4 days. Effects of product use were assessed at baseline and 24-hours after each application by colposcopy, vaginal pH and microbiology measures. Acute shifts in pH and microbiology were also assessed 30-minutes after each product application. Finally, vaginal and cervical biopsies were collected at baseline and 24-hours after the final product application, to determine presence of product-induced inflammatory infiltrate.

The 1% and 3% SPL7013 gel formulations performed similar to placebo gel, for all the parameters assessed and no measures of tissue irritation were noted. Repeated applications of the 5% SPL7013 product did not cause any changes to vaginal flora and no abnormalities were detected in biopsy samples although abnormal colposcopic findings were detected in 4 of 6 animals.

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02343_2 CELLULOSE SULFATE SAFETY AND EFFICACY STUDIES IN THE MACAQUE MODEL

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Cellulose Sulfate (CS) is a high molecular weight polymer being developed as a microbicide and for contraception efficacy. In these studies, CS was tested under a NIH contract for topical microbicide safety and efficacy testing in a macaque model. Safety evaluation included colposcopic, microbiologic, pH and histologic assessments, after each of four daily product applications. CS was shown to have an acceptable safety profile in these studies. No adverse findings were noted after multiple applications, by any parameter tested. A preclinical efficacy study was conducted to evaluate the product's ability to prevent Chlamydia trachomatis (CT) infection. In this study, a single intravaginal application of the topical microbicide is followed (30 minutes) by cervical challenge with CT inoculant. Five of six animals that received CS application 30 minutes prior to chlamydial inoculation tested positive for cervical chlamydial infection during follow up. Three developed circulating IgG antibody against Chlamydia trachomatis. One additional animal had evidence of chlamydial antigen detected in biopsy tissues. All six control animals tested positive for cervical chlamydial infection, two of which developed a short-lived infection. Three control animals developed circulating IgG antibody, two of which also had chlamydial antigen detected in biopsy tissues. The CS was kindly provided by CONRAD.

This work supported by NIH contract N01-AI-95388 and U of WA National Primate Research Center RR-00166.

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02343_3 PRECLINICAL SAFETY EVALUATION OF ACIDFORM IN THE MACAQUE MODEL

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ACIDFORM is an acid-buffering formulation that was evaluated for preclinical safety in NIH-contracted macaque studies as a topical microbicide. In these standardized studies, four daily applications of topical microbicide product are delivered vaginally. Immediately prior to each application, tissues are assessed by colposcopy, microbiology, and pH. Thirty minutes after product application, microbiology and pH are assessed again, to understand product-induced alterations to the cervicovaginal environment present at a potential time of pathogen exposure. Repeat assessments are made 24 hours and three days after the final product application to document recovery. Additionally, vaginal and cervical tissue biopsies collected one day after the final product application are assessed histologically for inflammatory infiltrate.

No abnormal colposcopic observations were noted in any animals. The vaginal microbiology remained largely unchanged throughout the experiment in test and placebo animals. Populations of H2O2-producing lactobacilli and viridans streptococci fluctuated slightly in animals treated with ACIDFORM, though no pattern of product-induced suppression of these organisms emerged. Vaginal pH consistently decreased (in general was measured at 4.0 – 4.5) in all animals at 30 minutes after test gel application. Vaginal and cervical biopsy specimens collected 24 hours after the 4th gel application showed no signs of product induced inflammatory infiltrate. ACIDFORM was kindly provided for testing by CONRAD.

This work supported by NIH contract N01-AI-95388 and U of WA National Primate Research Center RR-00166

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02346_1 THE EVALUATION OF THE LOCAL TOLERANCE OF VAGINAL FORMULATIONS USING THE SLUG MUCOSAL IRRITATION TEST

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Vaginal irritation may be associated with increased susceptibility to sexually transmitted pathogens. Therefore, it is important to evaluate the local tolerance of vaginal formulations. There is a tendency to reduce, refine, and replace the use of vertebrates for pre-clinical safety studies.

In this study the relevance of the slug mucosal irritation test was investigated by means of several vaginal gels. The irritation potency of the gels on the mucosal tissue was assessed by the mucus production caused by a repeated 30-minute treatment on 5 successive days. Additionally, the protein and enzyme release from the mucosa of the slugs was measured after treatment.

The hydroxyethyl cellulose gel induced no irritation as was demonstrated by the low mucus production and protein release and the absence of enzyme release. Replens" and K-Y" jelly resulted in an increased mucus production, however no increased protein and enzyme release were detected. The nonoxynol-9 containing gels Protectaid", Gynol II", Gynol II" Extra Strength, Advantage S", and Conceptrol" caused a higher mucus production and an increased protein release and/or enzyme release, indicating severe irritation. The results were comparable with the findings of other studies for all the formulations except for Protectaid". It can be concluded that the slug mucosal irritation test can be used to evaluate the effects of a repeated treatment with vaginal gels.

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02346_2 EVALUATION OF THE LOCAL TOLERANCE OF VAGINAL FORMULATIONS CONTAINING TMC 120 USING RABBITS AND SLUGS

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Vaginal irritation might increase the susceptibility to sexually transmitted pathogens upon sexual intercourse. Therefore, it is important to evaluate the local tolerance of vaginal formulations. Pre-clinical safety studies are often assessed in rabbits. However, there is a tendency to reduce, refine, and replace the use of vertebrates for this purpose.

In this study the local tolerance of a vehicle gel and 3 gels with different concentrations of TMC120 (obtained from Tibotec) was evaluated with the rabbit vaginal irritation (RVI) test and with an alternative mucosal irritation test using slugs. Conceptrol" was used as positive control. The effect of the gels on the rabbit vaginal mucosa was evaluated after intravaginal treatment for 10 consecutive days by means of microscopical examination of the vagina and cervix. The irritation potency of the gels on the mucosal tissue of the slugs was assessed by the mucus production (caused by a repeated treatment for 5 successive days) and by the protein and enzyme release from the slug mucosa after treatment.

Conceptrol" caused epithelial loss and atrophy in the rabbits and severe irritation of the slug mucosa (increased mucus production, protein release and enzyme release). The vehicle gel and the TMC120 gels induced no epithelial loss and atrophy in the rabbits and also no irritation of the slug mucosa (low mucus production and protein release, no enzyme release). So both the RVI test and the slug mucosal irritation test showed that the vehicle gel and the TMC120 gels are non-irritating gels.

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02349 IS GLYCERIN A NATURAL MICROBICIDE AGAINST HIV IN THE UPPER GASTROINTESTINAL TRACT?

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We studied the natural digestive product, glycerin, for anti-HIV activity. We found that, in vitro, glycerin inactivated HIV production by infected leukocytes, and also inactivated cell-free HIV. Glycerin

inactivated infected leukocytes within five minutes, which resulted in inhibition of infectious HIV production by greater than 25- to 100-fold. Glycerin also rapidly inactivated cell-free HIV by 10- to 30-fold. Glycerin was active at a minimum concentration of 4%. This anti-HIV activity suggests that glycerin, as a product of fat digestion, may play a natural role in vivo as a biological inhibitor of HIV infection of the upper gastrointestinal tract. This protective role of glycerin in the upper gastrointestinal tract may be due to the breakdown of fats into glycerin and fatty acids. The released glycerin may inactivate HIV, thereby contributing to the rarity of HIV transmission in the upper tract. In comparison, HIV transmission in the rectum and lower tract is more common, and might be due to the absence of glycerin in the lower tract, due to the prior absorption of glycerin in the upper tract. Our findings support the possibility that glycerin, as a product of digestion, may contribute to the total anti-HIV activity in the upper gastrointestinal tract.

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02352 THETA-DEFENSINS PROTECT CELLS FROM INFECTION BY HERPES SIMPLEX VIRUS

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Theta (q)) defensins are cyclic octadecapeptides that are encoded by ?-defensin (DEFT) genes. Intact DEFT genes exist in various non-human primates, including Old World monkeys (rhesus and pigtail macaques), lesser apes, and orangutans. Three rhesus ?-defensin peptides (RTD-1, -2, and –3) were purified from the leukocytes and bone marrow of rhesus macaques. However, although the human genome contains at least six different DEFT genes, all of them contain a premature stop codon that stops translation. Thus, ?-defensin peptides are not present in human neutrophils. Retrocyclins 1, -2, and -3 are ?-defensins that could be expressed in human leukocytes if the human DEFT gene sequences lacked the premature stop codon. Previous studies have shown that retrocyclin-1 protected human cells from infection by T and M-tropic strains of HIV-1.

Herpes simplex virus (HSV) is also a sexually-transmitted viral pathogen, and herpes infections may predispose to infection by HIV-1. We tested the ability of 20 synthetic ?-defensins to protect ME-180 cervical epithelial cells from infection by HSV-1 and HSV-2 using an MTT assay. The peptides included RTDs 1-3 and retrocyclins 1-3. We also tested 14 retrocyclin analogs, including the retro, enantio and retroenantio forms of retrocyclin-1. Peptides and viruses were co-incubated for 2 h before being added to target cell monolayers. Cells were then incubated at 37oC. for 72 h and viral infection and cytotoxicity were assessed. To study the mechanisms of retrocyclin action, we examined the binding of retrocyclin-2 to the HSV-2 glycoprotein gB2 in surface plasmon resonance studies. Temperature shift experiments were employed to determine whether q-defensins blocked viral attachment, penetration, and nuclear transport. To delineate the steps inhibited by theta-defensins, synchronized infections were induced and monitored to examine transport of the tegument protein VP 16 to the nucleus or expression of the immediate early gene product, ICP4.

Retrocyclin-2 provided 100% protection from HSV-2 without causing cytotoxicity or requiring pre-incubation with the virus. Retrocyclin-2 additionally blocked viral attachment and markedly diminished HSV-2 nuclear translocation of VP 16 and ICP4 expression. Human ?-defensins HNP 1-3 also protected human cells from HSV-2 but had little effect on binding. Also, retrocyclin-2 bound to immobilized glycoprotein gB2 with high affinity (KD, 13.3 nM) but did not bind to enzymatically deglycosylated gB2. Given its small size (18 residues), minimal cytotoxicity, and effectiveness in

inactivating both HSV-2 and HIV-1, retrocyclin-2 provides an intriguing prototype for topical viral microbicide development.

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02387 EUROPEAN MICROBICIDES PROJECT

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The European Microbicides Project (EMPRO) is a consortium of 35 principal investigators from 29 institutions or SMEs that has been funded by the European Union as part of the Sixth Framework Programme in the area "Confronting the major communicable diseases linked to poverty". The programme aims to develop new topical microbicides, with defined molecular targets, that block entry of HIV at mucosal sites with the aim of establishing a pipeline of candidate microbicides while taking selected microbicides through Phase I clinical trials. Members of the consortium have expertise in analyses and design of molecular structure, investigation of mechanisms of HIV infection at mucosal sites, testing efficacy in animal models, methods for large-scale production of microbicides and the conduct of clinical trials. Novel molecules and combinatorial peptide, polypeptide and oligosaccharide libraries will be screened for inhibitors that are specifically targeted to viral envelope proteins or host receptors. Microbicidal efficacy and effect on normal microbial flora of inhibitors will be tested in vitro. The most promising candidate microbicides will be formulated and tested in animal models. The developmental process for candidate agents will be target-driven according to a preclinical selection algorithm designed to fast track the most promising candidates and/or combination. Emphasis will be placed on development of compounds demonstrating synergistic activity either with others from this programme or with first generation compounds developed by other groups that are further ahead in the developmental process. As well as identifying novel candidate microbicides, the programme should provide a rational basis for the design of 2nd or 3rd generation microbicides.

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02395 CHARACTERIZATION OF AN EX VIVO/IN VITRO INTESTINAL EXPLANT MODEL FOR RECTAL MICROBICIDE DEVELOPMENT.

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Introduction: In vitro models of rectal mucosal HIV-1 transmission are required for the preclinical evaluation of candidate rectal microbicides. Here we describe the use of endoscopic biopsies for this purpose. Methods: Endoscopic biopsies were collected 30cm from the anal margin from three HIV-1 seronegative subjects. Five of the biopsies were immediately processed for histology and flow cytometry and the remaining ten were each set up on Gelfoam rafts. Explants were harvested after 24 hours and one week of culture. Intestinal mononuclear cells were isolated from the remaining four explants by collagenase digestion. Cell viability was assessed using trypan blue exclusion and flow cytometry was performed after staining for CD45, CD3, CD4, and CD8. Trucount beads were used to

quantify individual cell populations. Results: Intestinal biopsies processed immediately had normal morphology. After 24 hours of culture, significant deterioration of the mucosal architecture occurred with subtotal loss of intestinal crypts and epithelial detachment. At one week, stromal elements remained but intestinal crypts were absent. The mean cell viability at baseline was 91% (range 89 – 96), 63% at 24 hours (range 60 – 70) and 36% at 1 week (range 25 – 50). At 24 hours mean CD3+ lymphocyte count was 61% of baseline (range 59 – 63) and 50% of baseline (range 30-70) at 1 week. No preferential loss of CD4/CD8 subsets was seen. Challenge studies at Day 0 with R5 (SF162), X4 (LAV.04) and dual tropic R5/X4 (89.6) HIV-1 variants resulted in productive HIV -1 infection at Day 7 that was evidenced by increasing p24 levels in culture supernatant and by the accumulation of intracellular p24. Conclusions: These data suggest that endoscopic intestinal explants are a useful ex vivo/in vitro model for the evaluation of candidate rectal microbicides.

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02421 MICROBICIDAL DETERGENTS INCREASE HSV SUSCEPTIBILITY IN MICE W/O CAUSING VISIBLE EPITHELIAL DEFECTS

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Background: To block HSV infections, a detergent must be delivered at a concentration that rapidly disrupts epithelial cell membranes, and even at much lower concentrations, detergents still disturb cellular functions. In the mouse rectum, N9 (a nonionic detergent) delivered at a viricidal concentration rapidly injures columnar epithelium cells and later markedly increases rectal susceptibility to HSV (Phillips and Zacharopoulos, Contraception 1998). In the vagina of the mouse, when pre-treated with Depo-Provera to transform the entire epithelium to become columnar, a single application of N9 causes a long-lasting inflammatory response (Milligan et al, STDs, 29:597-605, 2002) and also causes a prolonged and marked increase in susceptibility to HSV (Abusuwwa et al, Microbicides 2002, Antwerp). Here we report tests of four major categories of detergents that are now used as spermicides and/or are being evaluated as microbicides: cationic (benzlkonium chloride), anionic (SDS – sodium dodecyl (lauryl) sulfate), zwitterionic (cetyl betaine; myristyl dimethylamine oxide), and nonionic (nonoxynol-9). Methods: Mice pretreated with DepoProvera were exposed to a single application of the test detergent (2% in PBS). (This concentration was selected since it is the minimal concentration of N9 that provides detectable protection of mice against HSV infection.) Twelve hours after delivering the test detergent, mice were inoculated with a low-dose of virus (0.1 Vaginal Infectious Dose50 of HSV-2). One group of control mice (PBS w/o detergent) was inoculated with this same low-dose inoculum, and another control group with a high-dose inoculum (10 Vaginal Infectious Dose50). Infections were detected 3 days later by culturing vaginal lavage fluid on human foreskin fibroblasts. Results: Every detergent tested to date markedly increased the susceptibility of mice (range:10-30 fold) when challenged 12 hours after one exposure to the detergent. Also, this increased susceptibility occurred without inducing epithelial defects as visualized by colposcopy. Conclusions: A detergent applied only once to a columnar epithelium can cause a prolonged and marked increase in the susceptibility of the epithelium to HSV. Our results suggest that in clinical trials, this toxic effect on columnar epithelium would not be detected by colposcopy.

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02438 DEVELOPMENT OF AN IN VITRO DUAL-CHAMBER MODEL FOR EVALUATION OF CANDIDATE MICROBICIDES

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A dual-chamber system of an endocervical epithelial cell line ME-180 (in the apical chamber) and co-cultures of monocyte-derived dendritic cells (MO-DC)/CD4 T cells (in the basal chamber) was used to model sexual HIV transmission. For microbicide evaluation, a confluent layer of ME-180 cells was cultured in a laminin coated apical chamber, of which the bottom consisted of a microporous membrane (pore size:3 µm). ME-180 cells were pre-treated with compound (1 h). The apical chamber was inserted into the basal chamber and cell-associated HIV-1 Ba-L was added to the apical chamber, which was removed 24 hours later. Cells of the basal chamber were cultured for 14 days, without compound or added cytokines. Culture supernatants were analysed by ELISA for the presence of HIV antigen. Several compounds were evaluated, including non-nucleoside reverse transcriptase inhibitors (NNRTIs) (UC-781, TMC120) and polyanionic entry inhibitors (PRO2000, DS-5000, Cellulose Sulphate). Toxicity of the compounds towards the epithelial layer was analysed both microscopically and by FACS. Infection was prevented with 0.1 µM TMC120 or 1 µM UC-781. Surprisingly, none of the entry inhibitors completely blocked infection at a concentration of 100µg/ml. Cell death was induced above 1 µM TMC120 or 10 µM UC-781. No cell death was induced by the entry inhibitors. However, intercellular contacts between epithelial cells were broken and cells detached from the culture plate after a 24-hours treatment with 250 µg/ml or more of an entry inhibitor . These results indicate NNRTIs might be potent candidate microbicides.

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02439 COMPARISON OF DRUG ABSORPTION FOLLOWING INTRAVAGINAL ADMINISTRATION TO RATS AND RABBITS

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Objective of the study was to compare rabbit and rat as models for evaluation of vaginal uptake and tissue distribution of drugs following intravaginal administration. Radioactive lamivudine (well absorbed orally) and ganciclovir (poorly absorbed orally) were formulated in Replense, administered in 0.5 ml, and animals placed in metabolism cages (n=3/group). Fluids/feces were collected for 48 hrs and tissue content of radioactivity was compared at 4 hrs. Rat tissues were also analyzed at 12 and 48 hrs. Less than 1% of the administered dose of either drug was found in the blood of either species at any time point, although high concentrations found in urine suggests that there was significant systemic uptake. Rats excreted 32% of lamivudine dose in 4 hr, and rabbits excreted 5%. By 48 hr, total amount of radioactivity in urine of rats and rabbits was 45% and 37%, respectively. Percent of dose in feces at 48 hr was 37% for rats and 13% for rabbits. After administration of ganciclovir to rats, 15% of the dose was found in urine and 51% in feces at 48 hr. In rabbits, 9% and 8% were recovered in 48 hr urine and feces, respectively. Less than 5% of total radioactivity from either drug remained in tissues at the end of the study. Rat tissues with the largest fraction of dose were vagina, GI tract, and large organs (muscle and skin). A similar quantity of radioactivity was recovered in most tissues for both drugs. A notable exception was rat vagina, which at 4 hr contained 8-10% of the dose for both drugs, in contrast to rabbit vagina, which contained only 0.1% of the administered dose. No drug was found in rat bladder, although from 13%-19% of total radioactivity was found in rabbit bladder. These

high levels may be due to urethral transit of drug from the vagina into the bladder of rabbits. In summary, significant systemic absorption of both drugs occurs following intravaginal administration. Thus, possible systemic effects may be a concern following intravaginal administration of drugs.

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02442 PMPA- NNRTI COMBINATION STUDIES DEMONSTRATE POTENT SYNERGISM AGAINST HIV-1 INFECTION IN VITRO

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Background: Combination products may maximise microbicide efficacy through: blockade of multiple targets involved in HIV transmission; increased activity through potential synergy; and minimizing potential development of resistance. We have investigated the synergistic potential of PMPA (9-[2-(Phosphonomethoxy)Propyl] Adenine), an acyclic nucleoside phosphonate (NRTI), with non-nucleoside reverse transcriptase inhibitors (NNRTIs) and PRO 2000, a candidate polyanion microbicide.

Methods: Synergistic potential was evaluated in cellular and cervical explant studies. Cells or tissue were treated with each drug alone or in a fixed ratio combination for 1 hour. R5 or X4 HIV-1 isolates were then added and incubated for a further 2 hours with subsequent washing to remove free drug and virus. Viral replication was monitored by measurement of supernatant reverse transcriptase activity (RT), p24 release or quantitative proviral PCR. The 50% inhibitory concentration (IC50) for drugs alone and in combination was determined. Analysis of combined effects was accomplished using the median effect principle developed by Chou and Talalay, (Calcusyn, Biosoft).

Results: PMPA in combination with UC781 demonstrated anti- HIV- 1 synergism with combination indices <1 in RT based assays, while PMPA in combination with PRO 2000 did not. These results have been extended in a cervical explant model to evaluate the efficacy of single and combination drugs against HIV infection and potential dissemination by migratory cells.

Conclusions: PMPA, in combination with candidate NNRTIs demonstrate good anti-HIV-1 activity in vitro and the capability of these drugs to demonstrate synergy is promising. Although PRO 2000 in combination with PMPA might improve the effect of PRO 2000, the combination is not synergistic and would not enhance the efficacy of PMPA.

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02444 MANNOSE-SPECIFIC PLANT LECTINS AS POTENTIAL HIV MICROBICIDES

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A variety of mannose-specific plant lectins selectively inhibit in cell culture the replication of HIV-1 and HIV-2 strains, including virus strains that show resistance to other classes of anti-HIV drugs (EC50: 0.1-1.0 µg/ml). They also prevent syncytium formation between persistently-infected HUT-78/HIV and CEM/HIV cells and uninfected T-lymphocyte cells. Preexposure of the lectins to HIV-1 particles or persistently HIV-infected cells markedly increased the antiviral efficacy of the plant lectins. They interrupt the virus entry process by interfering with the virus envelope glycoprotein gp120. When exposed to escalating plant lectin concentrations, HIV-1 strains with decreased drug sensitivity could be isolated. A variety of amino acid changes were observed at the N-glycosylation sites and/or the serine or threonine residues that are part of the N-glycosylation motif in gp120. The degree of virus-drug resistance correlated with an increasing number of mutated glycosylation sites in gp120. These virus strains kept full sensitivity to other entry inhibitors such as dextran sulphate, bicyclam AMD3100, chicoric acid and enfuvirtide. The plant lectins under investigation were found to be not mitogenic, colorless and stable at lower pH and higher temperature (50°C). In conclusion, the plant lectins represent a well-defined class of anti-HIV drugs with a microbicidal potential and with a novel drug resistance profile different from that of other existing anti-HIV drugs.

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02445 CARRAGUARD PREVENTS MACROPHAGE TRAFFICKING FROM VAGINA - IMPLICATIONS FOR MICROBICIDE DEVELOPMENT

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Considerable evidence suggests that HIV infected macrophages and/or lymphocytes may mediate sexual transmission of HIV. Our laboratory and other laboratories have previously demonstrated that when vitally stained donor mouse lymphocytes or macrophages are placed in the vaginas of mice, some of the stained cells can later be found in the iliac lymph nodes. The aim of this study was to assess the extent of mononuclear cells trafficking from the vagina and to test the possibility that CarraguardTM (PC-515), a vaginal microbicide, would prevent vaginal transmigration of macrophages. When we inoculated mouse mononuclear cells with supravitally stained macrophages; Carraguard TM reduced the number of macrophages in lymph nodes and the spleen by greater than 90%. In contrast, the placebo formulation reduced the number of vitally stained macrophages in the lymph nodes by only 50%. Both formulations were minimally toxic to macrophages over a 4-hour period as compared to no treatment, whereas they were not toxic to human cervical cells. Our findings suggest that CarraguardTM blocks cell trafficking of macrophages from the vaginal vault. Blocking does not appear to result from cytotoxicity. We speculate that blocking cell trafficking may help to prevent sexual transmission of HIV.

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02446 PC-815, A NOVEL COMBINATION MICROBICIDE

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The following is a report on PC-815, a novel microbicide that combines the microbicide Carraguard® and the non-nucleoside reverse transcriptase inhibitor (NNRTI) MIV-150 (Medivir AB). Pre-clinical studies indicate that Carraguard is effective in preventing HIV, SIV, HPV, HSV, and Neisseria gonorrhoea infection in vitro or in animals, and clinical trials show that the formulation is stable, safe, and acceptable in humans. Studies done by Medivir show that MIV-150 is highly efficacious in blocking infection by many HIV strains including strains resistant to other RT inhibitors. Animal studies show that MIV-150 is non-toxic, and clinical trials demonstrate that the compound is well tolerated and not easily systemically absorbed. We present evidence that MIV-150 in Carraguard can neutralize free virus. Strong evidence suggests that PC-815 is more efficacious in blocking infection in lymphoma cells than Carraguard or MIV-150 alone. PC-815 also prevents infection of all clinical isolates of HIV tested in PBMCs. In most cases, PC-815 is an order of magnitude more efficacious than Carraguard. By testing efficacy against HIV in vitro, using HPLC, and measuring the viscosity of the formulation, PC-815 was found to be stable for 3 months at 40OC. PC-815 is, therefore, a promising safe, stable and, efficacious microbicide.

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02451 MIV-150, A POTENT HIV-1 INHIBITOR SUITABLE FOR USE IN MICROBICIDES

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MIV-150 is a non nucleoside reverse transcriptase inhibitor (NNRTI) with a tight binding to HIV reverse transcriptase. This results in an inactivation of free virus particles as well as an inhibition of HIV replication at low nanomolar concentrations. MIV-150 is a more potent inhibitor that sustiva of NNRTI resistant mutants also in the presence of human serum. The rate of in vitro resistance development to MIV-150 is 3 times slower than to sustiva.

MIV-150 has shown a potent activity against SHIV in monkeys and prevented infection when dosed after SHIV inoculation and showed a good profile in preclinical safety and toxicology. A phase I clinical study showed a low oral bioavailability. Taken together these results strongly indicate the use of MIV-150 in a topical microbicide and combination studies with carraguard has shown synergy in vitro.

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02460 UC781 PROTECTS EX VIVO LYMPHOID TISSUE FROM HIV-1 INFECTION.

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Thiocarboxanilide UC781 is a potent non-nucleoside HIV-1 RT inhibitor that is being developed as a microbicide (Biosyn, Huntington Valley, PA). We studied anti-viral activity of this compound against HIV-1 variants of different coreceptor tropisms in human lymphoid tissue ex vivo. This system supports productive HIV-1 infection without exogenous stimulation. UC781 inhibits HIV-1 replication in a dose-dependent manner. If it is present constantly at concentrations of 1 mM, UC781 completely inhibits R5SF162 and X4LAV.04 HIV-1 strains, while 0.1 mM totally inhibits only R5SF162.

To test the potential "memory" effect of the drug on virus replication, human lymphoid tissue was pretreated for 2 h with UC781 (10 mM and 1 mM), thoroughly washed, and than infected with HIV-1 either immediately or after 24 h or 48 h. Viral replication was assessed 10–12 days post-infection. Under these conditions, 10-mM UC781 completely inhibited both R5 and X4 replication. At 1 mM, UC781 inhibited X4 replication (by 50%) only when tissues were inoculated with virus immediately after drug removal; it did not inhibit replication if tissue was inoculated 24–48 h after drug removal. In contrast, R5 replication was inhibited by 95% when tissue was inoculated with virus 24 h after drug removal and by 90% 48 h after drug removal.

Thus, UC781 is a strong inhibitor of HIV-1 replication in human lymphoid tissue ex vivo. Brief treatment of tissues with UC781 renders them resistant to HIV infection even in the absence of this drug. R5 HIV-1, which is known to transmit infection, is more sensitive to UC781 inhibition than is X4.

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02466 OPTIMIZING EXPRESSION OF PROTEIN MICROBICIDES IN LACTOBACILLI: BENEFITS OF GENOMIC SEQUENCING

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Osel is actively pursuing genetic modification of native lactobacilli as a vehicle to deliver protein microbicides to vaginal mucosal membranes as a novel means of impeding the transmission of HIV and STDs. The success of this approach, termed MucoCept, largely depends on whether human vaginal isolates of lactobacilli are amenable to genetic manipulation thereby enabling expression of active virus-binding proteins to intercept infectious viruses at the mucosal surface.

To support the facile genetic manipulation and overcome inefficient heterologous expression in vaginal lactobacilli, the genomic sequence of Lactobacillus jensenii 1153 was determined. Detailed reporter-based analyses of the genomic data containing over 1600 ORFs have identified novel cell wall anchor domains, unique signal sequences, powerful promoter elements, and possible sites for chromosomal integration of heterologous genes. These proprietary native sequences have been used to direct more efficient expression of heterologous proteins, including those anchored

covalently to the cell wall of L. jensenii, such as CD4 and cyanovirin-N. Some of these sequences have also been employed to stabilize heterologous fusion proteins. Furthermore, novel promoter elements have enabled expression of these proteins over a 50-fold range of concentrations. It is anticipated that all of these native regulatory components will be used in our final MucoCept HIV product format.

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02467 A PATHOGENIC CCR5-UTILIZING SHIV162PT CAN IMPROVE MACAQUE MODEL FOR TOPICAL MICROBICIDE EVALUATION

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Improved animal models that have biologic and virologic relevance to human HIV infection would facilitate current research. Rhesus macaques challenged with a chimeric CCR5-utilizing SIV/HIV, SHIV162P3, have been used to evaluate topical microbicides. However, vaginal challenge of pigtailed macaques (Macaca nemestrina; Mne) with SHIV162P3 results in poor infectivity and non-persistent replication. To improve these viral characteristics, we serially passaged SHIV162P3 in four adult female Mne. The first animal (P1) was inoculated intravenously with both cell-free and cell-associated SHIV162P3 grown in Mne PBMCs. Two weeks after inoculation, 10 ml of whole blood from P1 were transferred to a second macaque (P2). This passage schedule was performed consecutively in two additional macaques (P3 and P4). The animals were clinically monitored and lab assays were performed on blood samples. Results indicated that SHIV162P3 evolved during passage to a variant (SHIV162Pt) with increased infectivity and pathogenicity. SHIV162Pt was propagated in macaque PBMCs. Virus from this stock replicates in macaque and human PBMCs and CCR5+ cell lines but does not replicate in CXCR4+ cell lines. Evaluation of this stock in vivo should indicate whether this SHIV can improve the Mne model for topical microbicide evaluation.

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02479 BIOCHEMICAL EVALUATION OF FUNGISTATIC PROPERTIES OF AQUEOUS GARLIC EXTRACT AGAINST HIV1/AIDS CANDIDA ISOLATES FROM NIGERIA

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Candidiasis as a multidrug resistance opportunistic infection in HIV1/AIDS patients has become a global concern and several studies have demonstrated the anticandidal and fungistatic properties of garlic *in vitro* and *in vivo*. However, the mechanisms involved in the growth inhibitory property of this microbicide have not been completely understood.

This study investigated the avirulent properties of aqueous garlic extract (AGE) at fungistatic concentrations (0.75 – 1.5xMIC) and in 1hr human plasma sample following ingestion of 100g of garlic clove homogenate against 25 *Candida* isolates (*Candida albicans* (n = 17); *C.glabrata* (n = 5); *C.krusei* (n = 3) recovered from Nigerian HIV1/AIDS patients with candidiasis.

Compared to control values, spectrophotometric analyses revealed significant decreases ($P<0.05$) in phosphatase activity (26.84 ± 3.3 vs 9.58 ± 1.9^{broth} - 9.22 ± 1.7^{plasma}U/L), extracellular protease activity (43.34 ± 5.4 vs 21.16 ± 2.6^{broth} – 17.28 ± 2.8^{plasma}U/L) and membrane levels of trehalose (3.07 ± 0.2 vs 0.97 ± 0.2^{broth} – 1.05 ± 0.3^{plasma} mM) and ergosterol (12.79 ± 0.5 vs 2.42 ± 0.8^{broth} – 2.96 ± 0.2^{plasma} µg/g) coupled with loss of cell dimorphism in the tested isolates. The observed disparity in mean values of these virulence determinants in broth and plasma was found significant ($P<0.05$) for protease activity only. Multiple regression analyses further showed that these virulence factors were independently reduced by AGE. The results of this study provide a support for the complimentary use of garlic in the management of HIV1/AIDS with candidiasis.

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02499 DIETARY FLAVONOIDS REDUCE THE PRODUCTION OF HERPES SIMPLEX VIRUS (HSV)

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Flavonoids are low molecular weight compounds, which are common plant pigments. Dietary intake of flavonoids is far greater than that of vitamin E and beta-carotene. Flavonoids are also synthesized by plants in response to microbial infection and have been found to inhibit the binding of some viruses to their receptors. The present study was undertaken to determine whether flavonoids could inhibit the production of HSV. Myricetin inhibited the replication of HSV-2 by more than 100-fold at a concentration of 40 µg/ml and by more than 50,000-fold at 80 µg/ml. Interestingly, myricetin can distinguish between HSV-1 and HSV-2 since HSV-1 was not inhibited by this flavonoid. Quercetin also inhibited only HSV-2, which required a concentration of 100 µg/ml to reduce viral replication by more than 500-fold. Flavon did not have activity against either HSV-1 or HSV-2 even at a concentration of 400 µg/ml. These results suggest that it is possible to inhibit specific sexually transmitted viruses using flavonoids. These compounds could be used as one of the active components of a combination microbicide. Studies are currently underway to identify flavonoids, which inhibit HSV-1 and HIV.

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02503 K5 POLYSACCHARIDE DERIVATIVE: POTENTIAL CANDIDATE MICROBICIDE FOR PREVENTION OF HIV-1 INFECTION

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We have previously described that a derivative of Escherichia Coli K5 polysaccharide with high degree of sulfation [K5-N,OS(H)] inhibits HIV-1 attachment and/or entry (AIDS 17, 177-181, 2003). Here we have investigated the potential inhibitory effects of K5-N,OS(H) on the replication of several primary HIV isolates. In addition we have tested the efficacy of K5-N,OS(H) in preventing dendritic cells (DC)-mediated infection of peripheral blood mononuclear cells (PBMC). K5-N,OS(H) potently inhibited the replication of all (30 out of 30) tested primary HIV isolates including 16 R5, 4 X4 and 10 R5X4 viruses in T cell blasts. The 50% inhibitory concentration (IC50) was 2.1± 1.6 µg/ml, without evidence of cytotoxicity even at the maximal concentration tested (100 µg/ml). K5-N,OS(H) (100 µg/ml) abolished R5 HIV replication in either DC cultivated alone or in DC-PBMC co-cultures. X4 HIV replication was only detected in DC-PBMC co-cultures and it was also suppressed by this concentration of K5-N,OS(H).

In conclusion, the K5-N,OS(H) antiviral activity against several primary HIV-1 isolates with different coreceptor usage in both T cell blasts, DC, and DC-mediated PBMC infection coupled with the lack of penetration into cells, render this molecule a potential candidate as a topical microbicide for preventing sexual HIV-1 transmission.

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02507 SAMMA BLOCKS HIV-1 AND HSV-2 INFECTION IN CELLULAR AND HUMAN CERVICAL TISSUE MODELS

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Background
Epidemiological data show that HSV-2 infection of the genital tract is very common among HIV-1 +ve patients and enhances HIV-1 acquisition. Consequently, it is important to develop topical microbicides that block transmission of both viruses. SAMMA (mandelic acid condensation polymer) is a potentially cheap and effective microbicide against HIV-1, HSV-2 and several other STDs. Its precursor, mandelic acid, has a long history of safe usage in humans, having been utilised as a urinary antiseptic. We have investigated the activity of SAMMA against HIV-1(R5 and X4) and HSV-2 using cellular and human cervical explant models.

Methods.
Anti-HIV-1 and anti-HSV-2 activity of SAMMA was evaluated in human cervical explants, human monocyte derived macrophages and other cell lines. Blockade of DC-SIGN mediated HIV-1 infection was investigated using THP-1/DC-SIGN transfectants and biocompatibility was assessed using viability assays and cytokine profiles from mucosal tissue exposed to SAMMA and Nonoxynol-9 as a control.

Results
Our data show that SAMMA potently inhibits HIV-1 activity across a variety of strains both as cell free and cell associated virus. It inhibits trans infection via DC-SIGN in cellular models and, in addition, it shows strong inhibition of HSV-2 infection and good tissue biocompatibility.

Conclusions
SAMMA has shown strong anti-viral activity against both HIV and HSV in cellular, macrophage and cervical explant models and is biocompatible at the concentrations tested. These data along with its established safety record and low manufacture costs make it an ideal candidate for further development as a topical microbicide.

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02509 PREVENTION OF HIV-1 INFECTION BY PLATINUM TRIAZINES

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To explore the functions of a novel class of compounds as anti-HIV agents, we have investigated platinum compounds containing N-donor aromatic ligands, platinum triazines (ptt). From screening of over 50 agents, including the ligands and the metal precursors, we have identified platinum(II)2-pyridyl-1,2,4-triazines derivatives and formulations with these derivatives as having the highest anti-HIV activity. The maximum activity was observed when compounds were added immediately post-infection. However, they were not found to block cell fusion activity of HIV-1 Env proteins in cells bearing CD4X4 or CD4R5 receports, indicating a lack of interaction with the Env protein. The compounds were found to block RT activity of virus particles, and they exhibited low toxicity for human epithelial cells. The results show that these ptt compounds are promising candidates for use as microbicides or antiviral agents against HIV.

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02515 HIGH-EFFICIENT MEMBRANE-ACTING NORBORNENE- AND NORBORNANE-CONTAINING ANTI-HIV MICROBICIDES

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More than 90% of new cases of HIV-infection occur via heterosexual route; as a consequence, HIV-1/2 is quickly spread among women. Because of this, the development of efficient local remedies for prevention of HIV infection is undoubtedly urgent.

As we demonstrated previously (Timofeyev D.I. et al., 2003), membrane-acting compounds based on polycarboxyacilic matrix and norbornene exhibit high anti-HIV activity toward different strains of HIV-1 and in different virus-cell systems at early stages of interaction; because of this, they can be proper candidates for designing a high-efficient microbicide preparation on this basis.

We synthesized a series of compounds of "matrix-norbornene" type differing by matrix structure, hydrophobic-hydrophilic balance of norbornene derivatives, framework structure of membrane-acting modifier, length of spacer groups and stereo isomerism of modifiers (exo/endo versions of norbornene); we evaluated toxicity and antiviral activity of these compounds. Taking into account the above-listed parameters, we chose an optimal chemical structure of the complex compound providing the highest level of anti-HIV efficiency in the in vitro system for the purpose of perspective development of microbicide preparation for local intravaginal application.

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02562 MUCOSAL DELIVERY OF MICROBICIDES BY COMMENSAL BACTERIA: EXPRESSION OF CYANOVIRIN-N IN LACTOBACILLUS

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Vaginal delivery of microbicides can be achieved using recombinant commensal bacteria. Human strains of Lactobacillus engineered to express HIV-inactivating polipeptides such as cyanovirin-N (CV-N) can colonize the vaginal mucosa, releasing locally the recombinant microbicide. We developed a new genetic system for expression of heterologous proteins in Lactobacillus. It is based on construction of transcriptional and translational fusions with fusion partners of lactobacillary origin. The gene fusions are integrated in the bacterial chromosome within a conjugative transposon, and fusion proteins are either secreted or expressed on the bacterial cell surface. Conjugative transposons carrying the recombinant gene can be transferred to the chromosome of different Lactobacillus species.

Previously we obtained a recombinant CV-N expressed in Gram-positive bacteria, which was able to bind gp120 of HIV (Giomarelli et al., AIDS 2002, 16(10):1351-6). In the present work, we also improved the biological activity of the recombinant CV-N, by (i) including a different portion of the fusion partner, and (ii) a linker peptide at the N-terminal end. The new recombinant CV-N showed a gp120-binding activity equivalent to that of native CV-N.

Further developments include testing the in vitro HIV-inactivating capability of CV-N expressed by recombinant Lactobacillus, and microbicidal evaluations of CV-N-producing commensals in animal models.

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02591 TMC120 BLOCKS HIV-1 INFECTION IN CELLULAR AND HUMAN CERVICAL TISSUE MODELS

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Background
TMC120 is a non-nucleoside reverse transcriptase inhibitor (NNRTI) that demonstrates potent anti HIV-1 activity, a good resistance profile and efficacy in the vaginal hu-SCID mouse model of

transmission. To evaluate the potential of this drug as active ingredient in a microbicide formulation, we have investigated TMC120 as a base compound and a formulated hydroxyethyl cellulose (HEC) gel using cellular and human cervical explant models.

Methods
Anti HIV-1 activity of TMC120 was assessed by treatment of virus, T-cell lines, or human cervical explants with either base compound or formulated gel. Results were obtained by p24 ELISA, quantitative PCR or reverse transcriptase assay. The effect of various concentrations of TMC120 on the viability of both vaginal epithelial cell lines and cervical tissue was determined using MTT assay, with Nonoxynol-9 as a control.

Results
TMC120 inhibits HIV-1 infection by X4 and R5 strains of virus in both cell based assays and cervical explant models, including migratory cells emanating from human cervical explants. Furthermore, TMC120 demonstrated significant anti-HIV memory effects, with cervical tissue resisting viral challenge up to 6 days post treatment (2 hours) with TMC120. These studies have been extended to assess the activity of TMC120 against cell-associated virus, and in the presence of semen.

Conclusions
TMC120 demonstrates good anti-viral activity in cellular and cervical explant models, and shows no toxicity at therapeutic levels, making it a good candidate microbicide.

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02594 NEUTRALISING CAPACITY OF TMC120 (DAPIVIRINE) ON A RANGE OF CIRCULATING HIV-1 PRIMARY ISOLATES

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The most ideal microbicidal must be able to neutralise a wide range of circulating HIV-1 subtypes to prevent new infections, especially in the third world. A pre-treatment system previously developed was used to study the neutralising capacity of TMC120 (R147681, dapivirine) and UC781, on Ba-L (NSI/R5) virus and six primary isolates (subtypes A, A/G, B, C and CRF02_AG) mostly from seropositive African individuals. Monocyte derived dendritic cells (MO-DC) and autologous CD4 T cells co-cultures were used as target cells, because they mimic early in vivo targets of the HIV sexual transmission (including interstitial DC and mucosal T cells). Cell-free virus was first immobilised on a poly-l-lysine (PLL) treated 96-well plate and pre-treated with drug for 1 hour. Afterwards, the drug was thoroughly washed away (6X); target cells were added and cultured for 2 weeks. Viral production was measured on supernatant with HIV antigen ELISA. Negative results were confirmed by showing absence of proviral DNA in the cells. TMC120 inhibited replication of Ba-L with an EC50 value of 49nM, it had a more potent inhibition capacity on the primary isolates with an EC50 value ranging from 22nM - <10nM. UC781 inhibited replication of the reference strain Ba-L with an EC50 value of 500nM. EC50 values on the primary isolates ranged from 34nM – 588nM. Both drugs were able to completely prevent HIV infection at 10nM-100nM (TMC120) or 1,000nM-10,000nM (UC781), hence TMC120 is a promising potentially sterilizing microbicide.

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02595 CONTRACEPTIVE ACTION OF CELLULOSE ACETATE PHTHALATE (CAP)

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We previously reported that CAP containing formulations 803-39 and 803-40 at 0.6 gram of formulation/mL semen were able to render human sperm completely immotile, non viable and acrosome reacted. At 0.3 gram/mL, they were also 100% effective in preventing sperm penetration into bovine cervical mucus. Here, we report the preliminary results of our ongoing investigations on the contraceptive action of CAP using a rabbit model. Additionally, we are utilizing electron and confocal microscopy as well as calcium influx to further investigate the nature of CAP impact on sperm. New Zealand albino rabbits were either inseminated using pre-treated sperm (CAP at 0.3-0.6 gram/mL semen) or allowed to mate following intravaginal placement of CAP gel at similar concentrations. No rabbits achieved pregnancies following inseminations with pre-treated sperm. However, intravaginal application of the compounds followed by mating of the does resulted in less than marginal effectiveness (20%, n=5 for each experiment). Multiple mating, dilution with vaginal secretions and difficulty in assessing the volume of semen following natural mating (to adjust for the concentration of intravaginal CAP) were contributory to the marginal in vivo contraceptive performance of CAP. Remedies are currently being implemented/investigated. Irritation of the vaginal epithelium in the rabbits studied was non-significant. Compared to controls and CAP vehicles, CAP formulations induced a significant ($p<0.003$) increase in calcium influx at 0.3 gram formulation/mL semen. Results of complete evaluations (i.e., histological) along with the confocal and electron microscopy studies assessing the impact of CAP on sperm will be presented.

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02598 HUMAN CERVICAL AND COLORECTAL EXPLANTS FOR TOXICITY AND EFFICACY TESTING OF TOPICAL MICROBICIDES

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In this study, we investigated the value of human cervical and colorectal explants in the preclinical assessment of microbicides with anti-HIV activity. Normal tissues were obtained 2-4 hours after surgery. Colorectal explants (placed on gelfoam and embedded in Matrigel) and cervical explants (embedded in 2% agarose) were cultured in transwells with the epithelium oriented on top. After tissue activation, HIV-$1^{Ba\text{-}L}$ with or without product (diluted 1:10) was applied and incubated overnight. Residual virus and microbicide were removed, and the explants were cultured for 2 weeks. HIV replication was determined by p24gag levels in the basolateral medium and by immuno-histochemical (IHC) analysis. Products tested were cellulose acetate phthalate (CAP), Carraguard™, PRO 2000 (0.5% and 4%), K-Y plus nonoxynol-9 (KY-N9), UC781 (0.1% and 1%), and Vena Gel™ along with their placebos. In both models, CAP, 0.5% and 4% PRO 2000, and 0.1% and 1% UC781 blocked HIV infection. IHC analysis demonstrated an absence of $p24^{+}$ cells in cervical explants treated with these products. With the exception of KY-N9 and 4% PRO 2000, histological analysis showed minimal damage to the epithelium and submucosa. The low toxicity and anti-HIV activity of CAP, 0.5% PRO 2000, and 0.1% and 1% UC781 suggest further testing in human trials. These explant models may be useful for preclinical toxicity and efficacy testing of microbicides.

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02600 AN IN VITRO COMPARISON OF TOPICAL MICROBICIDES FOR THE PREVENTION OF HIV TRANSMISSION

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A standardized protocol was used to compare cellular toxicities and anti-HIV activities of candidate microbicides that are formulated for human use. The microbicides evaluated were cellulose acetate phthalate (CAP), CarraguardTM, K-Y plus nonoxynol-9 (KY-N9), PRO 2000 (0.5% and 4%), UC781 (0.1% and 1%), and Vena GelTM along with their accompanying placebos. Products were evaluated for toxicity on cervical and colorectal epithelial cell lines, peripheral blood mononuclear cells (PBMCs), and macrophages (M?) using an ATP release assay. Additionally, they were tested for their effect on a polarized epithelial monolayer (trans-epithelial resistance; TER). Anti-HIV activity was evaluated by blocking transfer of infectious HIV from epithelial cells to activated PBMCs and blocking PBMC and M? infection. CAP, CarraguardTM, PRO 2000, and UC781 along with their placebos were 20- to 50-fold less toxic than KY-N9 and Vena GelTM. At their nontoxic concentrations, none of the products disrupted the TER. Exposure of the epithelial cell lines to HIV-1Ba-L with all products but KY-N9 and Vena GelTM blocked the transfer of virus to PBMCs. Likewise, all products with the exception of KY-N9 and Vena GelTM inhibited PBMC and M? infection with laboratory-adapted HIV-1(Ba-L and LAI) strains. These results indicate that a comparison of candidate microbicides using this protocol may predict their effect on tissues and anti-HIV activity and may help to determine which product(s) to advance to clinical trials. However, the model still needs to be validated against results from human trials.

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02605 SULFATED POLYMERS TARGET HSV GLYCOPROTEIN B, PREVENT VIRAL BINDING, ENTRY, AND CELL-TO-CELL SPREAD AND MAY IMPACT MUCOSAL IMMUNITY

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The observation that herpes simplex virus (HSV) and human immunodeficiency virus (HIV) bind heparan sulfate provided the rationale for development of sulfated or sulfonated polymers (SP) as topical agents. Although several have advanced to clinical trials, the mechanism of anti-viral activity and effects on soluble mediators of inflammation have not been evaluated. These studies address these gaps. Results indicate that PRO 2000, polystyrene sulfonate, cellulose sulfate, polymethylenehydroquinone sulfonate, and a mandelic acid condensation polymer designated SAMMA, which has no surfactant properties and does not contain sulfur, inhibit HSV infection 10,000 fold and are active against clinical isolates including an acyclovir resistant variant. The compounds form stable complexes with glycoprotein B and inhibit viral binding, entry, and cell-to-cell spread. The

effects may be long lasting due to the high affinity and stability of the SP-viral complex, evidenced by surface plasmon resonance studies. The microbicides retain anti-viral activity in the presence of cervical secretions and over a broad pH range. There is little reduction in cell viability following repeated exposure of human endocervical cells to SP, although a reduction in secretory leukocyte protease inhibitor (SLPI) levels was observed. Prior to the initiation of large-scale clinical trials, rigorous evaluation of topical microbicides should include a thorough investigation of the changes in inflammatory cells, cytokines, and effects on host defenses following repeated application.

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02610_1 WHI-07 PREVENTS VAGINAL AND RECTAL TRANSMISSION OF FELINE IMMUNODEFICIENCY VIRUS INFECTION IN CATS

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WHI-07 [5-bromo-6-methoxy-5,6-dihydro-3'-azidothymidine-5'-(p-bromophenyl)-methoxy alaninyl phosphate] is a novel nontoxic dual-function aryl phosphate derivative of zidovudine (ZDV/AZT) with potent anti-HIV and contraceptive activities. WHI-07 was active against the feline immunodeficiency virus (FIV). This study evaluated whether topical application of WHI-07 as a single agent and in combination with an organometallic vanadium complex, vanadocene dithiocarbamate (VDDTC) via a nontoxic gel-microemulsion can block vaginal as well as rectal transmission of feline AIDS (FAIDS) by chronically FIV-infected feline T cells in the natural host model. Genital transmission of FIV was monitored in recipient cats by the appearance of viral antibodies to FIV gag proteins and by virus isolation of blood leukocytes measured by FIV reverse transcriptase activity and FIV-specific polymerase chain reaction. Microbicide activity was considered effective when the treated cats did not show evidence of FIV infection for up to 18 weeks post challenge. An aggregate analysis of 46 specific pathogen-free cats revealed that a single dose of the infected cell inoculum efficiently transmitted FIV infection when delivered into the vagina (100%) or rectum (66%). Pretreatment of the vagina or rectum with 2% WHI-07 alone or in combination with 0.25% vanadocene dithiocarbamate (VDDTC) significantly (P = 0.004) protected cats from genital transmission by the highly infectious inoculum (7 million FIV-infected feline T cells). Collectively, using the vaginal and rectal transmucosal model for FAIDS, our studies demonstrated that WHI-07 either alone or in combination with a vanadocene has clinical potential for the development of a contraceptive anti-HIV microbicide for sexually active women. Supported by: NIH grants HD 37357, HD 42884, HD 42889 and amfAR grant 02667.

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02610_2 STAMPIDINE IS A POTENTIAL NONCONTRACEPTIVE BROAD-SPECTRUM ANTI-HIV MICROBICIDE

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Stampidine [2',3'-didehydro-2',3'-dideoxythymidine 5'-[p-bromophenyl methoxyalaninyl phosphate], a novel aryl phosphate derivative of stavudine (STV/d4T) is a potent broad-spectrum anti-HIV agent with potential as a new class of noncontraceptive microbicide. Stampidine was 100-fold more potent than STV/d4T against clinical HIV-1 isolates of non-B envelope subtypes (A, C, F and G). Stampidine inhibited the in vitro replication of 20 genotypically and phenotypically nucleoside analog reverse transcriptase inhibitor (NRTI)-resistant and 6 non-nucleoside-resistant HIV-1 isolates at nanomolar concentrations. Stampidine exhibited potent in vivo anti-HIV activity in Hu-PBL-SCID mice against a NRTI-resistant clinical HIV-1 isolate and dose-dependent antiretroviral effect in chronically feline immunodeficiency virus-infected cats. Stampidine was non toxic even at cumulative dose levels as high as 8.4 g/kg and exhibited favorable pharmacokinetics in mice, rats, dogs, and cats. We investigated the potential utility of stampidine as a noncontraceptive microbicide for prevention of sexual transmission of HIV via semen. Exposure of human semen to stampidine, even at a concentration 106-times higher than its in vitro anti-HIV-1 activity had no effect on sperm functions or the viability of genital tract epithelial cells. In the rabbit model, reproductive indices were not affected by pretreatment of rabbit semen with stampidine prior to artificial insemination and gel formulations of stampidine did not induce mucosal toxicity. These attributes are particularly useful for the clinical development of stampidine (i) as a noncontraceptive anti-HIV microbicide and; (ii) as a prophylactic antiviral agent to curb the transmission of HIV via semen.

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02611_1 THE DEVELOPMENT OF A CYNOMOLOGOUS MACAQUE MODEL TO EVALUATE CANDIDATE VAGINAL MICROBICIDES

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The cynomologous macaque primate model is a useful animal model for assessing the safety and efficacy of candidate vaginal microbicides. A comprehensive toxicity examination following compound application is currently in progress using the candidate microbicide -2 RANTES. The impact of microbicide exposure to the cervicovaginal mucosa was determined by colposcopic evaluations for evidence of gross tissue irritation and by examination of cervicovaginal biopsies for disruption and inflammation of the mucosal epithelium. Cervicovaginal lavage fluid was collected to determine pH changes, fluctuations in chemokine expression profiles and quantitation of specific immune cells types following microbicide treatment. Cervicovaginal swabs were collected for cytology studies and to assess changes within the vaginal microflora following compound exposure. In addition, formulation design can be optimized in this model with respect to variables such as distribution and absorption. Vaginal challenge studies in cynomologous macaques are essential to determine the efficacy of candidate microbicides in the prevention of viral transmission. Studies examining the efficacy of –2 RANTES in preventing infection by SHIV-BaL are currently in progress. Overall, the cynomologous macaque primate model provides critical safety and efficacy data to evaluate candidate vaginal microbicides.

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02611_2 PRECLINICAL EVALUATION OF CANDIDATE VAGINAL MICROBICIDE -2 RANTES

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The development of topically-applied, female-controlled, vaginal microbicides for the prevention of HIV-1 sexual transmission has gained support as an alternative strategy for women to protect themselves against viral infection. The ideal microbicide would have substantial activity against HIV-1, while possessing no or minimal toxicity. Inhibiting HIV-1 entry can be achieved with CCR5-targeted ligands. In this study, we examine the synthetic -2 isoform of RANTES, a natural and selective CCR5 ligand, as a candidate microbicide for the prevention of HIV-1 sexual transmission. MTS cytotoxicity assays demonstrated that levels up to 1 mg/mL of –2 RANTES were non-toxic to HeLa cell cultures following short-term (30 minutes) and long-term (24 hours) exposures. Preclinical toxicity profiles were examined in vivo utilizing the murine Swiss Webster vaginal model and the New Zealand white rabbit vaginal irritation model. These studies measured cervicovaginal tissue integrity and inflammation following exposure to –2 RANTES formulations. The formulation vehicles, Novasomes, 7474, a non-phospholipid liposome, K-Y Jelly, a commonly used vaginal lubricant, and hydroxymethyl cellulose, have been demonstrated as safe for vaginal application. Formulations with 1 mg/mL of –2 RANTES have exhibited minimal toxicity to the mucosal epithelium following short-term (10 minutes) and long-term (24 hours) exposure with single and multiple applications. Overall, these preclinical studies suggest that –2 RANTES has an excellent safety profile for use as an anti-HIV-1 microbicide.

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02612 PRODUCTION OF A RECOMBINANT HUMAN ANTI-SPERM ANTIBODY, RASA: IMPLICATIONS AS A SPERMICIDAL AGENT

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Nonoxynol-9 (N-9), the most widely used spermicide, has recently been shown to offer no protection against HIV/STI transmission and, in fact, increase the risk of infection when used frequently. As an alternative to N-9, a mouse monoclonal antibody, S19, which agglutinates sperm and exhibits significant contraceptive effects in laboratory tests, has been identified. A second generation of S19 was made as a single chain variable region antibody (ScFv) called RASA (Recombinant Anti-Sperm Antibody). To develop RASA into a spermicidal candidate, two objectives must be achieved: 1) establish a large-scale expression system; and 2) humanize RASA to prevent human anti-mouse antibody (HAMA) responses. Various expression systems for large-scale production were tested, including E. coli (bacteria), P. pastoris (yeast), N. tabacum (tobacco), and a cell-free system (Roche). Both yeast and tobacco systems produced reasonable yields of soluble protein and proteins were easily extractable. Indirect immunoflourescence staining showed that RASA expressed in tobacco bound to human sperm in a manner similar to S19. Additionally, RASA was humanized by site-directed mutagenesis of amino acids in the variable region framework to resemble those found in human IgG using overlap extension PCR. Humanized RASA will be expressed in yeast/tobacco systems and evaluated for sperm agglutinat-ing abilities. Conceivably, RASA can replace spermicides like N-9 to reduce the incidence of HIV/STI transmission to women who are already at high risk and be combined with microbicidal agents provid-ing dual protection to women wishing to protect themselves against disease and unplanned pregnancy.

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02616 INTRAVAGINAL PSC-RANTES PROTECTS AGAINST VAGINAL TRANSMISSION OF SHIV-162P TO MACAQUE MONKEYS

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We are currently developing microbicides that may block HIV-1 infection by binding to receptors on susceptible cells and interfere with HIV attachment and/or fusion on mucosal surfaces. Since HIV-1 utilizes one or more chemokine receptors for attachment, we are testing the potential for RANTES analogs to block HIV-1 transmission in rhesus macaques. We have developed an amino-terminus modified RANTES analog called PSC RANTES that is several orders of magnitude more potent than native RANTES for inhibition of HIV replication. To assess its efficacy as a microbicide, Depo-provera treated macaques were intravaginally administered 4 ml of PSC RANTES diluted in saline at concentrations of 1 mM (n=5), 330 uM (n=5), 100 uM (n=5), or 1-10 uM (n=5). Five received saline alone as controls. 15 minutes after dosing, animals were intravaginally exposed to 300 TCID50 of the CCR5-using SHIV162P3. Viral loads in plasma were monitored weekly by RT-PCR. All five macaques treated with the highest dose (1 mM), 4/5 treated with 330 uM dose and 3/5 treated with 100uM dose of PSC RANTES were completely protected against vaginal transmission, as evidenced by undetectable virus in plasma. In contrast, 11/15 macaques in the low-dose groups or control group became infected. These results clearly demonstrate that PSC RANTES provides complete protection against vaginal transmission of a CCR5-utilizing SHIV. Since CCR5- utilizing strains predominate in early mucosal transmission, these findings suggest that this may be an effective strategy for preventing mucosal HIV-1 transmission.

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02619 CICLOPIROXOLAMINE: A MARKETED VAGINAL PRODUCT WITH POTENTIAL AS A MICROBICIDE

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To move the development of microbicides forward rapidly in India, where AIDS and other STDs are a serious problem, 2,200 marketed topical products from that country were reviewed and 50 pharmaceutical ingredients or formulations were tested for anti-HIV and cytotoxic activity. Those selected were evaluated for their gonococcal, chlamydial, lactobacillus, and sperm inhibitory properties, and the best products for their safety in the rabbit vaginal irritation (RVI) assay. Ciclopiroxolamine (CO) was one agent with desirable properties. It inhibits HIV-1 (IC50 = ~1 mg/ml), gonococci (IC50 = 1 mg/ml), chlamydia (IC50 = 1.6 mg/ml), has broad spectrum antibacterial and antifungal activity, and is minimally spermicidal. A RVI study with a marketed vaginal CO (1%) formulation confirmed the vaginal safety reported previously in the rat, rabbit, dog, and human. According to the literature, CO penetrates the vaginal wall but is minimally absorbed into the systemic circulation; has an excellent safety profile; and is not mutagenic, genotoxic, teratogenic, or carcinogenic. CO is widely marketed as a vaginal and cutaneous antifungal agent, and GMP-manufactured product can be purchased at reasonable cost. Its antibacterial and anti-inflammatory properties may help prevent bacterial vaginosis and maintain vaginal health. Development of CO for vaginal prophylactic purposes will be initiated in collaboration with the Indian drug industry.

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02620 COMPARISON OF THE IN VITRO ACTIVITY OF MARKETED INDIAN PRODUCTS AND NONOXYNOL-9 AGAINST VAGINAL LACTOBACCILLUS

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In a search for marketed Indian products with anti-HIV activity, a number of formulations were identified. Their effect on lactobacilli was compared to that of N-9, using 9 H2O2- producing vaginal strains (L. jensenii [2], L. gasseri [3], L. acidophilus-crispatus [2], L. salivarius [2]) in the agar dilution (AD) and macro-broth dilution (MBD), and a time-kill (TK) assay to determine survival time. Brucella agar (SBA) or broth supplemented with 5% lysed sheep blood, vit K and hemin (SBB) was used for most tests. The TK study was done at pH 4.7 and 6.0, and the AD study at pH 4.8 and 7.2. MICs for N-9 by AD ranged from 0.04% to 10% at pH 7.2, but were typically reduced by one fourfold dilution at pH 4.8. The MBD tests yielded similar results with MICs of 2% to 10%. In the TK study in SBB, 8 of 9 strains survived at least 7 hours in 10% N-9. A solution of 10% N-9 in PBS at pH 4.7 was cidal for 4 strains within 1 hour, but all survived for >7 hours in 2% N-9. The results at pH 6.0 were very similar. Inhibitory activity of N-9 was strain dependent. In the TK assay (for those formulations difficult to dissolve), the skin products, Amrut Malham (Amrut Pharm) and Dermal (Amrutanjan), at 1%, showed inhibition but Pama Malham (Amrut Pharm; 1%) and Moiste (Genix Pharm; 10%), did not. In the MBD assay, the skin products, Emolene (Fulford India), and the vaginal products, Fain gel (Elder Pharm), and V-gel (Himalaya Drug) had no effect at 10%.

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02625_1 STUDY OF GANODERMA LUCIDUM POLYSACCHARIDE ON EFFECTS OF CELLULAR IMMUNE FUNCTION IN MICE

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To study the effects of Ganoderma lucidum polysaccharide (GLB7) on cellular immune function in mice. The experimented mice are divided into four groups, which are poured into GLB7 of different dosage (high, medium, low) through stomach respectively for 14 days. Every day they are poured once. In the contrasted group of mice, distilled water is used instead of GLB7. On the 15th and 28th days, both of them will examine in cellular immune function in mice. Two weeks after GLB7 is used. The lymphocytes transformation test of mouse spleen cell and murine celiac macrophage ability of engulfing CRBC in high?medium?low dosage treatment; murine delayed type hypersensitivity ability and murine macrophage engulfing carbon granula ability in low dosage treatment; the splenic natural killer cell activity of the mice in high dosage treatment were significantly higher than that of the contrasted group ($p<0.05$). Four weeks after GLB7 is used: The experimented result has no significant changes ($P>0.05$); this result indicated the GLB7 might enhance no specific and specific cellular immune function.

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02626 PREFORMULATION EVALUATION OF UC-781, A POTENTIAL ANTI-HIV TOPICAL MICROBICIDE CANDIDATE

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UC781 is a tight binding non-nucleoside reverse transcriptase inhibitor (NNRTI) exhibiting excellent activity against HIV. Due to its ability to bind tightly to target enzymes and efficiency at inactivating HIV at the virion level, it is now being considered for use in a vaginal microbicide formulation to prevent HIV infection. Present work reports the preformulation studies conducted on UC781. Stability of UC781 was evaluated using stress stability studies in which the compound was exposed to accelerated conditions of temperature, humidity, light, oxidation, and hydrolysis. UC781 was prone to oxidation and to some extent photolysis and hence needs to be protected from light and oxygen during formulation development. Given the hydrophobic nature of this compound, solubility of UC781 was determined for a number of solubilizing agents. Acute tissue toxicity was evaluated for UC781/solvent combinations. Enhancement of UC781 solubility was achieved and permeability studies conducted in human cervical tissues. Permeability of UC781 through human cervical tissue was examined using three different solvent combinations (Transcutol, Cremophor+PEG+PBS, and Cremophor +PBS) in the Franz cell system. No significant diffusion of UC781 to the receptor compartment was observed with the assay used. Although no UC781 was detected in the receptor compartment after 8 hours, mass balance calculations suggested that UC781 might be absorbed into the tissue. An HPLC assay with greater sensitivity is currently being developed to quantify UC781 at lower concentrations. Once this assay is validated permeability studies will be repeated.

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02627_1 SAMMA, A NOVEL CONTRACEPTIVE MICROBICIDE, INDUCES CGMP-DEPENDENT INDUCTION OF ACROSOMAL LOSS

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SAMMA, a low molecular weight non-sulfonated oligomer, is of interest as a contraceptive microbicide because it is structurally dissimilar to sulfonated high molecular weight polymers currently in development. Understanding SAMMA-activated signal transduction pathways common to sperm and sexually transmitted microbes may lead to a more efficacious product. The present study examined the roles of several protein kinases in SAMMA-induced acrosomal loss (SAL) in human sperm. Neither 25 µg/mL genistein (protein tyrosine kinase inhibitor) nor 0.5 µM KT5720 (cAMP-dependent protein kinase inhibitor) affects SAL. However, 0.5 µM calphostin (Ca2+ - phospholipid- dependent kinase (PKC) inhibitor) inhibits SAL by 94%. Without added Ca2+, soluble guanylate cyclase activation and AL by 20 µM nitroprusside (produces nitric oxide) is unaffected by 2 µM KT5823, a cGMP-dependent protein kinase (PKG) inhibitor. With added Ca2+, KT5823 by itself induces 66% maximal AL, and inhibits SAL by approximately 82%. Further, 0.5 µM S-methyl-L-thiocitrulline (nitric oxide synthase inhibitor) has no effect on SAL. These data suggest that SAL is mediated by PKG, in turn activated by cGMP, likely produced by a receptor-linked guanylate cyclase. Although nitric oxide increases cGMP and causes AL in human sperm, it is not likely involved in SAL. PKC may be involved in SAL, but it isn't clear if activation of PKC is due to upstream activation of phospholipase C (PLC). Our studies suggest that one of the co-products of PLC-g action (inositol trisphosphate; IP3) has little, if any involvement. This is in contrast to suggested action of IP3 in AL induced by physiological stimuli, such as oocyte zona pellucida protein (Mol Human Reprod 3: 195,

1997). The relation between PKG and PKC as mediators of SAL remains to be determined. Supported by NIH grants HD41763 and AI37940

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02627_2 T-TYPE CA 2+ CHANNELS MEDIATE SAMMA-INDUCED HUMAN ACROSOMAL LOSS

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Work is ongoing to understand the actions of the contraceptive microbicide, SAMMA, a novel low molecular weight carboxylated oligomer. Past work suggested that SAMMA induces acrosomal loss (AL) in human sperm by activating voltage-dependent Ca2+ channels, though probably not L-type. The present study extended observations with Ca2+ channel antagonists and examined selected Ca2+-dependent pathways. Thapsigargin (THG; releases intracellular Ca2+ stores) also induces AL; 1 µM THG causes a 93% (90% confidence limits = 84.0-98.5%) maximal AL; 10 µM nifedipine inhibits this response by 68%. 2-aminoethoxydiphenylborate (2-APB) prevents inositol triphosphate-mediated release of intracellular Ca2+. Consistent with inhibition by nifedipine of THG-induced AL and its failure to block SAMMA-induced AL, 2-APB is without effect. Diphenylhydantoin, a T-type Ca2+ channel blocker, inhibits SAMMA-induced AL (IC50 - 200 µM). Neither trifluoperazine nor calmodulin binding domain affect SAMMA-induced AL, arguing against a role of Ca 2+ /calmodulin-dependent protein kinase II (CaMKII). The data suggest that Ca2+ entry, via either L- or T-type calcium channels, causes AL. CaMKII, involved in AL caused by sustained increases in intracellular Ca2+ (Fert. Steril. (Progr Suppl): S181, 1992), isn't important in SAMMA-induced AL. The oocyte zona pellucida (natural AL stimulus) may cause Ca2+ entry through L-type channels, activation of which are triggered by release of intracellular Ca2+ stores (Mol. Hum. Reprod. 3: 195, 1997.). Similar signalling may accompany epithelial cell infection by HSV (J Cell Biol 163: 283, 2003). SAMMA may be contraceptive and microbicidal by altering the normal Ca2+ responses to viral and sperm entry into target cells. Supported by NIH grants HD41763 and AI37940.

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02629_1 DEVELOPMENT OF ACID-BUFFERING FILMS AS NOVEL MICROBICIDE: COMPARATIVE EVALUATION WITH ACIDFORM GEL

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Maintenance of acidic environment in presence of infections and after intercourse may be an effective mechanism for microbicides. ACIDFORM and BufferGel act by this mechanism and are in advanced stages of clinical development. Solid unit dose formulations such as tablets and films are more preferred due to user convenience and higher stability as compared to gels. The present paper reports acid-buffering vaginal films as novel microbicide with performance characteristics similar to ACIDFORM gel. All ingredients used are either GRAS-listed or reported for vaginal use. Films of 2.5¥2.5 inch2 were prepared using glass casting technique. Dissolution time, pH, osmolality of film were

evaluated in normal saline (10 ml) at 37oC. Buffering capacity of film was determined by titrating with standard alkali (1N NaOH) and human semen samples. Bioadhesive properties and tensile strength of film were evaluated using a texture analyzer. Films dissolved in 3 minutes, yielding a smooth dispersion with osmotic pressure of 540 mosmol/kg (for 5% w/w gel, 390 mosmol/kg). 1.23 meq of NaOH and 6 ml of semen was required to raise the pH of film from 3.52-4.98 as compared to 1.32 and 7 ml for 4 g of gel. Bioadhesive strength of film (sheep vagina model) was higher (21.3 g) as compared to gel (16.1 g). Tensile strength of film (22 g) was similar to vaginal film, VCF" (25 g). In conclusion, acid-buffering films were found to possess similar performance characteristics as that of ACIDFORM gel.

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02629_2 DEVELOPMENT OF RAPIDLY DISINTEGRATING BIOADHESIVE VAGINAL TABLETS OF CELLULOSE SULFATE (CS)

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CS gel is currently being developed as a microbicide. Considering the region specific needs, climatic and socio-economic conditions of India and other tropical countries, novel vaginal tablets of CS were developed. Tablets containing 200 mg of CS per unit and GRAS listed excipients were formulated, which disintegrated in less than 30 seconds in 10 ml of fluids and formed smooth, homogenous, viscous and bioadhesive dispersion that is likely to be retained in vaginal cavity for prolonged intervals. Developing a rapidly disintegrating bioadhesive tablet was highly challenging, since these two properties normally act against each other. At accelerated stability conditions (40∞ C/75% RH) recommended by ICH for Zone IV countries, tablets were found to be stable for a period of three months and the process of preparation of tablets was amenable for large scale production.

Formulation of CS into tablets did not have any adverse effect on its activities and safety profile. Inhibition of sperm enzyme and sexually transmitted pathogens (HIV, HSV, Chlamydia) caused by tablets was comparable to that of CS. Further, the absence of cytotoxicity and Lactobacillus inhibition demonstrated the potential of CS tablets as safe and effective vaginal microbicide. These can be taken up for clinical studies after necessary toxicololgical studies and regulatory approvals.

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02639_1 PRECLINICAL EVALUATION OF LEAD CANDIDATE POLYANIONIC MICROBICIDES

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Background: With 5 million new cases of HIV-1 in 2002, there is an urgent need for strategies to reduce its transmission. The potential of microbicides to reduce transmission across mucosal surfaces has been clearly identified, and some agents are currently under evaluation in clinical trials. Many of these "first generation" microbicides consist of polyanionic compounds. We have evaluated a panel of

polyanions, including PRO 2000 and dextrin sulphate, to determine their mechanism of action and efficacy in different model systems.

Methods: In vitro activity of compounds was determined using both cell-based assays and an established ex-vivo, human cervical explant model.

Results: Pretreatment of viral strains prior to culture with permissive cells demonstrated differential activity, with compounds being more active against an X4 (HIV-1 RF) than an R5 (HIV-1 BaL) strain. While compounds showed little or no prevention of viral binding to THP-1 DC-SIGN+ cells, the transfer of bound virus to permissive cells was inhibited, with a higher concentration of compound necessary to block transfer of the R5 strain compared to the X4 strain. The presence of test compound during viral exposure demonstrated highly potent activity directed towards both viral phenotypes, with some differential activity also observed. Additionally, the infection of cervical explants with HIV-1 BaL was significantly inhibited when exposure occurred in the presence of compound.

Discussion: Polyanion compounds such as PRO 2000 and dextrin sulphate demonstrate highly potent activity against HIV-1 when present during viral exposure and thus show promise as candidate microbicides about to enter Phase III clinical trials.

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02639_2 THE EVALUATION OF MICROBICIDES TO PREVENT HIV-1 INFECTION OF HUMAN COLO-RECTAL TISSUE EXPLANTS

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Background: With 42 million people now living with HIV-1/AIDS, suitable strategies for the prevention of HIV transmission need to be developed. The potential of microbicides to reduce transmission across mucosal surfaces has been clearly identified. The development of microbicides for vaginal application is now well advanced, with some potential agents already having entered clinical trials. However, the prevalence of anal intercourse amongst heterosexual couples highlights the urgent need to assess the effect of these microbicides on HIV infection of rectal tissue. Assessment of their efficacy to prevent transmission across the colorectal mucosa needs to be completed within a suitable tissue model to ensure their efficacy. We present a model of colorectal explant culture to evaluate the efficacy of potential microbicides.

Methods: Tissue explants, exposed to HIV in the presence of candidate microbicides were assessed for viral replication by the presence of p24 in culture supernatants, and proviral DNA within Proteinase-K digested tissue.

Results: Experiments using microbicidal compounds demonstrated that such compounds have the ability to block HIV-1 infection of colorectal tissue. Inhibition of HIV-1 BaL infection was observed with both polyanionic compounds such as PRO 2000, dextrin sulphate, cyanovirin-N, and cellulose acetate phthalate, and reverse transcriptase inhibitors such as PMPA and UC781.

Conclusions: The colorectal explant culture model can be used for the pre-clinical assessment of potential rectal microbicides to prevent HIV-1 infection.

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02639_3 UC-781 BLOCKS LOCALISED INFECTION AND CELL DISSEMINATION PATHWAYS WITHIN HUMAN CERVICAL TISSUE

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Background: In the absence of an effective vaccine, microbicides provide a female controlled method of preventing HIV-1 infection that could significantly reduce worldwide transmission rates. UC-781 is a highly potent and selective thiocarboxanilide non-nucleoside reverse transcriptase inhibitors (NNRTI) of HIV-1. The compound exhibits high affinity for viral reverse transcriptase and is hydrophobic in nature, characteristics desirable for a microbicide. Thus, UC781 has potential as a lead candidate in microbicide development for both vaginal and rectal application. We have tested the hypothesis that UC781 can blockade both the localized infection of human cervical tissue, and dissemination of the virus.

Methods: In vitro activity and toxicity was determined by pretreatment of virus or target cells. The efficacy of UC781 to prevent localised mucosal infection and the potential uptake of infectious virus by migrating cells was assessed using an established ex-vivo, cervical explant model.

Results: UC781 potently inhibited HIV replication in cervical tissue explants and the transfer of infectious virus from migratory cells to coculture cells. In cervical explants pretreated with UC781, protection against viral challenge was still detectable 6 days post drug treatment, suggesting a potent memory effect. Pretreatment of tissue explants also demonstrated significant inhibition of viral dissemination by migratory cells. This inhibition was shown to occur by means other than the inhibition of viral attachment.

Conclusions: The NNRTI UC-781 demonstrates potent and prolonged activity against HIV-1 without being toxic to target cells. Thus, UC-781 is a promising candidate for continued pre-clinical and clinical development for use as a microbicide.

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02639_4 CONCORDANCE BETWEEN DIFFERENT IN VITRO CULTURE MODELS DESIGNED TO PREDICT VAGINAL IRRITATION AND/OR TOXICITY.

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The aim of this study was to examine concordance between different in vitro culture models designed to predict vaginal irritation and/or toxicity. For that purpose 5 agents (KY Jelly, SLS, N9 and silicones 300CP and D5 were tested using ME180 vaginal epithelial cells, reconstructed epidermal and vaginal models (EPI-200 and VEC-100, from MatTek Corporation), and cervical and epidermal tissue explants. Measured parameters included percent viability in the MTT reduction assay, with ED50 determination, and extracellular release of proinflammatory and chemotactic cytokines (inc IL-1_, IL-6, IL-8, TNF-_, GM-CSF, MIP-1_, MIP-1_, MCP-1, RANTES, and Eotaxin) after topical application of compound for 2 or 24 h. Silicone products did not cause any toxicity (to any system) following overnight exposure to a 10% dose. Epithelial cells (single cell layers) were more sensitive to toxic effects of N9 and SLS (10X) than multilayered epithelium. Explant cultures (skin & cervix) showed similar results to multilayered epithelial cultures (eg 0.028% (Cx) vs 0.047% (VEC-100) for SLS. Cytotoxic reagents modified cytokine production, specifically causing a suppression of IL-6, IL-8 and

MCP-1 secretion. Silicones and KY Jelly had no effect on cytokine production. These data show good correlation between different culture models and suggest that assessment of both toxicity and cytokine production may be predictive of in vivo irritation.

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02643 DESIGN AND PRECLINICAL DEVELOPMENT OF DENDRIMER BASED TOPICAL MICROBICIDES FOR HIV & STI PREVENTION

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Dendrimers are a relatively new class of macromolecule characterized by highly branched, 3D architectures that are assembled in a precise, step-wise manner. This controlled synthesis allows the assembly of highly defined structures that radiate out in generations from a central initiator core. The result of this iterative growth process is a SINGLE macromolecular entity that contrasts with the mixture of molecules in traditional polymers or naturally occurring carbohydrates.

In developing dendrimers as pharmaceuticals, we have had a focus on the prevention of HIV and STIs and the development of microbicide candidates. One approach investigated was the presentation of anionic groups on a variety of dendrimer scaffolds. Early examples of our polyanion coated dendrimers had activity against HIV and HSV which triggered a lead candidate optimization process and dendrimer SPL7013 was identified as a development candidate. Following a range of preclinical studies, we submitted an Investigational New Drug application (IND) for SPL7013 gel (VivaGel™) to the United States FDA. SPL7013 represented the first time a dendrimer based product has been submitted to the FDA. Phase I safety studies are currently in progress.

This presentation will describe the dendrimer based microbicide discovery phase, the lead candidate optimization process and selected data from the preclinical development of SPL7013.

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02646_1 EFFICACY OF PRO 2000/5 GEL IN A HU-SCID MOUSE MODEL FOR VAGINAL TRANSMISSION OF CELL-ASSOCIATED HIV.

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Sulfonated polymers are considered promising candidate topical agents for the prevention of sexually transmitted diseases, including HIV infection. Within this group, the naphthalene sulfonate polymer PRO 2000/5 has been shown to inhibit infection by cell-free virus in both in vitro and in vivo assays. Our study focuses on the use of a hu-SCID mouse model of cell-associated HIV transmission at the vaginal level. Gels containing PRO 2000/5 at two different concentrations (0.5% and 4%) were evaluated for protective efficacy vs a matched placebo gel. Animals received a single intravaginal

application of 25 ml of PRO 2000/5 or placebo gel 15-20 minutes prior to a non-invasive vaginal challenge with 2x106 human peripheral blood lymphocytes (hu-PBL) previously infected in vitro with a dualtropic laboratory-derived R5X4 strain of HIV-1 (1/BX08). Vaginally applied 0.5% and 4% PRO 2000/5 gel each prevented vaginal transmission of cell-associated HIV in 5 out of 5 hu-SCID mice as shown by p24. All animals receiving the placebo gel became infected.

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02646_2 HU-SCID MOUSE MODEL FOR RECTAL TRANSMISSION OF HIV: TESTING PRO 2000/5 GEL.

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Topical microbicides for the prevention of HIV-1 transmission between sexual partners should ideally be safe and effective when used both vaginally and rectally. Few animal models are suitable for evaluating both mechanisms of sexual transmission. Our study focuses on the use of a hu-SCID mouse model of cell-associated HIV transmission at the rectal level. This recently developed rectal model is currently being used for evaluation of rectally applied topical gel containing PRO 2000/5 at two different concentrations (0.5%, and 4%) vs a matched placebo gel. Animals received a single intra-rectal application of 50 ?l of PRO 2000/5 or placebo gel, 15-20 minutes prior to a non-invasive rectal challenge with cell-associated dual-tropic laboratory-derived R5X4 strain of HIV-1 (1/BX08). Cell to cell transmission was assessed by p24 determination and by quantitative PCR. Systemic infection was inhibited by PRO 2000/5 gel in this model: 4 out of 5 animals (80%) receiving 4% PRO 2000/5 gel resulted negative for infection as shown by p24 and PCR results, and 4 out of 5 animals (80%) receiving 0.5% PRO 2000/5 gel resulted negative as shown by p24 results. All 5 animals receiving the placebo gel became infected.

We are currently confirming these preliminary results and investigating the effect of PRO 2000/5 gel in preventing the rectal transmission of cell-free virus.

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02662 POTENTIAL REMEDY'S FOR DELIVERY OF HIGH-EFFECTIVE MEMBRANE-ACTING ANTI-HIV MICROBICIDES

data not supplied

Annually several million persons get infected with HIV via sexual route. To protect those who do not use contraceptives, efficient preparations are necessary: microbicids of vaginal application. As a rule, preparations exhibiting efficient anti-HIV action in vitro cause irritation when applied locally on vaginal mucous membrane, which can cause a decrease in antiviral activity, perhaps due to involvement of ?D4+ cells. In the present work, we investigated routes for the creation of efficient pharmaceutical form of microbicid preparation based on conjugates of polymeric carboxylic acid with adamantane, norbornane, norbornene, and peptide imitators of HIV-1/2 coreceptors. In order to eliminate irritating action and increase microbicid activity, we included efficient membrane-acting anti-HIV compounds into the ??-dependent interpolymeric complex (IPC) which is stable into weakly

acidic media and decomposes with the release of active anti-HIV preparation in neutral and/or alkaline media, with one of the following polymers: sodium alginate, polyvinylpyrrolidone (PVP), partly hydrolyzed chitosan, polyvinylimidazole, or included into the complex: PVP-polyacrylic acid. We propose to use carbopole, hyaluronic acid, sodium alginate, or chitosan (depending on the IPC used) as a gel-forming component for the final pharmaceutical form. The anti-HIV efficiency of some IPC proposed has been demonstrated experimentally in vitro, along with a decrease in local toxic action of preparation included in the IPC in vivo when applied on

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02656 DESIGN OF ANTI-HIV MICROBICIDES WITH INCLUSION OF PHARMACOPHORE MODIFIERS AND PSEUDO-LIGANDS

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At present, the whole humanity can be considered as a risk group for AIDS. Radically efficient medicines which could allow curing HIV infection have not been created yet; available preparations only somewhat slow down the development of AIDS. On the basis of co-polymers of divinyl ether with maleic anhydride, polymeric matrixes modified with hydrophobic pharmacophores and peptide imitators of pseudo-ligands of HIV-1/2 coreceptors have been synthesized. It was demonstrated previously that the prototypic preparations (like "Amant") are membrane-acting compounds exhibiting a clearly expressed antiviral effect toward shell viruses (influenza, parainfluenza, respiratory syncytial virus etc.). By evaluating the newly synthesized complex membrane-acting compounds in vitro, their low toxicity was revealed (CC50>1,5mg/ml) for human lymphocitic cells (MT-4, PBMC), as well as high anti-HIV activity (by means of viral procedure: suppression of reproduction of virus [EC50], and by means of ELISA [IC50]– measuring inhibition of the production of ?24 HIV-1 protein), which was 1-30mg/ml upon the culture of permissive cells (MT-4), infected with different strains of HIV-1, and upon PBMC under infection with R5 and X4 tropic strains of HIV-1. Maximal level of antiviral efficiency was revealed when preparations were introduced at the stage of virus adsorption and were during the whole of cultivation. From our point of view, these compounds can be promising for the development of microbicid preparations. Questions concerning the development of optimal means of transporting the complex microbicide compounds of this class are under investigation.

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02664 DEVELOPMENT OF MICROBICIDE VEHICLES: SELECTION LINKED TO PROPERTIES GOVERNING VAGINAL DEPLOYMENT

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A set of 12 prototype gels was created for potential use as vehicles for new microbicides under development. These gels were of four types: cellulose/polymer-cationic (A), cellulose-nonionic (B), block copolymer-nonionic (C), and poly acrylic acid/cellulose-anionic (D). The different combinations of molecular composition were intended to produce gels with different biophysical properties that

govern vaginal distribution and retention (deployment). Variation of these properties was intended to enable testing of hypotheses regarding how different combinations of gel characteristics lead to better or worse deployment. The rheological properties of these gels were studied for whole gels and after dissolution with vaginal fluid and semen simulants. The gels exhibited a wide range of rheological properties. For example, the gels of type C and D exhibited yield stresses while gels of type A and B did not. The four types of gels also exhibited different viscosities and shear thinning behavior. Dissolution studies indicated substantial differences in the propensity of the gel layer to be washed off by the simulants. Some gels swelled while the gel layer remained intact while others rapidly dissolved with loss of the gel layer. The results suggest significant differences in the vaginal deployment of the test gels. (Sponsored by NIH Grant # U19AI051650-02 to Biosyn Inc and, NIH Grant # AI48103 to Duke University).

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02665 IN VITRO RELEASE OF DEXTRAN SULFATE FROM SILICONE INTRAVAGINAL RINGS

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Dextran sulphate is a polymeric species containing a negatively charged glycoprotein surface which potently inhibits the absorption of HIV to CD4+ cells by binding to the neutralising domains of gp120. It is currently being evaluated in vaginal microbicidal gel formulations for the prevention of heterosexual transmission of HIV. However, from the perspective of providing long-term, female-friendly, patient-compliant, continuous protection against HIV transmission, microbicides incorporated into vaginal gel formulations are far from ideal. For example, the retention of gels (and thus the microbicidal substance) within the vagina is poor, they are messy and difficult to adminster, there is the need for gel application before every act of intercourse, and the nature of a gel is such that it is unlikely be used without the knowledge of the male partner. Silicone intravaginal rings (IVRs) are controlled release drug delivery devices that have been specifically designed to overcome the numerous disadvantages associated with gel formulations. In this study, dextran sulfate (weight average molecular weight 5000 and 10,000 daltons) has been incorporated into various matrix-type and reservoir-type IVR formulations and the in vitro release characteristics (employing an aqueous dissolution medium) evaluated using HPLC in conjunction with an evaporative light scattering detector (ELSD). The results demonstrate that dextran sulfate may be released in milligram quantities per day, dependent upon molecular weight and loading.

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02666 PSC-RANTES: DEVELOPMENT OF A POTENT HIV ENTRY INHIBITOR FOR USE AS A VAGINAL MICROBICIDE

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We are currently developing microbicides that prevent HIV infection through blockade of a chemokine receptor, CCR5, which is used by the virus during entry into target cells. Our work is based on the development of analogues of RANTES, a natural protein ligand of CCR5. RANTES itself has been noted for its capacity to block infection by viruses that use CCR5, but some of our analogues are several orders of magnitude more potent. The remarkable anti-HIV activity of these analogues appears to be due to a novel inhibitory mechanism: they induce prolonged intracellular sequestration of the receptor, making it unavailable to the virus for entry.

Although they are proteins, our RANTES analogues are stable for months in solution at ambient temperature. They also retain activity when formulated in hydroxymethylcellulose gel. Our recent experiments show that our most potent analogue, PSC-RANTES, fully protects female macaques from vaginal transmission of a CCR5-tropic SHIV. Taken together, these results suggest that PSC-RANTES is a promising candidate for development as a vaginal microbicide.

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02689 EFFECTS OF SQUEEZING FLOWS ON DISTRIBUTION/RETENTION OF MICROBICIDE FORMULATIONS: EXPERIMENTAL SIMULATIONS & MATHEMATICAL MODELS

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Microbicide vaginal distribution depends on formulation properties, ambient fluids, vaginal geometry, and applied forces. Macroscopic forces – gravitational and squeezing – significantly affect vaginal coverage and retention. We characterize the macroscopic flows via experiments in vitro and theoretical mechanistic models. We measured rheological properties of 7 formulations: 3 cellulose gels (Conceptrol, Gynol II, and KY Jelly), 3 polyacrylic acid (PAA)-based gels (Advantage, KY Plus, and Replens), and a carrageenan gel (Carraguard). Squeezing experiments applied physiologically-relevant forces and monitored the resulting thickness and strain. Unlike cellulose and carrageenan gels, PAA gels exhibited yielding and non-yielding regions, as well as a limiting coating thickness, which ranked KY Plus > Replens > Advantage. For all gels, the coating was dependent on applied force and initial thickness (applied volume). The non-PAA gels experienced the most strain, with strain rankings: Carraguard > KY Jelly > Conceptrol/Gynol > Advantage > Replens > KY Plus. These strain rankings relate to squeezing distribution in vivo. Theoretical models of squeezing flows are compared to in vitro experiments and are used to specify formulation properties that optimize distribution and retention in vivo. For example, differences in rheological properties of Carraguard and KY Jelly may produce a 30% difference in epithelial coverage and a 40% difference in coating thickness. A 43% increase in applied volume may produce an 18% increase in coverage. The above results reveal large differences between formulations and suggest distribution differences in vivo due to squeezing flows. (Supported by NIH #AI48103)

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02690 CONTEMPORAY MATERIAL CONCEPTS FOR THE NEXT GENERATION MICROBICIDE VEHICLES

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In the last 20 years there has been a revolution in understanding the underlying principles of bioresponsive materials for drug delivery and formulation science. These principles, developed by material scientists and pharmaceutics researchers, are now being applied to first generation microbicides, e.g. in the pegylated active ingredients such as PEG-cyanovirin and in thermo-gelling systems. We are developing a number of approaches to create novel bioresponsive materials and formulations for drug delivery in the vagina that are potential prototypes for 2nd and 3rd generation microbicidal formulations. Our approach is to engineer new materials that are designed to undergo changes in their properties in response to interactions with biological triggers that exist in the vagina, including pH, temperature and shear fields. By utilizing contemporary materials we are able to affect significant changes in rheological and other salient physico-chemical properties in response to these triggers. We hypothesize that these changes will enhance the bioactivity of the active ingredient and the carrier, as well as the biodistribution in the vagina. We are currently designing and testing several polymer systems which leverage these bioresponsive signals to create carriers that in themselves are active, and/or modify the properties of the active pharmaceutical in the vagina.

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02698 MC 1220 AS KNOCKING OUT NNRTI TO PREVENT SEXUAL TRANSMISSION OF HIV

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Background. Although progress has been made in post-infection treatment strategies for HIV-infected individuals, the development of effective topical microbicides to control sexual HIV transmission has lagged behind. However, microbicides are urgently needed because it has become increasingly clear that viral loads in vaginal mucosa and seminal fluid are strictly related to HIV transmission rates. Since non-nucleoside reverse transcriptase inhibitors (NNRTIs) are among the agents proposed as microbicides, following up the report of the virucidal activity of UC781 and L737,126, we comparatively evaluated the capability of the latter, of other NNRTIs used in the clinic and of MC-1220 to irreversibly knock out the HIV infection in vitro.

Methods. Long-term assays were set up to discriminate between virustatic and virucidal activities of NNRTIs. Compared to standard assays, our experimental conditions were characterized by: i) the use of a 20 to 40 fold higher m.o.i, ii) culture splitting conditions which avoid losing infected cells, iii) evaluation of HIV-1 multiplication up to day 40 post infection (p.i.), iv) testing of virucidal activity at every 4-day interval by recording cell viability, presence of syncytia, p24 levels, infectious virus yield, presence of viral DNA or RNA sequences.

Results. Following a chronic treatment started immediately after infection, MC-1220 and L-737,126 are the most potent NNRTIs (1 mM) in irreversibly knocking out the HIV-1 multiplication, followed by UC-781, Efavirenz (4 mM) and Nevirapine (20 mM). Following up a treatment limited to the first 4 hrs p.i., MC-1220 is the most potent (11 mM) knocking out drug, followed by UC-781 (50 mM). On the

contrary, Nevirapine, Efavirenz and L-737,126 are totally ineffective (>100 mM). Following up a treatment limited to the 2 hr infection period (see graph on the left), only MC-1220 (11 mM) irreversibly knocks out the HIV multiplication, whereas UC-781, Nevirapine, Efavirenz and L-737,126 are ineffective in preventing the viral breakthrough at concentrations as high as 100 mM. Following up a 4 hour treatment before infection (see graph on the right), MC-1220 (11 mM) and UC-781 (50 mM) are both capable of irreversibly knocking out the HIV-1 multiplication in the absence of extracellular drug. Viceversa, Nevirapine, Efavirenz and L-737,126 are inactive at concentrations as high as 100 mM. It is worth noting that MC-1220 is not cytotoxic following up a 40-day long-term treatment at concentrations up to 200 mM. Moreover, MC-1220 lacks inhibitory activity against vaginal commensals, such as Candida spp. and Lactobacillus spp.

Enzyme kinetic assays with the HIV-1 reverse transcriptase (RT) show that MC-1220 is the best tight-binding inhibitor with a Koff = 8x10-5 s-1. Last but not least, the dissociation rate of MC-1220 is unusually low when compared to the other tight-binding NNRTIs.

Conclusion. MC-1220 may have considerable promise as a virucidal agent to prevent mucosal HIV transmission.

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02700 VAGINAL COATING BY MICROBICIDE FORMULATIONS: DIRECT MEASUREMENT IN WOMEN AND BIOPHYSICAL PREDICTION

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Rational microbicide design must objectively link formulation properties to biological functionality, which depends, in part, on extent and durability of epithelial coating. We measured quantitative details of vaginal gel coating in women (custom fiber optic device), in relation to predictions of biophysical theory and experiment. Five gels with different chemical structures and biophysical properties: KY Jelly and Conceptrol (cellulose); Replens and Advantage (polyacrylic acid); and Carraguard (carrageenan) underwent paired human in vivo studies plus in vitro measurements of salient properties, flow and surface adhesion. Mathematical models of flow and adhesion were also applied. We found significant differences in measures of in vivo vaginal distribution and retention by the gels (e.g. extent, uniformity, bare spots). These related to formulation properties as interpreted using principles of biophysics. For example, initial coating by Conceptrol was less complete and uniform, and more prone to bare spots, than that by Advantage. This was predicted, in part, by differences in viscosity and surface properties (whole, and diluted with simulants of vaginal fluid and semen), as explained by gel coating models. KY and Replens have distinct biophysical properties, and these are altered differently by interactions with ambient vaginal fluids – suggesting different in vivo distributions. Initial in vivo analyses confirmed this. Formulation properties interact with details of formulation application (volume, location) as well as posture and movement, in governing coating distributions. (Supported by NIH AI48103, NIH HD41752 & FDA A60872).

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03206 THE PROGRAM OF THE MICROBICIDE DEVELOPMENT IN RUSSIA

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Background: The creation of topical microbicides against HIV and other sexual diseases pathogens is so important as vaccine development. Today more than 60 microbicide preparations pass clinical trials. They suppose the use of microbicide preparations will result in 1 million of the new HIV cases decrease. The most important part of the microbicide program is the search of novel specific anti-HIV-1 agents. Our investigations were performed to find perspective compounds and their combinations to employ them in topical microbicides which possess the ability to block the HIV transmission on different stages of virus cell interaction. We have studied original compounds from different groups: sulfated chitosanes, humic acids and plant polyphenol derivatives.

Methods: anti-viral activity as well the cytotoxicity of compounds was defined using clinical isolates and laboratory adapted HIV-1 strains and human PMBCs (peripheral mononuclear blood cells) and T-lymphoblastoid cell lines. The level of virus reproduction in infected cells was detected with p24 HIV-1 antigen ELISA detection system.

Results: Sulfated chitosane derivatives possessed low cytotoxicity and blocked HIV-1 infection in T-cells (ED50 = 0.08-2.0 ?g/ml). The inhibitory effect depended on the localization and the amount of the sulfated groups and saccharide monomer, the type of anionic groups and the charge of molecules. The ED50 values of the humic acid derivatives against HIV-1 laboratory strain and HIV-1 M-tropic AZT-resistant wild-type strain were 0.85 and 3.5 µg/ml respectively, without appearance of any detectible resistance. The most of studied plant polyphenol derivatives possessed strong cytotoxicity. The consideration of the cytotoxicity and inhibitory effect allowed us to choose the number of compounds with the essential selectivity index: IS = 100 - 1000.

Conclusions: We found the number of original compounds with high anti-HIV activity and sufficient selectivity indexes, which should be useful for new microbicide preparations. We are going to use new immunomodulator – polyoxidoniy for the improving of the microbicide compositions.

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03265 A NOVEL EX VIVO MODEL OF VAGINAL HIV-1 TRANSMISSION REVEALS PARALLEL RATHER THAN SEQUENTIAL TARGETING OF INTRAEPITHELIAL LANGERHANS AND T CELLS

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Sexual HIV transmission is thought to occur with the initial uptake of virions by mucosal dendritic cells (DCs), followed by the delivery of HIV to CD4+ T cells. This sequential model has arisen primarily from studies utilizing monocyte-derived DCs and epidermal Langerhans cells (LCs) rather than direct observations in the human genital tract, which are precluded by technical limitations and ethical considerations. Here, we introduce a novel ex vivo model that elucidates the initial intraepithelial transmission events. Vaginal epithelial sheets were obtained without the use of digestive enzymes by gentle ex vivo suction blistering of surgically excised mucosa. We then challenged these sheets with green-fluorescence protein (gfp)-tagged infectious virions by spinoculation. Examination by confocal microscopy revealed that both R5-tropic HIV-1 JR-CSF and X4-tropic HIV-1 LAI

simultaneously bound to intraepithelial vaginal T cells and LCs. Electron microscopy and blocking studies with monoclonal antibodies and mannan demonstrated that HIV-1 entered both cell types via CD4 and coreceptor-mediated fusion. In trans viral passage and C-type lectin receptors did not significantly contribute to this process. Thus, although vaginal LCs were also able to sequester intact virions in endosomes, our findings point to a parallel rather than a sequential mode of transmission, where infection occurs simultaneously in both intraepithelial LCs and T cells.

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TRACK B POSTERS

02062 THREE DESIGN ISSUES

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Three controversial design issues bearing on large-scale microbicide trials are discussed: a "condom only no-gel" trial arm; standardization of a common placebo across trials; and the ease and efficiency of applying a vaginal microbicide.

A study with a "condom-only no-gel arm," necessarily unblinded, is subject to unmeasurable variation among trial groups. Adding to this, new evidence from a prior field trial of gel-users points to confounding because of "emigration" from condom use; this undoes their comparability with the "no-gel" condom only arm.

The existence of a "universal placebo" strengthens the arguments for the use of product common to all large trials. This product, if used in every trial, allows for direct comparisons across trials, to the advantage of validity and economy in the numbers required.

Methods of application are insufficiently user-friendly and need improvement. Applicators in current use require time and privacy for preparation and insertion into the vagina, and unfailing mindfulness to sustain the routines. Insertion will on occasion interrupt the first stages of sexual encounter even among mindful women.

Each of these problems is discussed and improvements proposed.

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02073 LUBRICANTS CONTAINING N-9 MAY ENHANCE RECTAL TRANSMISSION OF HIV AND OTHER STI'S.

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It has been shown that men who have sex with men seek lubricants that contain nonoxynol-9 (N-9) because they believe that N-9 may help to prevent infection by HIV. However, there is indirect evidence to suggesting that N-9 may actually enhance infection. A clinical study was undertaken to determine whether N-9 causes sloughing of the rectal epithelium and if epithelium repair rapidly following application of N-9. Biopsies and rectal lavages were used to determine if application of the 2% N-9 product K-Y®Plus caused sloughing of the rectal epithelium. To ensure consistency and compliance all procedures for the study were carried out by a clinical investigator. Lavage and biopsy specimens were collected at 15 min and 2 hr post-rectal use of K-Y®Plus in addition to a later time point. Specimens were fixed in buffered glutaraldehyde and embedded in plastic and stained. Blinded slides were examined by light microscopy. Pronounced sloughing was observed in rectal

lavage and biopsy specimens collected at 15 min post application of K-Y®Plus. Sloughing was not observed in specimens collected at 2 hrs or 8 hrs post application K-Y®Plus and appeared similar to baseline specimens. Since rectal epithelium protects target cells in the submucosa from HIV; we conclude that lubricants containing N-9 should be avoided during rectal sex.

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02092_1 AN OPEN PHASE 1 TRIAL OF 13% CELLULOSE ACETATE PHTHALATE (CAP) VAGINAL MICROBICIDE.

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MRC/DFID Microbicide Development programme (MDP)

Background
Cellulose acetate phthalate (CAP) is a widely used pharmaceutical excipients that has been shown to block HIV-1 infection. In vitro studies confirmed that interaction between HIV-1 and CAP led to rapid virus adsorption onto CAP, gp41 six-helix bundle formation, virus disintegration and shedding of envelope glycoprotein with rapid loss of infectivity. In vivo experiments using animal models confirmed CAP is non- toxic, non-mutagenic and non-teratogenic. A new gel formulation for use as a vaginal microbicide has been developed.

Methods
A phase 1 vaginal microbicide safety study has been approved by the local research ethics committee. 60 women will be recruited. The study will be conducted in 2 parts. Informed consent will be obtained from women who meet the entry criteria. Part A will study 10 HIV-ve volunteers using CAP once a day for 14 days and will include a post-first dose Colposcopic assessment. The DSMC will review safety data from part A before proceeding to part B. Then 40 HIV-ve (randomised to gel, n=30 or observation, n=10) and 10 HIV+ve women (all will receive gel) will be recruited in Part B of the study. Outcome parameters will include local vaginal, clinical and laboratory adverse events.

Results
Enrolling 50 women in CAP arm enables to estimate the incidence of clinically significant adverse events. Thus if one person experiences such an event the 95% CI for the estimate will be 0.05% - 10.6%

Discussion
Our study will provide the first human CAP vaginal microbicide safety data.

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02092_2 MAGNETIC RESONANCE IMAGING STUDY OF THE DISTRIBUTION AND RETENTION OF DEXTRIN SULPHATE

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Background
Phase 1/2 studies have confirmed the safety and acceptability of Dextrin Sulphate (DS) as a vaginal microbicide. To provide effective protection against sexually transmitted diseases, DS should maximally cover the cervix and vagina before and after sex. Magnetic resonance imaging (MRI) can be used to monitor the intravaginal distribution of microbicide gels. In this study we will determine whether sexual intercourse affects the distribution and retention of the gel over 24 hours.

Methods
The study has been approved by the local research ethics committee. It will be an open label prospective single centre trial with 6 subjects. Subjects will be scanned twice over two 24 hour periods, once having sexual intercourse following gel application and once abstaining from intercourse. DS will be mixed with gadolinium chelate and introduced intravaginally by the female volunteers using a conventional applicator. MRI assessments will be made prior to, and immediately after gel application and 12 hours and 24 hours after gel administration. Study end points will include signal intensity readings for gel at predetermined sites within the vagina, assessment of the degree of cervico-vaginal mucosa covered by gel and visual assessment of the uniformity and distribution of gel within the genital tract.

Results
Women will act as their own controls to enable us to estimate the effect of intercourse on the retention and distribution of gel over 24 hours. The data obtained from the assessment will be analysed using a paired student T test and 95% confidence intervals.

Discussion
Although there has been one previous report of N9 distribution after coitus, we will use MRI signal intensity readings to analyse the distribution and retention of DS following intercourse over a 24 hour period.

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02340 FEASIBILITY OF CONDUCTING MICROBICIDE PREPAREDNESS STUDIES IN URBAN & RURAL KWAZULU-NATAL

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Hptn Grant No: 1 UO1 A148008

Background: There are several microbicide agents ready for Phase III clinical trials. Adequate population size, basic clinical and laboratory infrastructure, and estimates of HIV incidence are required. Preparedness studies are necessary for appropriate site selection. Preliminary baseline outcomes of a preparedness study are described.

Method: Between May and July 2003, 251 and 250 women from an urban clinic (Durban) and a rural clinic (Hlabisa) were screened for participation in the feasibility study. Of those, 116 and 92 women from Durban and Hlabisa respectively were enrolled in the study. At screening participants were tested for HIV, STI, and pregnancy. A demographic questionnaire was administered. At enrolment, women were screened for genital abnormality (colposcopy) and were administered a behavioral questionnaire.

Results: The median age of women in Durban and Hlabisa was 28 years at both clinics. 66% and 78% of the women in Durban and Hlabisa, respectively, were unmarried. 35% of the women in Hlabisa believed that their husband/partner had more than one partner. 54% of women in Durban and 42% of women in Hlabisa had incomplete secondary education. HIV prevalence was 31.3% and 35.5% in Durban and Hlabisa respectively, with a significantly higher prevalence in the 26-35 years age group in Hlabisa (p = 0.0046) Infections with T.vaginalis, candida and syphilis were significantly higher in Durban (p= 0058, 0.0141, and 0.0004 respectively). 85% and 87% of the women in Durban and Hlabisa respectively had vaginal sex without condoms in the past 3 months. Only 29% and 18% of the women in Durban and Hlabisa respectively used condoms in the last sexual act. Vaginal douching was not highly prevalent at both the sites.

Conclusion: Despite the high prevalence of HIV at both sites, these sites were able to enroll a cohort of HIV negative women in a short period of time. Risky sexual behaviors are still very prevalent which will likely result in high HIV incidence in these cohorts. Therefore, these sites are ready to be part of a microbicide Phase III clinical trial.

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02344 MULTIVARIATE ANALYSIS OF RISK FACTORS FOR HIV SEROCONVERSION IN THE COL-1492 PHASE III TRIAL

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Objective: To assess risk factors (including treatment arm) for HIV seroconversion among female sex workers (FSWs) participating in the COL-1492 microbicide phase III trial.

Methods: FSWs were recruited and followed monthly from 1996 to 2000 in Benin, Côte d'Ivoire, South Africa and Thailand. They were randomly allocated to receive either the COL-1492 gel or a placebo. At each visit, a questionnaire was administered and samples collected for HIV and STI testing. Multivariate analysis used a Cox proportional hazard model with time dependent covariates.

Results: The overall HIV incidence among 765 women followed for 837.5 person-years (PY) was 12.4 per 100 PY. Independent risk factors for HIV seroconversion were: inconsistent condom use with clients [Hazard ratio (HR): 1.8, 95% confidence interval (95%CI): 1.2-2.7); gonorrhea (HR: 2.4, 95%CI: 1.3-4.3); and being in the COL-1492 treatment arm (HR: 1.6, 95%CI: 1.1-2.4).

Conclusions: The association between COL-1492 and HIV acquisition is similar to that of the intention-to-treat analysis. Results on condom use and gonorrhea underline the effectiveness of condoms as a protective device as well as the importance of STI control in HIV prevention.

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02345 RISK FACTORS ASSOCIATED WITH HIV INFECTION IN URBAN AND RURAL POPULATIONS OF SOUTH AFRICA

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Background: As part of the screening process of enrolling women in a vaginal microbicide site feasibility study, women were tested for HIV at 2 settings; urban (Durban) and rural (Hlabisa). We describe the outcomes of the assessment of risk factors associated with HIV infection at baseline.

Method: Between May and July 2003, 251 and 250 women from an urban clinic (Durban) and a rural clinic (Hlabisa) respectively were screened for participation in the feasibility study. At screening, participants were tested for HIV, STI and pregnancy. A demographic questionnaire was administered. Univariate and multivariate analyses were conducted to assess the risk factors associated with HIV at both centers.

Results: The HIV prevalence in was 31.3% and 35.5% in Durban and Hlabisa respectively. Significant univariate factors associated with HIV infection in Durban were age (OR 0.934; p =0.0035), unmarried (OR 9.709; p<0.0001); husband/partner with more than 1 wife (OR 2.539; p=0.0047), not currently living with a husband or partner (OR 1.992; p=0.0184), having her own income (OR 3.424; p=0.0001), and ethnic group Zulu (7.558; p<0.001). In Hlabisa the factors associated with HIV were age (OR 0.957; p=0.0053), unmarried (OR 3.846; p= =0.0012), not currently living with a husband or partner (OR 2.506; p=0.0181), and at least some secondary education—or higher (OR 1.817; p=0.0413). Infections with N.gonorrhoeae, C trachomatis and syphilis were not significantly associated with HIV.

Conclusion: Young women, unmarried and of the ethic group Zulu are at high risk of HIV in Kwazulu Natal, Durban. These sites are in urgent need of prevention efforts targeted at women.

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02351 DISPOSABLE UNIT-DOSE VAGINAL APPLICATOR DEVELOPMENT

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Objective: Develop a non-proprietary, pharmaceutically acceptable unit-dose vaginal applicator.

Results: Commercial and prototype applicators were evaluated in terms of product delivery, residual product left in spent applicators, weight loss during storage, cap tightness and safety. Results convinced us a new vaginal applicator needed to be developed for microbicide use. A smooth tapered barrel tip was designed for elegant appearance and ease of insertion. A new piston design was developed to reduce product weight loss and one-direction movement for single use. A synthetic elastomer was selected for the piston to achieve these aims and meet strict regulatory chemical extraction/safety requirements. Barrel and cap material was selected based on USP package extraction requirements, and cap tightness, weight loss and mold performance test results. Regulatory required extraction tests were performed on all package components. Clinical evaluation was performed.

Conclusion: A superb non-proprietary unit-dose vaginal applicator has been developed and qualified for clinical and commercial use.

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02353 POTENTIAL PREVENTION OF HIV BY USING THE NEW CERVICAL BARRIER "FEMCAP" WITH MICROBICIDES

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Objectives:
A) To block, mechanically and chemically, the main portal of entry used by the virus—the cervix.
B) To minimize the disruption of the cervical and endometrial epithelium caused by microbicide.

Methods: The cervix was found to be the main portal of entry for HIV. This is due to the presence of chemokine receptors CCR-5 and CXCR-4 in the endocervical epithelium. These receptors must be present in order for HIV to enter and infect the CD4 cells. They are absent on the surface of the vagina.

The vagina is a muscular conduit that transports its contents in both directions. Unlike currently available female barriers, the FemCap has a unique groove to store and deliver microbicide on the vaginal side. This ensures immediate exposure of sperm, bacteria, and viruses to the microbicide upon deposition. Most importantly, the FemCap's microbicide storage groove protects the cervical and endometrial epithelium from the damaging effects of microbicides.

Results: Clinical and epidemiological studies have demonstrated that though many microbicides, including Nonoxynol-9, can destroy the fragile HIV virus in the lab, none have proven effective in the vagina. In fact, Nonoxynol-9 increases HIV transmission if applied over the cervix. This is due to its deleterious effect on the cervical and uterine epithelium.

Conclusion: To minimize the transmission of HIV, it is critical to use both chemical and mechanical barriers. The FemCap covers the cervix completely and is designed to store and deliver the microbicide on the vaginal side, unlike currently available female barriers. This ensures immediate and prolonged contact of the microbicide with invading microorganisms without disruption to the cervical and endometrial epithelium and vaginal ecology by the microbicide.

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02407 VAGINAL FLORA CHARACTERISTICS OF HIV+ WOMEN ENROLLED IN A PHASE I CELLULOSE SULFATE STUDY: HPTN 049

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For The HPTN 049 Study Team

Background: Vaginal microbicides, if effective, may be used by HIV+ women to prevent sexual transmission of HIV. These products may affect vaginal flora.. However, there are few data on the vaginal flora characteristics of HIV+ women..

Methods: Eligibility criteria included CD4+ lymphocyte count >200cells/mm3, HIV-1 RNA <50,000 c/mm3, negative pregnancy test, normal Pap smear, no sexually transmitted infections (STI) in the preceding 6 months and no vaginal symptoms or discharge. A pelvic examination, including pH measurement and wet mount exam of vaginal fluid, was conducted prior to any microbicide use.

Results: 55 HIV+ women enrolled thus far: mean age 37.9 y, 64% African American, 15% Latina, median CD4 583 cells/mm3, viral load 184 c/mm3. Antiretroviral therapy (ART) was used by 71%. Mean vaginal pH was 5.0 (range 3.5-7.0, SD 0.7), and 69% of women had a pH above normal pH of 4.5. Using clinical criteria (ph> 4.5, positive amine test and >20% clue cells), 15% of the women had bacterial vaginosis (BV). Wet mount exam did not reveal T.vaginalis or C.. albicans. Neither vaginal pH > 4.5 nor BV were associated with age, ART use, CD4 count, viral load or history of STI.

Conclusions: These asymptomatic, highly selected HIV-infected women had a high prevalence of elevated vaginal pH and incidental BV at baseline. As BV may act as a co-factor in the heterosexual transmission of HIV, the impact of vaginal microbicides on BV warrants further study.

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02420_2 OPTIMAL ANALYSIS OF MRI DATA TO QUANTITATE THE DISTRIBUTION OF A VAGINAL PRODUCT

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Introduction: MRI can be used to safely and acutely visualize and quantitate spread of a potential microbicide formulation. We have used MRI to characterize the spread of a number of vehicles and active compounds including Gynol II, 1.0% C31Gg, 6% Cellulose Sulfate, Replens and KY jelly; at a variety ofvolumes. By combining the experience of these trials we have been able to analyze MRI as a technique to compare gels and optimize experimental conditions. This abstract summarizes some of these conclusions.

Methods: Raw data from 5 experimental protocols and greater than 30 women were combined. When possible, data were aggregated. We explored a variety of analytic techniques, statistical methods and experimental designs to determine the optimal use of MRI to quantiate intra-vaginal spread of a potential microbicide.

Results: MRI has outstanding intra-person validity and reproducibility. Using this data the best characterization of intra-vaginal spread of a vaginal gel is a linear relationship with time (linear mixed model). The slope of the curve is dependant on the specific gel, the volume, time and the baseline vaginal dimensions. The baseline vaginal dimensions of length below the cervix and transverse measurement at the flexion may be dependant on weight and gravity respectively. Spread is best characterized in two distinct anatomical categories: the upper and lower vagina, using the pelvic diaphragm to delineate the two. Individual gels do not spread equally in both the upper and lower vagina.

Conclusions: MRI can be reproducibly used to assess and compare intra-vaginal spread of a microbicide. Given the complex anatomic shape of the human vagina a simple linear measurement in one plane is inadequate to characterize spread. A summary measurement of multiple assessments of both the upper and lower vagina best characterizes vagina coverage. Paired study designs provide the most efficient comparison of two products or volumes. This research was funded by CONRAD

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02433 ENROLLMENT FAILURES IN HIV+ AND HIV- WOMEN SCREENED FOR 2 PHASE I MICROBICIDE TRIALS: HPTN 049/050

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For The HPTN 049 and 050 Study Teams

Background: Increasing attention has been focused on the development of vaginal microbicides for the prevention of sexually transmitted infections (STIs) and HIV. Reasons for failed enrollment into microbicide studies among HIV+ and HIV- women are not well described and may assist in defining eligibility criteria in future studies.

Objectives: To identify reasons for failed enrollment among HIV+ and HIV- women screened for two Phase I microbicide studies: HPTN 049 (6% cellulose sulphate) and HPTN 050 (PMPA gel).

Results: Of 267 women who completed screening, 174 (65%) failed enrollment. The most common reasons included having an abnormal pelvic exam (30%) or Pap smear (25%) and evidence of a recent STI (24%). Overall rates of failed enrollment were similar between the 131 HIV+ (64%) and 136 HIV- (66%) women screened. Compared to HIV- women, HIV+ women who failed enrollment more often had an abnormal Pap (29% vs 21%) or a recent STI (29% vs 19%). While abnormal CBC (41% vs 14%) or chemistry (21% vs 7%) tests were more frequent among HIV+ women, grade 3 or 4 laboratory values (enrollment exclusion criteria) were similar. Rates of abnormalities found on pelvic exam did not differ between HIV+ and HIV- women who failed enrollment.

Conclusion: Despite pre-selection through strict eligibility criteria, most screened women failed enrollment. HIV+ women who failed had higher rates of abnormal Paps and evidence of recent STIs compared to HIV- women. Eligibility criteria should be carefully assessed in order to allow for enrollment of larger proportions of screened women. This need for screening of large numbers of women should be strongly considered in the development and implementation of future trials.

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02434 CHALLENGES IN THE RECRUITMENT OF HIV+ AND HIV- WOMEN IN US VAGINAL MICROBICIDE TRIALS: HPTN 049/050

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Background: Effective microbicides are needed for HIV-infected and uninfected women. There are limited data on how to recruit women and their male sexual partners into these studies.

Objective: To identify challenges in participant recruitment in two ongoing Phase I vaginal microbicide trials. HPTN 049 is (6% Cellulose Sulfate Gel) and. HTPN 050 is (PMPA Gel).

Methods: Survey of project staff at four US trial sites (Birmingham, AL; New York, NY; Philadelphia, PA; Providence, RI) conducting two Phase I microbicide studies of cellulose sulfate and PMPA vaginal gels.

Results: Challenges included: lengthy study visits (100%) of sites, stringent eligibility criteria (100%), participant work schedules and limited transport from distant locations (100%), identifying eligible HIV+ and HIV- women at one venue (25%), inability to enroll non-English speaking participants (25%), difficulty obtaining HIPAA waivers to accept referrals (25%), insufficient incentives (25%). For HIV+ women challenges included: need for HIV concordant couples and high rates of co-morbid diseases and abnormal PAP smears.

Conclusions: Phase I vaginal microbicide studies can be successfully conducted among HIV + and HIV- populations but recruitment strategies should be specific to the respective population. Future studies should consider the high rates of serodiscordancy among HIV+ couples likely to be eligible for these studies and explore the safety of using discordant rather than concordant couples.

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02463_2 ACCEPTABILITY OF CARRAGUARD® AMONG HIV-INFECTED WOMEN AND MEN IN A SAFETY TRIAL IN SOUTH AFRICA

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Introduction: Microbicides may offer HIV-infected women and men protection against sexually transmitted infections, and may protect their partners from HIV and other infections. It is therefore important to understand acceptability of potential microbicides among this population.

Methods: We assessed acceptability during a Phase I safety study of Carraguard", the Population Council's lead candidate microbicide, among 20 healthy HIV-positive sexually abstinent women and men, and 20 HIV-positive sexually active women in Durban, South Africa. Participants were randomized to use Carraguard, placebo (methyl cellulose), or condoms only. Women inserted gel vaginally every evening for 14 days, and men applied gel to the penis every evening for 7 days. Acceptability data were collected in interviewer-administered questionnaires and in-depth interviews.

Results: Preliminary, blinded, quantitative findings for 20 sexually abstinent women and 20 men are included here; results for sexually active women and qualitative findings will be included in the final presentation. Gel application did not cause any pain or irritation in men. Fifteen percent of women (2 out of 13) reported pain or irritation during some gel insertions, and 8% (1 out of 13) after some gel insertions. Men and women gave the same overall ratings for the study product: 62% liked it very much, 30% liked it somewhat, and 8% were neutral. Few men (23%) and women (15%) disliked the amount of gel they had to apply/insert. Few women and men (between 0 and 8%) disliked the gels' color, smell, or packaging. Most women (63%) reported that they prefer sex to be somewhat lubricated, but 62% of women (8 out of 13) and 54% of men (7 out of 13) felt the gel was sometimes, often or always too wet. About half (54%) of men and 39% of women felt the gel could be used

without their partner's knowledge. All participants said they would buy the gel to use with their spouse/steady partner if available as a microbicide, and 69% of women (11 out of 16) and 63% of men (12 out of 19) said they would prefer to use a microbicide alone over condoms alone or both.

Conclusion: The study gels were generally acceptable to the HIV-positive sexually abstinent women and men in this study.

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02496 PHASE I 14-DAY SAFETY AND ACCEPTABILITY STUDY OF 6% CELLULOSE SULFATE

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Cellulose sulfate (CS) is a non-cytotoxic antifertility agent that exhibits antimicrobial activity in vitro against sexually transmitted infections. A gel containing 6% CS has been shown to stimulate acrosomal loss, inhibit hyaluronidase and impede sperm penetration into cervical mucus in vitro. Clinical studies have shon it to be safe for use up to 6 days in women and 7 days in men. Expanded safety studies in developing countries have been completed and a non-comparative contraceptive effectiveness study and HIV prevention trials are planned. Based on pre-clinical and clinical data, CS gel appears to be a promising candidate microbicide.

This multi-center, Phase I, placebo-controlled, randomized, closed label study will determine the effect of CS on irritation of the vulva, vagina and cervix, vaginal microflora, vaginal cytokines, systemic safety and acceptability. The female study participants applied 6% CS gel or K-Y® Jelly intra-vaginally twice daily for 14 consecutive days. A total of 60 healthy female volunteers (30 sexually abstinent and 30 sexually active) were enrolled at three sites and seen in 4 scheduled visits.

Data presented will include the following specific endpoints: symptoms and signs of genital irritation including coloscopy, wet mounts, gram stains, semi-quantitative vaginal cultures, cytokines recovered on vaginal lavage, adverse events and acceptability.

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02576 RECRUITMENT FOR A TRIAL OF MICROBICIDE SAFETY AND ACCEPTABILITY AMONG HIV-INFECTED WOMEN, THAILAND

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Background: Vaginal microbicides to prevent HIV transmission may be used by HIV-infected women because they do not know their HIV status or they believe the product may protect sex partners from HIV infection. Therefore, we investigated the safety and acceptability of a candidate microbicide in HIV-infected women. Recruiting HIV-infected women for microbicide safety and acceptability studies may be challenging.

Methods: Our objective was to recruit 54 healthy, HIV-infected women for a safety and acceptability study of a candidate vaginal microbicide (Carraguard") in Northern Thailand. Study information sessions were held with women attending hospital and community HIV care and support programs. Eligible women were referred to the study clinic for screening for study eligibility.

Results: We conducted 115 study information sessions over ten months, including 68 (59%) with district health centers, 21 (18%) with non-governmental organizations, 15 (13%) with hospital-based HIV programs, nine (8%) with expanded access to antiretroviral drug programs, and two (2%) with antenatal clinics. Overall, 660 individuals attended the information sessions, including 578 potential participants and 82 family members. Among the 533 women assessed for eligibility, 281 (53%) were ineligible; reasons for ineligibility included antiretroviral therapy, irregular menstrual cycles, and family/privacy concerns. Overall, 252 (47%) met initial eligibility criteria, and 145 (58%) were screened. Of women screened, 68 (47%) attended information sessions at district health centers, 23 (16%) at non-governmental organizations, 38 (26%) at hospital HIV programs, 12 (8%) at expanded access to antiretroviral drug programs, and four (3%) at antenatal clinics.

Conclusions: Recruitment of healthy, HIV-infected women for candidate microbicide studies is feasible, but requires substantial resources and active involvement of HIV care programs. A high percentage of recruited women were ineligible. Our experience suggests that family and privacy concerns regarding HIV disclosure may limit participation in recruitment sessions and study screening.

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02577_1 EVALUATION OF HIV-INFECTED WOMEN SCREENED FOR A CLINICAL TRIAL OF MICROBICIDE SAFETY, THAILAND

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Background: Few candidate microbicide safety trials have been conducted among HIV-infected women. We screened HIV-infected women for participation in a safety and acceptability trial of a candidate microbicide (Carraguard") in Northern Thailand. Eligibility criteria included abstinence or an HIV-infected husband/steady sex partner, regular menstrual cycles, not currently taking antiretroviral (ARV) therapy, and a CD4 cell count of 50-500 cells/µL. We report the clinical findings from women screened.

Methods: HIV and syphilis serological tests and CD4 cell counts were performed for all women screened. Women were referred for HIV clinical evaluation, including chest radiograph, and received pneumocystis carinii (PCP) and/or fungal prophylaxis, if indicated. For women meeting preliminary eligibility criteria, a pelvic examination with Pap smear was performed. Husbands/steady sex partners were offered HIV testing.

Results: Overall, 144 women were screened; nine (6%) tested HIV negative. Among 135 HIV-infected women, 40 (30%) did not meet CD4 cell count criteria; 26 (19%) had <50 CD4 cells/µL, and 14 (10%) had >500 CD4 cells/µL. Overall, 64 (47%) women had CD4 cell counts <200 cells/µL. Among 114 women with HIV care evaluations, 40 (35%) received fungal and/or PCP prophylaxis. Among 95 women with CD4 50-500 cells/µL, 53 (56%) were abstinent. Thirty-four (36%) had a husband/steady sex partner who was tested for HIV, and 19 (56%) tested HIV positive. Six (4%) had reactive serologic tests for syphilis and were treated. Pap smear results were available for 57 women tested; eight (14%) were > Class II, and these women were referred for colposcopy and excluded from participation. One woman was diagnosed with active tuberculosis, received treatment, and was excluded. At this time, 35 women have been enrolled.

Conclusions: As part of screening for this study, women learned their CD4 count and received care for HIV-related conditions. For those eligible, knowledge of CD4 count may increase their ability to access to antiretroviral treatment. Overall, 47% of women screened may be eligible for ARVs as the Thai government expands HIV treatment programs for persons with CD4 cell counts <200 cells/µL; many may not have been previously aware of their eligibility. We identified many discordant couples who received intensive counselling to reduce the risk of HIV transmission to the uninfected partner.

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02577_2 CLINICAL TRIAL OF MICROBICIDE SAFETY AND ACCEPTABILITY AMONG HIV-INFECTED WOMEN IN NORTHERN THAILAND

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Background: Vaginal microbicides to prevent HIV transmission may be used by HIV-infected women because they do not know their HIV status or they believe the product will protect sex partners from HIV infection. Few studies evaluating candidate microbicide safety among HIV-infected women have been conducted.

Methods: We designed a study to evaluate safety, acceptability, and vaginal HIV viral shedding with vaginal use of 3% carrageenan gel (Carraguard“) among HIV-infected women in Northern Thailand. Eligibility criteria included a CD4 cell count of 50-500 cells/µL, not currently taking antiretroviral therapy, abstinence or a steady sex partner who was also HIV-infected, and regular menstrual cycles.

Results: The study was a three-arm, crossover design, including carrageenan gel, placebo (methylcellulose) gel, and a “no product” arm. Participants were randomized to one of the six possible study arm sequences. Primary endpoints included cervico-vaginal cell-free viral load, cellular viral replication, infectious virus, and epithelial disruption following seven days of product use. Secondary endpoints included vaginal symptoms, bacterial vaginosis, yeast infection, and other reproductive tract infections. Following a three-week washout period, participants crossed over to the next study arm, with each woman serving as her own control.

Conclusions: A cross-over study design may be an efficient method of evaluating safety of candidate microbicides among HIV-infected women, enhancing comparability of study arms and minimizing sample size requirements.

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02586 HIGH RATES OF CO-MORBID CONDITIONS & PELVIC FINDINGS IN HIV+ WOMEN ENROLLED IN HPTN049

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Background: The availability of effective vaginal microbicides is a key HIV prevention strategy. The assessment of the safety of these products HIV-infected persons is important as they are likely to be used by these populations.

Objectives: To describe the characteristics of HIV-infected women enrolled in an ongoing phase I double blind placebo controlled microbicide study of cellulose sulphate

Methods: HIV-infected women were enrolled at 4 US sites after screening for exclusion criteria. Baseline demographic and HIV disease characteristics, prior medical history, a pelvic examination and colposcopy were conducted.

Results: A total of 55 women were enrolled with mean age of 37.9 years, 64% African American, 15% Latino and 20% white. At baseline, mean CD4+ lymphocyte count was 588+245 cells/mm3 and viral load 4,275 copies/mm3. Antiretroviral drugs were used by 71% at baseline. History of depression was reported by 40%, anemia 24%, hepatitis C 24%, asthma 16%, hypertension 15% and diabetes 5%. History of bacterial vaginosis was reported by 9%, trichomonas by 5%, and chlamydia, gonorrhea, syphilis by 1 woman each. At enrollment, 7% and 49% had abnormal pelvic and colposcopic exams, respectively. The following colposcopic findings were noted: erythema (22%), petechiae/echymosis (20%), abrasion (5%), ulceration (4%), cysts (15%) and peeling (2%).

Conclusions: A high rate of co-morbid conditions, prior pelvic infections and colposcopic findings were noted in this highly selected group of HIV+ women. These findings highlight the complexities of enrolling such women and the need for pragmatic eligibility criteria. The data also support the need for determination of the safety of microbicide candidates in this population.

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02588 PARTIAL USE OF COLPOSCOPY IN THE SAFETY EVALUATION OF A CANDIDATE MICROBICIDE

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Background. Colposcopy can be employed to evaluate the genital epithelium in microbicide safety trials. However, more genital findings may be identified during colposcopy than during naked-eye examination, and its partial use might bias safety outcomes.

Methods. Safety of vaginal use of Carraguard" (3% carrageenan gel) was compared with that of a placebo gel (2.5% methyl-cellulose) in a year-long, randomized, triple-blinded study among 165 HIV-negative women recruited from family planning clinics in northern Thailand. Colposcopy was performed at enrollment, day 14, and during monthly follow-up visits at the discretion of the study nurses. The use of colposcopy by five study nurses was recorded and patterns of use in the Carraguard and placebo gel groups were compared.

Results. Study nurses reported performing colposcopy mostly to better visualize findings that were already visible by naked-eye examination. All five nurses evaluated roughly the same proportion of the 165 women enrolled in the study. Two study nurses performed colposcopy during one-quarter of the visits or less, while the other three used it during 40-50% of visits. However, rates of colposcope use by an individual nurse did not differ by Carraguard and placebo gel group. Although women with genital findings visible by naked eye may have been more likely to undergo colposcopy and women who underwent colposcopy may have been diagnosed with more genital findings, this occurred equally in both study groups.

Conclusion. Safety outcomes were not biased by partial use of colposcopy. However, colposcopy was not systematically performed and we did not record which genital findings were only seen during colposcopy. We could therefore not evaluate the added value of performing colposcopy in the safety evaluation of a candidate microbicide, which we are currently investigating in another safety trial in Thailand.

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02593 DETECTION OF HIV-1 RNA LOADS IN THE PRESENCE OF MICROBICIDE FORMULATIONS INTENDED FOR HUMAN USE

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The clinical evaluation of topical microbicide formulations should include an analysis of how daily applications of a product affect HIV-1 vaginal shedding in infected women. Therefore, accurate measurements of cell-free HIV-1 in vaginal secretions containing microbicide formulations are necessary. This study investigated the impact of microbicide and available placebo formulations of CarraguardTM, cellulose acetate phthalate (CAP), PRO-2000 (0.5%), UC781 (0.1 and 1.0%), and VenaGelTM on HIV-1 RNA virus load measurements using the Roche Amplicor HIV-1 Monitor® Assay (version 1.5). Microbicides were diluted in PBS to 10 and 50% of their original formulations and spiked with cell-free plasma virus (5,000 HIV-1 RNA copies/ml). HIV-1 RNA was extracted directly from the diluted formulations and from pelleted virus (1 hr at 105xg) using the NucliSens® 9-ml and 0.9-ml silica-based protocols, respectively. Virus-spiked 50% concentrations of CarraguardTM, its methylcellulose placebo, CAP, and VenaGelTM with direct RNA extractions had the same virus loads as those in the virus-spiked PBS only controls (< 0.5 log10 difference). In contrast, virus-spiked 10 and 50% concentrations of PRO-2000, UC781 (1.0%), and their placebos completely inhibited the virus load assay. However, a normal virus load (< 0.5 log10 difference versus the PBS control) was obtained from a 10% concentration of UC781 (0.1%), but not of PRO-2000, by pelleting virus before RNA extraction. These results indicate that the ability to accurately measure the effect of microbicide formulations on HIV-1 vaginal shedding will require a knowledge of the RNA extraction methodology and virus load protocols best suited for each product.

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02597 EXPANDED PHASE I SAFETY AND ACCEPTABILITY TRIAL OF 6% CELLULOSE SULPHATE GEL AS A VAGINAL MICROBICIDE

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Background: Sodium cellulose sulphate is a non-cytotoxic polymer with antimicrobial activity in vitro. An expanded Phase I trial was done to assess the safety and acceptability of 6% cellulose sulphate (CS) compared to K-Y® Jelly.

Methods: Sexually abstinent (cohort I) and sexually active (cohort II) women were recruited in India, Nigeria and Uganda. Participants were randomized to twice daily vaginal applications of either 3.5 ml 6% CS or 3.5 ml K-Y® Jelly for seven consecutive days. Safety was determined in cohort I before enrolling cohort II and was assessed by symptoms and signs (including colposcopy) of genital irritation and by changes in vaginal health as assessed by microscopy. Product acceptability was assessed by a structured questionnaire.

Results: One hundred and eighty women (90 on CS and 90 on K-Y® Jelly; equally distributed between centres and cohorts within each centre) were enrolled. Compliance with gel use was 94% overall. Baseline characteristics of women in both gel groups were similar. In cohort I, 6 (14%) women on CS and 12 (27%) on K-Y® Jelly reported genital symptoms, two of whom withdrew from study. New colposcopy findings were detected in 4 (9%) women on CS and 9 (21%) women on K-Y® Jelly in cohort I. Two women on CS and three on K-Y® Jelly in cohort II reported genital symptoms. Five women (11%) in each gel group in cohort II had new colposcopy findings. Differences between gel groups were not statistically significant. Over 80% (151/175) of women had no problem with their product, and 65% found their assigned gel very easy to use.

Conclusion: Twice daily vaginal applications of 6% cellulose sulphate appears to be as safe and well tolerated as K-Y® Jelly. Further studies of the effectiveness of CS to prevent HIV and pregnancy are planned.

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02604 IMPACT OF CERVICOVAGINAL SECRETIONS ON HERPES SIMPLEX VIRUS (HSV) INFECTION

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Cervicovaginal secretions have intrinsic antimicrobial activity, which may be important in protecting women against sexually transmitted infections (STI). Defining these innate factors and identifying how they protect against infection is essential for microbicide development because candidate topicals must not interfere with the innate protective activity and these factors could be exploited to facilitate the development of novel microbicides. The anti-HSV activity of cervicovaginal secretions is unknown. Objective: To evaluate the impact of cervicovaginal lavage (CVL) on HSV infection and explore the mechanism(s) of anti-viral activity. Results: CVL was obtained from 20 women (10 age 18-

25 and 10 age 26-45) on two occasions 14 days apart and evaluated for anti-HSV activity. We found that CVL (pH ~ 5.0) inhibits HSV infection in all subjects. There was a geometric mean reduction of > 10-fold in HSV-2 recovered in cervical cells cultured in the presence of CVL compared to cells cultured in the presence of control buffer (saline, pH 5.0 + 0.2mg/ml BSA) ($p < 0.0001$). There was no significant difference in anti-HSV activity in samples obtained on Day 0 compared to Day 14 and between the two age groups. The CVL is active against clinical isolates of HSV-2 and using immortalized human endocervical cells. CVL appears to inhibit viral entry post-binding as evidenced by its ability to prevent nuclear transport of the viral tegument protein VP16, but not to block HSV-2 binding to cells. The anti-HSV activity is retained if cervical cells are pre-treated with CVL, washed, and then inoculated with HSV-2. In contrast, the activity is diminished if virus is first pre-treated with CVL, and diluted prior to inoculating cells. Conclusions: CVL has intrinsic anti-HSV activity, independent of pH, and may interact with the cell surface preventing subsequent viral entry. Candidate components for this anti-viral activity include defensins, SLPI, lactoferrin or mucins

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02609 THE HEC PLACEBO: DESIGNED FOR "NO EFFECT"

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"Vehicle controls" are commonly used as placebos for two reasons: the vehicle (usually) provides a good physical match to the active product, and a vehicle placebo provides a comparison arm in which the absence of the active ingredient is the only difference between arms. Despite these common reasons for using the vehicle as the placebo, another consideration is arguably more important: the placebo must not cause unintended protection, and it certainly must not cause toxicity that increases susceptibility. Here we describe a placebo designed to minimize both protective and toxic effects. The design considerations included using: 1) a non-ionic gelling agent, HEC, (hydroxyethylcellulose) with no intrinsic microbicide properties (avoiding potentially active polyanionic gelling agents); 2) a preservative that is non-virucidal, non-inflammatory, and metabolizable (sorbic acid); 3) a formulation that has negligible buffering capacity (to avoid acid-mediated microbicidal effects even when formulated at pH ~4 to match the pH of the healthy vagina); and 4) a formulation that is isotonic to avoid causing an osmotic stress to the epithelium (and also to avoid the hypertonicity of many existing vehicle formulations, since hypertonic formulations cause osmosis that dilutes the gel and increases leakage from the vagina). In vitro studies document that the HEC Placebo has minimal cytocidal activity (by sperm motility and vaginal epithelial cell MTT assays), minimal stimulation of a proinflammatory response (IL-1 alpha release by vaginal epithelial cells), and minimal HIV inhibitory activity (2h virus-compound-cell incubation). In all four assays, the HEC Placebo had even less effect than K-Y® Jelly, a product that is generally assumed to be inert, and is commonly used as a control gel. In vivo experiments show that the HEC Placebo was not protective in an HSV-2 mouse vaginal challenge model. Moreover, unlike detergent spermicide/microbicides, when given 12 hours prior to HSV-2 challenge, it did not induce an increase in susceptibility to HSV-2. The minimal effects of the HEC Placebo should make it useful as a control gel for microbicide safety and efficacy trials

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02613 CLINICAL SAFETY AND ACCEPTABILITY OF IOCIDE VAGINAL GEL

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Iocide ® gel is a novel, iodine-based, topical microbicide developed for vaginal use. Initial clinical studies have evaluated the safety of a single treatment (targeted for use intrapartum to prevent early-onset neonatal group B streptococcal infections). Further studies, including multiple exposure testing, are planned. Following IND approval, Phase I human safety trials were initiated (currently on-going). Women were examined and tested for vaginal infections prior to any treatment (those with vaginal lesions or infections are excluded). Treatment visit (3-7 days later) included examination and safety tests obtained immediately prior to and 1 hour after placement of Iocide gel. Participants returned at 1 and 7 days post-treatment for repeat examination and safety testing. Women were questioned at the final visit regarding product acceptability and suggestions for improvement. Thus far, 9 women have completed the study. Post-treatment, none of the women reported vaginal itching, irritation or discharge. No inflammation or lesions were noted on exam. No significant changes were noted on haematology, chemistry, urinalysis or thyroid function. No persistent changes in vaginal flora were noted by culture. BV scores decreased in 2 women (from 10 to 7 and 7 to 4) and remained unchanged in the other 7 women (3 with BV, 4 without). All of the women found the product acceptable and if available for vaginal cleansing would recommend it to their friends.

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02614 VALIDITY AND FEASIBILITY OF SELF-SAMPLING FOR REPRODUCTIVE TRACT INFECTIONS IN SOUTH AFRICAN WOMEN

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Objectives: To determine the validity of self-sampling (using tampons or vaginal swabs) for reproductive tract infections (RTIs) with swabs obtained during speculum examinations as the gold standard, and to evaluate feasibility and acceptability of self-sampling procedures. Validity and feasibility results are presented here.

Methods: Four hundred and fifty women from a Community Health Centre in Gugulethu, Cape Town were enrolled in a cross-sectional study: Half the women were randomized to use either tampons or vaginal swabs. All specimens were tested for bacterial vaginosis (BV) and yeasts (Gram stain), Trichomonas vaginalis (TV)(culture), Neisseria gonorrhoeae (NG)(PCR), Chlamydia trachomatis (CT)(PCR) and human papillomavirus (HPV)(Hybrid Capture II). Questionnaires and focus group discussions provided feasibility and acceptability data.

Results: Overall 62%, 28%, 11%, 7%, 11% and 45% of clinician obtained specimens were positive for BV, yeasts, TV, NG, CT and HPV respectively. The self-sampled specimens performed favorably against the gold standard with the exception of TV (sensitivity of self-sampling 40.4%, specificity 99.5%) and HPV (sensitivity 69.9%, specificity 87.4%). Vaginal swabs and tampons performed similarly for diagnosing BV, yeasts, NG and CT, but vaginal swabs were more sensitive than tampons for diagnosing HPV ($p = 0.002$) and possibly TV ($p = 0.056$). Both self-sampling methods were found to be feasible.

Conclusions: This study demonstrates that self-sampling methods are valid and feasible methods for the diagnosis of most RTIs; they could be used for data collection in microbicide trials. However when using culture to detect TV, self-sampling methods cannot be recommended. Tampons are a less sensitive method for the diagnosis of HPV in comparison to vaginal swabs when diluting the tampon specimen to detect multiple pathogens and using Hybrid Capture II technology.

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02615 UNDERSTANDING THE ACCEPTABILITY OF SELF-SAMPLING METHODS FOR REPRODUCTIVE TRACT INFECTIONS IN SOUTH AFRICAN WOMEN

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Objectives: To determine validity, feasibility and acceptability of self-sampling (using tampons or vaginal swabs) for reproductive tract infections (RTIs). Acceptability results are presented here.

Methods: Four hundred and fifty women from a Community Health Centre in Gugulethu, Cape Town were enrolled in a cross-sectional study: Half the women were randomized to use either tampons or vaginal swabs. All specimens were tested for a range of RTIs. All participants were interviewed about their experiences with self-sampling and pelvic examinations in face-to-face interviews and nine focus group discussions were held.

Results: The majority of participants found the self-sampling procedures acceptable; the interview data showed hardly any acceptability differences between the tampon and swab groups. Women found taking their own sample very easy or easy (93%) and experienced no pain during sampling (97%). Almost all women felt confident, at ease, or okay with the self-sampling procedures (94%) but the majority was also comfortable with the pelvic examination (67%). Most women (64%) felt that it should be possible to do self-sampling at home, but 36% did not (mostly due to worries about making mistakes or forgetfulness). When asked for a preference, 42% would prefer a pelvic examination at the clinic, 31% would prefer self-sampling at the clinic, and 24% self-sampling at home, with 3% not having a preference. The focus group data supported these results and provided some additional insights about the underlying reasons for participant preferences.

Conclusions: Both self-sampling methods were found as acceptable as a speculum examination. Further research is needed to determine if the availability of self-sampling could improve RTI screening in resource-poor settings. Self-sampling in combination with certain types of lab testing could be used for data collection in microbicide trials (see also abstract on validity and feasibility).

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02618_2 CLINICAL SAFETY EVALUATION OF MICROBICIDE APPLICATORS

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Program for Appropriate Technology in Health (PATH) in collaboration with Profamilia in the Dominican Republic conducted a clinical evaluation of three microbicide applicators. The purpose of the study was to assess and compare the effect of these applicators on symptoms and signs of irritation of the external genitalia, cervix, and vagina as seen on colposcopy after a single applicator use. The three applicators evaluated were a single-use applicator from HTI Plastics, a reusable applicator from HTI Plastics, and a single-use applicator from Norden-Pac International. Both the HTI single-use and Norden-Pac International single-use applicators are currently being used in microbicide clinical trials. Twenty women were enrolled in this study through a Profamilia Clinic in Santo Domingo. Over the course of three months, each participant evaluated each of the three applicators in a separate clinic visit. At each visit, the participant underwent a baseline colposcopy, then vaginally inserted and removed a single applicator, and then underwent a follow-up colposcopy. All applicators were empty and therefore did not deliver any gel or product during the course of this study. Results of this study will be discussed, including implications for further applicator safety research and applicator selection for future clinical trials.

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02624 MINIMALLY INVASIVE ASSESSMENT OF MUCOSAL INFLAMMATION USING RECTAL SWABS

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Rationale: Previous studies have linked mucosal inflammation and disruption to increased risk of HIV-1 infection. Nonoxynol-9 has been linked to increased HIV transmission, possibly via IL-1b mediated activation in vaginal mucosa. For assessment of safety of topical microbicides, minimally invasive, sensitive techniques are needed to assess biologic correlates of mucosal inflammation. We report pilot data on the measurement of IL-1b and calprotectin expression by RT-PCR in cells eluted from rectal swabs. Both IL-1b and calprotectin are known to be increased in mucosal inflammation Methods: Investigations using cell lines were performed to optimize cell number and RNA recovery from swabs. Rectal swabs (n=29) were collected from five antiretroviral naïve Peruvian HIV+ subjects (median CD4 492 cells/?L; range (313-581), enrolled in an ongoing randomized, double blind, placebo controlled trial evaluating the effect of valacyclovir on herpes and HIV shedding. Swabs were inserted 3 cm from the anal margin and rotated once 360o and immediately stored in RNAlater. IL-1b and calprotectin expression were determined by real time PCR and expressed relative to normal, uninflamed colon RNA. Results: b-actin signals were seen for all the samples processed. IL-1b expression was determined in 20/29 subjects with a range of 0.2-2000 fold increase over normal; calprotectin in 27/29 subjects with a range of 3-5000 fold normal. Conclusions: These preliminary data demonstrate the feasibility of using rectal swabs to determine the presence of biologic markers of rectal inflammation in clinical trial subjects. Future studies are required to prospectively evaluate the correlation between the expression levels of IL-1b and calprotectin in rectal swabs with endoscopic, histological, and fecal calprotectin derived evidence of inflammation.

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02640 CHALLENGES OF IMPLEMENTING QUALITY MANAGEMENT IN CLINICAL RESEARCH IN URBAN AND RURAL SOUTH AFRICA

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Introduction
Implementing the Quality Control/Quality Assurance systems and determining the accuracy of research records, varies at different sites, posing challenges especially in developing countries and more especially in rural areas. Key functional areas require close supervision and adherence. The day to day review of work for correctness and completeness involves the various components of the research process, ensuring adherence to Protocol, Policies, Standard Operating Procedures and most important compliance to Good Clinical Practices.

Challenges of Key Indicators
Quality Management is an evolving process which ensures minimum errors and discrepancies, good research practices and most important "Quality Data". This abstract will seek to have a holistic approach of all areas of Clinical Research encompassing Good Clinical Practice, the implementation and sustainability of good Quality Management.

Listed below are some of the challenges: details will be included in the full presentation if accepted.
1. Regulatory Essential Documentation - differences in requirements and stipulations from Regulatory bodies from a developed country.
2. Informed Consent Process - problems with the high level of illiteracy among participants particularly from rural areas, problems with the diversity across rural communities and language barriers.
3. Training- the unavailability of experience and expertise from the rural environment (eg. clinicians, nurses, counsellors, medical technologists etc.)
4. The lack of resources to train staff in Good Clinical and Laboratory Practices as clinical trials require international standards but people have usually adapted to local standard and practices.
5. Implementing effective GPS systems to ensure the tracking and retention of participants.
6. Lack of appropriate management tools-lack of knowledge of general office administrative functions and systems limits the implementation of adequate management tools as required by the funders.
7. Inability to develop effective tracking tools that are key instruments in follow-up and retention rate of participants.

Consideration
a) Good Clinical Practice guidelines from developed countries should take cognizance of the limitations and challenges in developing countries.
b) Appropriate capacity building (human and financial resources) is essential for the implementation of a Quality Management system.

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02641 SEXUALLY TRANSMITTED INFECTIONS AMONG A COHORT OF FEMALES IN A MICROBICIDE FEASIBILITY STUDY

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Background: Women in a Microbicide Trial will need to be free from genital ulcers, and treated for any other STIs, at enrollment. Objective: To assess the prevalence of STIs among sexually active women attending FP and immunization clinics, who are in a microbicide feasibility study in rural KZN. Methods: After establishing reported symptoms of STIs, the vulva was inspected, followed by pelvic examination during which cervical and vaginal swabs were collected. Neisseria gonorrhoea and Chlamydia trachomatis infections were diagnosed by a strand displacement assay (ProbeTech BD ®). An in-house PCR was used for Trichomonas vaginalis. Bacterial vaginosis (BV) was defined as a Nugent Gram stain score >=7 in the absence of other cervico-vaginal pathogens. Syphilis was diagnosed with a RPR > 1:8 and a positive TPHA. Women with signs and symptoms of STI's were treated syndromically; others were treated on follow-up based on laboratory results. Results: STI results are available for 93 participants so far. No genital ulcers were observed. The overall prevalence of STIs was 18% if BV was excluded and 62% if BV was included. Of the 58 women with infection and/or abnormal vaginal flora, 35 (60%) were asymptomatic. Of the 27 women who were observed to have abnormal vaginal discharge, 19 (70%) were infected and 17 (63%) had BV. N.gonorrhoeae, C.trachomatis and T.vaginalis infection was diagnosed in 3, 3 and 11 (12%) women respectively. BV was found in 51 (55%) and 2 had syphilis. None of the women with syphilis had an ulcer or signs of secondary syphilis. Dual infections were found in 2 women. Only 11 of the 23 symptomatic women had an abnormal discharge. Conclusion: The prevalence of STIs and BV in this population is high and many women are or perceive themselves to be asymptomatic.

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02645 DO SITE FEASIBILITY STUDIES CONTRIBUTE TO THE PLANNING OF PHASE III MICROBICIDE TRIALS?

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Background The high cost of Phase III microbicide trials require careful selection of clinical sites capable of meeting the study end points. The current trend is to conduct site feasibility studies to ascertain site capability, adequate clinical and laboratory infrastructure, trained professional staff, adequate "at risk population", baseline behavioural characteristics, high HIV prevalence and incidence rates and high retention rates. Objective To describe the challenges and the lessons learnt from the microbicide development program funded feasibility study undertaken at 2 sites in Durban.

Results The sites selected for the studies were research "naïve" hence community entry and education played a crucial role in getting approval and support for developing infrastructure. Enormous amount of time was invested in basic education of HIV/STD, prevention strategies, ethics of research and the role of microbicides to not only the community but service providers at clinics in and around the area. Recruitment of trained staff was a challenge as many lacked clinical trial experience. The study initially targeted women from family health and post-natal clinics. The study generated enormous amount of interest hence recruitment was expanded to the community at large. Study specific development of case report forms was challenging as they were not only expensive but required several amendments after the study was implemented. The HIV prevalence rate in the community is high (>40%) suggesting that we had targeted the right population. The baseline behavioural characteristics were helpful in ascertaining behaviour risk factors and to develop the focus of risk reduction counseling. Retention of participants have not been difficult as the study has a high retention rate (>90%) after one year. Conclusion Sponsors should invest in site feasibility studies as they provide a "trial run" of the Phase III study. These studies provide an opportunity to address problems ranging from community entry to retention rates in preparation for a relatively "trouble free" Phase III implementation.

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02652 INHIBITORY EFFECT OF VAGINAL MICROBICIDES ON MOLECULAR AMPLIFICATION ASSAYS

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Background: Clinical trials to assess the safety, acceptability or efficacy of vaginal microbicides are conducted. Chlamydia trachomatis (Ct) and Neisseria gonorrhoeae (Ng) molecular amplification assays are performed at screening, follow-up and last visit of the clinical trial. Inhibition of the amplification assays introduced by the microbicide can jeopardize the study outcome.

Methods: The inhibitory activity of the microbicide was assessed by the recovery of Ng and Ct from known positive samples mixed with a volume of microbicide active product: Acidform, PSS, CS, or placebo gel: K-Y Jelly, PSS placebo, HPTN035 placebo. The samples were tested with Amplicor (Roche), Probetec SDA (B-D), and in-house PCR for Ct, Ng, and Beta2- microglobulin (inhibition control). The inhibitory activity was assessed in vivo on 1 volunteer/gel after 48 h of 1 dose gel-use.

Results: The CS gel inhibited in vitro as well as in vivo all assays, except the SDA. The PSS gel inhibited all assays in vitro, but not in vivo. The inhibition of the assays by acidform was resolved after sample dilution (2x), and no inhibition was detected in vivo. The HPTN035 placebo did not introduce inhibition, but the PSS placebo inhibited the Amplicor assay in vitro.

Discussion: Before starting a clinical trial with microbicides, the gel's inhibitory effect on amplification tests should be assessed, as this may influence the choice of assay, or may require modification in the test procedure.

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02661 CHARACTERISATION OF RECENTLY TRANSMITTED HIV-1 VARIANTS IN SUBTYPE C INFECTED WOMEN

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Characterization of recently transmitted HIV-1 variants is crucial to our understanding of mechanisms of transmission and the development of interventions. The majority of investigations show genetically homogeneous viral populations. However, a few studies suggested that gender differences exist, with women being more susceptible to multiple variant transmission. We identified and characterized HIV-1 populations in 19 recently infected women belonging to a sex worker cohort from Kwazulu/Natal. This cohort was established as part of a nonoxynol-9 vaginal microbicide, CoI-1492, phase III trial. Samples from these women were obtained within 3 months post infection. In a subset of five samples, taken from before seroconversion, diversity was assessed in both the envelope C2C3 and p17p24 region through heteroduplex tracking assays (HTAs), remaining samples were screened for diversity by C2C3 heteroduplex mobility assays (HMAs). The majority of samples (79%),

including all collected preseroconversion, harboured highly homogeneous HIV-1 populations. Four individuals (21%) exhibited high diversity in env, of whom three were dually infected with phylogenetically distinct subtype C strains. Preseroconversion samples, which best reflect the transmitted population, exhibited very little intraperson genetic diversity ranging from 0% to 1,8% (average 0,52%) in C2C3 and 0% to 1,2% (average 0,42%) in p17p24. Two of the five preseroconversion women had lower diversity in env compared to gag, suggesting selection associated with transmission and subsequent establishment of infection.

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02676_2 ACCEPTABILITY OF CARRAGUARD AMONG HETEROSEXUAL COUPLES IN A SIX-MONTH CLINICAL TRIAL IN THAILAND

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In phase II trials Carraguard use has been shown to be safe and acceptable in women. To evaluate safety and acceptability among heterosexual couples, we conducted a six-month, randomized, triple-blinded trial of Carraguard (3% carrageenan) compared to 2.5% methyl cellulose placebo in Chiang Rai, Thailand. We enrolled 55 low-risk couples who were in good health, were monogamous, did not use condoms regularly, and were free of HIV or other sexually transmitted infections (STIs). Couples were randomized to Carraguard or placebo gel and were asked to use the gel each time they had vaginal sex. The couples came for monthly follow-up visits including genital/pelvic exams, STI testing, interview and counseling.

Follow up and adherence with gel use instructions were >90% at each scheduled visit. There were no significant differences in acceptability between the two study arms, and acceptability remained high for the duration of the study. At study close, 85% of men and 92% of women reported they liked the gel somewhat or very much; 73% of men and 67% of women reported increased sexual pleasure; and 63% of men and 56% of women reported increased sexual frequency during the study. None of the men thought the gels had caused them any symptoms; 44% thought women could use the gel without her partner noticing it, and 94% thought that any increase in lubrication during sex was an advantage. Carraguard use was acceptable to low-risk heterosexual couples in northern Thailand.

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02679 HIV-1 RNA IN RECTAL MUCOSA SECRETIONS AND SEMINAL PLASMA; CONSIDERATIONS FOR MICROBICIDE EFFICACY

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Objective: High levels of HIV in rectal secretions and semen likely increase the risk of HIV transmission. An understanding of the natural variability of mucosal HIV shedding and the factors

that influence HIV levels in anogenital secretions is important for studying microbicide efficacy at the mucosal surface. Methods: HIV-infected men who have sex with men (MSM) made 2-3 visits over 4 wks at clinics in Seattle, WA USA and Lima, Peru to assess rectal, seminal and plasma HIV RNA levels. Mixed effects models were used to estimate the effect of factors on HIV shedding from the two mucosal sites. Results: Twenty-seven (42%) of 64 men were taking antiretrovirals (ART) and regardless of ART use, median HIV RNA levels were higher in rectal secretions (4.96 log10 c/mL) than in blood (4.24 log10 c/mL) or seminal plasma (3.55 log10 c/mL, P<0.05, each comparison). ART was associated with 1.3 log10 reduction in rectal RNA in a model without plasma RNA; with plasma RNA in the model, ART was not significantly associated with rectal HIV RNA levels. With and without plasma RNA in models, ART accounted for >1 log10 decrease in seminal HIV RNA level. Thus, controlling for plasma HIV, ART had an independent effect on seminal but not rectal HIV levels. Additionally, levels of HIV in rectal secretions were 0.5 log10 higher in Peruvian than in Seattle participants after controlling for ART use, CD4 count and plasma VL, and could not be explained by the examination findings or behavioral factors that we assessed. Conclusions: Factors that affect HIV levels in rectal secretions and seminal plasma have implications for understanding the risk of transmission associated with different sexual exposures with HIV-infected partners. Studies of microbicide efficacy need to account for highly variable mucosal HIV shedding in MSM.

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02699 A STUDY WITH THREE IMAGING TECHNIQUES OF VAGINAL GEL DISTRIBUTIONS

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Background: This study evaluated factors that influence vaginal distribution of microbicidal gels, and 3 techniques for imaging and analyzing these distributions: a fiberoptic probe to detect fluorescein-labeled material, gamma scintigraphy to detect radiolabeled material, and MRI to detect gadolinium-labeled material. Methods: Replens® and K-Y® were applied in a 3.5 ml bolus in 3 parous and 3 nulligravid women at each site. Vaginal distribution was compared when the woman did not ambulate after insertion to when she did ambulate, over time intervals up to 50 min after insertion. Results: Most spreading took place in the first 20 minutes. All techniques showed better spreading of KY when women ambulated, but better spreading of Replens when they did not. MRI was best able to detect the greater linear spread of Replens than KY when women did not ambulate (p=0.06) and greater linear spreading of KY when women ambulated compared with when they did not (p=0.06). The gels are known to have different rheological properties, suggesting different vaginal distributions. Scintigraphy and MRI results were generally similar but some probe results differed since it simulated penile intromission. The degree of observed spreading was greatest with the probe due to its pushing the gel into the posterior fornix. Conclusion: Gel properties interacted with ambulation and time in influencing distributions. Each of the 3 imaging techniques provides somewhat different but complementary information about vaginal formulation distributions. The choice of which to use in research will depend on the scientific context.

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TRACK C POSTERS

02014 ACCEPTABLITY OF DEXTRIN SULPHATE GEL IN WOMEN PARTICIPATING IN A PHASE II TRIAL IN KAMPALA, UGANDA

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Background: Social, cultural, and economic gender inequalities limit women's ability to protect themselves from infection. Microbicides offer a real possibility to help women to protect themselves from HIV/AIDS and other STIs. A phase II trial which included data collection on acceptability of microbicides was conducted in Kampala, Uganda.

Methods: Women aged 18 to 45 years were randomised to receive Dextrin Sulphate, twice daily (65) or placebo twice daily (15) or Dextrin sulphate pre-sex (10). They were interviewed after two and four weeks of gel use using a standardised closed questionnaire to explore gel acceptability.

Results: Responses are available from 69/80 women who were to use Dextrin Sulphate or placebo twice daily, and 8/10 of the women who were to use the substance pre-sex.

None of these respondents reported difficulties in inserting the substance, neither at 2 nor at 4 weeks.

27/55 women in the twice-daily arm using active gel and 5/14 of those using placebo and all eight women in the pre-sex arm expressed that the best characteristic of the gel was it's possible capacity to prevent HIV transmission. 53/55 women using active gel twice daily and all women in the placebo and in the pre-sex groups stated that they would continue to use the gel if it was available for free. The same respondents said that they would recommend the use of the gel to others. The two remaining respondents declared that they would not use it, and would not recommend it to others.

11/55 women using active gel twice daily found the gel interfered with sex, due to too much lubrication (3), continuous itching (4) and being too slippery (4). Women using gel twice daily stated that the worst characteristics they felt about the gel included- irritation, bleeding, too frequent application, and a cold feeling.

Only 1/77 partners of trial participants using the gel was reported to have had a problem with the gel because it was too cold.

Conclusions: The findings of this research on acceptability of dextrin sulphate gel so far are encouraging. The majority of study participants expressed generally positive attitudes towards the use of Microbicides.

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02023 KNOWLEDGE, PERCEPTION & ACCEPTABILITY OF MICROBICIDES AMONG HEALTH CAREGIVERS IN LAGOS STATE NIGERIA

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Background: Availability of a safe and effective microbicides will certainly be the most practical way to protect one against HIV/STI. Objective: To assess, the knowledge, perception and acceptability of microbicides among healthcare givers in Nigeria. Method: Data was derived from individual interviews using structured questionnaires. Knowledge, perception, as well as readiness to participate in the clinical trail of microbicides were evaluated. Result: A total of 240 respondents consisting of female 66%, male 33% with a mean age of 27 years, Clinicans 37.5%, Pharmacists 25%, MLS 16.6%, Nurses 12.5% and HIV/AIDS activists 8.3% and 58.3% single. On microbicides development, 20% Doctors, 19% Pharmacists, 16% MLS and 4.2% Nurses knowa bout the development. On willingness to participate, unmarried respondents were more willing P=0.04. There was a significant acceptance of microbicides by both married and single female P=0.05. Conclusion: Awarenessby Nigerian Health workers on Microbicides is very limited. There is urgent need for more information to be impacted to the general populace.

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02053 ASSESSMENT OF SEXUAL BEHAVIOUR AND CONDOM USE AMONG FEMALE ADOLESCENTS IN AWASSA, ETHIOPIA

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Objective: in Ethiopia, HIV infection rates continue to increase in female populations and women's health with regard to HIV transmission is severely compromised. Majority of females can easily affect by HIV due to unable to get best alternative method of prevention like Microbicides. This study intended to assess the sexual behaviour and condom use among of your female adolescents in Asawwa, Ethiopia. Methods: the study is a mixed qualitative and quantitative study carried out among sample of participants of female adolescents of family life skills education project recruited through Hope for The Generation Organization (HTGO), a non government organization working among youth, women and children in Asawwa, Ethiopia. 68 unemployed females adolescents age 12-24 years were selected on a convenience basis. A questionnaire with a combination of closed and open-ended questions was administered to the selected respondents and information on adolescent's sexual behaviour and condom use gathered. Focus Group Discussion and in depth interviews were also conducted. Results: In Asawwa, Ehtiopia females indulge in sex earlier than males. 10.29% of females start sex at the age 12-15 years. However, the best age for starting sex was 16-24 years, which is containing 89.7% of the respondents. The average age at first coitus is 17 year with a deviation of 2.15 years. 54.41% of females had more than one sexual partner in the past 12 months. The best reasons they mentioned were frequently changing sexual partners is considered as adventure, they easily get fed-up with one sexual partner, fall in love with new partners and tend to shift to others, etc. The other reason is that females have received money in exchange for sex. 47.05% of females had performed sex within the last 7 days prior of the last date of collection. 44.11% of females practice sex within the last 4 week. Only, 52.94% females mentioned to have sex longer ago. 28.23% of the females said they used a condom at the last sex. The reason for condom usage were: - curiosity 42.30%, disease protection and family planning 26.92%, family planning 19.23%, and disease protection 11.53%. The main source of condom if they need one today were peer educators (30.76%), family planning centers (23.07%), pharmacy (15.38%), partner (11.53%), and bicycle boys (7.69%). (87.3%) of the females responded that they knew where they can get condom when they need it. But 61.77% of the respondents were not used. The reason for not using condom

were 38.9% partners refused, 23.80% they don't like condoms, etc. Conclusion: Sex perceives as a means and recreation and passing time activity since majority of the young female adolescents do not have jobs. However, condom buying is considered as a shameful act among female adolescents. Advocating microbicides for the young females adolescents to protect themselves against all sexually transmitted diseases including HIV without making them difficult with the enjoyment of sex.

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02118 GENESIS OF MICROBICIDES CAMPAIGN IN INDIA

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Background:According to WHO, women and men both have reproductive health concerns but the nature of the problems, their causes and consequences differ since gedner roles and societal attitudes differ. In India, after half a century of freedom, the status of women in the country continues to be unsatisfactory –in the field of health,education, employment, political participation and decision making. Inequity of women is extended to all spheres of life, needless to say even in the sexual life. The HIV epidemic is largely driven by gender inequalities. Many women do not have the social power necessary to insist on condom use and fidelity or to abandon partnerships that put them at risk. Women need and deserve access to prevention options that are within their personal control. HIV/AIDS epidemic, creates the imperative need to pursue vigorously every means possible to stregthen women's immediate ability to protect themselves, through new women controlled technologies.

Genesis of the Campaign:Understanding the potential of microbicides as a tool bringing a new hope for prevention, after attending the Microbicides 2000, INN started to sensitize and and mobilize CBOs/NGOs and other stake holders broadening the campaign for microbicides in India. In the 5th National Convention of the Indian Network of NGOs on HIV/AIDS, for the first time in India the Microbicides and Female Condom were introduced through technical papers. For the first time, prevention options for women were discussed in a national forum. Education and Training services by INN members have conducted over 75 workshops for social workers, doctors and counsellors. Handouts and fact sheets were published in local languages, thus creating an enabling environment for education and a community preparedness. In October 2002 and in September 2003, national meetings were held for community stake holders and national policy makers. The campaign continues through the 'working groups' at a national level. Effective media coverage has already been promoted.

Forces in our favour: *Microbicides are included in the UNGASS declaration as a global priority *Microbicides is a priority of Indian Council of Medical Research (ICMR) and research and trials are on-going.

What we need to do : To develop networks of programmes for providers and policy makers and stakeholders to deal with numerous health, regulatory, gender, social and cultural biases that can facilitate and accelerate the research and facilitate the availability of microbicides for Indian woman.

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02131 ANITICIPATED ACCEPTABILITY OF A VAGINAL MICROBICIDE AMONG MEN ATTENDING THE MULAGO STD CLINIC IN KAMPALA, UGANDA

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Introduction: The study examined the feasibility of conducting a clinical trial of vaginal microbicides in high risk women in Uganda.

Methods: Semi-structured interviews were conducted with 155 women and 123 men, selected from among attendees of the Mulago Hospital clinic in Kampala, Uganda. Interviews collected data on personal characteristics; perception of risk of HIV & knowledge & attitudes regarding means of protecting oneself & one's partner from HIV/AIDS. A sub-sample of 14 women and 13 men were recruited for a product use study to test the acceptability of the K-Y gel as a mode of delivery of microbicides.

Results:Most participants, male and female (68%) are willing to participate in a future clinical trial of a microbicides product. Most men (94%) reported that they are likely to use a microbicide & they w'd approve of their partner using a microbicide. However, they are not willing to accept that one can be used without their knowledge. Most men would not use a condom if their partners are using a microbicide. Participants in the product test were positive about using K-Y gel, moting that it made the sexual experience more pleasurable.

Discussion: Data on the likelihood that microbicides will be accepted by women and men are important because clinical trials are informative only if people in them are willing to use the product

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02149 RESEARCH COMMUNITY AND THEIR NEEDS. HOW CAN WE HELP?

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Background: HIV prevention interventions such as microbicides or vaccines to reduce HIV transmission may take several years before being marketed among populations who participated in their testing. Current perception among research communities is that researchers enter and leave the community without making significant contribution to their welfare.

Objectives: 1. to assess the needs of the rural community of Hlabisa and to address those needs that were relevant to the research being undertaken.

Results: The needs identified were basic HIV/AIDS education and training within the community, training in home based care and social needs such as water, unemployment and alleviation of poverty. The researchers could only address issues related to HIV.

Addressing needs: We undertook to provide a certified HIV/AIDS education and home based care course to 50 participants from each of the 4 tribal wards in Hlabisa with the understanding with the community that each of the 50 individuals will undertake to train additional 50 and so on so forth.

The Hlabisa community working group approached the traditional leaders to seek approval to conduct training. Each leader was requested to select 50 individuals. A training programme was developed ensuring that it was not in conflict with other programmes. The community was consulted on appropriate use of language. The training manual was simple and user friendly with pictorial and graphic illustrations.

Training out come: Most trainees were women ranging in age from 17-42 years. Most lacked basic knowledge on HIV/STD. Majority believed in myths and misconceptions about HIV. Traditional healers were trusted for health care then primary health care clinics. Each trainee was able to comprehend the education provided and was confident of training other participants. A graduation ceremony will be held soon in the community to acknowledge their participation and their role in the community as educators.

Conclusion: Providing education and training to the community should be included in preparative studies for HIV prevention intervention. Community empowered with basic HIV prevention and care is a legacy the researchers can leave behind once the trial is over.

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02150 A PRELIMINARY COMPARATIVE STUDY ON CONDOM SOCIAL MARKETING VERSUS THE PROSPECT OF INTRODUCING MICROBICIDES AS AN ALTERNATIVE FOR HIV PREVENTION IN KATSINA STATE, NIGERIAPREVENTION

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ISSUE: Despite the intensive Condom Social Marketing [CSM]as a method of HIV/AIDS prevention in Katsina State, northwestern Nigeria, there has been associated poor compliance rate. This preliminary study is therefore to ascertain the reasons,possible options and the prospects of introducing microbicides as a more effective option in the near future.THE PROJECT: Public Enlightenment Projects[PEP NIGERIA], a national non-governmental organization based in Katsina, northern Nigeria. Katsina State is a core islamic state and one of the states that are currently implementing the Sharia as the legal code of conduct. The state like other northwestern states in Nigeria is made up of predominantly illiterate, highly religious and culturally [traditionally] motivated individuals. Early marriage is not only predominant but well accepted. The organization conducted a preliminary comparative study to CSWs, students, traders, single and married women and some men by random selection method. The use of simple standardized questionnaires was employed and a total number of three hundred [300] respondents sent in their responses.Questions asked ranged from: Knowledge of HIV/AIDS, its modes of transmission & prevention, knowlwedge of barrier prevention methods & their limitations, need forpossible options to available barrier prevention methods & the expected qualities of such e.g. microbicides RESULTS: A total of three hundred responses were received from respondents with ages ranging 15 -45 years and an average age of 24 years. About 50% of the respondents were female CSWs, 28% married women while the rest were men. 83% of the respondents had basic knowledge of HIV/AIDS as a disease while 67% had knowledge about its treatment/ARVs. 74% identified at leaset one mode of transmission while 26% identified four or more modes . 23% were aware of their HIV status while 35% were aware of their partner's HIV status. 50% of the sexaully active respondents used condom as a barrier method to prevent HIV/AIDS while only 25% used it always. Reasons offered for the inconsistency include: fear of perforation, ignorance of its effectiveness and reduced sexual pleasure. 71% prefer an alternate HIV preventive methods other than the condom which the female can only control. Qualities of such include effectiveness, reliability, prevention against other STIs, availability, and very low cost. CONCLUSION: Respondent demonstrated above average knowlwege of HIV/AIDS, its prevention, clinical features and transmission methods. The current most availaible barrier preventive method in Katsina State as in most other northen States in Nigeria has an identified low conpliance [25%] rate. From this study,

there is a need for an alternate which will be more reliable, effective and acceptable. PEP is currently conducting an advanced study to educate sexually active women and health service providers in the state about microbicides as an alternate barrier preventive method against HIV/AIDS, STIs and unwanted pregnancy and then assess the level of acceptability, preferred form of the product [gel, cream, pessaries e.t.c.], cost, undesirable side effects and products reliability.

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02170 ATTITUDES TOWARDS, AND EXPECTATIONS FOR, VAGINAL MICROBICIDES AMONG THAI HIV PREVENTION POLICYMAKERS

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Objective: To define attitudes, biases and expectations of key participants in the Thai HIV prevention arena regarding vaginal microbicides as a HIV prevention modality. Core questions to be addressed include: perceived advantages/drawbacks; potential user groups; distribution channels; sources of resistance to introduction; and expectations of efficacy.

Methods: Twenty-one selected participants were interviewed over a 4-week period utilizing a 20-question semi-structured questionnaire encompassing all core research questions. Respondents were both Thai and expatriate, representing the Thai Ministry of Public Health (MoPH), the Thai MoPH-U.S. CDC Collaboration, UN agencies, and NGOs.

Results: Several suggestive trends emerged: efficacy was the most important factor in determining future availability; potential for use without knowledge of a partner was seen as an advantage; the MoPH was regarded as the most important potential source of resistance to introduction; expectations of efficacy were higher in Thai vs. non-Thai respondents, especially MoPH officials; a mix of private (commercial) and public (governmental) channels was favoured for distribution; and over-the-counter distribution was highly preferred over prescription-based methods.

Conclusions: Direct collaboration with the Thai MoPH prior to introduction of a vaginal microbicide is essential; microbicides should not initially be introduced as a stand-alone prevention modality; and a combination of public health and commercial channels will be required for effective and wide-spread distribution.

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02198 ACCEPTABILITY OF FEMALE CONDOM AND VAGINAL MICROBICIDE USE AMONG AT RISK FEMALES IN THE GAMBIA

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Gambia is one of the few countries in sub-Saharan Africa with adult HIV rates lower than 2%. Keeping this rate low is imperative. The subordinate roles of females make many of the current HIV/AIDS prevention strategies inadequate. A female controlled HIV prevention option would be appropriate. We carried out a cross-sectional questionnaire-based study to assess the acceptability of female

condom and vaginal microbicide use by 'at risk' females in the greater Banjul area of The Gambia. 111 women (aged 16 to 52 years; mean 28.01 SD 7.24 years) were sampled. 69.4% were married. 54.1% felt they were at risk of HIV infection. 27.9% have used the male condoms before, while 17.1% were presently using it. 86.5% and 97.3% respectively had never heard of or seen a female condom, of whom 54.5% will be willing to use it if available. Perception of HIV risk was positively correlated with willingness to use the female condom (Pearson's Correlation = 0.352, p = 0.000 [2 tailed]). 72.1% of the respondents would use a hypothetical vaginal microbicide while 88.3% would support its use. Educational status but not marital status was associated with willingness to use the vaginal microbicide. There was unanimity among the respondents that women should be allowed to determine their HIV/STI prevention options. We conclude that in urban Gambia, many sexually active women are likely to use the female condom and vaginal microbicide if available, however the vaginal microbicide would be more acceptable than the female or male condom

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02216 KNOWLEDGE, ATTITUDE AND PERCEPTIONS OF NIGERIAN CHURCHES AND FAITH ORGANIZATIONS TOWARDS MICROBICIDES

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Background: the recently introduced mandatory HIV and VRDL screening as preconditions for marriages among members by churches and faith organizations in Nigeria not only prevent the spread of HIV and other STIs to unsuspecting spouses, but also from mother-to-child. This strategy is of significant role in STIs/HIV prevention and was explored to assess members understanding and perceptions about Microbicides.

Objective: to assess the knowledge, attitude and perceptions towards Microbicides by members in churches and faith organizations in Nigeria.

Method: Members of churches and faith organizations were identified, trained and assigned to counsellors as well as interviewers. Data collection tools were structured questionnaires, focus group discussions and individual interviews. Two churches and two faith organizations were selected for this study from November 2002 to May, 2003. Sociodemographic data obtained age, sex, marital status, level of education as well as occupation.

Results: Out of 246 respondents, 53% were female, mean age was 25±18 years. Participating groups included married 64%, divorced 19%; bachelors & spinsters 61%; widowed 15% and 29% of adolescents. Level of education were primary, secondary and post secondary consisting of varying forms of occupation while 10% were illiterates. On knowledge, married 45%, divorced 30%, batchelors and spinsters 49%, widowed 22% and adolescents 19% indicated knowing what Microbicides are. On acceptability, only 40% accepted regular use. Perceptions for non-acceptability included side effects, ignorance, religious beliefs, interference with fertility if stop and inducing excessive vaginal lubrication. Degree of knowledge and acceptability was proportional to level of education

Conclusion: Immense levels of ignorance exist about Microbicides and resistance to use among members of churches and faith organizations in Nigeria. Sensitization programmes among clergy and leaders of these groups about microbicides is urgently needed to enable enough information and benefits to be imparted to their members.

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02219 INVOLVEMENT OF MEDIA EXECTIVES/PRACTITIONERS AS MEMBERS OF CONTRACEPTIVE SOCIAL INFORMATIONSYSTEM TOWARDS MICROBICIDES: THE NIGERIA INITIATIVE.

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Issues: Nigerian, media organizations form the strongest pivots in disseminating information in the fight against the spread of HIV infection since its discovery two decades ago. Despite this , the disease has continued to be a major public health problem with devastating effects on families being hard-pressed to meet the social and medical needs of members down with AIDS. This poster presentation is designed to describe the need to integrate private media executives/practitioners as partners into existing contraceptive social information system (CSIS) for the campaign against the spread of HIV including other STIs through the use of vaginal Microbicides.

Project: In the absence of vaccine or cure, AIDS prevention brings a new urgency to making vaginal Microbicides more acceptable, desirable and viable product in the developing world. In May 2003 the Nigeria HIV/AIDS Research Network, an NGO, organized a two day workshop tagged "Enhancing Nigerian Microbicides Information Initiative" for 25 private media personnel drawn from print and electronic departments aimed at reviewing current knowledge as well as identifying specific strategies needed to be addressed for the inclusion of vaginal Microbicides into the existing CSIS in Nigeria. This workshop poised to enhance the perceived value and desirability of vaginal Microbicides through branding strategies, audience segmentation exploring adequate spectrum of action, not harmful to the vaginal flora and safety for vaginal use.

Results/Lesson Learned: Results of the pre-test on the existing CSIS showed that, knowledge, attitudes on information dissemination towards vaginal Microbicides still remain rudimentary among media executives/practitioners who are institutions for information dissemination in Nigeria. Though the post test assessment indicated increase awareness in the level of willingness to participation the ongoing campaign, there are more to be done to achieve the most expected goals. Involvement of media executives/practitioners as partners of CSIS promise to be a major component of the efforts to overcome consumer acceptable barriers and misconceptions towards vaginal microbicides in a developing country like Nigeria.

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02224 AWARENESS AND POTENTIAL FOR USE OF NEW HIV PREVENTION TECHNOLOGIES AMONG GAY MEN IN THE UK

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Background: Approximately 80% of people living in the UK who acquire HIV are gay men. Awareness & knowledge of new prevention technologies (NPT) as well as practical access are needed in this population for NPTs to make a contribution to reducing HIV incidence.

Method: Web-based national self-completion survey of gay & bisexual men recruited on Gay.com & Gaydar over summer 2003. Qs include: demographics; HIV testing history; sexual behaviour; HIV prevention needs; awareness and potential for use of 4 new HIV prevention technologies (vaccines, microbicides, home HIV-testing & post-exposure prophylaxis).

Results: N>10,000 men living in UK, 82% sex with men only, 94% white, 45% university educated, 10% unemployed, 6% tested HIV positive; 12% thought they had been involved in sexual HIV exposure in the last year & a further 20% thought they may have been involved. 21% has heard of PEP, 22% of home-testing, 23% of microbicides & 66% of vaccines. If needed, 71% said they would consider using PEP, 53% home-testing, 59% microbicides & 50% vaccines. The majority of the rest said they may consider using.

Conclusions: PEP, the only NPT even partially available in the UK, had the largest proportion who would consider using but the lowest level of awareness. Products from all four prevention technologies have large numbers of potential users among gay men in the UK.

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02255 INSTITUTIONAL CAPACITY AS A LIMITING FACTOR FOR MICROBICIDE RESEARCH IN NIGERIA

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Aim: The paper takes a look at the institutional capacities of institutions in Nigeria saddled with the responsibilities to review proposals for microbicide research using universally acceptable ethical guidelines

Method: A survey was carried out to assess the number of institutions in Nigeria that could possible undertake a microbicide research in Nigeria. The capapcity of these institutions to review microbicide research proposals was also assessed in terms of structures, facilities and manpower

Results: Of the over 80 Medical and Health Institutions in Nigeria were microbicide research could possibly be conducted, only 21 have established Ethical Review Committes with FWA accreditation. There is no National Ethical Review Board in place in the country presently which could accredit and monitor the activities of these Ethical Review Boards.Of the 21 registered with the FWA, less than 10 have properly constituted and functioning Ethical Review Committees. Only one institution has a number of the offices of its members connected to the internet to enable individuals search for information on microbicde if the need arises in view of dearth of information on the subject matter in the country. All institutions compalian of inadequate staffing thus their inability to monitor and evaluate research proposals approved.

Conclusion: There are inadequate institutional capacities in Nigeria to review proposals for microbicide research for ethical considerationin Nigeria. There is an urgent need for capacity building in this area to enable microbicide research to be conducted with internationally acceptable standards in Nigeria

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02262 ADVOCACY AND POLICY DEVELOPMENT TOOLS CAN ENHANCE MICROBICIDE CAMPAIGN

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HIV/AIDS prevention is relevant to all categories of people. Apparently many people still do not understand the usefulness of all HIV prevention methods. The problem has been or is lack of advocacy to fill he gap between a researcher and end users. Involving intermediates like program managers, coalitions (alliances), media, communities and policy makers initiates this development: People for instance who can identify HIV/AIDS/STI issues and assist in documenting the prevalence of particular problems, provide an information base for developing or revising policies. People who can bring issue that affect their target audiences to the attention of policy makers. Those who can join or build coalitions which can demonstrate collective concern about, those who have direct access to policy makers, or provide them with critical information, and may even recommend actions for the policy makers to take and those who have impact or influence to the people. The overall scope is to bridge the gap to heighten awareness of HIV/STI as a national issue vertically and horizontally, to contribute to a favourable political and social climate for HIV/STI, prevention and care, to mobilize the community and relevant social organizations for prevention and care, to popularise technical information about prevention and care, to deal with specific Community problems through appropriate messages and media directed at identified target audiences and create no barriers between science and the public. This will enhance a common understanding and inclusive ideology for microbides campaign.

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02269 MICROBICIDE ACCEPTABILITY AMONG HIGH-RISK URBAN U.S. WOMEN: EXPERIENCES AND PERCEPTIONS OF SEXUALLY

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We conducted a study of microbicide acceptability among high-risk women in Hartford, Connecticut to assess their readiness for and interest in vaginal microbicides as a possible method to prevent HIV/STI. The study combined qualitative ethnographic (cultural-cognitive interviews and focus groups) and quantitative (risk and acceptability survey) methods to explore women's perspectives on HIV/STI risk and prevention, and their experiences with and attitudes about vaginal contraceptives that are similar to many microbicides being tested. We developed a scale of microbicide acceptability to use in assessing their general attitudes toward microbicides, and to compare perceived acceptability among subgroups within the sample. This study assessed women's willingness to use microbicides during regular sexual activity with their primary, casual and paying sex partners in

various contexts of sexual activity and risk. Ethnographic and survey data from the study indicated that these predominantly inner-city African American, Puerto Rican, and non-Hispanic White women have had very limited prior experience with vaginal products, particularly vaginal contraceptives, but were highly interested in having an option like microbicides for HIV/STI prevention as an alternative to condoms. They also expressed willingness to use a microbicide in research trials and during their regular sexual activity with their partners. These findings confirm the potential value of vaginal microbicides to improve prevention outcomes for high-risk inner city women in the United States and suggest promise for broader acceptability and application as well.

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02311_1 ACCEPTABILITY OF MICROBICIDES AMONG MALE PARTNERS OF THE COL 1492 TRIAL PARTICIPANTS

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Nih Grant No: Hd40154

Introduction
Effectiveness of microbicide is dependent on acceptability by both sexual partners. We undertook a post-trial study to assess acceptability among male partners of women (sex workers) who participated in the COL 1492 (52.5mg N9) trial from 1996-2000.

Methods:
73 male sexual partners of sex workers were recruited for the study. Semi-structured interviews were administered to 73 men (43 steady partners and 30 clients). Data was collected on partner communication, gel use disclosure and microbicide acceptability.

Results:
All steady partners and only six (20%) clients were informed of gel use by the sex workers. 49% of the steady partners and all clients (n=6) reported that the gel had no effect on their sexual pleasure while 37% steady partners reported an increase in sexual pleasure. 20% said the gel decreased sexual pleasure when it thickened in the women's vagina. 80% of men liked the gel and reasons were: belief that the gel had cleansing effect on the penis, healed penile sores, prevented diseases and increased sexual pleasure. Clients (52%) and steady partners (42%) will use the microbicide on all occasions even if it is less effective than condoms for disease prevention.

Conclusions:
Perspectives of male partners will contribute to the use and acceptability of microbicides. These findings suggest male partners' involvement in clinical trials of vaginal microbicides may be an important determinant of adherence to gel use during and after the trial.

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02320 USE OF A SIMULATED MICROBICIDE IN TWO-WEEK TRIALS BY HIGH-RISK WOMEN IN HARTFORD, CONNECTICUT

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A study of microbicide acceptability conducted with high-risk, primarily African American and Puerto Rican women in Hartford, Connecticut explored issues affecting the acceptability and feasibility of using a microbicide with their primary, casual, and/or paying sex partners. As part of this study, we conducted a two-week behavioral trial in which 102 participants used an over-the-counter vaginal moisturizer to simulate microbicide use during sex with these kinds of partners. Trial participants documented their sexual activity through encounter forms and follow-up self-report at 2-weeks, and were offered the option to participate in a repeat trial for a second two weeks. The microbicide simulation trial showed significant willingness of these women to use a vaginally inserted microbicide-like product, and success in using the simulation product in a wide variety of locations with all types of sex partners. The trial also showed they used the microbicide-like product with greater frequency than they used condoms, indicating the potential of a microbicide to increase the number of protected sexual encounters among high risk US urban women. The women also demonstrated an ability to document their sexual activity, product use and condom use during the trial period through completed sexual encounter forms, verified by returned tabs from the product applicators. These findings have important implications for developing studies of microbicide use by urban U.S. women at high risk, possibly including clinical trials. They also confirm the potential value of microbicide availability as an HIV prevention option for these women.

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02355 MICROBICIDES DEVELOPMENT PROCESS IS A CHALLENGE: INDIA EXPERIENCE

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ISSUE: The risk of HIV among the women of North East region of India is reflected by high risk of IDUs of men. Women are the disadvantaged group because of historical, geographical, socio-economy, religions & cultural factors, law and practices. As a result they cannot negotiate for safer sex and their right to self determination has been denied. Policy makers need serious concern about the innovative approaches in dealing with microbicides to give better choice.

DESCRIPTION: This paper is to investigate the nature and the extent of the involvement of stakeholders, community leaders, politicians, judiciaries and policy makers of the region in developing and access to microbicides. These ongoing informal survey draw opinion and feedback and which can really help to analyze and to determine what factor contribute in order to ascertain the success of this development.

LESSONS LEARNED:
1] Suspicion-
Many of them asked about the safety of microbicides
Assurance about non-contraceptive microbicides as well as dual action.
Availability of the microbicides and its affordability.
High price due to TRIPS, PATENT & Drug and Cosmetic laws.

2] Suggestion-
From the users opinion
It should be less irritating, longer lasting, biodegradable, pleasing and easily removed.
It should also have pleasant taste and smell.

3] Expectation-
If effective microbicide will be the better choice than condom.
It will help in having pleasing and exciting sex and the practice of safer sex will be increased by all.
Applicable to anal sex will reduce HIV infection.
Many of them refused to comment as they did not take interest.

RECOMMENDATION:
Participation of special task force in the campaign, comprising Civil societies, NGOs, Academic institution and Manufactures for effective advocacy to educate elected and appointed policy makers for their greater involvement.

Policies and procedures for feasibility assessment, planning, implementation, oversight and evaluation are required. As trial proceeds, individuals and public interest should be protected with informed consent. Acceptability issues and ethical aspects of this research should be addressed.

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02377 MICROBICIDE TRIAL FEASIBILITY STUDY IN HIGH-RISK WOMEN IN MWANZA, TANZANIA: LESSONS LEARNED

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OBJECTIVES: To investigate whether high-risk women in Mwanza City, Northern Tanzania are a suitable study population for a phase III clinical trial of vaginal microbicides.

STUDY POPULATION: 2,400 women working as mamalishe (in makeshift eating places selling food cooked outdoors), or in bars, guesthouses, video halls, vilabu (shops selling locally brewed beer), hotels, restaurants and disco halls ("facilities") in ten wards in Mwanza City.

METHODS: A community-based sexual & reproductive health service has been established in 10 city wards. Field staff conduct mobilisation activities at facility level. Participants are enrolled and followed-up at mobile clinics conducted at guesthouses and hotels. Free reproductive health services, including syndromic management of STIs, family planning, health education and voluntary HIV counselling and testing (VCT) are provided. Field staff visit women at home and at the workplace to remind them to attend for scheduled 3-monthly follow-up appointments.

RESULTS: 1,463 participants were recruited over 12 months to end-Aug 2003. Re-attendance at 3, 6, 9 and 12-month follow-up was 78-83%; 9.2% (135/1,463) of participants enrolled were lost to follow-up. HIV prevalence at entry was 24.4% (344/1412) but varied by facility type from 18.2% (69/379) in mamalishe to 34.9% (45/129) in bar workers. 68.7% (1016/1478) of participants requested VCT at entry. 70.8% (719/1016) of these attended to receive their test result. Estimated annual HIV incidence (Mar 03) was 6.1% [0.1-12.1%]. Condom use at last sex with spouse/main partner was 16.3% (154/945) at enrolment, 28.9% (135/467) at 3 months and 19.3% (67/348) at 6 months follow-up. Condom use last time had sex for gifts/money was 58.6% (154/263) at enrolment, 67.2% (39/58) at 3 months and

63.8% (30/47) at 6 months follow-up. 10.1% (143/1416) of women at enrolment and 8.2% (25/306) at 6-months follow-up had a positive urine pregnancy test.

CONCLUSIONS: Evidence to date suggests that women working in food and recreational facilities in Mwanza are a suitable study population for a phase III clinical trial of vaginal microbicides. Developing locally appropriate strategies for health care provision, community mobilisation and participant tracing were key to successful recruitment and retention of the cohort.

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02379 EVALUATION OF KNOWLEDGE AND ACCEPTABILITY OF MICROBICIDES BY COMMERCIAL SEX WORKERS IN LAGOS NIGERIA

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Background:
There is widespread interest and hope in a safe and effective microbicide as a potential way of prevention of transmission of sexually transmitted diseases and HIV/AIDS.

Objectives:
To evaluate the knowledge of, and acceptability of microbicides by female commercial sex workers in Lagos, and to assess their willingness to participate in trials involving the use of microbicides.

Methods:
Data was derived from a multicentric cohort of female commercial sex workers, through focus group discussions, individual interviews, and use of structured questionnaires covering socio-demographic data including age, religion, marital status, parity, education, and "primary occupation". Sexual health and vaginal practices, HIV/STDs status and knowledge, types of microbicides known /used, reasons for use and specific beliefs, as well as readiness or willingness to participate in any trial were evaluated.

Results:
Total number of 851 females, mean age 24±11 years, 28% married, 32% were graduates, 45% high school certificates, while 23% had primary education. On knowledge of microbicides, products identified included foaming tablets, gels, antiseptics, antifungal creams and ointments, antibiotic powders, douches, vaginal tablets, petroleum jelly, 'alum', and tradomedical preparations. Knowledge and use of foaming tablets, gels, antifungal and antibiotic powders was proportional to level of education. Reasons for use included to ensure healthy state of the vagina (65%), personal sexual pleasure (45%), sexual pleasure for male clients (52%), to prevent contact of infection (62%), keep the vagina tight (45%), and for contraception (45%). Generally where substances were used, men or clients were not made aware. Most preferred products that disintegrated without much wetness in the vagina, and not coloured. On vaginal practices, 35% reported regularly cleansing the vagina just before sex, while 26% used routinely, antifungal creams like Canesten, and Gynostatin also believed to have antibacterial effects. Non-acceptability was due to physical discomforts such as itchiness in the vagina, dysuria, vaginal ulcerations, and excessive wetness by some vaginal pessaries. Some respondents still use "alum" and some trado-medical preparations for tightening of the vagina. On willingness to participate in microbicide studies, 57% were ready provided they are not long term studies. Single young respondents were more ready to participate than married.

Conclusion
There is increased knowledge by commercial sex workers in Lagos about microbicides. Since they constitute a risk group, they need protection. However, there is much concern about cost, availability, safety, effectiveness and comfort in use.

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02384 THE ASSESMENT OF DIFFERENT METHODS OF COLLECTING SEXUAL INFORMATION DATA ON CONDOM USE

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Background: Collection of accurate sexual behaviour data is not often possible. However such data must be collected for the assessment of the efficacy of microbicides during the phase III clinical trial. It is hoped that the feasibility study could try alternative methods to collect quantitative data to supplement case record forms (CRFs).

Objective: To estimate condom use through the CRF and compare results to information collected through different methods to ascertain sexual practices and condom use, at baseline and following active health promotion including access to free condoms

Methods: Different methods were used to collect condom use data, which included CRFs at enrolment and follow-up, a survey involving 400 subjects from the study population, 12 focus group discussions (FGDs), 6 with men and 6 with women, and 6 in depth interviews (IDI) with community key informants, and recently coital dairies have been used to collect data; currently data has been collected from 44 participants.

Results: CRF findings from 375 women at baseline showed, frequency of condom use with husband/regular partner as never 65.6%, sometimes 28.4%, most of the time 0.9%, and always 5.0%. At 3 months follow up condom use since last visit was, never 68.1%, sometimes 22.5%, most of the times 4.4% and always 5.0%. Condom use the last sexual act with husband/regular partner at baseline was 13.1% and at follow-up 14.4%. In the survey population 60.7% said they never used condoms, 22.6% sometimes, 8.3% quite often and 9.0% always. The 44 women who completed coital diaries had reported very similar condom use to the rest of the 375 women on CRF. Using the diary over the course of one week 81.8% reported that they never used condoms, 11.3% sometimes and 6.8% used them on each occasion. FGDs and IDIs discussants considered that, condom use was good for the prevention of sexually transmitted infections; however condom use within marriage is seen as inappropriate. Most discussants felt it would promote mistrust between couples and may eventually bring conflicts. The other problem associated with condom use was reduction of sexual pleasure and promotion of promiscuity.

Conclusions: The results from the different quantitative research methods used show similar findings, and suggest that consistent condom use in this population of women is low. This may be explained by the fact that the majority of women completing CRFs and coital dairies are in monogamous relationships, and there is a perception that condom use in this context is inappropriate.

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02385 DRY SEX PRACTICE IN A ZAMBIAN COMMUNITY

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Background: The practice of dry sex can have an effect on the acceptability and use of the microbicides. A feasibility study has been established in preparation for a clinical trial and 382 women living on the Nakambala sugar estate have been enrolled since January 2003. The study assessed among other things sexual practices that could influence acceptability and use of a microbicide.

Methods: Focus group discussions (FGDs) were conducted among men and women and in-depth interviews (IDIs) were conducted with key informants as part of the on going feasibility study. A survey was also conducted in the same community as a follow-up to the qualitative methods. A total of 12 FGDs (6 with women, 6 with men), and 6 IDIs (4 women, 2 men) were conducted. 400 questionnaires were administered to men (174) and women (226) from the six communities of Nakambala sugar estate for the survey using a stratified random sample.

Results: The data from the survey show that out of 226 female respondents, 96 (42.5%) reported that they practice dry sex. Asked what they used to have dry sex, 53.1% drank medicinal porridge, 5.2% drank traditional medicine, 3.1% had tattoos on the body, 9.4 % inserted traditional medicine in the vagina, 21.9% put a cloth inside the vagina and removed it before having sex and 8.3% used salt in water that had traditional medicine.

FGDs and IDIs reported that participants understood dry sex as having sex when the vagina is not lubricated. The women usually keep their vaginas dry because they believe a man enjoys dry sex. To keep themselves dry, women usually insert things in the vagina like, a piece of lemon, a dry cloth. They also add some herbs in porridge and wash their genitals with very cold water. However women do not enjoy dry sex because it causes bruises. Family planning pills, promiscuity among women and witchcraft are perceived to be the causes of 'water' in the vagina. Some men felt that dry sex is more enjoyable than wet sex since it enhances friction and warmth. However there were a few men who acknowledged that dry sex causes bruises and increases the chances of getting HIV infection.

Lessons learnt: Dry sex practices are common in the population. It is important to understand the nature of dry sex since it could increase the transmission of HIV and other sexually transmitted infections (STI). It could also influence the effective use of a microbicide. This understanding is important for the design of the protocol for the efficacy trial.

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02388 SEXUAL BEHAVIOUR AND ATTITUDES TOWARDS VAGINAL MICROBICIDES AMONG COUPLES IN RURAL SW UGANDA

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Background: Female controlled methods of HIV prevention such as vaginal microbicides are being developed to offer increased protection against HIV infection. The objective of this study was to explore common sexual practices and perceptions about condoms and microbicide use among couples in rural Uganda.

Methods: HIV discordant and concordant negative couples in regular sexual relationships were identified in a serological survey (December-July 2003) and invited to participate in the preparation for a phase III microbicide trial. Individual questionnaire interviews and Focus Group Discussions (FGDs) were conducted. All participants were offered both individual and couple HIV voluntary counselling and testing.

Results: A total of 108 couples (76 HIV discordant, 32 HIV concordant negative) in regular sexual relationships participated in the study. A total of 206 individual questionnaire interviews (98 men, 108 women) and 12 FGDs [6 with male, 6 with female] each with 8-12 participants were conducted. 60% of all interviewees reported that it was acceptable to discuss condom use with their partners. Ever use of a condom with a regular sexual partner was 40% in men and 42% in women. Of those reported ever use of a condom 48% of men and 42% of women had used them at least once in the last 3 months, 35% of men and 24% of women used them in the last 4 weeks, and 33% and 22% male and female respectively at the last sexual contact. Reasons for not using condoms include: being in a stable marital relationship, desire to have children and fear of creating distrust among partners. Similar findings were reported in the FGDs. Both male and female FGD participants reported desire to use microbicides with their regular partners because of potential benefits in HIV prevention. Preference was for a microbicide gel that is "not too slippery" and "does not feel cold on use","does not reduce sexual pleasure" or "affect partners' sexual urge and energy".Women were concerned about the possible burning sensation in the vagina. Oral sex was mentioned in FGDs although it is not usually talked about in community. Anal sex was considered unacceptable.

Lessons learnt: In this rural population, men and women were able to discuss sexual matters including the potential use of microbicides. Current levels of condom use are unlikely to protect the HIV negative partner among discordant couples.

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02389 COUPLE HIV COUNSELLING AND TESTING IN FEASIBILITY STUDY FOR A PHASE III MICROBICIDE TRIAL IN UGANDA

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Background: A feasibility study in preparation for a phase III microbicide is presently being conducted among HIV discordant and concordant negative couples in rural Uganda. HIV Voluntary Testing and Counselling (VCT) is offered to study participants in order to identify discordant and concordant negative couples but also to address ethical issues.

Objectives: To assess the acceptability of couple HIV VCT and disclosure of couple HIV status to both partners in rural Uganda.

Methods: Adults who live as a couple in a regular sexual relationship were identified during an initial demographic survey. Consenting participants provided a blood sample for HIV testing in a subsequent house to house serological survey (December 2002-June 2003). These participants were offered VCT and disclosure of results at a locality of their choice (at individual home or a village based counselling office). Sera were tested using Capillus rapid test and confirmed by EIA, and Western blot testing when necessary. Counsellors offered pre-result counselling either to couples or individuals depending on clients' wishes, emphasising the advantages of couple counselling and result sharing between partners. Upon satisfactory pre result counselling, HIV test results were then shared with couples or individually. Further post- test counselling is offered to those who require it.

Results: A total of 2004 couple provided a blood sample. 88% of couples were HIV-negative concordant, 4% were HIV-positive concordant and 8% were HIV-discordant. 1684 participants (84%) have so far received results. Among those who got results, 688 (34%) received and shared the result as couples in the presence of a counsellor. In 238 (12%) couples results were disclosed to both individuals following participants' request. 758 individuals had partners who preferred not to know their test results and have not yet received them.

Conclusions: We observed a substantial HIV discordance rate among stable couples. There is however an encouragingly high proportion of individuals wishing to know HIV test results either individually or as couples. It is hopped that disclosure of HIV results within couples is likely to reduce transmission of HIV among those in discordance.

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02390_2 IMPLICATIONS OF CURRENT INTRAVAGINAL PRACTICES AMONG FEMALE SEX WORKERS IN NAIROBI, KENYA

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During 40 key informant interviews (KII) on sexual behavior among female sex workers (FSW) in Nairobi, Kenya, themes on intravaginal hygiene practices with implications for diaphragm acceptability and effectiveness trials, particularly as used with microbicide, emerged.

Post-coitus, FSW generally pushed fluids into the vagina, for example, coca cola from a bottle, and wiped the vagina with their fingers, tissue paper, cotton wool or cloth. They did this to feel clean, fresh, and to appear free of signs of sexual activity before the next client. The varied non-commercial products used may interfere with their vaginal mucosa and flora placing them at greater risk for STI/HIV infection and theoretically impacting on the effectiveness of microbicides and female-controlled barrier devices such as diaphragms.

Sex worker habits and needs vis-à-vis intravaginal hygiene may potentially be a problem for correct use of a diaphragm particularly with microbicide. Alternatives such as a clean finger dipped in boiled water for intravaginal hygiene should be considered. Counselling to dissuade potentially harmful practices and products used post-coitus is warranted.

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02391_1 SEXUAL BARRIER PRODUCT ACCEPTABILITY PREDICTS USE AMOUNG HIV-POSITIVE ZAMBIAN WOMEN

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HIV-positive (n = 359) Zambian women were assessed regarding the effects of a culturally tailored cognitive-behavioral based intervention on sexual risk behavior and sexual barrier acceptability and preference. Participants received vaginal lubricants as surrogates for vaginal chemical barriers (microbicides) in addition to male and female condoms. Mean age was 29, average education level 2 years; 34% had HIV+ partners. Women were Bemba (23%), Ngoni/Nsenga/Tumbaka (33%), Tonga/Mambwe/Namwanya (18%) and Other (26%); 78% were unemployed, 79% were sexually active and 11% practiced dry sex.

At baseline, 6 and 12 months post-intervention, Sexual Activities and Acceptability Questionnaires were administered to assess frequency of product use, acceptability and preference. At baseline, 34% reported consistent barrier use, male condoms (92%), and/or female condoms (13%). Protected sex increased over time ($F = 14.5$, $p = .001$). Following trial use, participants identified ease of use, comfort, ability to talk about sex and control as the most important characteristics of sexual barrier products, and the potential to use a product secretly as the least important. Product acceptability by women and their partners predicted use of gels ($F = 13.41$, $p = .001$) and suppositories ($F = 12.07$, $p = .001$) but not male or female condoms. Most preferred VCB was suppositories; acceptability of all VCBs increased over time. Results suggest VCB and condom use and acceptability may increase following trial use. Findings highlight the importance of interventions that increase acceptability of VCBs for risk reduction. This study was supported by NIMH R01-MH63630.

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02391_2 SEXUAL BARRIER PRODUCT ACCEPTABILITY PREDICTS USE AMOUNG HIV-POSITIVE U.S. WOMEN

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HIV-positive (n = 232) multiethnic women were assessed regarding the effects of a culturally tailored intervention on sexual risk behavior, sexual barrier acceptability and preference. Women received vaginal lubricants as surrogates for vaginal chemical barriers (VCBs; microbicides) in addition to male and female condoms. Mean age was 39, education level less than 12 years; 43% had HIV+ partners. Participants were African American (75%), Hispanic (9%), Haitian (4%), Caucasian (7%) and other (5%); 85% were unemployed and 72% were sexually active.

At baseline, 6 and 12 months post-intervention Sexual Activities and Acceptability Questionnaires were administered to assess frequency of product use, acceptability and preference. Of those assessed, 75% reported consistent barrier use, of these, male condoms (95%), and/or female condoms (31%) or VCBs (10%). Protected sex did not decrease over time ($F = .789$, $p = .463$). Following trial use, participants identified ease of use, effectiveness and comfort as the most important characteristics of any sexual barrier product, and the potential to use a product secretly as the least important. Product acceptability predicted use of female condoms ($F = 23.71$, $p = .001$), gels ($F = 5.86$, $p = .02$) and suppositories ($F = 7.83$, $p = .007$). Most preferred VCBs were gels. Acceptability of gels and male condoms increased over time. Results suggest VCB use and acceptability may increase following exposure with no decrease in condom use. Findings highlight the importance of interventions that increase acceptability of VCBs for risk reduction. This study was supported by NIMH grant # R01-MH63630.

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02413 PREFERENCE FOR GEL USE WITH DIAPHRAGMS IN ZIMBABWE

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HIV/STI effectiveness trials will likely consider testing diaphragms both with and without microbicide gel, thus it is important to know how much a gel affects its ease of use and acceptability.

In Harare, Zimbabwe, 20 women who had completed a diaphragm acceptability study (DAS) 5-16 months ago, came for a one-time visit. They practiced inserting/removing the diaphragm with (a) no gel, (b) gel on the rim and (c) gel in the dome and rim, then received an interview. Median age was 27 (range: 20-41), 60% completed high school, 95% were married, 90% were current diaphragm users. Thirteen (65%) disliked the diaphragm without gel most. They said it was dry, hard, difficult or painful to insert/remove, or uncomfortable to wear. Only 3 women (15%) liked this option best, saying it kept their vagina "naturally" dry. Most women preferred to use gel with the diaphragm: 95% were very comfortable inserting/removing the diaphragm with gel on the rim; and were very comfortable inserting (65%) and removing (85%) it with gel on the rim and dome. Thirteen (65%) liked gel on the rim best, as it eased insertion/removal, comfort wearing diaphragm and was unnoticeable. Concerns about gel in the dome included feeling "unnaturally" wet, gel oozing, diaphragm moving, and inability to use it covertly.

Most women preferred some lubrication with the diaphragm, and the paramount issue was preserving imperceptibility while wearing it or having sex. How the gel feels and its amount can influence diaphragm acceptability and should be addressed during method counselling.

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02418 BUILDING COMMUNITY MOBILISATION FOR MICROBICIDES - THE TIME IS NOW

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There is global debate on the best time to introduce the concept of microbicides to communities who are not specifically attached to Trial sites. Most community participation focuses on those communities involved in trials. The Gender AIDS Forum, a Southern NGO working in South Africa has developed and is piloting a model to introduce microbicides to broader communities in an attempt to mobilise a broad based response to microbicides for three key reasons: to get support for microbicide development and other female controlled methods, to ensure wider involvement in trials and to facilitate post devlopment rollout and availability of the products.

The Gender AIDS Forum works with a range of organisations in the HIV/AIDS, Women and development sectors. Facilitators from these organisations will be trained using materials which have been developed in English and Zulu. The facilitators will build capacity in both their organisation and also in the communities they work with, Mentoring and support will be provided by GAF and organisations will be encouraged to support advocacy campaigns.

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02422 ACCEPTABILITY OF VAGINAL MICROBICIDES IN PUNE, INDIA: DEVELOPMENT AND VALIDATION OF MEASURES

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A woman's ability to use microbicides will be influenced by psychological, social and environmental factors, including individual perceptions of HIV risk; patterns of sexual communication and other couple dynamics; and presence or lack of privacy within the household. Measurement of such constructs poses challenges, because of the role that culture plays in determining how each are characterized. Research was conducted in Pune, India to 1) identify factors that promote or inhibit correct, consistent and continuous use of risk reduction behaviours, or lead to non-use; and 2) develop and validate psychometric scales that measure these constructs for use in an up-coming Phase 2/2b Study of Microbicide Effectiveness.

Results will be presented from analysis of repeat in-depth interviews with 30 women and their partners, recruited from a range of clinics that serve high- and low-risk populations that will feed into the Phase 2/2b Trial. Ten of these women and their partners will have participated in a Phase I Safety Trial of Pro-2000. Specifically, the presentation will address 1) the relationship between constructs and levels of condom and/or microbicide use; and 2) similarities and differences in the ways that men and women conceptualise risk and communicate about and/or act on risk reduction behaviours. Finally, approaches to scale development and validation will also be presented.

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02441 SEXUAL PRACTICES OF WOMEN RECRUITED TO A MICROBICIDE TRIAL FEASIBILITY STUDY IN MWANZA, TANZANIA

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Introduction: The acceptability of vaginal microbicide gels is likely to depend on social and sexual norms within a particular social group. Coital and vaginal practices may affect efficacy. This paper presents characteristics of sexual behaviour of female food and recreation workers and the social environments affecting them in Mwanza, Tanzania.

Methods: Ethnographic research over a period of one month in food and recreational facilities included observing interactions and conducting informal interviews. Eight focus group discussions with individuals identified during ethnographic research provided in-depth data on sexual practices. Quantitative sexual behaviour information was collected in Case Record Forms (CRF) and coital diaries.

Results: Qualitative data show that vaginal products are used orally or applied directly to the vagina to increase and decrease lubrication, to control menstruation and to clean the vagina e.g. lemon juice is applied to decrease vaginal size and reduce lubrication. Frequency of douching after sex is dependent on access to washing facilities, type of partner and time of day. CRF data (July 2003) show that few women, 4.7% (57/1206) reported the use of products to increase lubrication, whilst only 1.25% (15/1197) applied products to decrease lubrication. Multiple partners are common as many women supplement low regular incomes by selling sex. This may be encouraged by owners/managers who may also request sex from workers. During ethnographic research anal sex

was reported to take place sometimes during transactional sex, but only 1% (12/1206) of women self-reported having had anal sex on the CRF. Qualitative data show that condom use may wane once a relationship is established as a demonstration of mutual trust.

Discussion: Qualitative data show a wide variety of practices to clean the vagina and increase sexual pleasure of self or partner, and indicate that anal sex is sometimes practised by food and recreational facility workers. The CRF does not include data on frequency of specific lubrication, menstruation and douching practices, and may underestimate the extent of anal sex and overestimate condom use. Sexual norms in the Mwanza cohort seem unlikely to prevent the use of vaginal microbicides although work environments and access to washing facilities may affect women's ability/willingness to use microbicides. Further data collection and analysis will allow presentation of vaginal/ sexual practice frequencies and conclusions on the likely effect of norms and environments on microbicide acceptability, use and effectiveness.

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02448 MICROBICIDES INTRODUCTION IN TAMIL NADU, INDIA: POLICY MAKERS' PERSPECTIVES

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Methodology & Results: This study assessed the opinions of 17 key policy-makers on the potential public health, political and socio-cultural issues that are likely to be barriers or catalysts for the introduction of microbicides in Tamil Nadu, India. Respondents were selected through purposive and snowball sampling and the assessment was conducted over three weeks in 2003 through in-depth interviews. Most stakeholders were in favor of microbicides introduction in Tamil Nadu either as an adjunct method or as an alternative to the condom when it cannot be used. A few respondents expressed fears of condom migration. Respondents saw a wide range of methodological advantages of microbicides such as use by sex workers or in marriage, clandestine use, control by the female, and an expansion of prevention options. Partial efficacy, potential side effect and product application were cited among some of the disadvantages. Most respondents listed sex workers and certain married women as potential user groups, in addition to several others. A range of formulation preferences was discussed with the main point of divergence around concerns of vaginal product acceptability among women. Most respondents strongly felt that microbicides should be affordable, available over the counter and through strategies that addressed potential issues of stigma.

Conclusion: There is strong support for microbicides introduction among policy makers in Tamil Nadu overall, but issues around women's preference of formulations, condom migration, partial efficacy and access need to be further explored if introduction in this state is to be accepted and successful.

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02449 PHASE III MICROBICIDE TRIALS: CONFRONTING THE SCIENTIFIC, REGULATORY AND ETHICAL CHALLENGES

Stone, Alan

Large-scale trials to evaluate the performance of microbicides in the field are complicated by unavoidable tensions between scientific and ethical ideals, as well as by logistic and economic constraints. Thus, the optimal trial design in terms of having the highest chance of giving reliable

answers to the questions we are asking must be tempered by other considerations, especially the need to minimise harms – physical, social, emotional – to trial participants and others involved. The urgent need to advance promising candidate microbicides into Phase III trials is widely recognised and microbicide developers, ethicists and drug regulatory authorities are actively working together to confront these challenges. Many of the central issues arise from the fact that microbicide field trials have to be carried out in populations at high risk of acquiring HIV, often in developing country settings where resources for providing care are limited. What level of clinical care should be offered, especially to those who seroconvert during the trial and, indeed, to those who are found to be HIV+ at initial screening? Who should provide it, and for how long, and who should pay for it, and how can this be done without creating unacceptable disparities between trial participants and the rest of the community? What can be done to ensure that the community will continue to receive the microbicide if the trial is successful? Another set of issues concerns the need to find an appropriate balance between the drug regulators' duty to ensure high levels of safety and effectiveness and what clinical trials can realistically achieve. What confidence limits should the trial's findings be required to meet? What minimal level of effectiveness would be of significant benefit in different epidemic scenarios? What are the arguments in favour of, and against, the use of a placebo product in the trial's control arm, or alternatively of having a condom-only (no-gel) group as the control, or of having both types of control within a single trial? How can an ethical Phase III trial be controlled when we need to evaluate a second-generation microbicide if an earlier product has already been shown to be safe and effective? A critical analysis of these and other central dilemmas will be presented.

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02468 ROLE OF COMMUNITY BASED ORGANIZATIONS IN ADVOCACY AND MOBILIZATION AROUND MICROBICIDES

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BACKGROUND: Since 1999 Nkumba AIDS Community Initiative has been raised microbicide awareness amon HIV/AIDS clients, youth groups, church groups and women groups. Currently we are working hand in hand with Ministry of Health to develop an empowerment intervention program that will incorporate HIV/STI prevention and microbicide education. Workshops are continuously updated and highly interactive advocating for enhanced microbicide education as integral to HIV infection.

RESULTS: Our activities have expanded to include other AIDS Organizations, policy makers at community and District levels. This community interventions facilitate the ongoing involvement of community members by linking them to international advocates for microbicides egg 'Alliance for Microbicide Development' which regularly updates us on new findings.

CONCLUSION: A powerful grassroots demand exists for more and better HIV prevention options for women. Using community based educational strategies it is possible to elicit, activate and focus the demand which will enable grass-root voices calling for women controlled tools to be heard collectively by national and international policy makers.

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02474 ASSESSING MEN'S KNOWLEDGE AND ATTITUDE TOWARDS MICROBICIDES

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Objective: To assess men's attitude towards vaginal microbicides.

Methods: The study was conducted from 8 STD clinics (n=98) and from general population (control group – n=101). Brief product demonstration of a vaginal microbicide gel was followed by private discussions. Survey included questions on demographics, sexual activities, gender, condom use and willingness for partners to use microbicides. Mean age from STD clinics was 31 years and that from the control group was 28 years. Married men included 19% (n=21) from STD clinics and 20% (n=22) from the control group.

Results: Among the men from the STD clinic, 83% (n=78) and 92% (n=90) from the control group wouldlike partner to use vaginal microbicide. Both groups 85% would like to be informed if partner was using the product. Other issues raised included concerns about safety of the product and its use should be the decision of both partners. Regarding preference between microbicide and condom 55% (n=51) among those from STD clinic and 70% (n=73) preferred microbicide to condoms.

Conclusion: This study shows that while men understand the need of women to protect themselves, they would like to be involved in decision making process. Introduction of microbicides will certainly influence use of condoms. Success of microbicides will be aided by support from men.

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02475 CHALLENGES IN ACCESS AND USE OF MICROBICIDES

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Issue: Women have always been at the center of HIV/AIDS. Prevention measures like condoms favour men. It is the man to decide whether to use it or not. Microbicide could break this gap by offering a woman-controlled method. The female condom did not gain popularity here due to lack of proper education and empowerment to women. Women must be empowered to negotiate for safe sex so as so to have a say in prevention programs. The way forward hs been to introduce a microbicide in our prevention programs. Our advocacy and mobilization department embarked on a program to integrate microbicide in our overall HIV/AIDS and reproductive program.

Results: Focus group discussions were conducted and knowledge, perception of risk and prevention strategies were looked at. Results show that women had information about HIV/AIDS and knew ways of HIV transmission and prevention. However, many did not use condoms with their stable partners (ie 65% n=125 out of 207 respondents). Many admitted lack of dialogue in issues relating to sex. Women welcomed information on microbicides. Questions raised included accessibility, costs, application, side effects and continuity of supply.

Conclusion: A woman-controlled HIV prevention method should be at the forefront of prevention programs. It is important to make such new methods affordable to the ordinary woman so they can play a central role in HIV/AIDS prevention

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02476 ASSESSING THE NEED FOR A NON CONTRACEPTIVE VAGINAL MICROBICIDE

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Issue: Available methods of protection from HIV and STIs also prevent contraception. Women with HIV positive partners and those with unknown sero status who wish to become pregnant must put themselves at risk of HIV infection. This is a bog problem in areas of high STI and HIV prevalence. In most of these areas women's status is closely linked to fertility and motherhood. Many reproductive advocates and scientists have stressed the need for a female controlled method that would allow contraception but prevent HIV and other STIs.

Project: Sixteen focus group discussions of seven to ten participants were held with women attending nine Family Planning Clinics run by Uganda Private Midwives Association including Seeta-Nazigo AIDS Project. Discussions centered on participants views of HIV/AIDS, need for contraceptives and non contraceptive microbicidal products. Women expressed a strong support for an HIV prevention method that is within their personal control stressing the need for both contraceptive and non contraceptive products. Women showed a desire to become pregnant but still protect themselves against HIV and STIs.

Conclusion: It is a fact that many women still put themselves at risk of HIV by their desire to get pregnant. A woman's role is still associated with fertility. Scientists should make every effort to develop effective contraceptive and non contraceptive methods to be easily used by women.

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02500 HIV PREVENTATIVE STRATEGIES AND THE USER OF ANTI RETROVIRAL DRUGS

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Issue: Users of anti retroviral drugs are aware of the need to avoid further infection, but are they effectively using the available HIV preventative strategy?

Approach: At The Joint Clinical Research Centre, 450 patients receiving anti retroviral drugs 250 women and 200 men were asked about the preventative strategies they were using. This was done through individual and couple interviews. Information about awareness about the need for HIV prevention and the microbicides in the making was given to individuals and during focus group discussions.

Findings: 5% were abstaining, 85% were using condoms but inconsistently with coitus interruption method (withdrawal) 5% were using condoms inconsistently while the remaining 5% were not using any methods because of poor couple communication.

Lesson learned: The HIV prevention strategies available are inadequate for the user of anti retroviral drugs. There is a longing for a more suitable method which a microbicide is likely to fulfil as either a single method or as a complementally method.

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02527 SELF-REPORTED CONDOM USE AND HIV/STD INCIDENT CASES: HIV PREVENTION TRIALS NETWORK STUDY 016A

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Background: Condom availability is an essential service provided to women participating in vaginal microbicide trials. The extent of condom use among participants can often affect the study design, sample size and analysis. The measure of condom use is participant self-report. Acquisition of an STD or HIV during a condom use evaluation period can be used as a valuation tool for self-reported condom use.

Methods: Women at risk of acquiring HIV in Lilongwe and Balantyre, Malawi and Harare, Zimbabwe attended 5, condom promotion counselling sessions over a 2 month period, then every 3 months (quarterly) for 9 months. At each visit, condoms were offered and women reported condom use in the previous 2 weeks. At the baseline and every quarterly visit, specimens were collected for HIV and STD diagnostics: blood for HIV by ELISA/WB, syphilis by RPR/MHA-TP; cervical for gonorrhea by culture, chlamydia by EIA; vaginal for trichomonas by wet mount. An incident case of HIV/STD was defined as a negative baseline result followed by a positive result at any follow-up visit.

Results: 1745 HIV/STD infected women were enrolled and 200 (11.5%) were lost to follow-up before HIV/STD incident data could be collected. 1545 women were followed for a median period of 477 da7s. 323/1545 (20.9%) had an incident HIV/STD infection including 284 women with an incident infection and self-reported condom use data in the period in which they acquired HIV/STD. Of these 83/284 (29%) repored <75% condom use, 33/284 (12%) reported >75% but <100% condom use, and 168/284 (59%) reported 100% condom use in that period. Of the 1220 women who reported 100% condom use at 1 or more visits, 168/1220 (14%) acquired HIV/STD during that reporting visit.

Conclusion: Incident HIV/STD data implies that condom use was over-reported by participants in this African cohort study. The design, sample size calculation and analysis of microbicide investigations must carefully weigh the bias and confounding potential of self-reported condom use

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02530 MICROBICIDES ADVOCACY: CHALLENGE OF RURAL WOMEN

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BACKGROUND: Vaginal product use may interfere with microbicides use and acceptability.

METHODS: Women were interviewed about their vaginal practices (vaginal cleansing, drying/tightening, medications, menstrual hygiene and the use of lubricants and spermicides) as part

of a Phase II trial of Carraguard™ gel (n=400), and a Phase III feasibility study (N=200), in Uganda. Vaginal product use was permitted under the Phase II protocol.

RESULTS: Women in Kasangati (near Kampala) and Lakai (near Masaka) reported to engage in vaginal product insertion before enrolment into the trial for the following reasons: cleansing (19%, 52%), drying and/or tightening (8%, 5%), medication (35%, 22%) and menstrual hygiene (27%, 21%). Use of vaginal lubricants and spermicides was rare at both sites. During the Phase II trial, women in Kasangati and Rakai continued to use vaginal products for cleansing (14%, 30%), medication (22%, 10%) and menstrual hygiene (15%, 18%), and almost all women (96% at both sites) regularly washed their external genitalia. Vaginal cleansing typically occurred once or twice per day while bathing, with plain water or water and soap, using a finger or a wet towel. Eleven percent of women reported to regularly cleanse the vagina just before sex. Many more women in Kasangati than Rakai preferred a dry and/or tight vagina during sex (63% versus 11%) and thought that their male partners preferred it dry and/or tight (65% versus 14%).

CONCLUSION: Women in Uganda commonly use vaginal products for a variety of reasons. Types of practices and preferences for vaginal lubrication vary by region and should be taken into account when studying microbicide acceptability. Education messages should clearly state that women should cleanse their vagina between microbicide insertion and sex.

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02571 READINESS OF A RESEARCH SITE TO DELIVER ON A PHASE III MICROBICIDE TRIAL IN DURBAN, SOUTH AFRICA.

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Background
Selection of Microbicide Phase III trial sites is based on sites having adequate clinical and laboratory infrastructure, trained staff, a population with a high HIV prevalence and incidence rates and the ability to retain enrolled participants for a period of time.

Objectives
To describe baseline socio demographic and behavioural characteristics
To determine baseline HIV/STI prevalence rates.
To ascertain age-specific HIV prevalence rates.
To determine HIV and STI incidence rates.

Methods
The study commenced in August 2002. As of August 2003, 919 women from the communities of Tongaat and Verulum were screened for this study. Women who were less than 18, pregnant, allergic to latex, planning to leave the study sites in the next year and HIV positive were excluded from the study. 421 consenting women were enrolled in the study. Women were followed up quarterly when a clinical gynecological exam was conducted for collection of swabs for STI testing; blood was collected for HIV, syphilis and HSV-2 serology. All STI were treated.

Results
The mean age of women was 30 years. (range 16-57 years). 67% had secondary education. 78% were unemployed and 51% had a household income was R500-1000. 53% of women lived with their partners. 29% used condoms last time they had sex. 8% practiced anal sex and 22% of these were protected by condoms. 3 women had more than 1 partner.

Baseline HIV prevalence was 47% with the highest prevalence rates in the 25-35 age group. HSV-2 prevalence was 85.1%. Prevalence of N gonorroheae, C trachomatis, T vaginalis and syphilis was 1.5%,6.4%,9,2% and 2%, respectively. HIV incidence after 133 women years of follow-up was 8%. Incidence of N gonorrohoeae (N= 230) ,C Trachomatis (n= 232) was 2% and 6% respectively. Over 90% of the women attended the last visit.

Conclusion
The sites selected for future microbicides study has demonstrated adequate clinical and laboratory infrastructure, trained staff, high participant follow-up rate, appropriately targeted population with a high HIV prevalence and incidence rates.

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02580_1 MALE PARTNERS ACCEPTABILITY OF PMPA GEL AS VAGINAL MICROBICIDE: HPTN 050

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Background: HPTN 050 is an ongoing Phase 1 Safety and Acceptability trial of the vaginal microbicide candidate PMPA (Tenofovir), a colorless, odorless, and transparent gel.

Methods: By design, 96 women will participate in the trial, 24 of them using the gel during vaginal intercourse with their male partners. We present the acceptability evaluation of the 10 men who completed the study to date (full sample data will be presented at the conference). Five men were African American, 1 was European American, and 4 were of other or mixed ethnicities; mean age was 38.9 years, and 5 participants were unemployed. They responded to a structured questionnaire and were also interviewed in-depth individually about their experiences using the product.

Results: Likes and dislikes: Overall, 8 of the 10 men reported liking the gel "somewhat;" 9 liked its color, 8 liked its consistency, and 6 liked its smell. Only one man reported burning sensation in the penis or genital area and itching, but characterized this as "rarely" a problem. There were no reports of pain when urinating, rash, or any other physical problems. Three reported that the gel soiled clothes/bed linens, although only one said this was a problem 'most of the time.' Four reported leakage of gel either before, during, or after sex; 2 reported the gel drying out during sex, and 3 said the gel got sticky during sex. All 10 men reported that the gel made sex feel "more wet;" yet, only one participant reported that wetness was a problem 'most of the time.' Sexual pleasure: 7 men said the gel increased their sexual pleasure or made no difference; 5 felt it increased or made no difference in their partners' pleasure; one man felt the gel decreased his pleasure, and 2 felt it decreased their partners' pleasure. Future use: 8 men said they would definitely or probably use the gel in the future. Only 2 said they would definitely or probably not use it. Eight of the men stated that they would likely use the gel with a condom as opposed to using the gel alone.

Conclusions: Overall acceptability of PMPA for vaginal use during intercourse was good among the male respondents. They manifested intentions to use the product in the future, if it became available over the counter, and they said they would use it with condoms. Exerpts from the qualitative interviews that provide further insight into the personal experience of the men will be discussed during the presentation.

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02580_2 INTENTIONS TO USE RECTAL MICROBICIDES AND PRIOR USE OF ANAL LUBRICANTS WITH NONOXYNOL-9 IN A PROBABILITY SAMPLE OF MEN WHO HAVE SEX WITH MEN

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We report the results of a telephone survey of a household probability sample of 879 adult men who have sex with men (MSM) living in San Francisco. Their mean age was 43.6 (range, 18-90, SD=0.44). Two-thirds had a 4-year college degree; 79.9% were European American, 8.8% Latino, 4.7% Asian-Pacific Islander, 3.7% African American, and 2.8% other; 26.9% were HIV-infected (all percentages are adjusted to population estimates). Data were collected between May 2002 and January 2003 by trained interviewers using CATI software. On average, the interview took 45 minutes.

Of the total, 761 men had had sex with men in the prior year. Two thirds of them had had anal sex, and half had had it unprotected; 35.8% of the sexually active men had had unprotected receptive anal sex (15.4% with multiple partners), and 44.8% unprotected insertive anal sex (20.0% with multiple partners); 90% of those having unprotected anal sex (UAS) had used lubricants.

58.6% of all respondents had heard about microbicides, and 82.9% had heard about Nonoxynol-9 (N-9). Of the latter, 30% had used products containing N-9 during the prior year. 38.6% of the sample believed that N-9 could irritate of injure the person's rectal tissue and/or increase the risk of getting HIV. Only 6.5% believed that it could prevent HIV transmission.

Intentions to use a microbicide regardless of its level of effectiveness were more prevalent among those who had had UAS (vs. those who had not) and the HIV infected. This seems to indicate that MSM who do not use condoms consistently or are HIV-infected may be especially receptive to using rectal microbicides.

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02583 HPTN 050

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Background: HPTN 050 is an ongoing clinical safety trial of PMPA gel (Tenofovir). It is a clear gel, inserted into the vagina prior to sexual intercourse using an applicator. The acceptability of microbicides will ultimately be key to their use and effectiveness.

Method: Women (n=75 to date) participated in this Phase I stepped parallel dose and frequency study. Participants used product either once- or twice-daily for 14 days. Cohorts were stratified by HIV serostatus and sexually abstinent vs. active. Mean age was 36.2 years; 13 were Latina, 61 non-Latina: 36 African American, 26 White, 2 Asian, and 11 'other.' Quantitative acceptability data were collected prior to and following product use. Qualitative focus group data collected following product use were analyzed according to both a priori research questions and emergent themes. Preliminary data are reported here (full sample data will be presented at the conference).

Results: Among 71 women who completed the follow-up acceptability questionnaire, most reported that they 'liked somewhat/a lot' the gel's color (92%), smell (80%), consistency (76%). One-fourth reported that the gel soiled clothing and/or bed linens. Among women who were in sexually active cohorts (n=13), many reported gel leaking out during (46%) and/or after (69%) sex and 85% reported the gel made sex feel more wet. 94% reported they would 'definitely/probably use' the gel if they had reason to be worried about HIV and this gel were available, while 6% reported they would 'probably/definitely not use' the gel. Of note, 73% reported that they would prefer a microbicide that could not be noticed by a sex partner. Qualitatively, product texture/consistency was acceptable, but its lubricating qualities and leakage during sex presented a challenge for some women. Women expressed varying preferences regarding the timing of product use (e.g., wait-time between application and sex) and for female-controlled HIV prevention methods in general and issues of covert use.

Conclusions: The candidate microbicide PMPA gel appears to be acceptable to study participants. Particular characteristics of the product's formulation and leakage and consistency during sex will be discussed both quantitatively and qualitatively.

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02585 THE ACCEPTABILITY OF A NOVEL VAGINAL MICROBICIDE, CELLULOSE SULFATE GEL, AMONG HIV-POSITIVE FEMALES: HPTN 049

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Background: HPTN 049 is an ongoing Phase I safety trial of Cellulose Sulfate (6%), a nonspecific inhibitor of HIV binding. As a microbicide, it is a thick and odorless gel, with a slightly hazy light brown tint. It is inserted into the vagina prior to sexual intercourse, using a pre-filled applicator.

Methods: Phase I, double blind, randomized controlled, frequency escalation study. HIV-positive women were exposed to product for 14 days. Cohorts are stratified by: sexually abstinent vs. active; and once- vs. twice-daily dosing. Quantitative acceptability data were collected before and after product use. Preliminary data from both the experimental gel and placebo groups are reported here.

Results: HIV-positive women (n=55 to date) have participated: mean age 38 years: 8 Latina, 35 African-American, 11 White, and 9 'other'. 18 reported prior use of vaginal lubricants during sex. 42 reported prior use of vaginal medications, with 18 using vaginal products in the form of gels. Among the 52 women who completed the follow-up acceptability questionnaire thus far, most reported that they 'liked somewhat/a lot' the gel's color (98%), smell (92%), consistency (85%). 31% reported that the gel soiled clothing and/or bed linens. Among women in the once-daily sexually active cohort (n=7), 4 reported gel leaking out during sex and 4 reported that it leaked after sex. All 7 reported the gel made sex feel more wet. Across the first 3 cohorts, 51 reported they would 'definitely/probably use' the gel if they were worried about HIV and this gel were available, while 1 woman reported she would 'definitely not use' it. Of note, 32 reported that they would prefer a microbicide that could not be noticed by a sex partner.

Conclusions: The majority of HIV-infected women reported that the gel (cellulose sulphate or placebo) was acceptable with primary issues raised being soiling of clothes and leakage of gel during sex. Further analyses will be conducted on completion of the study and unblinding of the arms, and will include data from all cohorts, male sexual partners of sexually active women's cohorts, and

comparisons between experimental product and placebo. Implications for the use of microbicidal products in HIV-positive populations will also be discussed.

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02587 PROJECT ON PROMOTION AND AWARENESS ABOUT MICROBICIDES

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Background: More then 90% of HIV new infection is spread through unprotected sex. Especially young women are biologically more vulnerable to HIV and other STI's than men. Because of gender inequality, condoms while effective if used correctly and consistently are simply not a feasible option for many women. The development of a prevention method that women control could save millions of lives. A Microbicide offer the potential for women to protect themselves and their sexual partners from HIV and other STI's.

Issue: Microbicides offer many potential advantages for increasing a women's control over her sexual life and for protecting women, men and children from infection.

Method: BOSS & CIPCA a unique CBO having 350 doctors and 6250 blood donors as its members working on HIV/AIDS since 1987, started a project "Awareness and promotion of Microbicides in 1998 onwards. Under this project 121 campaigns were conducted to educate 'Sexually Active Healthy female' (SAHF) aged between 20-40 years in the region about STI's/HIV/AIDS and microbicides. These campaigns targeted towards sex workers, women migrant labours, women with multiple sex partners and women students in colleges and universities.

Results: More than 52,501 sexually active healthy females have received awareness about STI's/HIV/AIDS and Microbicids through our campaigns. Especially women student groups have shown keen interest in microbicides use and availability. Sex workers are eagerly waiting for arrival of microbicides in the market.

Conclusion: In south India sexually active healthy females urgently need safe, effective, available and affordable microbicides to protect themselves from HIV and STI infection with a method under their control.

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02589 SWAA: USING FEMALE CONDOM TO PAVE THE WAY FOR MICROBICIDES AT AFRICA'S GRASSROOTS

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Like the Female Condom, microbicides will not require the intervention of a medical provider. Many health structures find it difficult to find the time to educate and distribute female-initiated prevention methods. Additionally, provider bias often determines whether or not a method is readily available and accessible. Africa's women have taken it into their own hands to educate and deliver

the Female Condom to grassroots women through the SWAA network, present in 39 countries across the continent.

The Women's Protection Initiative is a private/public, north/south collaboration between The Female Health Company, makers of the Female Condom and SWAA. This innovative partnership builds capacities in SWAA national branch offices to accept, program and distribute new HIV/AIDS prevention technologies. The origins of this partnership, the activities of the initiative and specifics as to how Female Condom is being used as a tool to prepare for microbicides will be discussed.

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02592 EUROPEAN ADVOCACY EFFORTS: WHY DO THEY MATTER?

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A considerable amount of microbicide research and development is underway in Europe and several European governments have made initial investments in this research. Despite this, public knowledge and understanding of microbicides is very low, even among EU officials, partly due to the fact that they are primarily aimed for use in developing countries. What does this mean for the future of a microbicide?

International Family Health is working in partnership with the Global Campaign for Microbicides to raise awareness of microbicides within Europe. This initiative is part of an IFH advocacy project funded by the European Union and the UK Department for International Development.

Drawing on the experiences of advocates building the European Campaign for Microbicides, this paper sets out why European advocacy efforts are strategically important in the search for prevention tools for the developing world. It examines the role of European advocacy efforts in raising wider awareness of microbicides and securing long-term political commitment to their development. The paper reviews and compares progress made to date in building campaigns across Europe and suggests future directions for pan-European strategies.

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02599 PREFERENCES FOR A HERPES-PREVENTION MICROBICIDE AMONG WOMEN IN CALIFORNIA

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Objectives: The overall study objective was to identify the qualities that women would consider desirable in a herpes prevention topical microbicide.

Materials and Methods: This study integrates market research approaches (i.e., conjoint analysis and demand forecasting) with epidemiologic and demographic methods more typically used in public health research. The sample includes 415 sexually active women aged 18-46 years old recruited from the San Francisco Bay Area.

Findings: Structured interviews were preformed targeting women aged 18-46 (N=415). A broad spectrum of races and SES were sampled Nearly half of the sample (45%) reported having had an unplanned pregnancy and 32% reported ever having had an STI; 9% reported a herpes diagnosis. Conjoint analysis indicates that the most important microbicide product attribute is product type (preference for a vaginal tablet vs a gel), followed by availability (preference for over the counter vs prescription), efficacy (preference for high efficacy vs moderate), spectrum of protection (preference for herpes plus pregnancy prevention), and duration of activity (preference for use at time of intercourse vs daily).

Discussion: By integrating epidemiologic and demographic methods with market research we are able to quantify how women make trade offs for different potential microbicide attributes. A product that offers protection against pregnancy as well as herpes appears to have the greatest appeal in this multistrata sample. This methodology could be incorporated into ongoing and planned trials of first-generation microbicides at national and international sites.

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02602 A NEW LOOK AT AN OLD METHOD: EXPLORING DIAPHAGM USE AMONG WOMEN IN TWO U.S. SAMPLES

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Research on the diaphragm suggests that it is effective in preventing some STIs, could potentially prevent HIV, and has advantages over other female-controlled methods. This method could also serve as a physical barrier device to hold in place microbicides. Very few women in the US, especially women at high risk for HIV/STIs, use the diaphragm. Given the immediate need to increase the acceptability of physical barrier methods like the diaphragm, it is important that we understand how to overcome obstacles to their use. In this presentation we will 1) examine the perceptions of the diaphragm among current and former diaphragm users and young women at increased risk for HIV/STIs; 2) assess diaphragm use self-efficacy among the 3 groups of women; and 3) explore factors that increase the acceptability of the diaphragm among high risk women. Data come from two studies that examined the acceptability of the diaphragm among women in the US. In the first study, telephone interviews were conducted with 215 current and 173 former diaphragm users. In the second study 140 racially/ethnically diverse women at risk for HIV/STIs participated in 25 focus groups and completed self-administered questionnaires before and after the focus group. Findings indicate that positive perceptions and diaphragm use self-efficacy are associated with continued use, consistency of use, and satisfaction with the diaphragm. Although young women at risk for HIV believe the diaphragm has some positive attributes, they also perceive that the method is not easy to use, is messy to use and report low diaphragm use self-efficacy. Nearly three-fourths of these women reported that they would be more likely to use the diaphragm if they were confident in their ability to correctly use it and if it protected against HIV and other STIs. Additional results and implications for HIV/STI prevention and the development of new methods will be presented.

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02621 USING Q METHODOLOGY TO ASSESS OPINIONS OF STAKEHOLDERS ABOUT USE OF CERVICAL BARRIERS IN LOW-RESOURCE SETTINGS

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Program for Appropriate Technology in Health (PATH) used Q methodology, also referred to as Q sorting technique, to assess individuals' viewpoints about the constraints, benefits, and related issues that may advance or inhibit the promotion and use of cervical barriers in developing countries. Q methodology combines both qualitative and quantitative techniques to examine subjective viewpoints about any topic. The methodology uses a set of operational principles and statistical applications of correlation and factor-analysis techniques that reveals a systematic and rigorous quantitative means for examining human subjectivity. A literature review and interviews with 19 experts were conducted to obtain the breadth of current discourse about cervical barriers. This was then used to develop a set of 36 statements representing 2 supporting and 2 opposing viewpoints for each of 9 issue categories (Q-sample size of N=36). Surveys were sent to 648 respondents worldwide and results were analyzed using a correlation matrix and factor analysis. Results summarizing the qualitative interpretation of statements for each factor will be used to develop a future advocacy strategy to promote the use of cervical barriers by women in the developing world. The Q Method technique provides an option for measuring subjective attitudes about a wide variety of health-related behaviors.

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02622 MARKETED VAGINAL PRODUCTS AS MICROBICIDES: A STRATEGY FOR INDIA

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India has the highest HIV incidence outside of South Africa. Other genital tract infections are also on the rise. Program for Appropriate Technology in Health (PATH), in an effort to accelerate development and marketing of microbicides, reviewed over 2,200 marketed topical Indian products. A succession of tests led to the selection of broad-spectrum active pharmaceutical ingredients as potential leads. Testing included in vitro anti-HIV, -gonococcal, -chlamydial, -lactobacillus and cytotoxic activity; sperm inhibitory properties; rabbit vaginal irritation; and latex condom compatibility studies. In addition to safety and efficacy, further selection criteria include ease of formulation, manufacturing, and scale-up; development cost and time to market; and marketability to target populations (i.e. acceptability, cost, and intellectual property). PATH is now partnering with Indian pharmaceutical companies with strong development and marketing capabilities in India and other developing countries in order to ensure cost-effective development and optimal access and supply. The product(s) will initially be marketed in India mainly following Indian regulatory approval requirements. We will first focus on a "vaginal health" concept, i.e. prevention of bacterial vaginosis and fungal infections, subsequently on non-HIV STIs, and ultimately on HIV. This escalating claims strategy will inform best practices and develop the vaginal prophylaxis market.

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02623 CLEANING EFFECTIVENESS STUDY OF A MICROBICIDE APPLICATOR

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While reusable vaginal applicators may result in lower cost of delivery of microbicides and lower environmental burden of disposal, an acceptable and feasible means of effectively cleaning the applicators must be investigated and provided to users. In order to develop recommended cleaning procedures, Program for Appropriate Technology in Health (PATH) conducted an evaluation of cleaning effectiveness. Three cleaning methodologies were evaluated for their effectiveness at cleaning a reusable microbicide applicator. The three methodologies evaluated were: (1) cleaning with plain tap water, (2) cleaning with tap water and Omo powdered laundry detergent, and (3) cleaning with tap water and Sunlight bar soap. Each cleaning method was chosen because of the availability of these materials in low-resource settings and its manual cleaning method (i.e. no tools required). The applicators were inoculated with a solution of simulated vaginal fluid containing a microbial marker (Bacillus subtilis). After cleaning, the bacteria remaining on the applicators were recovered and compared to bacterial recovery from control samples. With this data, cleaning recommendations for reusable vaginal applicators were developed.

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02628_1 THE BESTBET STUDY: A "BODY EMPOWERMENT" INTERVENTION TO HELP WOMEN USE VAGINAL HIV PROTECTION

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Background: Interventions designed to help drug-using women use vaginal HIV protection methods are few. We report data from the first 150 women enrolled in a randomized trial of a 5-session, peer-led, small-group intervention for active users based on Body Empowerment Theory.

Results: Mean age at baseline was 39.6 yrs. 63% of subjects were African-American, 32% white, 5% other. 49% had a HS diploma and 93% were unemployed. 11% had stayed in a shelter, 23% in jail, and 35% at a drug treatment facility at least once in the past year. 88% injected heroin (47% >1x dy); 32% snorted or smoked heroin; and 87% used crack (51% >1x/dy) in the past 3 mo. 40% were trichomonas positive. 82% had a primary sexual partner (PSP) and 74% had casual partner (CSP). 96% exchanged sex for drugs or money. At baseline, both intervention and control women reported (via audio-CASI) a mean % protected vaginal sex acts (PPA) with male or female condom of 7% with PSP. 63% of weekly intervention group sessions were attended; 61% attended all 5 sessions. 80% of all 150 women have completed a 6-mo FU to date. Mean PPA for controls was 15% with PSP, 45% with CSP. For intervention women, mean PPA was 32% (PSP) and 71% (CSP).

Conclusions: A "body empowerment" approach and 5-method hierarchy for women at high HIV risk demonstrated substantial protection gains at 6 months, mostly in male and female condom use.

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02628_2 WOMEN'S RIGHT TO MICROBICIDES: CONDITIONAL OR UNCONDITIONAL?

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In a recent publication "Microbicides and HIV: Help or Hindrance?", Karmon et al. argue that the introduction of vaginal microbicides into a population must be based on the relative probabilities of male condom "migration", otherwise such introduction may lead to decreases in population level protection against HIV. The authors argue that microbicide introduction should occur only in instances where male condom use is low, or, if not, that the likelihood of migration is low. Mathematical models are used to support the argument. The present abstract is submitted in the hopes of providing a forum for debate about the moral right of women to access microbicidal products. The issue of condom "migration" has long accompanied discussions of women's protection methods – whether it be female condom, diaphragm, spermicide, etc. At issue is whether women have an unconditional right to microbicides - as this paper will argue - or whether that right should be based upon men's use of condoms, and the probability of migration, whether modeled or real. Can the introduction of microbicides be at once pro-woman but anti-public health, as some are suggesting? Or are both goals compatible under a broader framework? Other analogous and/or possibly instructive cases - withholding HIV treatment, or curtailing the right to legal abortion services or to sex education, in view of possible unwanted behaviour change - will be examined.

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02632 STAINING STUDIES WITH SULFONATED HESPERIDIN (SH), A NOVEL MICROBICIDE

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A number of microbicides currently under development such as SH, Poly-methylene hydroquinone sulfonic acid etc, are coloured in nature. A question is usually posed on pursuing the development of such leads. User compliance of these microbicides is likely to depend on the staining properties of their formulations. In the present study, tablets and bioadhesive gel formulations of SH, synthesised, isolated and characterised in the laboratory, were subjected to an accelerated study to assess their staining nature on the clothes in contact. Fabrics of different fibre blends, ranging from 100% cotton to 100% polyester, including silk, were procured and stained with 1 ml of a 5% solution of SH in distilled water, vaginal gel of SH (1 gm of a 5% gel), and a tablet dispersion (1 ml, 200 mg) of the same, and observed for staining after accelerated drying and subsequent washing with standard detergent. The sample clothes were cut into 6 sq inch squares and the test solution/formulation were poured/applied in the centre of each. The stains were air-dried and the clothes left at 50ºC for 48 h to accelerate the drying. After leaving them at room temperature for 5 more days (total 1 week), they were washed with standard detergent (Surf) and water. After air drying the staining on the sample clothes was recorded. It was observed that neither the aqueous solution of the drug nor the formulations stained any of the fibres tested even after prolonged exposure and accelerated drying. This effect can be attributed to the high aqueous solubility of the compound.

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02635-1 THE PREVALENCE OF ANAL SEX IN RURAL SOUTH AFRICA

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Background: As part of an ongoing microbicide feasibility study in rural KwaZulu Natal, South Africa we are seeking to estimate the prevalence of anal sex in the general population. This is an important preliminary investigation because vaginal microbicides would not prevent HIV transmission through anal sex and therefore, populations with a high prevalence of anal sex would not be suitable as future trial sites. Objective: To describe the prevalence of anal sex practices in rural KwaZulu-Natal. Methods: A combination of quantitative and qualitative methods is used including self-reported sexual behaviour of study participants and focus group discussions (FGs)

with community members. Sixteen FGs were conducted with men and women selected on the basis of their age and place of residence (rural areas and township). Participants were asked about their knowledge and attitudes towards anal sex and its prevalence in the local population. FGs were recorded and transcribed in Zulu. These were translated into English and coded using Nud*ist 6 software to identify key themes and sub-themes using content analysis. Differentials in knowledge and attitudes to anal sex will be analysed by gender, age and area. These qualitative results will be compared with quantitative data collected in the feasibility study. Results: Preliminary findings suggest that there is difficulty in explaining the concept to respondents because no single word or phrase for anal sex exists in the Zulu language. Anal sex was generally confused with vaginal sex 'dog-style' and oral sex. Many respondents were unfamiliar with the concept of anal sex. Those with knowledge generally expressed negative attitudes towards anal sex associating the practice with marginalized groups such as ex-prisoners, male homosexuals and child abusers. Using qualitative and quantitative methods may help to answer the question whether prevalence of anal sex is low in this community or negative social attitudes inhibit reporting

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02635_2 COMMUNITY ATTITUDES TOWARDS INDIVIDUALS INFECTED WITH HIV IN RURAL KWA-ZULU NATAL

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Background: A microbicide feasibility study is being conducted in rural KwaZulu Natal, South Africa. Antenatal seroprevalence rates of 30% and more have been reported in this area since 1998, and over 50% of all adult deaths in 2000 were due to AIDS. As in all prevention studies, the changing social and cultural attitudes to HIV/AIDS is important contextual information to aid the design of these interventions. Objective: To examine community attitudes towards individuals with HIV/AIDS. Method: Sixteen focus groups were conducted with men and women selected on the basis of their age and place of residence (rural areas and township). Participants were encouraged to discuss how HIV infected individuals should be treated and how they are treated within the family and within community. The discussions were recorded and transcribed in Zulu. These were translated into English and coded using Nud*ist 6 software to identify key themes and sub-themes using content analysis. Analyses are ongoing. Gender, age and area differences will be investigated. Results: Preliminary analyses suggest that generally respondents expressed positive attitudes to the treatment of AIDS patients and felt that AIDS patients were being cared for within families. However, they reported more negative attitudes to HIV positive individuals by the general community and suggested these attitudes and acts of discrimination influence disclosure rates. Discrimination included not sitting next to someone, not sharing the same cup, friends running away, having a three

finger gesture used to identify them to others. Respondents also reported mixed responses to known HIV positive individuals ranging from sympathy to a lack of care on the grounds that the person is certain to die. Results of these analyses will be compared with other studies and surveys in the province.

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02637 NOTHING NEW?: A QUALITATIVE INVESTIGATION OF GAY MEN'S UNDERSTANDINGS OF MICROBICIDES

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Method: Men from London and Leicester who had completed the annual Gay Men's Sex Survey (GMSS) online were recruited to a qualitative study on gay and bisexual men and health. At a face-to-face interview lasting 90 minutes, men were asked a range of questions about health management including some on microbicides. Results are based on an analysis of the first twenty respondents.

Results: Recall and knowledge: Despite prior participation in GMSS (which required that they read a definition of, and answer questions about microbicides), the majority (n=13) reported never having heard of microbicides. Effectiveness and use: Most (n=12) expressed major concern about likely effectiveness. They did not see microbicides as a stand alone prophylaxis, assuming instead that they would be added to condoms during manufacture (as with spermicide).

Discussion: Because microbicides were seen solely as a component of condoms, they are unlikely to precipitate any major innovation in terms of personal HIV risk management strategies. They are not perceived to represent increased opportunity for the receptive partner to take control of preventing HIV transmission when exposure occurs. They are understood within a framework of risk elimination (condom use) rather than risk reduction (engaging creatively with partially effective technologies) and do not present a challenge to the current risk management strategies of gay men. We conclude that the introduction of partially effective microbicides is unlikely to represent a significant innovation for gay men (this may account for the lack of recall observed). Those responsible for advising on the marketing and use of microbicides need to attend to this as well as investigating the feasibility of stand-alone use of microbicides for anal intercourse.

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02642 ROLE OF MEN IN STUDIES INVOLVING FEMALE CONTROLLED PREVENTIVE STRATEGIES

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Several studies are underway to examine female-controlled preventive strategies. Lessons learned from studies on female condom can be used to provide better insights and inroads into future microbicides research initiatives. A study conducted at YRGCARE, Chennai: Phase-1 'functionality and safety' comparative study between the Reality-Female-Condom and the Modified-Reddy-Female-Condom randomly assigned to 30 monogamous couples from three urban low-income areas in

Chennai. Participants had to use each type of condom thrice over a 3- week period; other sexual acts were allowed with/without condom use. Female and male participants discussed the pros and cons of using such a product. The product was novel and their male partners felt encouraged to use it. Common reactions centered on satisfaction with some men reporting "same feeling and pleasure" as sex without the condom; others responded that there was a lack of complete sexual satisfaction as it seemed "different". The general feeling was that the condom kept moving and was uncomfortable and intrusive during sexual intercourse. Privacy in use and disposal of the condom and the gel were other issues that were raised. Cooperation of the partners during the sexual intercourse provided the women with better ability to discuss use of the condom. Participation of men in studies involving female-controlled preventive measures must go beyond mere informed consent when appropriate. Stealth use of such products by women may enhance violence, commonly reported in sexual relations. While it is important to understand the constraints/obstacles that men pose in the use of such products, it is equally important to recognise the advantages of involving them during product development. Studies at our centre have shown that the increased involvement of men significantly increases our understanding of their acceptability, perceptions about their advantages and difficulties with such products as well as triggers for sexual violence in the context of female controlled barriers.

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02644 MOBILISING COMMUNITY INVOLVEMENT IN RANDOMISED MICROBICIDE CLINICAL TRIALS: LESSONS FROM 6 MDP SITES

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Background: The Microbicides Development Programme (MDP) has established six feasibility study Sites in South Africa, Zambia, Tanzania, and Uganda. A variety of methods have been utilised to mobilise the local communities to ensure effective community involvement in the MDP feasibility study in all the Sites.

Objective: To review experience and describe lessons learnt from community mobilisation activities in 6 African sites during the microbicide development programme feasibility study.

Results: Data from the sites so far indicates that the community liaison approach adopted in the Sites has been oriented more towards selling the study as a product to the local communities. This may have engendered a sense of provider-client relationship between the local community and local MDP centre in the Sites. Thus, feedback from the communities has been centred on individual compensation for participation, immediate benefits to the local community, and expressions that somewhat indicate the quality of mutual trust in the relationship between the local community and the MDP.

Conclusion: Communication with local communities in the Sites should use a verbal and non-verbal language that promotes the MDP as a local partnership rather than as a product.

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02648 HIV/AIDS EPIDEMIC SITUATION AND DEVELOPING OF MICROBICIDES IN CHINA

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1 Situation
A total of 40560 HIV infections (including 2639 AIDS cases) were reported to the Health Ministry of the P.R. China at the end of 2002. The number of new cases reported in 2002 was 9824 an increase of 19.5 % from 2001 (transmission modes: 4928/9824 50.2% by drug use; 1042/9824, 11.0 % by heterosexual; age: 1.5% <15; 43.4.9% 20-29; 35.0 % 30-39; 9.89 % 40-49). It is estimated, however, that there are currently over 1,040,000 actual cases of HIV in China. The number of infections could reach to 10 million by 2010 if no effective countermeasures will be taken.

2 Describtion:
2.1 The current internal movement of temporary and permanent migration across China is without precedent. Estimates suggest that the total number of migrants, both temporary and permanent, may be as high as 120 million; that is, some 15% of the total labour force. This number, while extremely large, is actually increasing. A number of additional factors make the migrant labour force particularly vulnerable to HIV infection.
2.2 STDs have risen sharply to a level of 744848 reported cases in 2002. Again, experts estimate that the actual number of STD cases in the country is 6-8 million.
2.3 Prostitution is increasing year by year.The number of prostitutes and clients arrested in 1998 is 398 000, in the estimation the actual numbers of prostitutes about six million and clients about 14 million.
2.4 There are some 1,000,000 known drug users recorded by public security in mainland China. The actual number is estimated to be between 3-5 million.
2.5 Men have sex with men are estimated to 20 million. Most adult men had been married with women but some of them have men sex multipatners without protection.

3. Conclution:The above-mentioned situation has been brought attentions of governments and NGOs in China and further research and efforts at AIDS prevention and intervention for the high risk populations are conducted. But condom using rate is VERY LOW: 10% never using,<10% permanent using.A lot of people don't like using condoms. Therefore,microbicides is very needed for these populations. We are planing to keep abreast more information on micribicides at Mcrobicides 2004 and further to promote the microbicides in China.

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02649 MOBILISING MEDIA ADVOCACY AND COMMUNITY PREPAREDNESS FOR FEMALE CONTROLLED OPTIONS IN NIGERIA

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Background
An effective microbicide, made accessible and available to women in developing countries, who bear the brunt of the HIV epidemic will undoubtedly alter the course of the epidemic, by giving women the power to protect themselves and their partners from HIV and Sexually transmitted Infections(STIs).

Despite growing efforts from advocates and scientists in the developed world to ensure women's access to safe, cheap, effective and accessible female controlled female controlled HIV prevention options barrier methods such as microbicides, the voices of the affected communities in many developing countries remain unheard.

In Nigeria for instance, ignorance, lack of awareness and lack of involvement in policy advocacy issues regarding microbicides, contribute to the silence on the part of the media, people living with HIV, Sex workers ,community leaders, care providers, scientists, and other related stakeholders in the fight against HIV/AIDS. There is therefore an urgent need to accelerate community activism and participation in Nigeria in order to help create a demand for female controlled options particularly where it is most needed.

Description
Media Monitoring: Journalists Against AIDS (JAAIDS) Nigeria conducted a three month long base-line survey to determine the depth of coverage / focus and the level of media reporting in Nigeria on female controlled HIV prevention methods between June-September 2003. Reports from six major national newspapers in the country and three community based publications were analysed over the period in focus.

Focused Group Discussion: Two focused group discussions (FGDs) with representatives of the identified stakeholder groups will hold in November 2003 to examine the myths and misconceptions surrounding female controlled options, concerns, advocacy challenges in their respective localities, and how they can be overcome.

Capacity Building: Key issues in microbicide policy advocacy, research and development, public communication and enlightenment as well as recommendations from the FGDs will form the content of 3 JAAIDS training workshops for the media and community representatives which will hold between November 2003 and March 2004.The workshop content will be designed in collaboration with the newly established Nigeria HIV Vaccine and Microbicides Advocacy group (NHVMAG) with a view to broaden the knowledge base of participants and empower voices from the community with the knowledge and skills to mobilise and engage their constituencies in advocating for access to female controlled HIV prevention options.

Findings
Findings from the Media base line survey revealed that there is a dearth of focus on female controlled options in the media; which ought to be a key agenda setters in advocacy around such issues. It also revealed the need for media based organisations to bridge the media's knowledge gap on these issues. As a follow-up, JAAIDS Nigeria will hold a series of media discussion roundtables on female controlled options are planned for Media gatekeepers between November 20003 and February 2004.

Findings from the preliminary activities conducted by Journalists Against AIDS (JAAIDS)Nigeria clearly indicate the need for a co-ordinated strategy to engage a corps of advocates from the media and other identified groups to create community awareness, understanding, preparedness, support, demand as well as a conducive policy environment that will facilitate continued and sustained access to female controlled HIV/STI prevention options .

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02650 MICROBICIDES AND THE GROUND REALITY-A SITUATIONAL ANALYSIS INVISAKHAPATNAM OF ANDHRAPRADESH, IN

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Twenty million births occur in India every year, with 1-4 % of all pregnant women found to be HIV seropositive. That of the 5.3 million new HIV infections in 2002, half of them were in women. The STD clinics in Mumbai and Delhi noticed sharp rise(by 64 %) in their cases in past decade .In Andhrapradesh 28-30% of STD clients are HIV positive.Millions of women around the world need help now to prevent HIV infection and death from AIDS. . Even when women have only one partner, they can be at risk of infection through that partner's other sexual relationships. Many simply do not have the power to insist their husbands or partners to use condoms. For some, multiple sexual partnerships often serve as their only source of economic and social security. .

Under this scenario ther is an urgent need for the development of Microbicides, that could be added to gels, foams, and creams and used during vaginal and/or rectal intercourse to reduce the risk of HIV infection. Microbicides could be used with condoms or alone in situations where individuals will not or cannot negotiate condom usage with their partners.so that have protection against HIV without a partner's knowledge. Currently, almost 30 possible Microbicides hae been developed and are in the research pipeline. Microbicides can also provide protection to HIV positive women safeguarding the spread of HIV/AIDS to their partners, and protecting them from contracting other strains of HIV.

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02654 MALE INVOLVEMENT IN MICROBICIDES: INSIGHTS FROM SOUTH AFRICA

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Introduction: Vaginal Microbicides phase III clinical trials require a large cohort of women. Women are the primary user of the Microbicides product, thus trials have to enrol and follow up women participants. Women who are enrolled in these trials must be sexually active, and involved in heterosexual relationships. This raises a question of the role that men should play in these trials. There are different views about whether men should be involved or not, and also about what their involvement will mean. This paper outlines the views and perspectives of men and women from selected communities within South Africa with regard to male involvement in Microbicides trials.

Methods: The following methods have been used for gathering data: 1) Focus group discussions with; men from various organisations, women and health care providers 3) Interviews with researchers involved in Microbicides trials.

Preliminary results: Emerging issues are safety concerns, the benefits and disadvantages of male partner involvement, the effects of religion and tradition on the views/perspectives of men. Men described themselves as 'traditional or modern' in their outlook to life however, depending on the issue under discussion the views they expressed could change them from being in one group one to the other. Violence against women was an issue that came up repeatedly during the discussions as something that could result from either the involvement or non-involvement of men in the trials. The data collection and analysis is continuing and further findings will be elaborated in the paper.

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02660 PREPARING FOR MICROBICIDE INTRODUCTION: FINDINGS FROM SOUTH AFRICA

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Qualitative methods were used to explore diverse issues related to microbicide introduction in Langa, Cape Town. Researchers conducted FGDs with men (9), women (13) and nurses (1); and IDIs with service providers (7), community key informants (11), and national and provincial government and NGO leaders (20). Data was coded and sorted using Atlas.ti and analyzed using a modified grounded theory approach.

Study findings indicate keen interest in microbicides, underscored by desperation related to the HIV/AIDS epidemic, and widespread awareness of its impact on women. Community respondents saw the need for microbicide use among diverse user groups, and that routine use could potentially play a role in providing protection in case of rape and unplanned sex. Providers and policymakers expressed concern about partial effectiveness, and the challenge of balancing complex messages about partial effectiveness with widespread availability. In most cases, this evolved into a more positive view against the backdrop of the epidemic and limitations of condoms, suggesting initial views are not immutable. Other issues addressed include: partner involvement; need to ensure reliable supply before introducing; distribution and marketing strategies; and intravaginal product use. Findings suggest similar qualitative research on community and decision-maker perspectives will be important to inform introduction strategies in diverse settings.

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02667 AN ASSESSMENT OF SEXUAL PRACTICES AFFECTING THE FEASABILITY OF MICROBICIDE DEVELOPMENT AMONG MSM

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Clinical investigation of microbicide products requires thorough understanding of sexual practices to ensure appropriate experimental design. In order to determine practices of MSM in preparation for and during anal sex, focus groups were conducted with gay and bisexual men in Baltimore, Maryland. A total of 16 men, ages 19-61 (mean = 32, median = 37.5) participated in the focus groups. The racial/ethnic composition of the participants was 63% Caucasian, 31% African American, and 6% Latino. Enema use in preparation for anal sex was typical. The most commonly used enema was tap water; other enemas reported were over-the-counter products, soap and water combined, Epsom salts and glycerin. All participants reported using lubricants for anal sex, though the type of products used varied widely. Many preferred the use of water-based commercially available products specifically designed for sexual intercourse. Others preferred oil-based lubricants such as lotion, baby oil and petroleum jelly. The use of saliva as a lubricant was reported by only one participant, but saliva was used by many as a method to add lubricity to water-based gels that became sticky or gummy during use. All indicated that lubricants were typically applied using fingers, by one or both

partners, and that both the anus of the receptive partner as well as the penis of the insertive partner had lube applied to them. Water-based lubricants were frequently reapplied, while oil-based lubricants were seldom reapplied. The use of products in preparation for and during anal sex by MSM varies greatly and should be considered when designing microbicide trials.

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02669_1 RESULTS FROM A MICROBICIDE FEASIBILITY STUDY IN FAMILY PLANNING CLIENTS IN SOWETO, SOUTH AFRICA.

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Introduction: The use of condoms for the effective prevention of HIV transmission is well recognised. However many women who are at risk of acquiring HIV are not always in a position to negotiate the use of a condom. Vaginal microbicides have been identified as a possible method for the prevention of HIV transmission. Prior to the implementation of a phase III trial of vaginal microbicides, a feasibility study is being conducted in Soweto.

Objectives: The study aims to determine the (1) Incidence of HIV, (2) Rates of condom use, and (3) Rates of cohort retention over 12-18 months in this population. In addition, secondary objectives of this study are to determine (1) prevalence and incidence of sexually transmitted infections (STIs), (2) prevalence of abnormal cervical cytology (3) rates of pregnancy, (4) patterns of risk behaviour in this population during the study period, and (5) the effects of repeated risk reduction counselling on risk behaviour and condom use.

Methods: Female family planning clients between the ages of 18 and 35 are recruited from the Soweto area. These women are screened for eligibility and invited to attend for HIV and pregnancy testing at the study clinic. Socio-demographic, behavioural and clinical data are collected using a structured interview. Participants are testing using an HIV rapid test algorithm. Eligible women who are HIV sero-negative are enrolled in the study. Additional specimens are collected for STI testing at enrolment. Participants are required to visit the clinic every three months for further HIV testing. Participants receive counselling and testing for HIV, examination and treatment for STIs and free condoms at each visit.

Results: After 9 months of recruitment, 2241 women have been screened for eligibility with 1857 eligible for HIV testing. HIV prevalence at screening was 18%. 576 women have been enrolled in the study. The mean age of participants is 23. Although at enrolment the prevalence self-reported condom use at last sex was 57% (95% CI 52-62%), 12% and 4% were infected with chlamydia or gonorrhoea respectively. In addition, 55% were HSV2 positive suggesting previous high risk sexual behaviour. Follow up at 6 months is >85%. Additional 6-month follow up data on HIV incidence, STI prevalence and condom use will be presented.

Conclusions: The Microbicides Feasibility Study provides essential data on HIV incidence and cohort retention in planning for randomised controlled trials. In addition it provides important information on the effects of repeated risk reduction counselling on sexual behaviour.

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02670 LAUNCHING MICROBICIDES, HOW IMPORTANT IS PROMOTION? LESSONS FROM CONDOM SOCIAL MARKETING

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Background: To successfully launch microbicides, both consumer demand and a system of distribution need to be developed. This study explores how advertising and promotion impacts the quantity of male and female condoms distributed through social marketing (SM) in 26 countries, and how unit distribution costs change as projects mature. The implications for the successful launch of microbicides and the levels of initial investment in promotion are explored.

Methods: The financial cost data and project output from Population Services International for SM for 5 years (1997-2001) and 26 countries in Africa, Asia, Latin America and Eastern Europe relating to the distribution of male and female condoms are analysed. Multivariate regression analysis is used to understand the relationship between promotion expenditures and sales quantities, and the relationship between unit costs and project maturity.

Results: At the early stages of SM, an average 1.5 million male condoms and 21,000 female condoms were sold per country, after 5 years this grew to 8 million male and 246,000 female condoms. Promotion expenditures ranged from 15% to 33% of delivery expenditures. There is a strong and statistically significant relationship between promotion expenditures and quantities sold for both male and female condoms. Unit costs of distributing both types of condoms fell as projects matured and grew (average male and female condom cost were $1.15 and $17.72 in Year 1 and $0.20 and $2.03 in Year 5, respectively).

Conclusions: When launching microbicides, one must not under-invest in promotion activities. Higher initial investment in promotion is likely expedite a drop in unit distribution costs, through achieving higher distribution quantities.

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02672 COMBINATION PREVENTION: CONSIDERING THE IMPACT OF NEW PREVENTION TECHNOLOGIES ON HIV PREVENTION

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Canadian AIDS Society

As more products move into clinical trials, awareness of vaccines and microbicides will increase over the next few years. The impact of this increasing awareness, as well as the eventual availability of these new prevention technologies, will have a significant and lasting effect on HIV prevention and education efforts. This workshop will explore the potential impact of new prevention technologies conceptually (harm reduction, public health, health promotion) as well as practically across a range of vulnerable populations in Canada. Special attention will be given to policy and programming implications for community-based AIDS organizations, people living with HIV/AIDS and vulnerable populations.

Participants will have an opportunity to increase their understanding of the potential impact of new prevention technologies by exploring how they will affect their prevention education work and their

work with vulnerable populations. Participants will explore means of planning for shifts in policy and programming within their own organizations and communities.

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02673 COITAL DIARIES TO MEASURE FREQUENCY OF SEXUAL PRACTICES IN MWANZA, TANZANIA

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INTRODUCTION: Frequency estimates for condom use, vaginal hygiene practices and other vaginal/ sexual practices are vital to the calculation of the efficacy of microbicides under different behaviour scenarios. This paper presents methods used in Mwanza to pilot coital diaries (CDs) to record frequency of vaginal/ sexual practices among women working in recreational facilities and enrolled in a microbicide trial feasibility study.

METHODS: Following focus groups discussions (FGDs) with women from recreational facilities, 5 diary designs, ranging in the types of acts included and the balance between pictures and text, were produced. For each diary type 7 women were drawn randomly from those due to attend a feasibility study follow-up visit during the 4 weeks of the diary study. A field researcher was assigned to each group who visited each woman individually to obtain informed consent, then visited weekly to collect completed diaries and interview the women to record concerns and verify the diary information on a recall questionnaire. Semi-structured exit interviews (SSIs) and FGDs at the end of the 4 week period reviewed acceptability, comprehension, ease of completion and confidentiality. SSIs included recall questions on sexual behaviour. Results will be used to design a single instrument administered over 4 weeks to 150 randomly selected women, to generate frequency estimates.

DISCUSSION: The paper will review pilot data on issues such as acceptability of the method. It will compare vaginal/ sexual practice frequencies between CDs, the weekly and month-end recall questions and questions on the Mwanza case record forms. Recommendations will be made on the design of instruments for measuring the frequency of vaginal/ sexual practices in the Phase 3 trial.

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02677 HIGH LEVELS OF COMPREHENSION AND WILLINGNESS TO PARTICIPATE AMONG WOMEN AND MEN IN BOTSWANA

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Objective: Assess understanding of trial design and willingness to participate, and elicit issues about a microbicide efficacy trial in Botswana.

Methods: Questionnaires were interviewer-administered with 349 women and 135 men, ages 18-40, in Francistown and Gaborone from multiple recruitment sites (36% HIV testing centers, 30% primary health clinics, 19% University of Botswana, 15% other). After demographic questions and a 15-minute presentation about trial design, we asked open-ended and closed-response questions about trial design and willingness to participate. Men were questioned about partner's possible participation.

Results: Correct responses about trial design (e.g., eligibility, study intent, blinding, condom use promotion) were >95% for most items. 87% answered that the microbicide may not work, and 92% that gel-users won't know whether they are using the active microbicide. 28% of women were definitely willing to join (and 43% of men to encourage partner participation); 46% (36%) probably willing, 15% (14%) probably unwilling, and 11% (7%) definitely unwilling. Among those definitely or probably willing to join, the reasons most cited as important were: to help stop HIV (93%), to get risk-reduction counseling (93%) and because their safety in the trial would be monitored (93%). Gel use as a reason to avoid condoms (39%) was least cited. Among those definitely or probably unwilling to join, the reasons most cited as important were worry about safety (77%) or side effects (74%) and that their partners might have more partners (50%). Concerns about provoking gossip (27%) and not getting a gel (27%) were least cited. Among women, willingness to participate was associated in bivariate analyses (X2, $p<0.05$) with recruitment from clinics or testing centers; having children; having a steady partner; and higher perceived risk of HIV infection.

Conclusions: Women and men understood the trial design well and were highly willing to participate or encourage partner participation.

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02678 BELIEFS ABOUT HIV/AIDS TRANSMISSION AND PERCEIVED RISK AMONG WOMEN AND MEN IN BOTSWANA

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Objectives: Assess knowledge and beliefs about HIV transmission and perceived risk of infection and their relationship to willingness to participate in a phase III microbicide trial in Botswana.

Methods: Interviewer-administered questionnaires with 349 women and 135 men, ages 18-40, in Francistown and Gaborone from multiple recruitment sites (36% HIV testing centers, 30% clinics, 19% University of Botswana, 15% other sites). Interview included demographics, 15-minute script about trial design, assessment of understanding of trial design and willingness to participate, and questions about HIV/AIDS transmission.

Results: HIV is perceived to be very easily passed from women to men (97%) and from men to women (85%). When asked whether one partner could be uninfected if a couple had sex for a year without condoms, only 20% of women and 13% of men thought discordance was possible. Perceived risk of HIV infection was high. 40% of women (31% of men) reported that they will probably get HIV someday; 5% (7%) that they think they are already HIV-infected, 44% (44%) that they might or might not become infected; and 10% (18%) that they won't ever. Few university students believed they will probably become infected (15%), though most recognized they might (74%). Willingness to participate among women was high (74%). HIV knowledge items were not associated with willingness to participate but higher perceived risk of HIV acquisition was associated with greater willingness to participate (X2, $p<0.001$).

Conclusions: Women and men in Botswana have a good overall understanding of HIV transmission risk between men and women (in both directions) and perceive themselves at significant risk of HIV infection, although university students may underestimate their risk. The disbelief in possible discordance in couples not using condoms needs further exploration as it may have implications for counseling messages in HIV prevention trials.

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02680 MARKET POTENTIAL FOR A TOPICAL PREVENTION METHOD FOR RECURRENT UTI AND BV

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Objectives: The overall study objectives were to identify the current treatment modalities and the interest in LACTIN-V as a new non-antibiotic therapy for the prevention of recurrent urinary tract infection (UTI) and bacterial vaginosis (BV) among women with these disorders and their clinicians.

Materials and Methods: This study integrates qualitative and quantitative methods. The sample includes 33 women of diverse racial/ethnic backgrounds aged 18-61 years old with either UTI or BV in the past year as well as 10 clinicians who treat women with such disorders.

Findings: The majority of women in this study are white(42%) or African American (36%), are under the age of thirty (64%), and are married or have a steady partner (56%). Clinicians include physicians, nurse practicioners and midwives. Among women with UTIs and BV in the past year, 31% reported at least three and 27% reported at least three, respectively. Antibiotic resistence to existing UTI therapies is common and women and their clinicians report that existing therapies for recurrent UTIs and BV are not adequate. These disorders, in particular recurrent UTIs, can be debilitating and often result in emergency room visits. Based on a well-established purchase intent scale, 85% of all women reported they would buy a non-antibiotic therapy for prevention of recurrent infections and over 80% of clinicians would prescribe such a product to their patients. Women and clinicians are most interested in a product with high efficacy that has minimal side effects.

Discussion: There is a need for a non-antibiotic treatment and prevention for recurrent UTIs and BV, similar to LACTIN-V. Furthermore, since BV is associated with increased risk for HIV, a topical prevention method aimed towards BV could help reduce the risk for HIV as well. Based upon preliminary findings, there is great interest among women with these disorders and their clinicians for a LACTIN-V like product.

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02684 THE EFFECT OF INTRODUCING THE DIAPHRAGM ON MALE CONDOM USE

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Female controlled methods for protection against HIV are urgently needed because women cannot always negotiate 100% male condom use. The diaphragm is currently being evaluated as one such

option. One concern is that male condom, among those who can use it, might be replaced with less effective methods.

A total of 181 women attending a family planning clinic completed an 8 month prospective study to evaluate diaphragm acceptability. First, women had a 2month run-in condom intervention phase. Those who reported <100% male or female condom use enrolled in a diaphragm acceptability phase (phase II) and followed for another 6 months. At entry into phase II women were fitted with a diaphragm, and received a diaphragm educational intervention where they were told to use the diaphragm with male condoms every time they had sex. Women completed a survey on use patterns and acceptability at two month intervals during the entire follow-up period. The proportion of unprotected acts declined over phase II at month 2 15.3% to 8.5% at month 8 ($p < 0.05$). The proportion of acts where a male condom was used increased from 51.3% to 61.2% (ns). A diaphragm was used in approximately half of acts protected by a male condom. Acts where only the diaphragm was used ranged from 29.2% at month 4 to 19.7% at month 8 ($p < 0.05$).

The overall proportion of protected acts increased with the introduction of the diaphragm. The proportion of acts where a male condom was used did not change suggesting that women would continue to use male condoms with methods of unknown or lower efficacy.

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02692 PARTNER INVOLVEMENT IN A PHASE III CARRAGAURD TRIAL® (POPULATION COUNCIL)

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African culture plays a significant role in sexual relationships for both males and females. Males, in the dominant role as decision-makers, have control over women's sexuality. We found that these gender imbalances affected participation in a phase II Carraguard trial, as some participants withdrew their study participation due to partner disapproval. We are now planning for a Phase III efficacy trial to be conducted at several sites, including Ga-Rankuwa and Soshanguve, South Africa. This presentation will discuss our efforts to involve men in various aspects of planning for and implementing the Phase III trial. As part of our preparation, we held community meetings twice monthly over a period of a year. We informed a wide range of community representatives from government, non-government, private and religious organisations about clinical trials in general and specifically about microbicides, the past and upcoming Carraguard trial and the importance of community involvement, especially men as partners. The purpose of these meetings was to create awareness about microbicides trials, to dispel myths about HIV prevention and medical trials and to gain community trust. As a result of these meetings, some men decided to become involved by disseminating information to their organisations and to their partners about the trial and others chose to be involved in our Community Advisory Groups. The continued involvement of men in ongoing consultations and at recruitment sessions may have a substantial positive effect on women's study participation.

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02693 COMMUNITY PARTICIPATION IN A GA-RANKUWA/ SOSHANGUVE PHASE III CARRAGAURD TRIAL® (POPULATION COUNCIL)

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Community involvement in clinical trials benefits the community as a whole, researchers and individual study participants. The Department of Medical Microbiology at the Medical University of Southern Africa (MEDUNSA) recently completed a phase II trial of the candidate microbicide Carraguard® (Population Council) and is in preparation for a phase III efficacy trial. The trial will be conducted in two South African communities near Pretoria. A Community Outreach Team (COT) was established to foster community involvement in the trial preparation. To achieve this goal, the COT identified and established ongoing relationships with stakeholders; hosted community consultations; conducted formal presentations focusing on clinical trials and microbicides in general, provided feedback about the study, and educated the community about trial participation. Our networking approach resulted in mutual co-operation between and information sharing among study staff and key community stakeholders. Our consultative workshops encouraged community members, both men and women, old and young, to volunteer their participation as Community Advisory Groups (CAG) members. CAG members assisted in our planning of recruitment strategies and were crucial to the development of informed consent materials in simple, appropriate language. Engaging the community in preparation for a clinical trial benefits the community by raising awareness, benefits researchers by identifying recruitment and retention strategies, and benefits study participants by ensuring a truly informed consent process and a culturally sensitive approach.

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02695 WHO USES CONDOMS? EVIDENCE FROM POPULATION SURVEYS IN SUB-SAHARAN AFRICA AND ASIA

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Introduction Globally, significant resources have been invested in promoting condom use. This study summarises evidence of current levels of condom use in different relationships in Sub-Saharan Africa and Asia; estimates the extent to which condom use could potentially be increased, and identifies key gaps and their implications for microbicide introduction.

Methods Review of nationally representative population based survey data on reported sexual behaviour and condom use by women and men in sub-Saharan Africa. Data on the sexual behaviour of different populations (sex workers, men and women in specific occupations) in East Asia and the Pacific and South Asia were compiled from behavioural surveys. Country specific demographic data, in combination with the sexual behaviour data, were used to estimate the current gap in condom use.

Results Across all regions, the highest levels of reported condom use are in commercial sex, with high levels (>80%) of condom use in the last commercial sex act being reported in many settings. Generally the levels of reported condom use in non-commercial non-regular partnerships was lower, but were still high in some settings. Even in countries where HIV infection is highly prevalent there was limited evidence of condoms being used in long term or regular partnerships - surveys from 15 Sub-Saharan African countries suggest that less than 5% of women used a condom in the last sex act

with their main partner. The data suggest that globally the majority of sexual acts are not protected by condoms.

Conclusions Fundamentally, condom use is influenced by the nature of the sexual relationship – with associations with disease prevention, lack of intimacy or trust, and a desire to conceive inhibiting their use in long-term relationships. Thus, although investments in condom promotion may increase condom use in casual and commercial partnerships, it is unlikely to substantially affect condom use in stable and long-term partnerships. Microbicide promotion should target these relationships, where risk may be substantial, but where condom use is likely to remain low.

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02754 ANAL SEX AND CONDOM USE AMONGST PARTICIPANTS IN A MICROBICIDE FEASIBILITY STUDY

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Introduction:
Accurate and reliable data on sexual behaviors is critical to assess the efficacy of a microbicide. Sexual behavior research is however notoriously problematic due to the intimate and private nature of sexual relationships. Questions on sexual practices are distorted by respondents' ideas of the normative and socially desirable, and suffer from recall bias. Moreover, specific forms of sexual behavior may be hidden (for example anal sex).Questionnaire interviews are not always sensitive to these factors. This paper addresses these issues from the perspective of the microbicide feasibility study conducted amongst women in Soweto, Johannesburg.

Rationale
During the microbicides randomized control trial it is of utmost importance that the efficacy of the gel can be measured against the background of reliable data on sexual practices and condom use. Tools need to be developed that can validate sexual behavior data.

Methods:
In depth interviews were held with 25 enrolled trial participants. These explored responses to sexual behavior questionnaires. A series of five focus groups explored anal sex and vaginal cleansing. Twenty one enrolled women completed coital logs over two weeks and were debriefed in a second focus group. In addition, Audio Computer Aided Self Interviews (ACASI) were conducted with 20 enrolled study participants.

Results:
Coital logs appear to be an acceptable and effective method to measure condom use, condom failure and sexual behaviors. In addition, data from focus groups suggest that anal sex is often associated with forced sexual encounters. Comparisons between coital logs and ACASI are presented.

Conclusions:
Triangulation between different data collection methods (coital logs, ACASI questionnaires and interview questionnaires) is vital for validation of sexual behaviors data. Focus groups and interviews are important in raising new questions and exposing practices that may otherwise remain hidden but have an impact on HIV transmission.

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02755 BUILDING MULTISTAKE HOLDER CONSTITUANCIES TO SUPPORT MICROBICIDES DEVELOPMENT AND PROMOTION

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Building a multi stakeholder commitment to support the resource mobilization and political commitment needed to develop and roll out microbicides is essential. On 30 October 2003, researchers, private sector firms, government and community organizations met in Ottawa to assess Canada's progress in supporting microbicides development. Cosponsors of the symposium included: Interagency Coalition on AIDS and development (ICAD); Canadian International Development Agency (CIDA); Health Canada, Canadian Institute for Health Research (CIHR); International Partnership for Microbicides (IPM); Canadian AIDS Society (CAS); Microbicide Advocacy Group Network (MAG-Net); and Global Campaign for Microbicides (GCM)

The one day symposium was designed to updated participants on progress concerning microbicides research and development in Canada and provided opportunities for networking in order to promote joint research, advocacy and support.

This presentation will report on the outcome of the symposium and highlight the challenges and specific areas of action for each sector (government, researchers and community organisations). In addition, the presentation will describe why collaborative meetings are so important in building a strong constituency of stakeholders, committed to microbicide research and development.

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03115 MICROBICIDES: THE IMPACT OF RAPE IN MEETING DIVERSE NEEDS

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Introduction: HIV prevention strategies are limited as women's risk is frequently derived from their partners' behaviours, rather than their own. Microbicides may offer the possibility of reducing women's risk of HIV/STIs in cases where other more effective methods cannot be used.

Methods: The study involved qualitative research conducted in South Africa at three levels of enquiry: community, health service, and policy. Focus group discussions were held at community level, and in-depth interviews were held at community, health service and policy level. Data was analysed using grounded theory.

Results: Participants discussed diverse ways to best use microbicides for protection against HIV infection. Rape, coercion, and unplanned sex emerged spontaneously as major reasons to support microbicides, which was linked to being able to insert microbicides "before going out" and for them to have long-lasting protection against infection. Participants also wanted no age restrictions placed on use because of children's risk of rape. A preference for overt use emerged, and microbicide visibility was of concern to male participants. Gender power dynamics appeared to underlie all these issues. Implications of microbicides regarding possible contraceptive properties in a society where fertility is highly valued will be discussed.

Conclusion: Microbicides have the potential to meet diverse needs beyond what prior research suggested. The challenge will be to develop a microbicide that can meet diverse needs, especially in a South African context where women and girls face high levels of rape and concomitant HIV infection.

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03119 SITUATIONAL ANALYSIS OF HIV RELATED STANDARD OF CARE AVAILABLE AMONG TARGETED RESEARCH COMMUNITIES

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BACKGROUND: The current practice of care for research participants is to seek ways to improve or facilitate local health care services to ensure that a common or best standard of care is available and accessible to the community.

OBJECTIVES: To explore HIV related services available in community structures among targeted research communities. To assess HIV related standard of care provided by Health Care service providers. To establish an accessible and adequate referral pattern for trial participants.

METHODS: A geographic positioning system was used to identify community structures which provide HIV related care in the Verulam and Tongaat in the North of Durban.

RESULTS: 11 Public health services, 6 Non-governmental organizations (NGO) and 5 community based organizations (CBO's) were identified as providing HIV related health care.

Primary Health Centres: The centres provide basic health care, treatment of STIs and opportunistic infections, such as TB, chest infections, skin irritations and provide anti-biotics and immune boosters to HIV infected persons via the VCT/PMTCT programmes. They also provide nevirapine to pregnant women and babies on the PMTCT programme, who are monitored and followed for a period of a year. HIV positive clients are enrolled for on going counselling, monitoring, and ultimately become members of an HIV positive only support group. Osindisweni hospital has a VCT centre that also conducts CD4 counts. All of these centres hope to participate in the ARV roll out programme.

NGOs: They assist infected persons with food hampers, state grant applications, offer training on bead work; collaborate with other organisations in identifying and facilitating training of volunteers in Home Based Care and formation of support groups. One centre also functions as a temporal hospice for full-blown AIDS patients. The Haven of Rest also has a VCT programme for HIV testing and counselling. Some NGOs train communities on gardening projects and supply vegetables at a cheaper price.

CBOs: Are active in identifying volunteers to be trained in home based care. They train communities in beadwork and art, conduct education and awareness through drama and public gatherings. Encourage community members to form sustainable support groups. Those that have trained HIV counsellors offer this service to support groups.

CONCLUSION: The current best locally available standard of care for HIV is available in this research community. Co-ordination is required to minimize duplication of efforts in the same geographic area. Referral systems from research clinics are available provided a formal partnership is forged.

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ABSTRACT ONLY

02168 MICROBICIDES THE ULTIMATE PREFERENCE OF ALL THE WOMEN PREVENTION OPTIONS

WAIKHOM, RONNY
L, Lilabanta et al

ISSUE:
In the beginning the transmission of HIV in Manipur (a north-eastern state of India) were confined amongst the IDUs (injecting drug users) but now we are witnessing a paradigm shift in the transmission. It has started to take its root to the female spouses and further to their children. STIs have also become one major health problem amongst general women attending ante natal clinics. Unwanted pregnancies are yet another common unwanted happening. And use of prevention options such as male condoms is solely depended on the male partners.

DESCRIPTION:
As a working group member of a national campaign for initiating women prevention options such as female condoms and microbicides in India, the CARE Foundation in collaboration with 14 NGOs have conducted a preliminary survey for obtaining opinion on microbicides and other female initiated methods. Altogether 337 were involved in the said survey. 273 were women and 64 were men. The respondents included MSMs; CSWs; young married women; middle-aged housewives; HIV/AIDS service providers (male & female), school & college going girls and male IDUs.

LESSONS LEARNED:
95% of them never heard of microbicides.
30% have heard of female condoms but only 4% have actually seen it.
Use of male condoms is solely depended on the male partner.
All of them were explained regarding the microbicides, female condoms and other barrier methods.
All of them feared its (microbicides) side effects and 60% had doubts over its efficacy.
All of them would opt for microbicides, if prove safe and efficacious.
It would empower women and the choice over using of prevention options would be on their discretion.
Stigma attached to male or female condoms will no longer be there in case of microbicides and hence could procure over the counter.
Its conspicuous nature, lubricating factor and easy to apply would facilitate the sexual activity and will also enhance the pleasure.

RECOMMENDATIONS:
Mass campaign such as the present "Global Campaign for Microbicides" is a must.
People must be aware of its usage and importance and must also know its pros and cons.
Feasibility and acceptability or Phase III trials must be conducted equitably at the regional levels.
Proper law must be enacted for protecting the rights for those undergoing trials.
Need for advocacy to those key players in making or changing the laws.
Adequate funds must be available for conducting such trials or for developing effective microbicides.
The prices (of microbicides) should be affordable by all, especially by those poor end-users from poor or developing countries where the impact of STI/HIV is worst.

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02187 PHASE II OF KNOWLEDGE, ATTITUDES & PERCEPTIONS TOWARDS THE USE OF MICROBICIDES: TANGA RELIGIOUS LEADERS RESPONSES

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Objectives: Religious leaders play a very important role in a community, to Inform, Educate & Communicate. Our organization intend to involve religious leaders to jointly conduct MICROBICIDES awareness Campaign. But what knowledge to they have about MICROBICIDES? What is their attitudes and perceptions?, which religious leaders should be involved in our study, & how?

Method: We used questionnaire to generate data, out team interviewed 8 (eight) major Tanga religious leaders. Period of study was from Jan 2003 – September 2003.

Results: All 8 leaders (100%) did not have an idea about Microbicides, 3 Church leaders (38%) are interested to jointly conduct Microbicides awareness campaign through Health & Calamity Sections, Periodic meetings, joint HIV/AIDS Counselling & testing; women organizations; & PASADIT. Views about Microbicides jelly included: No objection 3 (38%); incomplete research 1 (12%), will encourage prostitution 3 (38%), worried about side effects 1 (12%).

Conclusions: Level of knowledge about Microbicides does not exist. We shall jointly conduct Microbicides awareness campaign for interested religious leaders ie. Tanzania Assemblies of God (TAG); Roman Catholic (RC); Seventh dat Adventist (SDA) and other NGO'S involved in HIV/AIDS research.

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02189 HIV PREVENTION AMONG SEX WORKERS IN SENEGAL

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Objectives: surveys reveal high rate HIV infection among sex workers in Senegal Vaginal Microbicides and virucides offered the possibility to prevent infection and HIV. The study also intended to provide detailet information on knowledge and prevention so our objective is to obtain user perspective on microbicide from sex workers.

Methods: 50 sex workers were recruited and followed up to 6 months. Focus group discussions to discuss the themes of the study (HIV prevention and Microbicides

Results: More than 95% would like to use microbicide. The reason for microbicide usage was:- Disease protection Family planning 11%, - Disease protection and planning 40% others 10%

Conclusion: sexuel relationship among sex workers is while risky pratices are widespread is expressed need for protection against STDs HIV/AIDS

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02201 GRASSROOTS MEDIA CRY OUT: WHAT MICROBICIDES?

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Issue:The need to create awareness, acceptability and readiness of microbicides at grassroot level via mass media relevant in Nigeria. The 2001 survellance survey was 5.44% result graduated to 5.8% in the 2002 survey with the rural(grassroot) areas recording a high level of prevalence.Description: A training workshop for media practitioners in Ekiti State in Nigeria was facilitated by JAAIDS, , a media based NGO for media practitioners in collaboration with Ekiti State Action Committee on AIDS (SACA)along with Department for International Development (DFID) for 45 journalists comprising of media managers, gatekeepers, reporters, programme producers and newscasters in both print and electronic media.. A pre -workshop questionnaire survey was employed to test the Knowledge, Attitude And Perspective (KAP)of the participants on HIV/AIDS prevetion, treatment, care and support and and a post workshop questionnaire was utilised. The Female Condom (FC) and microbicides.Also, the FC and microbicides section caused a quite a stir as they have never seen or heard of the FC less microbicides. The participants took a high interest in other preventive options particularly for women and requested for information flow so as to make information known to the general public. Lesson learnt: This experience encouraged JAAIDS to seek funding to support a national grassroot training of journalists on other prevention options as well as other issues relating to HIV/AIDS. The project is currently on-going Recommendation: Mass media and people at the grassroot very essential to successful acceptability and readiness for microbicides product

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02217 HIV/STIS PREVENTION THROUGH MICROBICIDES: A STUDY SURVEY AMONG FAMILY PLANNING CLINIC ATTENDEES IN NIGERIA

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BACKGROUND: globally HI/STIs remain a major public health problem. Data on HIV/STI in Nigeria remain rudimentary, due to under-reporting. More than 90% of these infections are though heterosexual and unprotected sexual behaviours with women more vulnerable. Effective vaginal microbicide remain the only open hope in the prevention strategy,

OBJECTIVE: To assess HIV prevalence and conventional STDs among women attending Family Planning clinic in Lagos, Nigeria.

METHODS: Semi-structured questionnaires after informed consent, were administered by trained health personnel to 92 attendees. Demographic data gained were age, marital status, number of sexual partners, history of STDs and blood transfusion. Serum samples obtained were tested fro antibodies against HIV and syphilis. Sero- positive cases were confirmed by Western Blot for HIV and TPHA for Syphilis. Cervical swabs also collected were bacteriologically analysed. Study period was from November 2002 to September 2003. Ninety two (92) attendees made up of 55 married and 37 ingle women participated in the study.

RESULTS: Eight (8.7%) were infected with HIV, six were infected with HIV-1 and two were co-infected with HIV-1 and HIV-11. Conventional STDs were Treponemal pallidium (6%) Neisseria gonorrhoea

(3%), Chlamydia trachomatis (4%), Staphylococcus aureus (8%) and Candida albicans (14%). 5% of the participants had two or more of the STI's.

Products commonly used among participants include antiseptics, antifungal cream, foaming tablets, gels, condoms, antibiotics and vaginal douches. The study showed that Candida albicans was the most prevalent, followed by HIV and Staphylococcus aureus. There was no significant differences in the 2 groups (married and single).

CONCLUSION: the study group was aware of the effects of HIC/STIs and welcomed the concept of effective vaginal Microbicides. Majority of women indicated willingness to participate in the country's microbicide trials when finally introduced.

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02223 PEER EDUCATION IN HIV PREVENTION WITH HIGH RISK YOUTH

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Objective: One percent of the newly diagnosed STIs and HIV cases in Baluchistan, Pakistan are individuals/youth at risk 8-17 years of age. Our epidemiologists indicate that STIs and HIV cases among Youth increased between 1998 and 2003. While clearly an at-risk demographic, youth are rarely targeted with STIs and HIV prevention education. To empower youth the pilot project at the Youth Empowerment Skills fills that gap by utilizing youth at risk/street children as peer educators administering STIs and HIV prevention programming. Methodology: In thirty-minute Life Skills education sessions, peer educators provide out of school going youth sound, reality-based information that increases their awareness about STDs/HIV and the spread of the virus. Sessions encourage vulnerable youth to recognize how the virus impacts their lives and gives them a forum to discuss the issue with people of their own age. Findings: Launching a Peer Education program, which includes awareness of self and body protection focusing on child sexual abuse and STDs/HIV, life skills, gender and human rights/children rights awareness, preventive health measure, and care at work. Opening care and counseling center for these working and street children and handling these centers over to local communities. During awareness sessions, Youth are informed about the nutrition, physical and psychological changes, masturbation, menstrual cycle, family planning and STDs/HIV. It was determined relationships among HIV related knowledge, beliefs and sexual behavior of young adults and found that reason for unsafe sex included, misconception about disease etiology, conflicting cultural values, risk denial partner pressures, trust and partner significance, accusation of promiscuity, lack of community endorsement of protective measures, and barrier to condom access. In addition socio economic pressure, physiological issues, poor community participation and attitudes, and low education level limited the effectiveness of existing HIV prevention education.

Conclusion: Presentations at centers by peer educators have demonstrated that audiences over 12 years of age typically have only basic information about STIs and HIV. Confusion regarding the difference between HIV and STIs and the specifics of risk related behaviors generated interest in the presentations. Additional conclusions will be drawn as the pilot progresses and administrators tabulate survey results and conduct focus groups with peer educators and participants.

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02338 MICROBICIDES, CONDOMS OR BOTH? VIEWS OF MEDICAL PRACTITIONERS IN TWO STATES OF NORTH EAST NIGERIA

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Forty-four doctors out of 49 responded to the questionnaire. Thirty eight were (86.4%) were males and six (13.6%) were females. Thirty-one (76.7%) were less than five years as doctors and 5(11.4%) were above ten years.

Fifty percent (22) of clinicians report HIV as the commonest form of STI in clinical practice, followed by gonorrhoea (18.1%) and Candida (11.4%).

Sixteen clinicians (36.4%), 12(27.3) and 11(25%) considered faithfulness, condom and abstinence respectively as the most practical and feasible methods to prevent HIV and other STIs.

Twenty nine (65.9%) of medical practitioners don't think microbicides when applied locally would be superior to condom in preventing STIs since they may not be effective against the various agents causing STIs. But 29(65.9%) think condoms should contain microbicides to improve effectiveness in preventing STIs. While 31(70.5%) will support the production and marketing of microbicides in Nigeria, Bio- terrorism, resistance and promotion of sexual promiscuity are some of the reasons for not supporting. Microbicides could be spermicidal (27.3%), carcinogenic (18.2%) or cause itchiness (13.6) are some of the anticipated problems with their use.

Twenty six (59.1%) think that microbicides should take the form of creams, lotions (9.1%), pessaries (9.1%) and suppositories (6.8%).Thirty –two (72.7%) would recommend the use of microbicides to both married and unmarried. Fifty four percent report that both the man and woman should use microbicides in sexual encounter. And 22 (50%) would recommend microbicides few minutes before sex, 15(34%) at the time of sex and 5(11.4%) an hour before sex. Although 95.5% of the respondents are not aware of any microbicides currently in use, 31(70.5%) would support the production and marketing of microbicides.

Conclusion: Doctors will support the production and marketing of microbicides and condom should contain microbicides to improve protection against STIs.

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02350 INTENTIONS TO BECOME PREGNANT: DATA FROM A FEASIBILITY STUDY FOR A PHASE III MICROBICIDE TRIAL

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Introduction: Vaginal microbicides are being developed to increase options of preventing HIV transmission. While current products are being investigated for both local and systemic safety profiles in phase I/II clinical trials, there are also potential effects of microbicides use on pregnancy, which also need to be considered when an effectiveness trial is planned. We therefore are investigating the willingness of women to delay pregnancy in a feasibility study for phase III microbicide trials.

Objective: To assess women's reported intentions to become pregnant, prevalence of pregnancy, and the willingness of women to delay pregnancy during a feasibility study for a phase III Microbicide trial in rural Uganda.

Methods: A cohort of 101 couples (76 HIV sero-discordant and 25 HIV sero-negative concordant) in regular sexual relationships were identified in a serological survey and invited to participate in a feasibility study in preparation for a phase III microbicide trial. Information on pregnancy prevalence and intentions of future pregnancies was collected from all women during the baseline questionnaire survey.

Results: Out of the 101 recruited couples, 98 women consented to individual interviews. Their median age was 32 years (range 17 – 63). 94 (96%) women had ever been pregnant. 14 (15%) reported to be currently pregnant and 5 (6%) were not sure. 65 (66%) of the women said they had no intentions to get pregnant within the next 2 years, 6 (7%) were not sure, while 22 (27%) intended to do so. Of those intending to become pregnant, 13 (60%) expected this to happen within the next 1 to 2 years, 3 (14%) in the next 3 months to one year and 6 (26%) within the next three months. 54 (68%) of the women not currently pregnant were not using any contraceptive because they were either breast-feeding, 13 (24%), or reached menopause 12 (22%), while 18 (33%) said they had no particular reason for using contraception and 11 (20%) wanted to become pregnant.

Conclusion: Two thirds of the women in this population have no intentions of becoming pregnant within the next 1 to 2 years, a result that argues for conducting a phase III trial in this population with a follow-up duration of 2 years or less. However, it will be necessary to see how the proportion of actual pregnancies compares with reported intention during the ongoing feasibility study follow-up.

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02356 EVALUATION OF KNOWLEDGE AND ACCEPTABILITY OF MICROBICIDES BY COMMERCIAL SEX WORKERS IN LAGOS

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Background:
There is widespread interest and hope in a safe and effective microbicide as a potential way of prevention of transmission of sexually transmitted diseases and HIV/AIDS.

Objective:
To evaluate the knowledge of, and acceptability of microbicides by female commercial sex workers in Lagos, and to assess their willingness to participate in trials involving microbicides

Methods:
Data was derived from a multicentric cohort of female commercial sex workers, through focus group discussions, individual interviews, and use of structured questionnaires covering socio-demographic data including age, religion, marital status, parity, education, and "primary occupation". Sexual health and vaginal practices, HIV/STDs status and knowledge, types of microbicides known/used, reasons for use and specific beliefs, as well as readiness or willingness to participate in any trial were evaluated.

Results:
Total numbers of 851 females, mean age 24+ 11years, 28% married, 32% were graduates, 45% high school certificates, while 23% had primary education. On knowledge of microbicides, products identified include foaming tablets, gels, antiseptics, antifungal creams and ointments, antibiotic powders, douches, vaginal tablets, petroleum jelly, 'alum', and tradomedical preparations. Knowledge and use of foaming tablets, gel, antifungal and antibiotic powders were proportional to level of education. Reasons for use include healthy state of the vaginal (65%), personal sexual pleasure (45%), sexual pleasures for male clients (52%), to prevent contact of infection (62%), keep the virginal tight (45%), and for contraception (45%). Generally where substances were used, men or clients were not made aware. Most preferred products that disintegrated without much wetness in the vaginal, and not coloured. On vaginal practices, 35% reported regularly cleansing the vagina just before sex, while 26% used routinely, antifungal creams like Canesten, Gynostatin also believe to have antibacterial effects. Non-acceptability was due to physical discomforts such as itchiness in the vagina, dysuria, vaginal ulcerations, and excessive wetness by some vaginal pessaries. Some respondents still use 'alum' and some trado-medical preparations for tightening of the vagina. On willingness to participate in microbicides studies, 57% were ready provided they are not long terms studies. Single young respondents were more ready to participate than married.

Conclusion:
There is increased knowledge by commercial sex workers in Lagos about microbicides. Since they constitute a risk group, they need protection. However, there is much concern about cost, availability, safety, effectiveness and comfort in use.

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02380 MICROBICIDES AN ANOTHER APPROACH TO KEEP STI/HIV INTERVENTION VIABLE

Bangkim, Chingsubam Bangkim

ISSUE: Manipur is famous for its high HIV prevalence rate and a major portion of it is also contributed by MSMs. The recent sentinel surveillance on 250 MSMs shows 30% are HIV positives. Despite of such a high rate the HIV prevention programmes amongst MSM are negligible.Targeting MSM and their need identification is the priority. Harassed and sexually abused by their family members and community, they are driven underground. Hence, it becomes difficult not only to reach them but also in designing & development intervention programs to address various issues such as discrimination, sexual roles & internalized homophobia etc.

APPROACH:
Field visits, FGD and interaction; workshops and sensitisation programmes; dissemination of legal ethical issues; health education; interviews -321 MSMs

KEYPOINTS:
Alienated by the family members
Physically abused by security personnel & youths
More than 83% has multiple sexual partners
34% has history of STI infection
Condom use very rare 12%, lack of knowledge, freely accessible and good quality
65% preferred water based lubricant condom
Male condom use solely depended on the partner
Sexual partners include middle aged married men, security personnel and ex-IDUs
The existing strict Indian law 377 in the country hamper the intervention programs.
After explaining about microbicides more than 76% of the participants would like to undergo Microbicides trial.

IMPLICATION: The general population do not realise the risk involved and thus neglect their involvement. Stakeholders including NGO and GO sectos are not aware about the issues pertained around MSMs. There should be more sensitization programme through various Medias including print and electronic. Microbicides if proved effective and safe then the entire intervention prevention programmes would be indeed efective thus preventing many from STI/HIV. Microbicides awareness programs should be initiated to other parts by organizing workshops, seminars among the GOs, NGOs, CBOs & community at large.

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02382 NEED OF THE HOUR – A WOMAN CONTROLLED PREVENTION TECHNIQUE

Archana, Oinam Archana
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ISSUE: The Serious epidemic of AIDS related death has increased in Manipur. HIV sero-prevalence rate among IDUs in Manipur which is one of the highest in the world has reduced from 73% in 1992 to 59.79% at present. The epidemic is now shifting from IDUs to their spouses/partners/children and general community. According to the MACS epidemiological report July 2003, the sero-prevalence rate among antenatal mothers is 3.12 %, thereby indicating that the infection is in the general population and no longer restricted to any specific target group.

Women are at high risk of HIV infection. For effective HIV prevention among women, the only option available is male condom. This is the only 'safe' barrier protection that has its own limitations. Inspite of different woman empowerment programs, women in general still lack the power to discuss and negotiate safer sex with their husbands/ partners.

APPROACH: Group discussion, Focus group discussion, one to one interactions among infected and affected women, local youth's female and Injecting drug users.

KEY POINTS:
Very less knowledge on sexual health issues
Out of 100 IDUs only 20% use condom, Baseline OXFAM/SASO
Rarely use due to non-availability of condom
IDUs used condoms while having sexual contact with the sex workers but not with their girl friends.
Women cannot negotiate for safer sex.
Female drug users are indulging in unprotected sex for their drug habits
Single women (widows) are being taken advantage thereby increasing their vulnerability to STIs and other blood borne diseases.

IMPLICATIONS:
Women need prevention method, which they can control, such as female condoms and microbicides. There is the immediate need for other alternative methods other than male condoms. The idea is that we should widen the range of 'safer sex' choices in order to complement the existing safer sex mechanism.

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02390 SEX WORKER CONDOM USE PATTERNS BY PARTNER TYPE

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We conducted key-informant-interviews with 40 female sex workers (FSW) living in Nairobi, Kenya to understand their continued risk for HIV acquisition in spite of periodic comprehensive training on correct condom use and negotiation for safer sex.

Two independent readers of the resultant transcripts identified four key themes relating to condom use practices and partner types. The FSW reported increased condom use with casual partners due to their increased awareness of HIV/AIDS. However, most felt unable or were unwilling to demand condom use from their regular clients because of 1) fear of angering them, 2) fear of losing them, 3) and consequently their financial support, and 4) desiring sexual intimacy.

The narrative data suggests that greater efforts should be made to help FSW negotiate for safer sex with their regular clients and to develop additional female-controlled and effective prevention technologies, such as microbicides with or without the female controlled barrier methods such as the diaphragm.

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02402 PREVALENCE AND TYPES OF STIS AMONG FEMALES OF REPRODUCTIVE AGE ATTENDING A REHABILITATION CENTRE IN LAGOS, NIGERIA

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Background: Previous studies have shown that asymptomatic patients with STIs/HIV constitute high risk groups in the spread of these diseases with developing nations highly affected due to poor health facilities, lack of adequate finances and reluctancy on the part of the patients in seeking prompt medical advice.

Objective: To determine the prevalence rate and types of STIs/HIV among females of reproductive age in a rehabilitation center in Lagos.

Methods: Data were derived through structured questionnaires and one on one interview. Sociodemographic data including age, marital status and symptoms suggestive of STIs were documented for all females of reproductive age attending the center for the first time. Clinical examinations were conducted and high vaginal speculum swabs collected for wet microscopy, gram staining and culture. About 2-3ml serum samples were collected from the participants for HIV and syphilis serological determinations. All reactive sera for HIV and syphilis were confirmed with Western blot and TPHA techniques respectively. The study period was from January 2002 to April 2003.

Results: Out of 312 participants, 158 (50.6%) had one or more STIs. Married and widowed (n = 200) had the highest prevalence of HIV (9.0%) with single women (n = 112) having the highest prevalence

of trichomoniasis of 32.1%. Candida albicans colonization stood at 42% in 131 of the women, while 9 (7.8%), 25 (21.7%) of gonorrhoea and syphilis respectively were found in 115 of the women who complained of vaginal discharge. Also 7.3% genital wart and 12.4% pubic lice respectively were noticed on the pubic region in 218 of the women before speculum examinations.

Conclusion: In order to effectively control the high prevalence of STI/HIV infections, the use of vaginal microbicide suggests the only viable and potentially useful option.

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02408 BEHAVIOURAL CHALLENGES TO MICROBICIDE GEL ACCEPTANCE AND USE IN SUB-SAHARAN AFRICA

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This overview paper discusses the behavioural and cultural challenges to microbicide gel acceptance and use in sub-Saharan Africa, a setting characterized by unique socio-economic circumstances and cultural norms relating to sexual behaviour and gender power relations. Given the relatively low status of women, men play a key role in reproductive health decision making and behaviour. Recent Demographic and Health Survey (DHS) data in the region suggest that more men than women have multiple sexual partners, and condoms are rarely used within regular sexual partnerships. This paper draws on the experiences of six sites in sub-Saharan Africa participating in the feasibility study of the microbicides development programme (MDP), coordinated by the UK MRC/CTU. Critical issues for consideration include: microbicide gel acceptance, especially where gel use is inconsistent with practices aimed at enhancing sexual pleasure such as dry sex; the extent of male partner involvement without compromising the case for a woman-controlled product; and the relatively poor socio-economic circumstances, including low literacy levels among the populations. Preliminary social science research at the sites indicate significant male dominance in reproductive health decision making and high prevalence of intravaginal practices that are likely to affect microbicide gel acceptance and use. These challenges apply during the microbicide trial phases and beyond. Behavioural research in these populations plays a critical role in the understanding of these issues to better inform microbicide development for sub-Saharan Africa communities and similar settings.

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02482 ENHANCING KNOWLEDGE TRANSFER FOR THE SUCCESSFUL INTRODUCTION OF MICROBICIDES IN DEVELOPING COUNTRIES

Clur, Brenda

This paper aims to provide new insights on how to develop the skills Health Professionals and HIV/AIDS Educators/Counselors need, to harness the brain's information processing system to enhance knowledge transfer, in order to facilitate the successful post-trial introduction of microbicides in developing countries.

Three case studies will be outlined, including experiences, key learnings and results achieved implementing projects in the Public and Private Sectors, that involved training Health Professionals

and/or HIV/AIDS Educators and Counselors on how to use thought management methods to enhance knowledge transfer. The experiences and lessons learnt provide new insights on how to develop the skills people need to convey knowledge more effectively, to establish a common understanding of the concept, proper use of microbicides, the benefits, risks and limitations, so that appropriate messages are conveyed from the start and people are empowered to make informed choices leading to safer sexual practices.

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02484 GENDER MARGINALIZATION - A CHALLENGE FORMICROBICIDES AS A PREVENTION OPTION FOR WOMEN IN INDIA

Kumaramangalam Lalitha
Prakriti

Fifteen years after the HIV epidemic began in India, today more women are being infected than men. As Indian women have no control over their sexual and reproductive lives they are vulnerable to STIs/RTIs. Furthermore, IEC and prevention campaigns have failed to address the needs of women, and they continue to lack the necessary skills to negotiate for safer sex. A patriarchal social system and the inability to voice their needs, opinions or feelings have exacerbated the situation. In India only men are permitted to have sexual desires. Sexual violence against women, including marital rape is not recognized as a crime and often goes unpunished. The onus for 100% condom use is often thrust on women, especially sex workers. Recent research on female condoms has demonstrated women's dependence on the concurrence of their male partners. Hence, in India, research into microbicides must be culture and gender sensitive, focussing on women's marginalization, including that of positive women. It has become imperative to integrate issues of RTIs/STIs/HIV and women's rights into all developmental programs directed at women. Simultaneously men's involvement must emphasize enhanced male responsibility, without reiterating/exacerbating the existing gender bias. Only then can microbicides be an efficacious and sustainable prevention option for India's women.

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02497 MICROBICIDES AWARENESS AMONG BIOMEDICAL STAFF AT THE UNIVERSITY TEACHING HOSPITAL IN LUSAKA,ZAMBIA

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Background: Biomedical workers are key persons in the promotion and use of microbicides. There is an urgent need to assess their knowledge about microbicides in a high HIV prevalence country like Zambia. Objective:To assess the current level of microbicides awareness among the biomedical staff at the University Teaching Hospital(UTH)Lusaka,Zambia. Method: A survey was conducted using the structured questionnaire from June -August 2003. Expected definition and types of Vaginal microbicides were pre-defined by the researchers. The points from 1 to 5 were awarded based on satisfactory responses. Points of 5 represented the optimum desired response. Results: Forty-nine staff members returned the questionnaires. There were 12(24%) women and 37 (76%) men with age ranging from 25 to 42 yrs. Respondent women were younger (mean age 30.2 yrs) as compared to men (mean 35.2 yrs). Eight(16%) were graduate degree holders and 15(31%) attained first degree and

26(53%) College Diploma. All the graduate degree holders had a satisfactory score of 4 points each. Twelve (80%) of the first degree holders scored 2 points each . Ten (38%) of College Diploma holders got one point each. Nineteen (39 %) of the respondents (3 first degree and 16 College Diploma holders) perceived microbicides to be spermicides used by women for contraception and were not given any point.Conclusion:Knowledge gaps about microbicides exist among majority of biomedical staff. There is a positive correlation between microbicides awareness and the level of education. Sensitisation programmes on microbicides must be put in place.

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02528 ACCEPTABILITY OF A VAGINAL GEL AS A PROTECTIVE BARRIER AGAINST STDS AND HIV IN ADOLESCENT GIRLS AND SEX WORKERS IN DAKAR

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Introduction: The STI center in Polyclinique of Dakar deals with nearly more 1000 sex-workers. In Senegal, the practice of prostitution has been tolerated since 1962 (Decree No 62036 dated 13 August 1962).

Objective: To evaluate the level of knowledge and acceptance of microbicides among authorized prostitutes and now for adolescent girls (50 adolescent girls sex workers are informed of microbicides). To warn against HIV infection and the STI. To inform prostitutes about the use, the effects and the signification of microbicides.

Methodology: In the Institut d'Hygiene Social site, selection of 300 prostitutes living with or no without the HIV and registered for the sanitary index, 50 adolescent girls sex workers; information is obtained from prostitutes through interviews based on a questionnaire about the knowledge and acceptance of ways of using preventive methods against the transmission of HIV, in particular (male condoms, female condoms or femidon, microbicides).

Result: About the knowledge of microbicides
300 prostitutes and 50 adolescent girls are sensibilized
14% have heard of microbicides
98% have accepted to be part of a study on microbicides mainly those who have fixed partners
1% have regained doing so.

Conclusion: The study in process sex workers need protection since they constitute a risk group. This microbicide can play a very important role in the prevention of STI/HIV/AIDS. The use of microbicides is an alternative method particularly with partners refusing to use male condoms. I think also the only alternative methods of prevention, which can be controlled by women, has led to interest in the development of microbicide.

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02578 CANADA: APPLYING RIGHTS-BASED APPROACH TO MOBILIZE COMMUNITY FOR MICROBICIDES

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As the AIDS epidemic enters its third decade, it becomes clear that enabling those who are not yet infected to protect themselves from HIV, and providing adequate and affordable treatment and care to people living with HIV/AIDS (PHAs) are two of the biggest challenges facing humankind today. From a global perspective, numbers of HIV infection in Canada seem quite low (52640 HIV-positive tests reported in adults and children), but they are significant to Canada's population of approximately 32 million. Women represent an increasing proportion of reported HIV cases in Canada, and since 2000 there has been an increase of HIV cases among gay men in urban settings.

Canada does not have a Microbicides Development and Delivery Strategy. Canada is yet to earmark funds specifically for microbicides development and delivery. Currently, there is only one candidate product in clinical trials in Canada, and the researchers often face financial constraints.

The general public as well as HIV/AIDS community often lack awareness about microbicides, and the importance of advocating for increased investment in microbicides development and delivery.

In 2003 Canadian AIDS Society (CAS) with funding from Health Canada and in close collaboration with the Global Campaign for Microbicides launched an advocacy initiative, seeking to raise community awareness, increase community participation in microbicides development and delivery, and enhance community advocacy efforts through applying the rights-based approach to HIV prevention. As a result of this project an advocacy tool "Microbicides in Canada: Legal, Ethical and Human Rights Issues" was published and disseminated among CAS membership (115 AIDS service organizations). This presentation outlines legal, ethical and human rights issues in microbicides development and delivery that were identified through research and extensive community consultations, and hi-lights the important role communities around the world, including in such industrialized countries as Canada, can play in advocating for the global access to microbicides

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02601 MICROBICIDES, DIAPHRAGMS, MALE CONDOMS, AND HIV VACCINES: INTENTIONS AMONG A SAMPLE OF U.S. STUDENTS

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Multiple HIV prevention methods are needed so that women and men have options. In this study, we examined intentions to use microbicides, the diaphragm, and male condoms as well as intentions to get vaccinated with a preventive HIV vaccine among a study population of college students. A total of 277 college students (187 women, 90 men) completed self-administered questionnaires that included questions about microbicides, the diaphragm, male condoms, HIV preventive vaccines, and related topics. We limited the present analyses to those respondents who reported having had at least 1 sexual partner in their lifetime. Among women, only 20% reported that, if microbicides were available today, they would be somewhat or extremely likely to use them in the next 3 months. In contrast, 45% reported that, if a preventive HIV vaccine were available today, they would be somewhat or extremely likely to get vaccinated in the next 3 months. Whereas only 1 woman reported that she would be likely to use the diaphragm in the next 3 months, 63% said they would be somewhat or extremely likely to use male condoms during that time period. Similarly, among men, intentions were highest for male condoms (61% somewhat or extremely likely), followed by an HIV vaccine (51%), microbicides (7%), and the diaphragm (0%). Thus, among this group of college students, intentions were relatively high for an HIV vaccine and low for microbicides and the diaphragm. We will also explore how intentions differ for subgroups other than gender. Results and implications for the development of new HIV prevention methods will be presented.

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02636 THE CHALLENGES OF NATIONALLY REPRESENTATIVE ACCEPTABILITY STUDIES IN A MULTI-CULTURAL CONTEXT

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Background: This paper seeks to highlight the challenges of attaining a nationally representative, probability based sample in a developing, multi-cultural setting. It aims to highlight the additional complexities of attaining such a sample when the research question pertains to sexual behaviour.

Methodology: South African researchers and fieldworkers working in an organisation specialising in primary data collection were asked about their experiences of in attaining nationally representative probability based samples.

Results: This presentation will report on issues such as the relatively large sample sizes required to ensure sub-populations are adequately sampled and the difficulties of developing sampling frames for such sub-populations. It will highlight the need for community preparation to obtain permission from traditional authority structures and to raise awareness of the research among community members. The challenges of physically mapping households in a defined geographical area, particularly in informal settlements and rural areas will be discussed. The impact of low response rates from particular groups on overall response rate and acceptability of the findings will be examined. Difficulties in obtaining informed consent from disempowered groups and the challenge of unambiguously translating questions about sexual behaviour into 10 languages without offending will be highlighed.

Conclusion: Those planning large scale microbicide acceptability studies need to consider these issues at the proposal stage of their projects to ensure adequate preparation to meet these challenges.

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02697 THE FEMALE CONDOM: SEEING THE READY BEATEN TRAIL TO START PAVING THE PATH

Philpott, Anne
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The Female Condom and the vaginal microbicide will share many product features and social challenges. An approved microbicide will require the prepared institutions, service delivery mechanism and trained networks of service providers for its delivery. Both products are female initiated, prevent or could prevent HIV transmission and are inserted into the vagina. Many lessons have been learnt internationally and at a country level about how organisational structure, policy response or political backdrop can affect uptake of female condoms. As yet there has been no other HIV prevention technology invented besides the male condom and none that is female initiated.

Female Condom programmes have proved most successful with clear targeting, product champions, adequate and consistent supply, cross-sectoral stakeholder support, face to face communication and

support for anatomical and sexual skills enhancement and training to avoid potential negative service provider biases. The challenge of resource allocation, the importance of female-controlled prevention methods and the right of women and men to have access to and choice among a range of methods are not at all unique to the female condom – they are central issues to a range of products and behavioural interventions. Delivering female condoms now paves the path for future delivery of a vaginal microbicide.

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The organisers accept no responsibility for errors and omissions

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